Newer Methods of Preparative Organic Chemistry

Volume III

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Preface

In this third volume of a series dealing with newer methods in preparative organic chemistry, the publishers continue to provide for the English-speaking chemist a useful survey of some of the more recent developments in this field. Like its predecessors, the volume consists of a number of selected reviews which originally appeared in *Angewandte Chemie;* these summarize a wide variety of topics in a comprehensive and authoritative manner. Detailed experimental directions are given, and the probable reaction mechanisms discussed; references to the original literature abound. This volume should, by its very nature, be of great value to all organic chemists, in both acamedic research institutions and industrial laboratories, who wish to keep abreast of modern techniques and developments in their field.

The translator should like to express his gratitude to Dr. N. A. Armstrong and Miss M. L. Bond for their kind assistance in the preparation of the English version of this book.

HENRY BIRNBAUM

Foreword

This volume is intended for all synthetic organic chemists.

The first series of these articles was originally collected in one volume, which went through numerous large editions. (Several editions were reprinted in the United States during the Second World War.)

The reviews in these three volumes are in the form of monographs, and have for that reason not appeared in systematic order. We have selected what seemed to us topical and important. (Reaction mechanisms according to modern theories are postulated only where they allow the prediction of fresh applications of the reaction described.)

The up-to-date character of the reviews is due to the exceptional cooperation of the authors.

W. FOERST

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The Reactions of Sulfur with Araliphatic and Aliphatic Compounds

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It seems opportune at this time to give a general survey of the reactions of sulfur recently published, special emphasis being accorded to those found in the patent literature. We should like, in this respect, to restrict ourselves to reactions undergone by aliphatic compounds or groups. Reactions between sulfur and the aromatic ring (e.g. phenol or aniline) are therefore not considered; the dehydrogenation of cycloaliphatic compounds introduced by Ruzicka in 1921 has already been reviewed (*1*). The important problem of the vulcanization by sulfur of rubber or unsaturated polymers generally, the mechanism of which remains unelucidated, is merely touched upon, and in some reactions a possible explanation of the vulcanization is alluded to.

We ourselves have also discovered fresh information concerning the action of sulfur on alkylated heterocycles. These results appear to link individual findings of various investigators, and may at the same time be of interest in relation to the largely similar course taken by the action of sulfur on organic compounds.

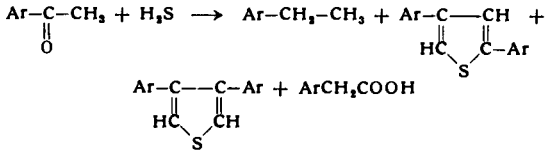
The Development of the Willgerodt Reaction

The best-known reaction between sulfur and methylene or methyl groups involving dehydrogenation or oxidation, is the so-called Willgerodt reaction (*2, 3, 4*). This consists in heating predominantly aromatic aliphatic ketones with an aqueous sulfur-ammonium sulfide solution in an autoclave (usually) above 200°. Carboxylic acids and their amides containing the same number of carbon atoms as the starting ketones are obtained. The reaction always proceeds, in effect, as though only the methyl group were oxidized to a carboxylic acid group, and the keto group simply converted into a methylene.

$$\mathrm{Ar{-}CO{-}(CH_2)_n{-}CH_3 + (NH_4)_2S_x + H_2O \longrightarrow Ar{-}(CH_2)_{n+1}{-}COOH}$$

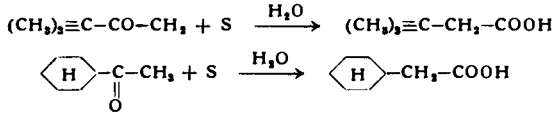
It was reasonable to expect that particularly those araliphatic ketones which can only be oxidized at one end should be conducive to a uniform

reaction course. Willgerodt, however, has already referred to the facile oxidation of enanthole to enanthic acid with ammonium sulfide (*5*). This reaction only illustrates the preferential attack by sulfur directly on the comparatively readily oxidized aldehyde group. Willgerodt proved conclusively that not only are oxidation processes in the Willgerodt reaction coupled with reductions, but that these can occur separately and are attributable to the hydrogen sulfide. The reducing action of hydrogen sulfide under the reaction conditions prevailing becomes clearly visible in the action of colorless ammonium sulfide on ketones; large quantities of hydrocarbons and thiophene derivatives are obtained together with acids and amides.



The acid and thiophene derivatives formed in this reaction are due to the oxidation products of hydrogen sulfide and their yields can consequently be lowered by the increased addition of the latter compound.

In its original form, i.e. the action of ammonium sulfide solution on araliphatic ketones under pressure at approximately 200°, the Willgerodt reaction found certain applications (see refs. *3,4,6*). Extension of the reaction was hampered by the (usually) modest yields of carboxylic acid. The use of water-miscible organic solvents such as dioxane or pyridine increased the yield of acid and lowered the reaction temperature to around 160°; this resulted in the decreased formation of by-products (*6*). In this ameliorated form, the Willgerodt reaction found wider application (*3,7*) (Example 1). Aliphatic ketones could now also be converted into carboxylic acids in a yield of 58%, though lower yields are generally the rule (*7–11*). In this class also, good yields are only obtained if one side of the ketone is oxidized less readily or not at all.

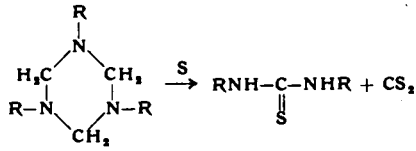


Whereas Fieser and his co-workers (*6*) also report the simultaneous formation of hydrocarbons in this example of the Willgerodt reaction (Example 2), Carmack and his collaborators no longer refer to it (*7*). The latter workers, however, used a larger excess of sulfur in the oxidation, whereby the reduction is probably largely suppressed.

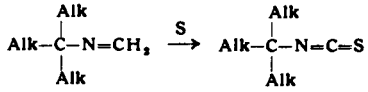
It is interesting to note moreover, as already mentioned by Willgerodt, that in the action of large quantities of sulfur or ammonium polysulfide on araliphatic ketones, the keto group may be oxidized as far as benzoic acid.

A substantial modification of the Willgerodt reaction was devised by K. Kindler. He proceeded from an observation of Wallach (*12, 12a*) that the action of sulfur above 180° on methylene groups adjacent to aryl groups, such as found, for example, in *p,p'*-tetramethyldiaminodiphenylmethane or even in benzylamine, results in their conversion to thiocarbonyl groups, thus forming thioketones from the former and thioamides from the latter. Kindler oxidized a series of benzylamines to thioacid amides (*13, 14*) (Example 3). He assumes the formation of Schiff bases as intermediates in the reaction between benzylamines and sulfur and conclusively demonstrates the ready conversion of these bases into thioamides by means of sulfur (*13*).

The trimeric Schiff bases of formaldehyde, existing as 1,3,5-trisubstituted hexahydro-*s*-triazines are correspondingly converted by sulfur into 1,3-disubstituted thioureas (*14a*).



An exception occurs in the case of the stable monomeric azomethines of tertiary alkylamines, which are converted into mustard oils on sulfurization (*14a*).



Not only Schiff bases, but aldehydes and ketones generally, undergo this reaction in the presence of primary and secondary amines or dry ammonia. Since the reaction takes place under anhydrous conditions, the thioacid amides are invariably obtained. This variant of the Willgerodt reaction has become generally known as the Willgerodt-Kindler reaction. The reaction is carried out at a maximum temperature of 180°.

Kindler's theoretical interpretation of the reaction, even if this does involve the initial attack of the nitrogen by sulfur, scarcely merits discussion today; the Willgerodt-Kindler method has nevertheless acquired great preparative significance and has been thoroughly developed (*15*). Morpholine is usually chosen as the hard-to-oxidize (*16*) amine com-

ponent, and the reaction proceeds at atmospheric pressure (*15*) (Example 4). The yields of thioamide amount to a maximum of 75%. Aliphatic ketones like methyl nonyl ketone may also be successfully subjected to the Willgerodt-Kindler reaction (*8*). It was even found possible to convert compounds as readily substituted in the ring as salicyl aldehyde into thioacid amides (*17*). Thermolabile furyl ketones, e.g. 2,5-dimethyl-3-furyl methyl ketone, could be converted into the thioamides at 100–110°, though the yields (10–27%) were rather modest. As anticipated, diketones are converted into dicarboxylic acids (*17a*). The Kindler method allows the surprisingly ready conversion of 1,3,5-triacetylbenzene into a 75% yield of benzenetriacetic acid (*18*) (Example 5).

The oxidation of benzylamines to thiobenzamides (*12*) is still one of the most convenient methods of synthesizing N-substituted thiobenzamides. It was subsequently more thoroughly developed by McMillan (*19*). Kindler's restricting the attack by sulfur to benzylamines only, though allowing its possibility in the case of, e.g. N-dimethylbenzylamine accompanied by the loss of one methyl group, has proved incorrect. Purely aliphatic amines also react readily on heating with sulfur to give thioamides, as was first indicated in the patent literature (*20*) (Example 6). The reaction proceeds readily in boiling pyridine at atmospheric pressure.

The oxidation of dibutylamine to N-butylthiobutyric acid amide proved to be the starting point of a more thorough elaboration, by us and by others, of oxidations effected by means of sulfur. When tested against tuberculosis in the laboratory of Prof. Domagk in Elberfeld, N-butylthiobutyric acid amide showed a specifically high tuberculostatic activity of 1:10 million. Even in Tb strains resistant to isonicotinic acid hydrazide, an activity of 1:1 million was still exhibited. Clinical use of the compound is unfortunately out of the question because of its excessive toxicity.

p-Nitrobenzylaniline with its highly active methylene group can be dehydrogenated to the Schiff base with sodium polysulfide at around 100°. *p*-Aminobenzaldehyde is obtained, as was already known in 1897 (*21*) (Example 7).

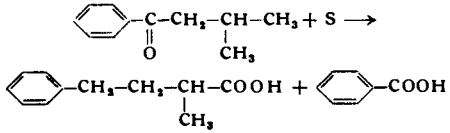
The Mechanism of the Willgerodt Reaction

The mechanism of the Willgerodt-Kindler reaction resisted numerous investigations. Even though it has not yet been elucidated in all its details, its major steps are known with some degree of certainty.

The old concepts of Kindler whereby a phenyl group migrates during the course of the reaction with sulfur are no longer considered a serious interpretation, since no definite indication has been observed of

the isomerization of a ketone during the oxidation. Willgerodt's older hypothesis, i.e., that the oxidation of the methyl group, e.g. in acetophenone, is preceded by the reduction of the keto group, is equally improbable as the corresponding hydrocarbons will not, or hardly, react under the prevailing reaction conditions.

When advancing a mechanism, it must be borne in mind that no isomerization occurs during the oxidation, and furthermore, that ketones differing only in the position of the keto group yield identical oxidation products (*9*). It must also be remembered that ketones in which the carbonyl group is adjacent to a phenyl ring and which contain a quaternary carbon atom give hydrocarbons exclusively and no carboxylic acids (*22*). De Tar and Carmack (*9*) believe that a reactive group—probably the amino group—migrates along the hydrocarbon chain during the course of the Willgerodt-Kindler reaction, via addition to triple bonds. The observation, reported almost simultaneously by McMillan (*10*) and Carmack (*9, 11, 23, 24, 25*) that olefins and acetylenes (Example 8) are also converted into thioamides or acids under the conditions of the Willgerodt reaction, supports the assumption of the presence of olefins or acetylenes as intermediates. On the other hand, the same authors point out that lower yields are obtained from the Willgerodt-Kindler reaction undergone by phenylacetaldehyde and β-phenylpropionaldehyde than by acetophenone and propiophenone, respectively. It is concluded from this fact that it is not merely a case of a carbonyl group's migrating along the carbon chain. It must, however, also be considered that a high initial concentration of mutually reactive aldehydes is conducive to side reactions of a different type. In argument against the intermediate formation of acetylenes, the fact is adduced that branched ketones incapable of possessing a migrating triple bond can also be oxidized by sulfur (*26*), though the yields are, to be sure, exceedingly small.

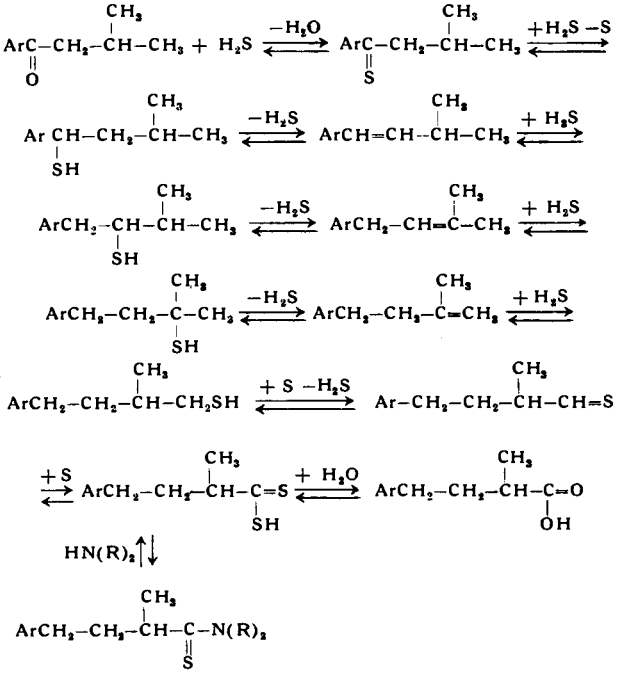


(The ketone can be degraded further, resulting in a shortening of the chain, an observation already noted by Willgerodt (*26, 27*) at the commencement of his work.) The degradation of a methyl ketone group as far as a carboxylic group has also been reported by other workers (*15*).

The oxidation of a branched ketone appears to contradict the migration of a carbonyl group along the chain; it also does not support the intermediate formation of olefins, for in this case the poor yield would scarcely be comprehensible. More probably, the oxidation can proceed

via several mechanisms, one of which involves the olefin stage. It would, however, appear that an intermediate devoid of the possibility of migration along a branched carbon chain does provide a substantial contribution to the reaction.

McMillan (*22, 28*) assumes that the reaction starts with the addition of H_2S to the keto group, followed by dehydration to a thioketone, the latter's reduction to a mercaptan, elimination of hydrogen sulfide to an olefin, renewed H_2S addition which can now proceed in two directions (to give isomeric mercaptans), again elimination of H_2S to give two isomeric olefins, and so on. The thiol group thus migrates along the whole aliphatic chain, including a carbon atom linked to only one hydrogen. The primary mercaptan finally obtained is dehydrogenated to the thioaldehyde and the latter irreversibly converted into the dithiocarboxylic acid; this last step may also involve stabilization to the thioacid amide or acid amide. Except for the conversion of the thioaldehyde into the thioacid amide, all the transformations are equilibrium reactions. It is understandable that this cycle of equilibria results in low yields in the case of compounds containing long carbon chains, since side reactions such as sulfide, or hydrocarbon formation interrupt the reaction sequence.



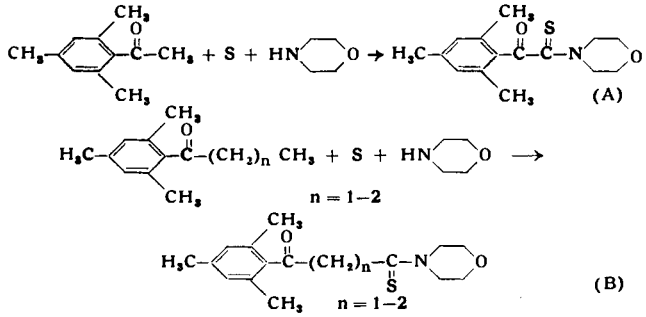
The reversible conversion of the secondary mercaptans into thioketones, possible at every step, is not included in the scheme. Nor is the formation of disulfides, which can be isolated in the careful reaction between sulfur and olefins, taken into account. They represent, in our opinion, labile compounds which will readily undergo further reaction without thereby being true intermediates. Other workers ascribe an important role to these disulfides in the reaction course (*29*).

A large number of observations is compatible with this reaction mechanism. Thus in the reaction of olefins, e.g. the oxidation of isobutylene to isobutyramide by means of sulfur, polysulfides are detected which could have been produced by the action of sulfur on thiols and which can be converted further into the thiocarboxylic acids (*29*). The reduction of a keto group by hydrogen sulfide to give a methylene group has been proved in various ways. Similarly, benzophenone can be reduced to diphenylmethane by hydrogen sulfide in the presence of morpholine; this reaction proceeds via the thiol compound, as is evidenced by the isolation of disulfides (*30*). The reduction of benzophenone to diphenylmethane with hydrogen sulfide is merely the reverse of the oxidation of tetramethyldiaminodiphenylmethane with sulfur to the thiobenzophenone derivative (*31*) (Example 9). Hydrogen sulfide itself need not be used, but can be replaced by a compound which generates hydrogen sulfide by reaction with sulfur, e.g. morpholine. The ready reducibility of the keto group is also shown by the notable yields of hydrocarbon (observed by Willgerodt in his original work) resulting from the reaction between araliphatic ketones and colorless ammonium sulfide, which contains hydrogen sulfide from the very beginning. Ammonium polysulfide reduces cyclohexanone to cyclohexanethiol (*32*). The straightforward conversion of thiols (present as intermediates) into thiocarboxylic acids has been confirmed experimentally by McMillan (*33*).

Newer Views Regarding the Course of the Reaction

In spite of these empirical observations, we do not believe this last route, commencing with the reduction of the carbonyl group, to be a completely true representation of the Willgerodt-Kindler reaction. Facts still to be discussed show that a methylene group—adjacent to a carbonyl group—reacts with exceptional readiness, even at room temperature, with sulfur to form a thiol group (see the Asinger reaction). It appears probable, therefore, that the primary attack takes place at the particularly reactive methylene group. This is followed by oxidations of the mercaptan, partly to the labile disulfide, but especially to the thioketone, accompanied by the formation of H_2S. The latter is then in a position to reduce the carbonyl group to a methylene group. The re-

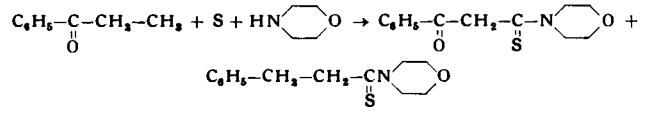
newed attack by sulfur can then take place at an activated methylene group once again. The oxidation-reduction cycle proceeds by a sequence of equilibrium reactions up to the end of the chain, when a dithiocarboxylic acid is irreversibly formed. The mechanism proceeding most readily would be that via olefins, accompanied by the formation of mercaptan intermediates to but a limited extent. This explains why branched ketones can be oxidized, though only in very low yields. The observation by Dauben and Rogan that araliphatic ketones containing a sterically hindered carbonyl group undergo a Willgerodt reaction without attack on the keto group (*34*), is also consistent with this reaction mechanism.



The oxidation of mesityl methyl ketone, involving the retention of the keto group (Eq. A) does not allow the intermediate formation of an olefin. In the case of higher ketones (Eq. B), the possibility of the interim formation of unsaturated compounds does exist.

On the basis of their own findings in connection with the Willgerodt reaction, Dauben and Rogan also advocate a primary attack by sulfur on the methylene group adjacent to the keto group.

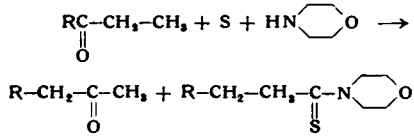
Barrett (*35*) has also been able to show recently that when the Willgerodt reaction is applied to simple araliphatic ketones, e.g. propiophenone, the terminal methyl group is partially converted into a carboxyl group without attack on the carbonyl group.



It was found possible to increase the quantity of oxothiomorpholide compound in the Willgerodt reaction by eliminating the reducing effect of the hydrogen sulfide produced during the course of the reaction, e.g., by the addition of nitrobenzene. Similarly, if the reaction is carried out

in an open vessel, fewer reduction products, i.e. true Willgerodt reaction products, are obtained compared to a reaction effected under pressure. Barrett was also able to accomplish the reduction of the oxothiomorpholides by means of hydrogen sulfide, though only in the presence of sulfur. He nevertheless rejects a definite intermediate formation of oxothiomorpholides on the grounds that the reduction of the ketones by hydrogen sulfide does not proceed sufficiently rapidly. He restricts his conclusions himself, however, by pointing out that the conditions during the Willgerodt reaction are different.

The above-mentioned theory of the course taken by the Willgerodt-Kindler reaction has been repeatedly supported experimentally. The formation of phenylacetaldehyde when acetophenone is subjected to a Willgerodt-Kindler reaction (*28*) agrees well with the theory. The action of ammonium polysulfide on α,β-unsaturated acids, e.g. cinnamic acid, results in the formation of saturated carboxylic acids containing one carbon atom less in the chain (*36*). Carmack and his collaborators do not actually explain the course of the reaction in detail, but this result is readily accounted for by the addition of hydrogen sulfide to the double bond followed by the oxidation to a β-keto or thioketo acid and decarboxylation of the latter. The thioketone obtained is further oxidized to the acid and reduced. Finally, Bible (*37*) actually detected the intermediate with a shifted carbonyl group required by the theory, in the Willgerodt-Kindler reaction of a complex ketone.



Furthermore, it is found that compounds deuterated at the position β to the keto group lose almost all their deuterium during the Willgerodt reaction (*38*).

Naylor and Anderson assumed that in the Willgerodt reaction involving olefins, the disulfide intermediates mentioned earlier are formed (*29*), and that these then react further via trithiones. The disulfides can then only be reversibly fissionable oxidation by-products of the thiols. No trithione intermediate is possible in the case of styrene.

The cyclic ketone α-tetralone reacts with morpholine and sulfur to give β-morpholinenaphthalene in 30% yield (*39, 40*). The reaction appears to be extremely involved. In our opinion, β-thiophenol could be formed as an intermediate which could then undergo a Bucherer reaction to give the morpholinenaphthalene.

Unsymmetrical aliphatic ketones react with sulfur to give predomi-

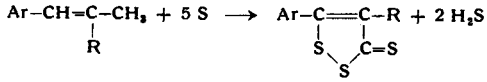
nantly carboxyl groups, formed by attack on the end of the shorter chain. Labelling of one chain end with C^{14} and subsequent Hoffmann degradation of the acid amide revealed the proportion of acid formed by attack on either side of the keto group (*41*).

In all the reactions with sulfur, amines or ammonia may convert the sulfur into a particularly reactive form via polysulfide intermediates, as found in the case of vulcanization of rubber by sulfur. Whether the basicity of the amine therefore plays an important role is rather doubtful (see below).

Trithiones

The reaction between sulfur and compounds of structure —CH=CH —CH_3 is related to the Willgerodt reaction and was not discovered until 60 years after the latter. Even though H. Erdmann (*42*) believed he had obtained thioözonides from the reaction of sulfur and linaloöl as early as 1908, it was not until 1940 that B. Böttcher (*43*) succeeded in isolating well-defined, pure products. Böttcher and Lüttringhaus were able to elucidate the constitution of the reaction products in the case of a large number of simple arylolefins (*44–48*).

Unlike the Willgerodt reaction, the synthesis of the trithiones proceeds in the absence of amines (no mention is made in the literature concerning a probable catalytic effect of small quantities of tertiary bases). The olefins subjected to the action of sulfur (approximately 1 hr at 220°) are chiefly araliphatic compounds containing a methyl group adjacent to the double bond.



The fact that anethole and estragole yield the identical trithione (Example 10) is of particular significance in terms of the reaction mechanism. The position of the double bond in the araliphatic olefin is consequently of no importance. Olefins only give trithiones when the carbon adjacent to the aryl group carries hydrogen, whereas the second carbon atom can be substituted by any group whatever. It is not known whether the substitution of the carbon α to the phenyl group at elevated temperatures is capable of effecting a conversion to saturated reaction products.

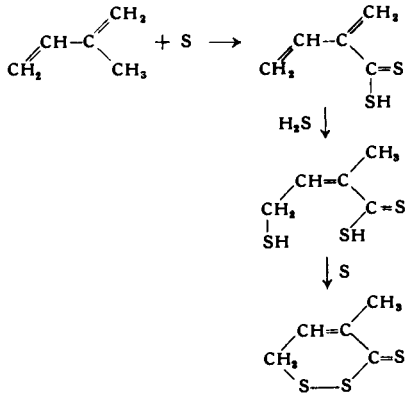
According to Lüttringhaus, the initial attack in the formation of the trithione appears to be restricted to the extremely reactive allyl group, which is oxidized to the dithioacid via the thiol. Lüttringhaus and Böttcher consequently assume that also in the Willgerodt reaction, an activated methyl or methylene group is initially attacked. The next step is less clear. Addition of hydrogen sulfide can occur, but only one isomer

can be detected via dehydrogenation to the five-membered ring as a trithione and thus stabilized. This would then have to be followed by a further dehydrogenation, resulting in the formation of a double bond. Alternatively, the secondary thiol could equally well be dehydrogenated to a thioketone, following the addition of hydrogen sulfide to the double bond. The thioketone could then be stabilized in the form of a thioenol, by trithione formation. This last route would explain why only olefins containing a CH group adjacent to the aryl group are capable of trithione formation. β-Ketoesters, in fact, also form trithiones with phosphorus pentasulfide (*49*). The preparation of saturated trithiones and their behavior under the action of sulfur would substantially contribute to a partial elucidation of the course of the reaction.

The facile conversion of 2,3-diphenyl-2-propene-1-thiol into the trithione under the action of sulfur supports the probable initial attack on the methyl group adjacent to the double bond (*50*). 3-Phenyl-1-mercapto-2-propene can be converted in the same manner into the corresponding trithione derivative by means of sulfur. The formation of very similar compounds from cinnamic esters and sulfur (Example 11) shows that the attack by sulfur alone or initially perhaps by hydrogen sulfide on a double bond, is also possible when the carbonyl group is already present (*51*).



The action of sulfur on isoprene apparently results in an anomalous behavior, inasmuch as a six-membered ring compound is formed.

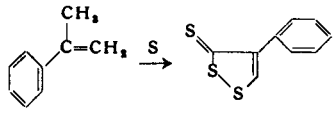


Dehydrogenations similar to those found in the case of 1-phenyl-1-propene probably occur during the course of this reaction, followed by

stabilization after the 1,4-addition of hydrogen sulfide, or via some other type of intermediate step, to give a six-membered ring.

The experiments on propylene illustrate the special position occupied by a double bond possessing an adjacent aryl group, resulting in a polarized double bond. Even the simplest trithione can only be obtained in very low yield. Detection of saturated hydrocarbons during the formation of the trithione indicates that this reaction also involves a sequence of equilibria between oxidative and reductive processes.

Trithiones may be prepared by an improved commercial process using sulfur/sulfur dioxide at 190°. The hydrogen sulfide generated is oxidized back to sulfur by the sulfur dioxide (*52*). Y. Mollier and N. Lozách (*52a*) also carried out work with a view to preparing trithiones from olefins. A recent patent describes the first conversion of α-methylstyrene into 4-phenyl-1,2-dithiole-3-thione, under the catalytic influence of diarylguanidines at 160° (*52b*).



Besides olefins, unsaturated aldehydes also yield trithiones by the action of sulfur. A number of other processes, of no interest in this connection, have also been discovered (*46–49, 53–57*).

It is interesting to note that saturated aldehydes also give trithiones; the double bond is therefore not an essential prerequisite (*58*). Benzoylacetaldehyde, in the form of its oxime, also gives a trithione derivative by the action of phosphorus pentasulfide (*58a*).

Even saturated hydrocarbons, e.g., isopropylbenzene, can be converted into trithiones with sulfur. In this system, the initial attack most probably occurs exclusively at the carbon atom adjacent to the phenyl ring. Somewhat surprisingly, the yields of trithione resulting from the action of sulfur on saturated alkylaromatic compounds are relatively good (78%) (*59*) (Example 12). The formation of trithione from isopropylbenzene is incompatible, however, with the earlier assertion, i.e., that trithiones are only formed from arylolefins if a double-bonded CH group is adjacent to the aryl nucleus, unless the reaction proceeds via a different route in the case of isopropylbenzene.

It follows from the above that suitable acetylenic compounds can also be converted into trithiones (*60*). Disulfides also react in a similar manner with sulfur to give trithiones (*57, 61*).

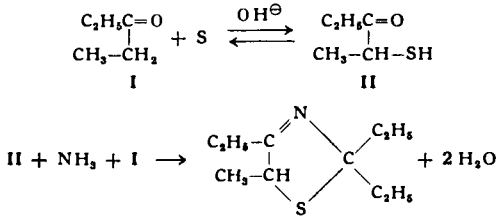
The action of sulfur on olefins or acetylenes leads to the reaction between sulfur and alkylaromatic compounds. It was mentioned earlier

that isopropylbenzene gives a trithione with sulfur. The intermediate formation of an olefin may be assumed in this instance. The reaction occurring between sulfur and toluene or xylene, however, must proceed differently. This work has been continued until very recently; it will be discussed at the end because of its more heterogeneous nature.

Action of Sulfur on Aliphatic Ketones in the Presence of Ammonia, under Mild Temperature Conditions (Asinger Reaction) (*61a*)

The action of sulfur on aliphatic ketones under mild temperature conditions in the presence of ammonia appears to be particularly important and unequivocal for the elucidation of the attack of sulfur on organic compounds. F. Asinger showed in 1956 that both aliphatic ketones, such as diethyl ketone, and cycloaliphatic ketones, such as cyclohexanone, react with sulfur and ammonia at room temperature (*62–64a*). Ammonia has a dual function in this reaction. On the one hand it forms polysulfides with sulfur, and these provide the reactive preliminary stage for the attack by sulfur, and on the other, it serves in the stabilization of the primary reaction products from the ketone and sulfur, even if this effect proceeds in a different manner from that in the Willgerodt-Kindler reaction.

The primary attack by sulfur on aliphatic ketones proceeds readily and evenly at the activated methylene group, to give an α-thiolketone, which is then stabilized by reaction with a second molecule of ketone and ammonia, and cyclization to 1,3-thiazolines (Example 13).

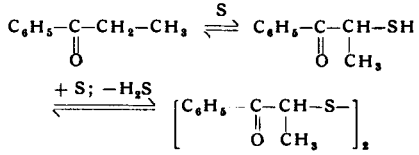


2, 2, 4-Triethyl-5-methylthiazoline

The reaction products could be accounted for unambiguously. The suspected thiolketone intermediates, prepared by another route, yielded the 1,3-thiazolines by reaction with the starting ketone and ammonia.

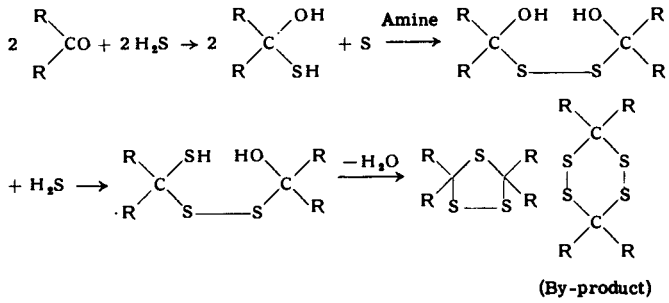
It is of but little significance here whether the enol form of the ketone adds sulfur during the initial attack to give an ethylene sulfide derivative or whether the methylene group is substituted directly. What is striking is the ease with which the reaction sets in even at room temperature or slightly higher, and the fact that the reaction proceeds very evenly and largely to completion. This also confirms that in the Willgerodt reaction

the initial attack occurs at the methylene or methyl group adjacent to the carbonyl. Another characteristic of the Asinger reaction is the ready reversibility of the first step, i.e., the formation of the α-thioketone. The action of e.g., *n*-butylamine on an α-mercaptoketone results in the almost complete regeneration of the ketone and sulfur. The equilibrium reactions occurring in the Willgerodt reaction, especially the coupled dehydrogenations and hydrogenations, have already been referred to. Asinger was also able to show that an equilibrium is set up between the mercapto compound and the disulfides resulting from the action of sulfur on ketones in the absence of ammonia (*64b*).

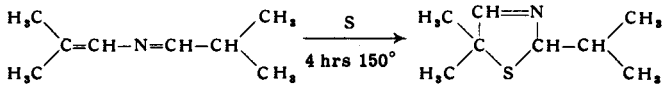


Amines exert a catalytic effect on the establishment of the equilibrium. Thiazolines are regenerated by ammonia.

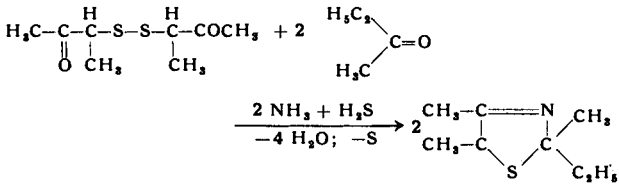
If ketones are treated gently with sulfur and a large amount of hydrogen sulfide in the absence of ammonia, the addition of hydrogen sulfide to the keto group is followed by the preferential oxidative formation of disulfide. Amines also exert a catalytic effect on this reaction (*64c*).



Thiazolines are also formed by 1,4-addition of sulfur to alkylidenevinylamines (*64d*).



Finally, thiazolines can also be prepared from α,α'-diketodisulfides and 2 moles of a keto compound in the presence of sulfur and ammonia (*64e*).



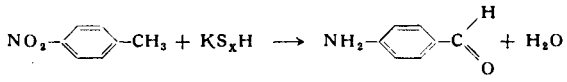
The observation (*65*) of the possibility of vulcanization shown by polyacrylic esters with sulfur can similarly be explained by an attack on the reactive methylene group. Cross-linking takes place via di- and polysulfide bridges (*65, 66*). Polymers with keto and adjacent methylene groups appear to undergo cross-linking with sulfur and ammonia exceptionally readily.

The Asinger reaction is also closely related to the long-known reaction between phenols and sulfur, which is catalyzed by small quantities of an organic base or alkali hydroxide. In this instance too, the sulfur enters in the position *ortho* or *para* to the phenolic hydroxyl group (which corresponds to an enolized keto group) to give a thiophenol; the latter is stabilized by further addition of sulfur, via di- and polysulfide formation (*67*) (Example 14). The action of sulfur on aromatic amines proceeds along similar lines (*68*). Aniline and sulfur yield *o,o'*-diaminodiphenyl disulfide almost exclusively. The reaction between 2,4,6-trichlorophenol and sulfur, on the other hand, is quite different. Under the influence of concentrated sulfuric acid, even the *m*-position undergoes condensation, and 3,3'-dihydroxy-2,4,6,2',4',6'-hexachlorodiphenyl disulfide is obtained in 93% yield (*69*) (Example 36). These reactions lie outside the scope of our review, however, and are not discussed in greater detail.

Action of Sulfur on Alkyl-Substituted Aromatic and Heterocyclic Compounds

A few years before the introduction of the reaction between toluene and sulfur mentioned below, the dye industry was concerned with the manufacture of *p*-aminobenzaldehyde. This compound was satisfactorily prepared for the first time in 1895 by the action of alkali polysulfide in boiling methanol on *p*-nitrotoluene, with its particularly reactive methyl group (*70*) (Example 15). The reaction can also be effected in conc. sulfuric acid solution (*70*), a less well-known fact. The nitro group

appears to possess a dual function, the activation of the *p*-methyl group and the capture of the hydrogen sulfide formed.



The process was employed by the I.G.-Farbenindustrie for the production of *p*-aminobenzaldehyde (*73*); see also ref. (*74*). Similar processes start from *p*-nitrobenzyl alcohol (*71*). It was not until much later that reports concerning this reaction began to appear in the literature (*72*).

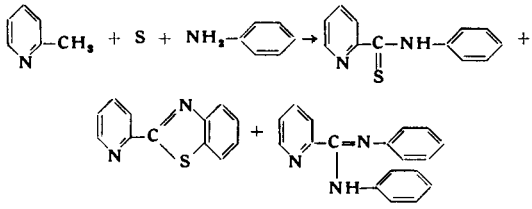
Unlike the above reactions, toluene does not react with sulfur below 200°. Aronstein and Nierop detected very small quantities of stilbene and tetraphenylthiophene during the course of this reaction (*75*). This is the first example of the vulnerability to attack displayed by a methyl group activated by only an aryl group. It was a long time before any substantial progress was achieved in this field. It was not until the end of the Second World War, and especially after 1950, that fresh insight was gained. The work developed in two, originally somewhat divergent, directions. The first was the action of sulfur, under the conditions of the Willgerodt-Kindler reaction, on alkyl heterocycles, i.e. on compounds containing a more reactive methyl or methylene group than that present in toluene. The second consisted in using more energetic reaction conditions, especially substantially higher temperatures; this results in the conversion of alkylaromatic and even aliphatic compounds into carboxylic acids in frequently surprisingly good yields.

Reaction between Sulfur and Alkyl Heterocycles

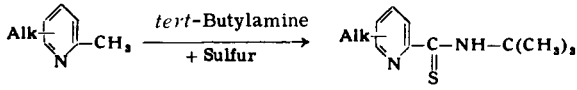
The first approach to the application of the Willgerodt-Kindler reaction conditions to alkyl heterocycles was introduced by Emmert in 1953 (*76,77*). A little later, reports by other workers on the identical or similar reactions appeared (*78*). Emmert initially confined his investigations to the action of sulfur on 2-methylpyridine in the absence of added amine and he obtained largely the same products as those previously described by Thayer and his collaborators (*79,80*). Experiments with quinaldine, sulfur, and a trace of sodium hydroxide have also been published (*81*).

According to Thayer, the alkali-catalyzed action of sulfur on 4-methylpyridine proceeds in the identical manner to the reaction between sulfur and toluene, though at temperatures as low as 140° and in far better yields, to give 1,2-di(4-pyridyl)ethylene and 2,3,4,5-tetra(4-pyridyl)thiophene. Besides these, 1,2-di(4-pyridyl)ethane and 1,2,3-tri(4-

pyridyl)propane were also detected (Example 16). The addition of a catalyst readily reduces the maximal yield (60%) of the ethane. The yield of the thiophene compound is increased, on the other hand, and up to 72% of the thiophene is obtained by effecting the reaction at elevated temperatures. This variation in the yield of individual products points to the stepwise course taken by the reaction. At the same time, however, the pronounced susceptibility of the primary reaction products to attack by sulfur and their final stabilization into a thiophene ring become manifest. In pursuance of these experiments, Emmert allowed 2- and 4-methylpyridine to react with sulfur in the presence of primary or secondary aromatic amines at 130° and obtained an approximately 40% yield of 2- and 4-pyridinethioaryl amides, respectively (Example 17). Thiazoles, and under special conditions an amidine derivative, are formed in a side reaction (*77*, *77a*).



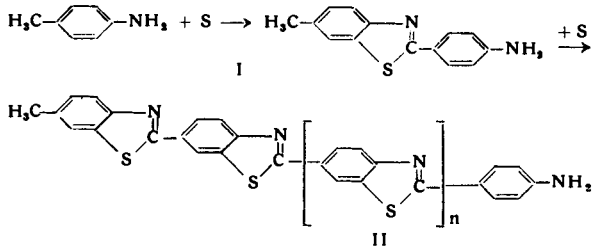
Mansfield (*77b*) allowed 2-methylpyridine, 2,3-, 2,4-, and 2,6-dimethylpyridine and 2-methyl-5-ethylpyridine to react with sulfur and tertiary alkylamines (e.g., *tert*-butylamine), and thus succeeded in selectively obtaining the corresponding 2-pyridinethioamides; we made the same observation in the case of other sulfurizations in the pyridine series (*87*).



The formation of thiazole from methylpyridine and aniline may be regarded as the definitely stabilizing capture reaction for the thioacid anilide initially formed. The 2-pyridinethioaryl amide stage is almost entirely passed over in the case of arylamines containing a particularly reactive *o*-position, e.g., *β*-naphthylamine.

The formation of thiazole during the action of sulfur on methyl-substituted aromatic amines, e.g. *p*-toluidine, is one of the oldest known reactions between sulfur and an aromatic sidechain (*82*, *83*). The primulin base II results from the further action of sulfur on the first stabilization product from *p*-toluidine, the so-called dehydrothiotoluidine I (*84*).

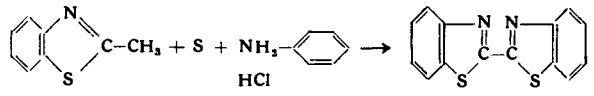
Reactions of this type have assumed a certain commercial significance in the chemistry of the sulfur dyestuffs (*85*) (Example 18).



Secondary reaction products from thioisonicotinic anilide with excess aniline to give an amidine compound command no interest within the present framework. The observation that tertiary amines, especially those containing two methyl groups linked to the nitrogen, also yield amides with the loss of one methyl group, points to the possibility of an oxidative elimination of a methyl group.

In 1952–1954 we were engaged in the synthesis of thioacid amides in order to examine their tuberculostatic action. Because of the considerable activity shown by some individual thioacid amides (unfortunately associated with excessive toxicity), we also investigated thionicotinic amides and isothionicotinic amides.

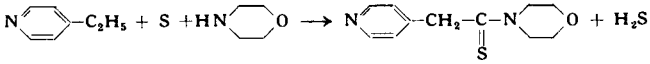
We found that low-boiling or gaseous aliphatic amines in the form of their salts are readily converted with picoline and sulfur. The process can also be applied to other methylheterocycles, e.g. methylbenzothiazole (*86*) (Example 19). When this method was extended to the salts of aromatic amines, however, the thioacid amides were no longer obtained but were almost exclusively replaced by 2-pyridylbenzothiazoles. The far less reactive 2-methylbenzothiazole is similarly only converted into the bisbenzothiazole by the action of aniline hydrochloride and sulfur at 200°.



The conversion of α- and γ-methylpyridine with sulfur and methyl- and dimethylformamide into the corresponding methyl and dimethyl amide, respectively, of the pyridinethiocarboxylic acids is also simple and trouble free (*87*) (Example 27 and Table 4). The mixture is usually easily worked up by distillation. Formylbutylamine and even formylallylamine react readily. This method allows the particularly facile conversion of all three methyl groups in 2,4,6-trimethylpyridine into thio-

amide groups via isolable intermediates. Lutidines (dimethylpyridines) and methyl- or dimethylpyrazines also undergo this reaction. α- and γ-Ethylpyridine yield the anticipated pyridylthioacetamides. Methylbenzothiazole can also be used as the oxidizable component. In the Willgerodt-Kindler reaction, we utilized low-boiling amines in the form of their formyl compounds, which underwent the reaction readily and mostly afforded very good yields. Styrene can similarly be converted with formyldimethylamine and sulfur, a reaction carried out by M. Carmack and De Tar, who used the free amines under pressure (*11*). Ammonia cannot readily be replaced by formamide, strangely enough, as the latter apparently undergoes a different reaction with sulfur. This is true both of the reaction with ketones and especially that with alkylpyridines. Other amides such as acetamide and benzamide or sulfonamides could not be substituted for amines in the Willgerodt reaction. Only N-methylurea is usable, but it offers no special advantage.

We were also able to convert the α- and γ-ethylpyridines, like the methyl analogs, into the pyridylthioacetomorpholides by means of sulfur and morpholine at 120–130°. Porter (*88*) subsequently published the same results for the conversion of ethylpyridine with sulfur and secondary amines (Example 20).



Other authors obtained the same products from pyridyl methyl ketones via a Willgerodt-Kindler reaction (*89*).

Intermediates Formed during the Action of Sulfur on Alkyl Heterocycles

The course of the reaction between sulfur and 2- and 4-alkylpyridine in the presence of amines appeared to merit closer investigation with regard to the possible isolation of pharmacologically interesting intermediates. Thus, we believed it might be possible to isolate Schiff bases as intermediates. We consequently briefly examined the behavior of Schiff bases under attack by sulfur.

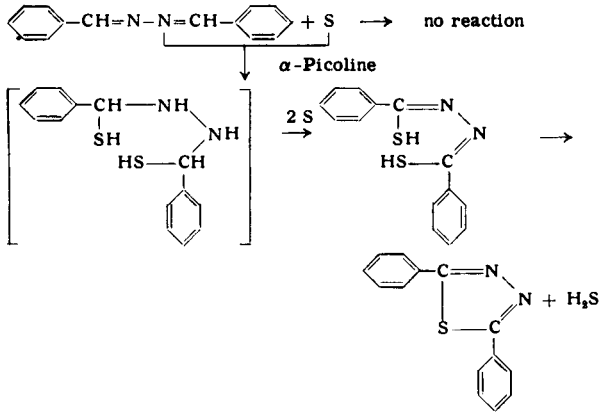
Kindler had already referred to the possible formation of Schiff base intermediates during the action of sulfur on benzylaniline. But whereas benzylaniline and sulfur react readily at 120° to give thiobenzoic acid anilide, our experiments showed that benzalaniline reacts but slowly and incompletely at 120–140° to give the same product. Our further assumption, namely that a thiolamine similar to that formed by the addition of hydrogen sulfide to the Schiff base may constitute the actual

intermediate stage, was confirmed by the fact that benzalaniline can already be converted into thiobenzanilide at 60–70°by means of sulfur and hydrogen sulfide (Example 21). This fact, however, does not yet prove whether it is not the free thioaldehyde, in equilibrium with the thiolamine and hydrogen sulfide, which represents the readily oxidizable intermediate. In support of this, it might perhaps be argued that the additional passage of hydrogen sulfide during the course of the reaction accelerates the attack by sulfur. The important part played by hydrogen sulfide during the reaction with Schiff bases is also clearly seen in the better yields of 2-phenylbenzothiazole obtained from benzylaniline at 220°, compared to those from benzalaniline under the same conditions (*90*).

The reaction certainly does not proceed as simply as it formally appears. The addition product of hydrogen sulfide and a Schiff base could not be isolated, even at a temperature of 20°. Depending on the strength of the base, thio- or trithioaldehydes or more frequently disulfides are obtained in its place. We should at the present stage prefer to assume that thioaldehydes are readily reduced to the mercaptans by hydrogen sulfide in the presence of aliphatic amines, with the liberation of sulfur; the latter then effects a partial oxidation, again catalyzed by strong bases, to give disulfides (Example 22). We have made no observations to date which would contradict this hypothesis. The disulfides readily react with the amines below 100° to give thioamides (Examples 23 and 24). Weaker bases, however, yield no disulfides under these conditions, although a Willgerodt reaction with the Schiff bases is nevertheless still possible.

Experiments have recently been published, according to which the aldehyde addition product of α- and γ-pyridinealdehyde and morpholine is converted into the thioacid morpholide by means of sulfur at 160–180° less readily than the methylpyridines themselves (*91, 92*). These experiments are also easily explained by the initial lack of hydrogen sulfide, which makes the conversion into the oxidizable thiolamines impossible.

We hoped we would be able to obtain bisthiobenzoic acid hydrazide more easily by the action of sulfur on benzalazine, since a retrogressive dissociation by hydrogen sulfide into the aldehyde and hydrazine components is more difficult in this case. Like benzalaniline, however, benzalazine undergoes no reaction whatever with sulfur at 130–140°. If, on the other hand, an equivalent amount of a compound is added which reacts with sulfur at this temperature to form hydrogen sulfide, e.g. α- or γ-picoline, a good yield of 2,5-diphenyl-1,3,4-thiodiazole is obtained via the bisthiobenzoic acid hydrazide.

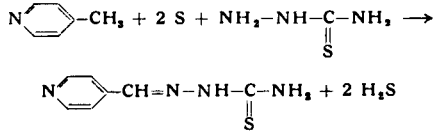


We attempted to synthesize the corresponding 2,5-(di-γ-pyridyl)-1,3,4-thiodiazole from γ-picoline, sulfur, and hydrazine (as the sulfate) directly, and this was readily achieved at 140°. Since this compound was also prepared by heating bisisonicotinic thioacid hydrazide (*93*) the formation of the readily oxidizable dihydrazide as intermediate is not improbable. It was also found possible to subject α-picoline to the same reaction.

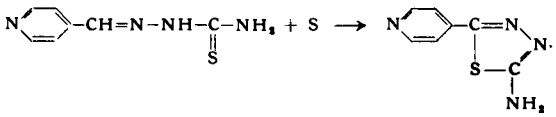
In order to elucidate the course of the Emmert reaction and to isolate an aldehyde or thioaldehyde intermediate, we hoped to obtain the aldehyde as a semicarbazone, thiosemicarbazone or phenylhydrazone during the course of the reaction. Semicarbazide, α- or γ-picoline and sulfur, however, only afford a small yield of the same thiodiazole which we had obtained with hydrazine sulfate, and its formation is due to the decomposition of the semicarbazide.

Action of Sulfur on Alkyl Heterocycles in the Presence of Thiosemicarbazide

The more stable thiosemicarbazide in an excess of α- and γ-picoline, on the other hand, reacts very readily with sulfur at the boiling point of the picoline; a reaction time of 2 hr resulted in a 40% yield of pyridinealdehyde thiosemicarbazone (Example 25 and Table 2).



This thiosemicarbazone represents the first aldehyde intermediate product ever isolated from the oxidation by sulfur of a methylheterocycle. A number of other not easily isolated products, including the 1,3,4-thiodiazole derivative are also present in the mother liquors. As is only to be expected, this thiodiazole is formed by prolonged heating of the pyridinealdehyde thiosemicarbazone with sulfur.

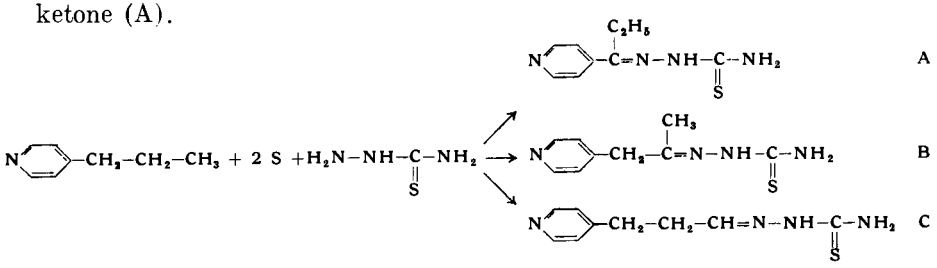


The oxidizability of diphenylmethane derivatives to benzophenone has been referred to earlier. Diphenylmethane itself was recently also converted into thiobenzophenone (*94*). In this instance, however, the oxidation must of necessity stop at the thioketone.

The reaction between sulfur, thiosemicarbazide, and α- and γ-picoline proceeds readily (*95*). On account of its solubility in alkali, the thiosemicarbazone is easily isolated. We believe this to be one of the simplest methods available at the present time for preparing the corresponding thiosemicarbazones, which have assumed importance in the treatment of tuberculosis, especially when the aldehydes are not readily accessible (*96*).

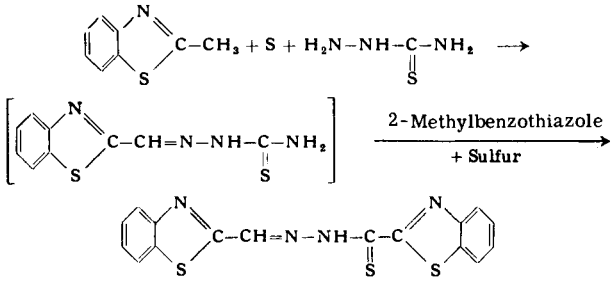
α- or γ-Ethylpyridine could be oxidized by sulfur in the presence of thiosemicarbazide to the thiosemicarbazone of the pyridyl methyl ketone (this compound shows strong activity against "Neoteben"-resistant strains of tuberculosis). The discovery of this thiosemicarbazone proves without doubt that the primary attack of the sulfur occurs at the methylene group (*97*). We have however, so far been unable to isolate a thiosemicarbazone of pyridineacetaldehyde in these experiments.

The reaction between 4-propylpyridine and sulfur in the presence of thiosemicarbazide merits great interest, since the possibility exists of isolating various intermediates. After a relatively short reaction time, the main product isolated was the thiosemicarbazone of 4-pyridyl ethyl ketone (A).



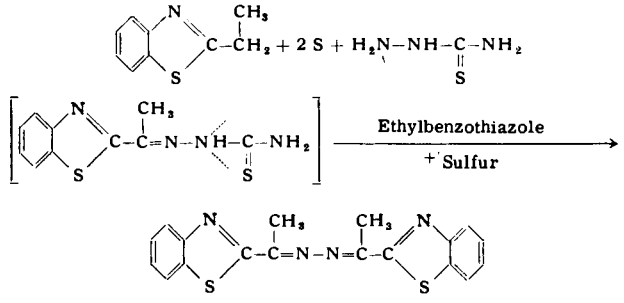
Another thiosemicarbazone having the same analysis was also obtained in small quantities; we could not be certain of its constitution since it does not correspond to the other possible thiosemicarbazones (B and C). (It is possible that the propylpyridine was not free from isomers.)

The action of sulfur on other heterocycles containing reactive methyl groups in the presence of thiosemicarbazide, proceeded somewhat differently with respect to the isolable end products. Thus only benzothiazole-2-aldehydebenzothiazole-2-thiocarboxylic acid hydrazone was obtained from 2-methylbenzothiazole.

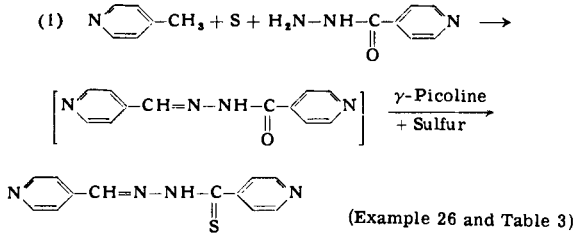


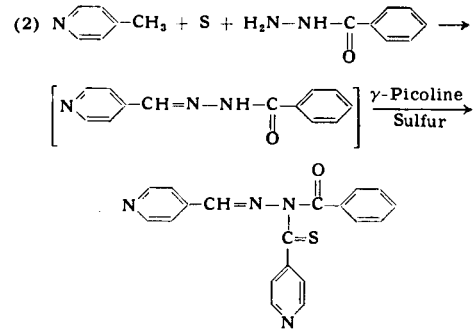
This seemingly divergent reaction course may primarily be due to the higher temperatures required by the reaction. The thiosemicarbazone of benzothiazole-2-aldehyde prepared via a different route is converted into the same compound by heating with sulfur and 2-methylbenzothiazole; the scheme therefore corresponds to the course of the reaction.

The reaction between 2-ethylbenzothiazole and sulfur in the presence of thiosemicarbazide results in a similar situation. The 2-acetylbenzothiazole thiosemicarbazone cannot be isolated in this case either, since further conversion to the azine is caused by the elevated temperatures. (No thioacylhydrazone formation is possible since the active methylene group in 2-ethylbenzothiazole, unlike the methyl group in 2-methylbenzothiazole, remains at the thioketone stage and cannot be sulfurized to a thioacyl group.)



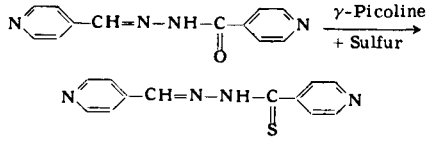
In the picoline- and the 2-methylbenzothiazole series, replacement of the thiosemicarbazide by other monoacylhydrazines results essentially in the formation of similar products, i.e. hydrazones, even if these are occasionally converted into more stable compounds under the influence of the elevated temperature (*98, 99*) e.g.,



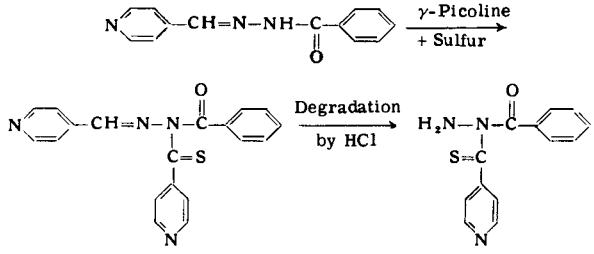


We were able to show that the nonisolable primary products shown in brackets are in fact formed as intermediates.

For reaction (1):

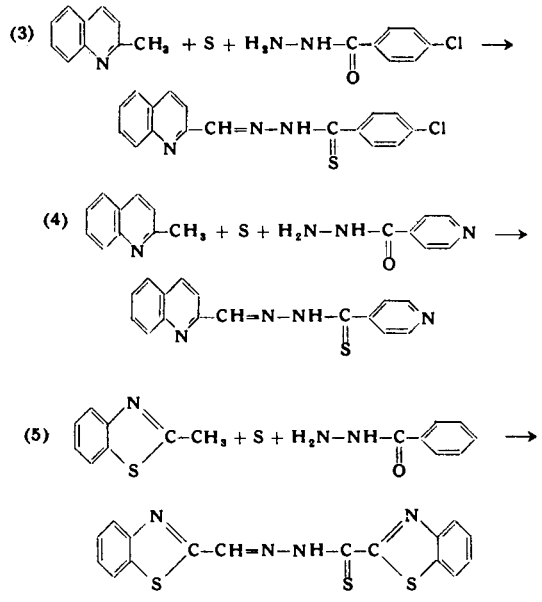


For reaction (2):



In spite of numerous similar reactions we are at the present time still unable to predict with certainty which secondary reaction products are formed.

The few reactions undergone by members of the quinaldine and methylbenzothiazole series are summarized below.



Oxidation of Alkylaromatic Compounds with Sulfur

Papers in the chemical literature as well as patent specifications of only a few years ago are in universal agreement regarding the poor yields resulting from the attempt to convert alkylaromatic compounds into arylcarboxylic acids by means of sulfur under the conditions of the Willgerodt reaction, in which the temperatures vary considerably and lie between 220° and 270° (*100, 101*). It is worthy of note that the possibility of oxidizing isopropylbenzene with ammonium polysulfide has already been dealt with, and both phenylacetamide and benzamide were detected, together with α-methylphenylacetamide; this observation points to the complete degradation of a branched side chain.

The oxidizing ability of sulfur is greatly increased, however, when the reactions are carried out around 335–345°. The lower members of even the saturated aliphatic hydrocarbons can then be oxidized to the carboxylic acids in relatively good yields with aqueous ammonium polysulfide. Thus 25% of isobutyramide can be isolated from isobutane (this figure is calculated from the amount transformed). The fact that,

e.g. acetamide, is obtained from propane also indicates further degradation of the carbon chain (*102*).

The oxidation of alkylaromatic compounds with sulfur at 320° proceeds particularly readily in the presence of aqueous alkali hydroxide even if no ammonium salts are added. The California Research Corp. in 1950 thus succeeded in obtaining a good yield of the benzenedicarboxylic acids from toluic acids (*103*). The possibility of using sulfur dioxide or sulfites as the oxidizing agent is also mentioned for the first time in the same patent; these compounds yield sulfates and sulfur under the conditions of the reaction (Example 28). The hydrogen sulfide generated by the action of sulfur on toluic acid is oxidized back to sulfur by the sulfite. It is only to initiate the reaction that a very small amount of sulfur is required. It is worth noting that this represents the first description of an oxidation with sulfur in a weakly acidic medium.

Another patent describes the general reaction of unsaturated hydrocarbons with sulfur in the presence of sulfur dioxide; here too the sulfur is entirely used up. The patent includes all the oxidations with sulfur without any particular restriction as to the corresponding products (*52*). Olefins sometimes yield trithiones at 190° (Example 34).

In the past few years a number of patent specifications have been published in which the oxidation of toluene or *p*-xylene with sulfur in the presence of ammonium sulfate and water at 320° (still below the critical temperature of water) under pressure, is described. The yields of terephthalic acid from *p*-xylene are reported to be quantitative. As we were engaged in similar experiments, we repeated the work described in the patents and succeeded in fully confirming the results given. This process, which is also being tried in pilot plants in the U.S.A., may represent the simplest and cheapest method for preparing terephthalic acid from *p*-xylene, since the latter cannot be oxidized directly with air to the dicarboxylic acid, oxidation stopping at the toluic acid stage. It is only by invoking the assistance of organic acids such as acetic acid, which yields peracetic acid, that a tolerably satisfactory oxidation of both alkyl groups can be accomplished. In the patents, however, the addition of diisopropylbenzene, which generates hydroperoxide readily, is invariably mentioned (*104*). Processes as yet unpublished in the patent literature, utilizing acetaldehyde as intermediate catalyst, are said to give better results.

The patent describing the oxidation by means of sulfur and ammonium sulfate also mentions the oxidation of ketones, olefins, and even aliphatic hydrocarbons without, however, quoting any yields regarding such oxidations of hydrocarbons (*105*). The high yield of phthalic acids may, nevertheless, be primarily due, not to the use of sulfur and a large

quantity of ammonium sulfate, but rather to the elevated reaction temperature (Example 29). *p*-Xylene similarly yields 91% of terephthalic acid by the action of ammonium polysulfide at 320° (*106*). By a special process, good yields of nitriles and dinitriles can be obtained by the action of sulfur on xylene and *p*-tolunitrile, respectively, in the presence of a tenfold excess of ammonia (*107, 107a*). After the reaction (effected around 220–340°) the hydrogen sulfide formed is driven off with ammonia at 220–300°. It is probable that the nitriles are only then formed from the thioamides.

The discovery that not only sulfur, but all sulfur-producing compounds such as, e.g. sulfites, can be used as the oxidizing agent is extended

TABLE 1

Compounds Which Can Be Oxidized with Sulfur and Aqueous Bases

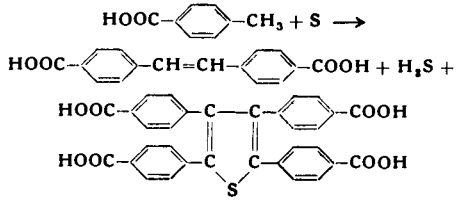
Compound oxidized	Base[a]	Product	Yield[b] %
m-, *p*-Toluic acid	1.0 NaOH	Iso-, Terephthalic acid	100.0
m-, *p*-Toluic acid	8.5 NaOH	Iso-, Terephthalic acid	97.8
p-Toluenesulfonic acid	2.0 NaOH	*p*-Sulfobenzoic acid	94.8
p-Toluenesulfonic acid	1.0 NaOH	*p*-Sulfobenzoic acid	38.5
		Benzoic acid	29.0
m-Xylenesulfonic acid	1.0 NaOH	Isophthalic acid	63.6
p-Xylenesulfonic acid	1.0 NaOH	Terephthalic acid	46.2
Toluene	2.0 $CaCO_3$	Benzoic acid	61.0
m-Xylene	2.0 NaOH	sophthalic acid	61.0
m-Xylene	1.3 Na_2CO_3	Isophthalic acid	70.8
		Benzoic acid	10.4
m-Xylene	2.0 $CaCO_3$	Isophthalic acid	11.1
		m-Toluic acid	12.0
m-Xylene	1.2-Disodium-isophthalate	Isophthalic acid	33.5
m-Xylene	10.0 NH_4OH	Isophthalic acid	87.2
m-Xylene	None	Isophthalic acid	29.0
p-Xylene	2.0 NaOH	Terephthalic acid	77.0
p-Xylene	1.1 Na_2S	Terephthalic acid	79.0
p-Xylene	2.4 Na_2CO_3	Terephthalic acid	86.0
p-Xylene	8.0 $Na_2B_4O_7$	Terephthalic acid	76.0
p-Xylene	10.0 NH_4OH	Terephthalic acid	96.2
Acetophenone	1.0 NaOH	Benzoic acid	28.0
1-Butanol	4.0 NaOH	Propionic and acetic acid	48.0
Furan	2.0 NH_4OH	Succinic acid	30.0
Thiophene	4.0 NH_4OH	Succinic acid	19.5
Propylene	1.1 KSH	Propionic acid	12.5
		Acetic acid	7.2
Acetone	1.3 NaOH	Acetic acid	4.5

[a] Mole per mole of compound oxidized.

[b] Calculated with respect to the quantity of starting material which could not be recovered.

in a patent to the utilization of alkali thiosulfate for the oxidation of aromatic hydrocarbons at 315–320° (*108*) (Example 30). The oxidation according to this method also affords almost quantitative yields. The oxidation can also be effected with sulfur dioxide over vanadium pentoxide at 350–450° (*108a*). W. G. Toland, Jr. and his collaborators have published a summary of the yields obtained via the various oxidation methods (Table 1). It appears to be essential that either the sulfur or the compound undergoing oxidation be dissolved in water.

The facile oxidation of *p*-toluic acid at 270–275° with sulfur in the absence of water and amines also deserves attention; this results in a 50–60% yield of *trans*-4,4′-stilbenedicarboxylic acid, which has thus become readily accessible (*109*) (Example 35).

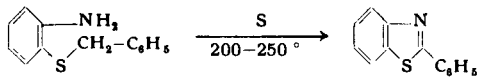


Tetra(*p*-carboxyphenyl)thiophene is formed as a by-product. *m*-Toluic acid can be oxidized in a similar manner but with lower yields and *o*-toluic acid cannot be oxidized by this method at all.

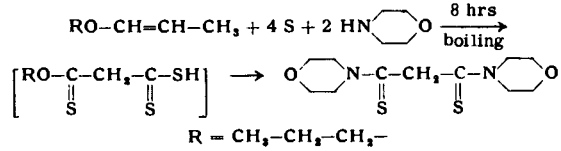
Action of Sulfur on Other Compounds

In contrast to these developments on the ready oxidation of alkylaromatic compounds with sulfur and sulfur-producing substances, succeeding advances published in the patent literature are predominantly directed towards the extension to substances which could undergo oxidation, i.e. to other most readily attacked classes of compounds.

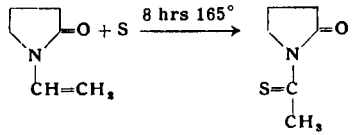
The particularly ready oxidizability of the mercaptans initially formed in the oxidation of hydrocarbons with sulfur, by means of aqueous ammonium polysulfide, is also mentioned in a patent (*110*). β-Phenylethylmercaptan is converted into phenylacetamide in 95% yield at temperatures as low as 200° (Example 31). The same compound results from the isomeric α-phenylethylmercaptan though in lower yield. Propionamide is obtained from isopropylmercaptan in a corresponding manner. Allylmercaptan is converted into propionamide; this reaction clearly demonstrates the reducing action of the hydrogen sulfide. A similar oxidation is undergone by the alcohols with lower yields. Benzyl thioethers have recently been oxidized at the methylene group above 200°, for example, the cyclization of *o*-aminophenyl benzyl thioether to 2-phenylbenzothiazole (*110a*).



Vinyl ethers can be converted into thioacetamides by the Willgerodt-Kindler reaction; attack therefore occurs at the double bond (*111*). Propenyl alkyl ethers undergo a double attack at the double bond and again at the methyl group with the elimination of the ether grouping, resulting in very good yields of malondiamides (*111a*).



The susceptibility to attack displayed by the vinyl group is also illustrated by the conversion of vinylpyrrolidone into N-thioacetylpyrrolidone (*111b*) (Example 31a).

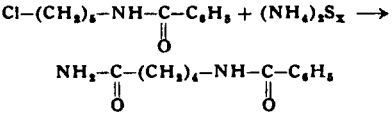


Acetylene in the presence of secondary amines readily undergoes a double attack by sulfur in the absence of water to give dithioöxalamides (*113*) (Example 32). No other data appear to exist regarding the degradation by sulfur on both sides.

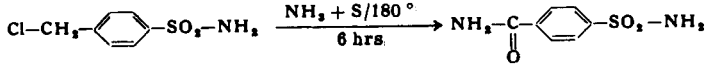
Propylene and ammonium polysulfide in the presence of water result in the formation of propionamide (*114*). Naylor observed the formation of di- and trisulfide intermediates during the course of the oxidation of olefins by the action of ammonium polysulfide at 200°; these sulfides are converted further into saturated carboxylic acid amides at 230–250° (*32, 115, 116*). If undecylenic acid is subjected to a Willgerodt-Kindler reaction, 1,9-nonanedicarboxylic acid is obtained (*23*) (Example 33). Patents describe similar reactions, in which the oxidation can also be effected, apart from the use of ammonium polysulfide, by the action of sulfurous acid in the presence of magnesium or zinc sulfide, and proceeds via the di- and trisulfides (*116*).

With reference to the oxidation of olefins with sulfur, anethole was subjected to a Willgerodt reaction in the presence of morpholine and phenylpropynoic acid thiomorpholide was obtained (*112*).

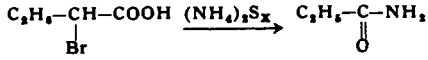
The reaction between N-(ε-chloro-*n*-amyl)benzamide, sulfur, and ammonium polysulfide results in the formation of aminocarboxylic acids (*116a*).



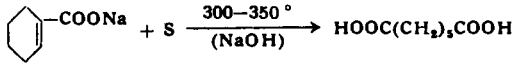
A number of chloromethylaromatic compounds and other halogenated hydrocarbons can be converted into amides or carboxylic acids under the conditions of the Willgerodt reaction (*116b–d*). Chloromethylbenzenesulfonamide in particular was utilized in this experiment.



In general, hydrocarbons containing nitro or thiocyano groups are attacked more readily under the conditions of the Willgerodt reaction than are the corresponding unsubstituted hydrocarbons (*116e*). This also applies to α-halocarboxylic acids, which are converted into amides containing one less carbon atom (*116f*).



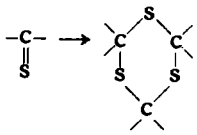
With reference to the repeatedly mentioned ready oxidation undergone by olefins, it is proposed that nitroölefins be converted into the saturated acid amides via a Willgerodt reaction without ascribing any significance to this process (*117*). The conversion of cyclohexenecarboxylic acid into pentane-1,5-dicarboxylic acid represents an interesting variant of the action of sulfur on olefins (*117a*).



Several of the reactions described are without doubt of significance in the elucidation of the reaction occurring during the course of the vulcanization of unsaturated high polymers by means of sulfur (*118*) in the presence of zinc oxide or polyamines. The action of sulfur on olefins at approximately 140° was investigated in model experiments (*119–120a*).

The primary attack by sulfur on the allyl position, already demonstrated in other reactions, probably also occurs in the case of the vulcanization (*118–123*). Whether the reaction proceeds via a (probable) free radical, or some other mechanism is not now under discussion. In

any event, mercaptans may be formed initially, and may then become linked under the influence of sulfur to give di- and polysulfides, a process which we have repeatedly encountered. By addition to a double bond, hydrogen sulfide can once again yield mercaptans capable of linking together, with the consequent disappearance of the double bond. The reaction course



involving the formation of a thioketone intermediate, discussed in the case of the Willgerodt-Kindler reaction, and during which cross-linking via trimers may occur, nevertheless also appears to be possible (*124*). Further cross-linking can also be effected by di- and polysulfides instead of sulfur. A readily dissociating disulfide such as thiuram can be added at the start. This does not necessarily require the cross-linking to be effected by dissociation into thiuram monosulfide and sulfur; it could conceivably also proceed by a symmetrical dissociation into two identical radicals (*125*).

The attack by sulfur on hydroaromatic or aliphatic hydrocarbons in the presence of a Friedel-Crafts catalyst appears to occupy a special position. Unlike the reactions described up to now and the conversion of aromatic hydrocarbons in acid conditions, mercaptans are predominantly formed (*126*). There is, however, no extensive information available as yet.

Although many observations have been made allowing dissimilar reactions to be considered from a common point of view, we are conscious of the incompleteness of this aspect; this is due to the fact that this work was not undertaken with a view to clarifying or explaining the common characteristics. We hope that this review will contribute to and stimulate the filling of gaps. We realize that more questions are perhaps raised than answered, as is so often the case in the progressive understanding of chemical problems. We intend to investigate further some of the problems which are of special interest to us.

Experimental Examples

Example 1: β,β-Dimethylbutyramide from pinacolone (*7*). Pinacolone (4 gm), ammonium sulfide solution (16 ml), and sulfur (12.8 gm) are heated in dioxane (8 ml) in an autoclave for 6 hr at 210°. After being allowed to cool to room temperature, the contents of the autoclave are

cooled further to 0° and filtered. β,β-Dimethylbutyramide (2.1 gm), m.p. 133–134° is extracted from the residue with boiling water (30 ml). The filtrate is evaporated to dryness under vacuum on a water bath, and the residue boiled up with water. On cooling, the aqueous solution yields a further crop of the amide (0.57 gm), m.p. 129–130°. Total yield: 2.68 gm, 58%.

Example 2: 1-Acenaphthoic acid, acenaphthene-1-amide, and 1-ethylacenaphthene from 1-acetoacenaphthene (6). 1-Acetylacenaphthene (19.2 gm), ammonium sulfide solution (96 gm), sulfur (9.6 gm), and dioxane (17 ml) are heated for 18 hr at 175–180°. On cooling, the amide of 1-acenaphthoic acid (6.8 gm, 33%) crystallizes. The filtrate is extracted with benzene; acidification of the aqueous phase gives 1-acenaphthoic acid (0.426 gm, 2.1%), m.p. 159–160°, and treatment of the benzene layer affords a further 0.385 gm, 1.7%. Conversion of the 1-acetylacenaphthene into the acid or amide has therefore proceeded to the extent of 36.8%. In addition, evaporation of the benzene yields an oil, which distills at 160–163°/6 mm. The compound obtained (8.3 gm, 46.7%) is found to be 1-butylacenaphthene, which crystallizes on cooling, m.p. 34.8–35.1°.

Example 3: N-Dimethylthiobenzamide from N-dimethylbenzylamine and sulfur (13). N-Dimethylbenzylamine is heated with sulfur (2 moles) for 4 hr in a sealed tube at 180°. The reaction product is taken up in ether, the crystallized sulfur filtered, and the filtrate concentrated to a small volume. More sulfur crystallizes and is filtered off. Addition of petroleum ether precipitates N-dimethylthiobenzamide, m.p. 67°.

Example 4: o-Benzyloxyphenylthioacetmorpholide from o-benzyloxyacetophenone, morpholine, and sulfur (15). o-Benzyloxyacetophenone (11.3 gm), morpholine (4.5 gm), and sulfur (1.6 gm) are boiled for 8 hr. Ice is added, the thiomorpholide extracted with ether and the ether evaporated. The residue is allowed to crystallize for several days, and the product is then recrystallized from dilute methanol. Yield: 12 gm, m.p. 118–119°.

Example 5: 1,3,5-Benzenetriacetic acid from 1,3,5-triacetylbenzene, morpholine, and sulfur (18). 1,3,5-Triacetylbenzene (26.4 gm, 0.13 mole), morpholine (78.3 gm, 0.9 mole) and sulfur (28.8 gm, 0.9 mole) are boiled together for 14 hr. The solution is added to water, and the precipitate is filtered and saponified by boiling in sulfuric acid/glacial acetic acid. The solution is basified with caustic soda and extracted with ether. The aqueous layer is then acidified to congo red and extracted with ether for 4 days. Evaporation of the ether yields 1,3,5-benzenetriacetic acid (24.6 gm, 75%) in the form of a yellow powder, m.p. 197–204°; m.p. after recrystallization from glacial acetic acid, 215–216°.

Example 6: N-Butylthiobutyramide from dibutylamine and sulfur (*20*). Dibutylamine (97 gm, 0.75 mole), sulfur (48 gm, 1.5 mole), and pyridine (200 ml) are boiled for 10 hr with stirring. Chloroform (400 ml) is added, and the solution washed with water, dilute hydrochloric acid, and again with water. Fractional distillation affords a pale yellow oil, b.p. 142–144°/6 mm. Yield 67.2 gm.

Example 7: p-Aminobenzaldehyde from p-nitrobenzylaniline and sodium polysulfide (*21*). *p*-Nitrobenzylaniline (114 gm) in alcohol (400 gm) is treated with a solution of sodium sulfide ($Na_2S \cdot 9H_2O$) (120 gm) and sulfur (32 gm) in water (100 gm). The mixture becomes warm and a red-yellow coloration develops. The liquid is maintained at the boiling point for 2–3 hr, the alcohol distilled off, and the residual oil washed with water. The *p*-aminobenzylideneaniline obtained is a red-yellow, nondistillable oil. Addition of dilute mineral acid results in the formation of a crystalline mass of the polycondensation product of *p*-aminobenzaldehyde.

Example 8: n-Heptanamide from 1-heptyne (*9*). 1-Heptyne is heated for 4 hr at 145° with a solution of ammonium sulfide and sulfur in pyridine, yielding *n*-heptanamide (35%), m.p. 97°.

Example 9: 4,4′-Bisdimethylaminothiobenzophenone from 4,4′-bisdimethylaminodiphenylmethane (*31*). 4,4′-Bisdimethylaminodiphenylmethane (50 gm) is intimately mixed with sulfur (15 gm) and heated in a porcelain dish in an oil bath at 230°. The reaction soon sets in, and is completed when no further significant evolution of H_2S can be detected (after approximately 40 min). The hot melt is dissolved in amyl alcohol (25 gm), the small quantity of unreacted sulfur removed by decantation, and the solution allowed to stand. On cooling, solidification to a crystalline mass occurs. The crude product is filtered and purified by recrystallization from chloroform/alcohol, yielding deep-red needles, m.p. 194–200°.

Example 10: 5-Thione-3-(4-methoxyphenyl)-1,2-dithiole (trithione of anethole) from 4-methoxy-1-propenylbenzene (anethole) (*44*). Anethole (103.2 gm) and sulfur (89.9 gm) are heated in a sulfonating flask in an atmosphere of CO_2 with slow stirring. The evolution of H_2S begins at 175°, and at 185° heat is spontaneously generated. The liquid foams and the flask is filled with green-brown fumes. The temperature rapidly rises to approximately 240°, when a colorless oil (3.8 gm) comes over, consisting mainly of anethole and 4-methoxy-1-propylbenzene. After the temperature has started to fall, stirring is continued for a further hour at 220°. The loss of weight incurred during the course of the reaction amounts to approximately 34.2 gm. Crystallization of the product commences on cooling and is promoted by the addition of ether (200 ml). On

the following day the crude product is filtered and washed with cold water (100 ml), yielding crude crystallizate (80.4 gm).

The crude product, which apart from trithione still contains sulfur, 2,5-dimethyl-3,4-dianisylthiophene etc., is purified by fractional sublimation under high vacuum in a horizontal sublimation apparatus 40 cm long, according to the method of Freudenberg-Friedrich (*127*). At a pressure of 10^{-3} mm of mercury, the trithione sublimes at 90°, and the sulfur and other by-products above 100°.

The trithione can also advantageously be separated via the mercuric chloride adduct. The crude crystalline product (66.6 gm), which is found to contain, for example, 53% of trithione by chromatographic analysis (cf. original literature) is dissolved in benzene (950 ml), and mercuric chloride (66 gm) in methanol (150 ml) added to the solution. The amorphous yellow precipitate becomes crystalline after boiling for 1 hr. Cooling, filtration, and washing with methanol yield the crude adduct (99 gm). The latter is suspended in benzene (500 ml) and shaken for several hours with a solution of hydrated sodium sulfide (400 gm) and potassium hydroxide (48 gm) in water (800 ml). The benzene layer is separated, washed with water and evaporated, leaving a residue of fairly pure trithione (34 gm, reported 35.3 gm). A first purification is achieved by recrystallization from a little carbon disulfide, when some sulfur still present is dissolved out. Final purification is best effected by recrystallization from butyl acetate. The pure trithione forms deep-orange prisms, m.p. 111°.

Example 11: 5-Oxo-3-phenyl-1,2-dithiole from cinnamic ester (*51*). Cinnamic ester (100 gm) and sulfur (50 gm) are heated with stirring in an oil bath for 8–10 hr at 250–260°, resulting in the elimination of alcohol. When the evolution of alcohol has ceased, the mixture is allowed to cool and is crystallized from alcohol, leaving a dark, sulfur-containing resin. Purification is effected by alternately recrystallizing from acetone and alcohol and clarifying with animal charcoal. 5-Oxo-3-phenyl-1,2-dithiole crystallizes in yellowish plates or flakes, m.p. 117°.

Example 12: 3-Thione-4-(p-tolyl)-1,2-dithiole from p-cymene (*59*). A mixture of *p*-cymene (1108 gm), sulfur (400 gm), and ditolylguanidine (8.2 gm) is heated under reflux for 21 hr at 185°; during this time hydrogen sulfide is continuously evolved. On cooling, the reaction mixture is maintained for 2 hr at 5° to assist crystallization. The red crystalline mass is filtered, washed with a benzene–hexane mixture (1:3) and sucked dry, yielding 3-thione-4-(*p*-tolyl)-1,2-dithiole (355 gm), m.p. 119–120°. A single recrystallization from benzene affords a product, m.p. 122.5–123°.

Example 13: 2,2,4-Triethyl-5-methylthiazoline. Finely ground stick sulfur (80 gm, 2.5 gm atom) and diethyl ketone (430 gm, 5 moles) are

placed in a 2 liter three-necked flask fitted with a stirrer, reflux condenser, and gas inlet tube, and a vigorous stream of ammonia is passed into the mixture. After a short time the reaction mixture becomes colored and the temperature rises to 50–60°. The temperature begins to fall after 3–4 hr, but the ammonia is passed in for a total of 7 hr. By that time the reaction mixture has turned dark brown, the sulfur has disappeared and water separates on the bottom of the flask. The reaction mixture can then be worked up in two ways: it can either be steam-distilled and the organic layer of the distillate fractionated, or it can be taken up in ether, the ethereal layer carefully washed with water and the dried ether extract treated as above after evaporation of the solvent. The first method affords very pure products and the yields obtained are similar in both cases. Apart from unchanged diethyl ketone (85 gm), 2,2,4-triethyl-5-methylthiazoline (315 gm, 85%), b.p. 96°/12 mm is obtained, as a colorless liquid of penetrating, characteristic odor, n_D^{20} 1.4862.

Example 14: Condensation of phenol with sulfur (128). Phenol (28.2 kg), powdered sulfur (9.6 kg), and sodium hydroxide (0.45 kg) dissolved in water (1.35 kg) are mixed, fused, and heated at 120–122° for 15 hr with slow stirring (the boiling temperature is regulated to 120–122° by the quantity of water present). The loss in weight due to the evolution of hydrogen sulfide amounts to 3.6 kg. All the volatile material is then distilled off *in vacuo* at a bath temperature of 60–130°, when the loss in weight—mostly phenol—amounts to 10.05 kg. The reaction mixture is finally subjected to a pressure of 4 mm of mercury for another 8 hr at a bath temperature of 60–130°, and a further loss of 4.8 kg is incurred. The residue consists of a solid, dark resin (31.6 kg) which softens around 60° and dissolves readily in methanol. The use of more sulfur affords higher-melting resins in better yields. Unreacted sulfur is detected by a turbidity in the methanolic solution.

Example 15: p-Aminobenzaldehyde from p-nitrotoluene and sulfur (74). Sodium hydroxide solution (82.3 gm, 48.6%, containing 1 mole of NaOH) is added to a stirred mixture of ethanol (147 gm), water (360 gm), sodium sulfide ($Na_2S \cdot 9H_2O$) (54 gm), and sulfur (7.5 gm). *p*-Nitrotoluene (90 gm) is added and the heterogeneous mixture brought to the reflux temperature; sulfur (15 gm) is added over a period of 2 hr and the mixture heated for a further 2 hr. The alcohol is then distilled and the residue treated with steam. After the reaction solution is cooled down to 2°, *p*-aminobenzaldehyde (81 gm, approximately 100%) is separated as a noncrystalline product.

A different method of working up the product (*73*) is advisable following the oxidation to the aldehyde: The mixture is cooled to 35°, the aqueous layer separated, hydrochloric acid (15%) added to the alcoholic

solution, which is then diluted with a large quantity of water, and the product salted out with common salt.

Example 16: 1,2-Di(4-pyridyl)ethane from 4-methylpyridine and sulfur (79). 4-Methylpyridine (3 moles) and sulfur (1.5 mole) are heated for 12 hr at 140–155°, resulting in the rapid evolution of H_2S. The unreacted 4-methylpyridine is then distilled off at a pressure of 45 mm of mercury, and 47% of the original quantity is recovered. The residue from the distillation is added to a mixture of ice and sulfuric acid (50%), the unreacted sulfur filtered off, and the filtrate basified with a 30% sodium hydroxide solution. The warm oil is separated and the aqueous layer extracted with benzene; the organic solution is added to the oil, and the combined solutions fractionally distilled after evaporation of the solvent. 1,2-Di(4-pyridyl)ethane (60%, calculated with respect to the quantity of 4-methylpyridine used up), b.p. 164–174°/3 mm is obtained, m.p., after recrystallization from cyclohexane/benzene (3:1), 110–111°.

Further fractions obtained under these conditions consist of 1,2-di(4-pyridyl)ethylene (4%), b.p. 175–205°/2 mm, m.p. 151–152° (benzene), and 1,2,3-tri(4-pyridyl)propane (14%), b.p. 230–242°/2 mm, m.p. 110–111° (acetic ester).

Example 17: Thiopicolinic acid anilide from α-picoline, aniline, and sulfur (76). α-Picoline (90 gm), aniline (45 gm), and sulfur (45 gm) are vigorously boiled, resulting in the immediate evolution of a continuous stream of H_2S. Excess aniline and α-picoline are removed after 48 hr by steam distillation and the residue twice extracted with a warm potassium hydroxide solution (3 *N*, 300 ml). On weak acidification with dilute hydrochloric acid, the thiopicolinic acid anilide separates as an orange-red oil which solidifies on cooling to a crystalline cake (85 gm crude product). Recrystallization from methanol (in the presence of animal charcoal) yields large, golden yellow prisms (75 gm), m.p. 52°.

Example 18: 6-Methyl-2-(p-aminophenyl)benzothiazole ("dehydrothiotoluidine") from p-toluidine (83). *p*-Toluidine (1200 gm), sulfur (430 gm), and sodium carbonate (1–2 gm) are heated at 180° for 2–3 hr, and the temperature then slowly raised to 220–230° until the evolution of H_2S has ceased. Unreacted *p*-toluidine (approximately 470–480 gm) is distilled off *in vacuo*. Following a first fraction (about 40–50 gm) below 200°/2–3 mm, dehydrothiotoluidine (600–610 gm) comes over. The crude product is recrystallized from alcohol (600 ml), yielding the pure compound (470–480 gm), m.p. 190–192°. (In the original directions, kg, and liter are given instead of gm and ml, respectively.)

Example 19: Isothionicotinic acid dimethyl amide from γ-picoline, sulfur, and dimethylamine hydrochloride (86). A stirred mixture of

γ-picoline (186 gm, 2 moles), sulfur (192 gm, 6 moles), and dimethylamine hydrochloride (162 gm, 2 moles) is heated for 6 hr at 170° and the reaction mixture extracted at room temperature with dilute hydrochloric acid. Addition of sodium hydroxide to this solution causes the separation of an oil, which consists of a mixture of γ-picoline and the thioamide. Drying with sodium sulfate and distillation yield isothionicotinic acid dimethyl amide (96 gm, 29%), b.p. 135–137°/0.8 mm, m.p. 64–65°.

Example 20: Pyridine-4-thiocarboxylic acid morpholide from γ-picoline and morpholine (87). A suspension of sulfur (96.2 gm) in a mixture of γ-picoline (93.1 gm) and morpholine (130.7 gm) is heated at 170° for 12 hr, during which time H_2S is continuously evolved. On cooling, the reaction product is dissolved in hot absolute alcohol (500 ml). Small, black needles separate from the cold solution, and are recrystallized from absolute alcohol (2 liters) containing animal charcoal, yielding pyridine-4-thiocarboxylic acid morpholide (66.2 gm). Concentration of the mother liquors and repeated extraction with *n*-hexane afford a further crop (20.5 gm) of a less pure product. Repeated crystallization from *n*-hexane gives a total of 83.1 gm of pyridine-4-thiocarboxylic acid morpholide, m.p. 141–147°.

Example 21: Thiobenzanilide from benzalaniline (129).

(a) Benzalaniline does not react with sulfur below 100°, and gives 2-phenylbenzothiazole at 150°.

(b) Hydrogen sulfide is passed for 1 hr into molten benzalaniline maintained at 50°. The temperature is then raised to 70°, one equivalent of sulfur added, and the temperature maintained for a further 5 hr. The thiobenzanilide is extracted from the reaction mixture by shaking with dilute sodium hydroxide; the alkaline solution is neutralized with dilute hydrochloric acid, causing the precipitation of a mixture consisting of a little sulfur and thiobenzanilide. Recrystallization from a minimum quantity of alcohol yields a product of m.p. 98–101° (m.p. according to the literature: 101°).

Example 22: Dibenzyl disulfide from benzalbutylamine and hydrogen sulfide (129). Hydrogen sulfide (68 gm, 2 moles) is passed into benzalbutylamine (161 gm, 2 moles) maintained at 0–5°. The viscous solution obtained solidifies overnight. The entire contents of the flask are dissolved in hot methanol and filtered hot. On cooling, crystals of dibenzyl disulfide (83 gm, 68%), m.p. 68–70° are obtained. The m.p. after recrystallization from methanol is 68–70°.

The mixed m.p. with a sample of dibenzyl disulfide obtained by the oxidation of benzyl mercaptan with hypobromite solution shows no depression.

Example 23: Di(4-pyridylmethyl) disulfide and the N-butylamide of

4-pyridinethiocarboxylic acid from 4-pyridalbutylamine and hydrogen sulfide (129). Hydrogen sulfide (30 gm, 2 equivalents) is passed into γ-pyridalbutylamine (71 gm) maintained at 0–5°, whereby the contents of the flask solidify. The reaction mixture is dissolved in hot alcohol and filtered hot. On cooling, crystals of di(4-pyridylmethyl) disulfide (25 gm), m.p. 158–163° are obtained. Recrystallization from alcohol raises the m.p. to 164–166°.

Concentration of the mother liquors gives an oil which soon crystallizes. Trituration with ether and filtration yield the N-butylamide of 4-pyridinethiocarboxylic acid (34 gm), m.p. 76–78°.

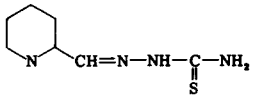
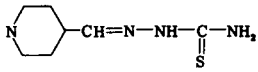
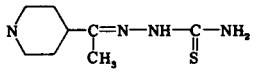
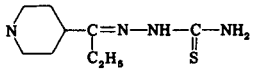
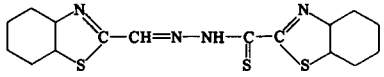
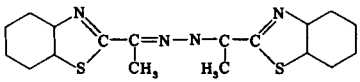
Example 24: N-Butylthiobenzamide from dibenzyl disulfide, sulfur, and n-butylamine (129). Dibenzyl disulfide (41 gm, 1/6 mole), sulfur (11 gm, 1/3 mole), and *n*-butylamine (25 gm, 1/3 mole) are warmed to 90–100°, resulting in the slow evolution of H_2S. The temperature is then raised to 140° for 10 min and finally, at 25°, the mixture is poured into methanol. The small quantity of sulfur which separates is filtered off and the solution distilled. The residual oil has a b.p. of 162–167° at 0.2 mm. Yield 42 gm, 65.5%.

Example 25: Preparation of thiosemicarbazones (e.g. 4-pyridyl methyl ketone thiosemicarbazone) (96). 4-Ethylpyridine (214 gm), sulfur (128 gm), and thiosemicarbazide (182 gm) are heated to 130° and maintained at that temperature for 2½ hours. Any unreacted 4-ethylpyridine is steam-distilled and the cooled crystalline residue filtered. The solid is dissolved in sodium hydroxide solution (2 *N*, 1000 ml), the undissolved sulfur filtered off, and the thiosemicarbazone precipitated from the clear solution by neutralization with dilute hydrochloric acid. Recrystallization from methanol gives a product of m.p. 229–231° (dec.). Yield 33%.

The compounds listed in Table 2 were prepared in analogous manner.

Example 26: Preparation of thioacylhydrazones (97). A mixture of γ-picoline (46.5 gm, ½ mole), isonicotinic acid hydrazide (68.5 gm, ½ mole), and sulfur (32 gm, 1 gm atom) is heated in an oil bath at 135–140° (internal temperature), for 5 hr, during which time H_2S is continuously evolved. Towards the end of this period, the temperature is raised to 150°. Acetonitrile (about 70 ml) is added to the still warm solution and the precipitate (83.5 gm) is filtered off after cooling. Concentration of the mother liquors yields a further crop of crystallizate (about 3 gm) and unchanged γ-picoline (10 gm). The combined precipitates are recrystallized from dimethylformamide, and pure pyridine-4-aldehyde thioisonicotinylhydrazone (28 gm), m.p. 238–240°, is obtained.

TABLE 2
Thiosemicarbazones

Reaction product	Reactants	M. p.
	α-Picoline, sulfur, and thiosemicarbazide	208–211° (dec.)
	γ-Picoline, sulfur, and thiosemicarbazide	228° (dec.)
	4-Ethylpyridine, sulfur, and thiosemicarbazide	229–231° (dec.)
	4-*n*-Propylpyridine, sulfur, and thiosemicarbazide	197°
	2-Methylbenzothiazole, sulfur, and thiosemicarbazide	342–344°
	2-Ethylbenzothiazole, sulfur, and thiosemicarbazide	285°

The mixed m.p. with a comparison sample prepared from thioisonicotinic acid hydrazide and pyridine-4-aldehyde shows no depression.

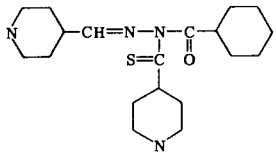
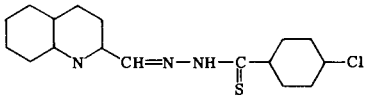
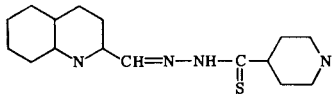
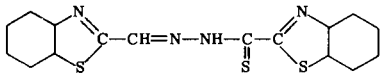
The compounds listed in Table 3 were prepared in analogous manner.

Example 27: Preparation of N-alkylthioacid amides (Dimethyl amide of isothionicotinic acid) (87). Picoline (186 gm), sulfur (192 gm), and dimethylformamide (146 gm) are heated for 20 hr at 140–160° until the evolution of gas has ceased, and the mixture distilled. The main fraction, the dimethyl amide of isothionicotinic acid comes over at 145–160°/0.6–1.3 mm, yield 66%. It is redistilled at 143–148°/0.9 mm and recrystallized from ethyl acetate, yielding pale yellow needles, m.p. 64–65°.

The compounds listed in Table 4 were prepared in analogous manner.

Example 28: Oxidation of xylene by means of sulfur dioxide in the presence of ammonium sulfide (103). Xylene (85% *m*-xylene and 15% *p*-xylene, 1 mole), sulfur dioxide (1.53 mole), ammonia (3.08 moles), and hydrogen sulfide (1.55 mole) are heated in water (58 moles) for 1 hr in

TABLE 3
Thioacylhydrazones

Reaction product	Reactants	M.p.
	γ-Picoline, sulfur, and benzhydrazide	183 - 184°
	Quinaldine, sulfur, and *p*-chlorobenzhydrazide	254 - 255°
	Quinaldine, sulfur, and isonicotinic acid hydrazide	237°
	2-Methylbenzothiazole, sulfur, and benzhydrazide	346 - 348°

an autoclave at 315°. A pressure of approximately 180 atm is reached. On cooling, a little activated charcoal is suspended in the liquid product and it is filtered in order to remove the coloring matter. Of the xylene used, 96.5% is converted into a mixture of iso- and terephthalic acid which has a saponification value of 86 and a neutralization value of 101.5.

Example 29: Oxidation of a mixture of m- and p-xylene by means of sulfur in the presence of ammonium sulfate (105). *m*- and *p*-Xylene (85:15, 225 gm), sulfur (34 gm), ammonium sulfate (464 gm), and water (960 ml) are heated for 1 hr in a high-grade steel autoclave at 328°. On cooling, the pressure is released and the reaction mixture treated with steam until a pH value of 6 is reached. Treatment with activated charcoal and filtration are followed by acidification to pH 2 with sulfuric acid. After standing for some time, the mixture is filtered, yielding a solid (311.6 gm) consisting of isoterephthalic acids and their amides.

Complete saponification is achieved by heating with dilute sulfuric acid. A special process recommends the saponification at pH 3 (4.65 gm sulfuric acid/liter) for one-half hour at 240° and 35 atm (*130*).

Example 30: Oxidation of m-xylene with ammonium thiosulfate (108). *m*-Xylene (75 gm, 0.707 mole) is placed in a tube and, with a solution of ammonium thiosulfate (60%, 262 gm, 1.06 mole) in water, (658 gm) is placed in a 2½ liter high-grade steel autoclave. The reac-

TABLE 4
N-Alkylthioacid Amides

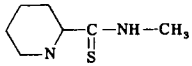
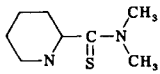
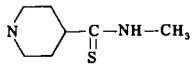
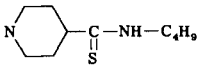
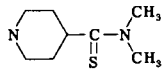
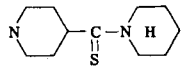
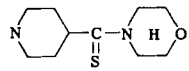
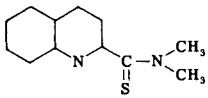
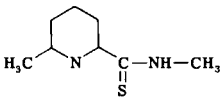
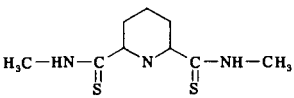
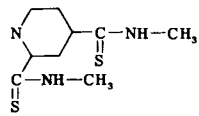
Reaction product	Reactants	M. p.	B. p.
	α-Picoline, sulfur, and methylformamide	74–78°	–
	α-Picoline, sulfur, and dimethylformamide	–	129–133° 0.55 mm
	γ-Picoline, sulfur, and methylformamide	94–97°	156–162° 0.5 mm
	γ-Picoline, sulfur, and butylformamide	75–78°	120–122° 17 mm
	γ-Picoline, sulfur, and dimethylformamide	64–65°	143–148° 0.9 mm
	γ-Picoline, sulfur, and formylpiperidine	113–116°	160–180° 0.9–2 mm
	γ-Picoline, sulfur, and formylmorpholine	151–153°	–
	Quinaldine, sulfur, and dimethylformamide	126–129°	–
	2,6-Lutidine, sulfur, and methylformamide	–	172–176° 12 mm
	2,6-Lutidine, sulfur, and methylformamide	168–170°	–
	2,4-Lutidine, sulfur, and methylformamide	150–153°	–

TABLE 4 (*Continued*)

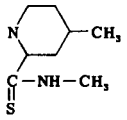
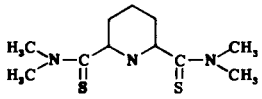
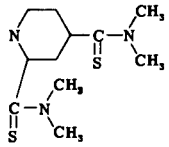
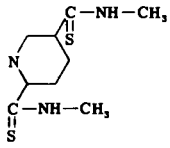
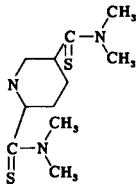
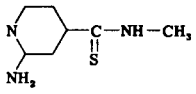
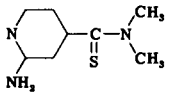
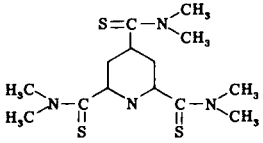
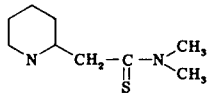
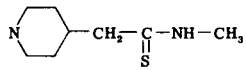
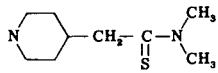
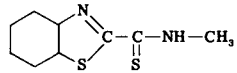
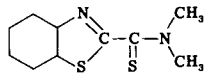
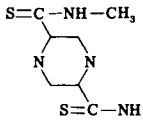
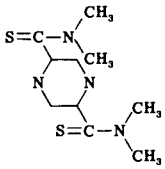
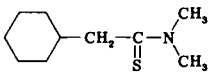
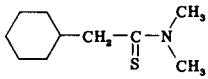
Reaction product	Reactants	M. p.	B. p.
	2,4-Lutidine, sulfur, and methylformamide	-	174 176° 13 mm
	2,6-Lutidine, sulfur, and dimethylformamide	195 - 197°	-
	2,4-Lutidine, sulfur, and dimethylformamide	168 - 171°	-
	2,5-Lutidine, sulfur, and methylformamide	163 - 166°	-
	2,5-Lutidine, sulfur, and dimethylformamide	158 - 163°	-
	2-Amino-4-methylpyridine, sulfur, and methylformamide	134 - 137°	-
	2-Amino-4-methylpyridine, sulfur, and dimethylformamide	116 - 119°	

TABLE 4 (*Continued*)

Reaction product	Reactants	M. p.	B. p.
	Collidine, sulfur, and dimethylformamide	239 – 242°	–
	2-Vinylpyridine, sulfur, and dimethylformamide	–	153 – 157° 1. 2 mm
	4-Ethylpyridine, sulfur, and methylformamide	136 – 140°	–
	4-Ethylpyridine, sulfur, and dimethylformamide; or 4-vinylpyridine, sulfur, and dimethylformamide	108 112°	–
	2-Methylbenzothiazole, sulfur, and methylformamide	116 119°	–
	2-Methylbenzothiazole, sulfur, and dimethylformamide	103 – 105°	–
	2,5-Dimethylpyrazine, sulfur, and methylformamide	307 – 310°	–
	2,5-Dimethylpyrazine, sulfur, and dimethylformamide	283 – 285°	–
	Acetophenone, sulfur, and dimethylformamide	79 – 81°	–
	Styrene, sulfur, and dimethylformamide	79 – 81°	–

tants are heated to 315° before the xylene is mixed with the solution by agitating the glass tube; the pressure then rises to about 135 atm. Heating is continued for a further 90 min; on cooling, the gases formed (20 gm H_2S) are released. Volatile material is removed from the liquid product by steam distillation at pH 6, and sulfur removed from the residue by filtration. The filtrate is heated with sodium hydroxide (60 gm), acidified to pH 6, treated with activated charcoal, and filtered. The filtrate is acidified to pH 2 with hydrochloric acid, and the isophthalic acid (90.5 mole %) filtered.

Example 31: Oxidation of mercaptans with sulfur (110). 2-Phenylethyl mercaptan (1 part) and ammonium polysulfide solution (5 parts) are heated in an autoclave for 4 hr at 205°. Phenylacetamide is formed in 95% yield. It is isolated by evaporating the reaction solution to dryness, extraction with hot alcohol, and recrystallization from the same solvent; m.p. 153–154°.

Similarly, if *n*-decyl mercaptan (1 mole) is heated with sulfur (2 moles) and aqueous ammonia (28%, 5 moles) for 12 hr at 200°, an almost quantitative conversion into *n*-nonanecarboxylic acid amide, m.p. 97–98°, takes place.

The corresponding alcohols only afford yields of 40–50% of the acid amides; nor do the yields obtained from secondary mercaptans quite compare with those from the primary compounds.

Example 31a: Conversion of vinylpyrrolidone into N-thioacetylpyrrolidone (111b). N-Vinylpyrrolidone (100 parts) is heated, with stirring or shaking, with sulfur (85 parts) and hydroquinone (2 parts) for 6–8 hr at 160–170°. The dark-colored reaction product is dissolved in tetrahydrofuran, treated with animal charcoal, filtered, and concentrated. A dark, noncrystalline substance (180 parts) of composition C_8H_9ONS is obtained, and can be shown to be the dimer of N-thioacetylpyrrolidone by molecular weight determination. The compound is completely soluble in water and melts in the range 48–93°. Boiling with dilute sulfuric acid and methanolic hydrochloric acid (20%) causes the elimination of H_2S. The substance is completely hydrolyzed after 8 hr, yielding acetic acid and γ-hydroxybutyric acid.

Example 32: N,N'-Dicyclohexyldithioöxalic acid diamide from acetylene (113). Cyclohexylamine (198 gm) is placed in a four-necked flask fitted with a stirrer, thermometer, reflux condenser, and gas inlet, and acetylene passed in until the saturation point is reached. Sulfur (106 gm) and dioxane (150 ml) are then added and the mixture heated to boiling. Acetylene is slowly passed for 3 hr, and heating continued for a further 2 hr. The dioxane is evaporated under vacuum, and the semisolid residue extracted with boiling alcohol (500 ml) and filtered. The solid

filtration residue is placed in boiling butanol (250 ml) and filtered hot. On cooling, N,N′-dicyclohexyldithioöxalic acid diamide (11 gm) m.p. 156–158° separates from the filtrate.

Example 33: Nonane-1,9-dicarboxylic acid from undecylenic acid (23). Purified undecylenic acid (3.68 gm) is heated with an oxidizing solution for 4 hr at 160°. The reaction product is saponified by alkali, and acidification yields nonane-1,9-dicarboxylic acid. Recrystallization from chloroform affords the pure acid (1.52 gm, 35%), m.p. 111–112.5°.

The oxidizing solution is prepared as follows: For every 0.1 mole of the compound to be oxidized, 7 *N* ammonium sulfide solution (7 *N* with respect to the sulfide and 12 *N* with respect to the ammonia) (25 ml), sulfur (0.5–1 gm atom) and pyridine or dioxane (12–25 ml) are used. Ammonium thiosulfate (0.1 mole) is also added.

Example 34: Preparation of a trithione from isobutylene and sulfur/sulfur dioxide (52). Isobutylene (170 gm), sulfur dioxide (213 gm), and sulfur (192 gm) are heated in a high-grade steel autoclave of 1600 ml capacity for 2 hr at 180–195°. A dark oil (426 gm) and an aqueous liquid (131 gm) are obtained. The oily product is distilled at 118–122°/1 mm, yielding $C_4H_4S_3$ (186 gm), m.p. 37–38.3°.

Example 35: 4,4′-Stilbenedicarboxylic acid from p-toluic acid and sulfur (109). A mixture of *p*-toluic acid, at least 97% pure, (1 mole) and sulfur (0.5 mole)—up to 1 mole of sulfur can be used—is heated in a three-necked flask for 4½ hr at 270–275°. A yellow precipitate of 4,4′-stilbenedicarboxylic acid gradually separates from the ever-darkening reaction liquid. When the evolution of H_2S has ceased, the mixture is cooled to 140° and hot xylene (5 ml/gm of *p*-toluic acid) added. The mixture is again heated under reflux for 30 min, filtered hot, and the filtration residue washed with hot xylene. After evaporation of the xylene, the filtrate contains impure *p*-toluic acid, sulfur, and acids of high molecular weight. The *p*-toluic acid can be recovered by distillation. The filtration residue is extracted with hot dioxane, when about 20 gm of higher acids dissolve in 100 ml of the solvent. The residue consists of 4,4′-stilbenedicarboxylic acid and a small quanity of yellow-colored higher acids. Purification can be effected by the crystallization of the potassium salt from water; the ammonium and guanidine salts are equally well suited. The free acid has a m.p. of 460° and a neutralization equivalent of 134.1. The crude yield amounts to approximately 60%, calculated with respect to 51% of reacted toluic acid.

The dioxane solution contains mainly tetra(*p*-carboxyphenyl)thiophene.

Example 36: Reaction between 2,4,6-trichlorophenol and sulfur (69). 2,4,6-Trichlorophenol (200 parts) is added to a cold solution of flowers

of sulfur (100 parts) in oleum (30%, 100 parts); the brown solution is stirred for several hours at 10–20° and poured on to ice. The separated product is dissolved in dilute sodium carbonate solution, freed from undissolved sulfur by filtration, and reprecipitated by pouring the solution into dilute hydrochloric acid. The crude product is filtered, dried, and if necessary recrystallized from glacial acetic acid or benzene.

3,3′-Dihydroxy-2,4,6,2′,4′,6′-hexachlorodiphenyl disulfide, m.p. 156–159°, is obtained in 93% yield as a pale yellow crystalline powder. It is readily soluble in most organic solvents as well as in dilute sodium carbonate solution.

If 2,4,6-tribromophenol is subjected to the same treatment, a good yield of 3,3′-dihydroxy-2,4,6,2′,4′,6′-hexabromodiphenyl disulfide is obtained as a yellowish crystalline powder, m.p. (after recrystallization from glacial acetic acid) 198–202°.

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The Introduction of Substituents into the Pyridine Ring

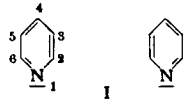
K. THOMAS AND D. JERCHEL

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The introduction of substituents into the pyridine ring presents an interesting problem to the synthetic chemist, as this aromatic heterocycle exhibits but limited readiness to undergo the substitutions so fruitfully effected in the benzene series. While satisfactory methods for preparing 2- and 3-substituted pyridines were discovered relatively early, substitution in the 4-position caused great difficulty for a long time. Apart from a short survey of the more common substitution reactions undergone by the pyridine ring, this review deals primarily with methods leading to the preparation of 4-substituted pyridine derivatives. Beside the use of pyridinium salts, these particularly include the reactions of pyridine-N-oxides, which have hitherto scarcely been discussed.*

Behavior of Pyridine during Substitution Reactions

The pyridine nucleus, like that of benzene, consists of a six-membered ring and possesses three π-electron pairs (I).



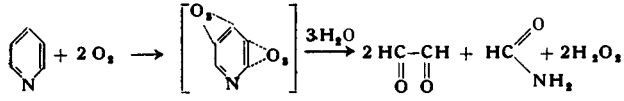
I

Pyridine, however, exhibits different reaction characteristics than benzene, due to the fact that the symmetry of the electron distribution of the ring is disturbed by the presence of the nitrogen atom (*1*).

In contrast to benzene, therefore, the ozonization of pyridine proceeds with the addition of only two molecules of ozone; hydrolysis of the non-

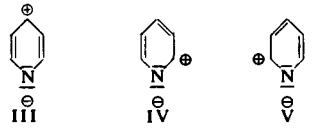
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isolable diozonide produces two molecules of glyoxal and one of formamide (II) (*2*).



II

Due to its higher nuclear charge, the nitrogen atom possesses an increased electron affinity compared to carbon; in the pyridine molecule this results in a higher electron density around the heteroatom. A series of resonance structures involving formal charge separation (III–V) can thus be written, and their contribution to the ground state is detected in the course taken by the substitution reactions undergone by pyridine.

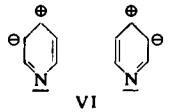


III IV V

The tertiary nitrogen atom is comparable to a benzene ring carbon atom linked to a substituent which induces a powerful positive charge, e.g., the grouping $=C—NO_2$ present in nitrobenzene (*1*).

Examination of the nuclear magnetic resonance spectra of pyridine and its homologs has recently confirmed the resemblance between these heterocycles and nitrobenzene (*3*).

Substitution of pyridine could accordingly be expected to proceed in a manner similar to the introduction of a second substituent into nitrobenzene. Thus, in the case of the electrophilic substitution of the pyridine ring, a general lowering of reaction velocity becomes evident, accompanied by a marked deactivation of the 2-, 4-, and 6-positions (see formulae III–V). An electrophilic attacking substituent therefore enters the pyridine ring at positions 3 or 5 (VI).



VI

Positions 2, 4, and 6, on the other hand, are vulnerable to nucleophilic attack (III–V), and in the event of free radical substitution, all five carbon atoms of the pyridine nucleus are equally susceptible. Since the introduction of substituents into pyridine is associated with a marked temperature effect (*4*), differentiation between the various reaction types is made possible; this is particularly well illustrated by the halogena-

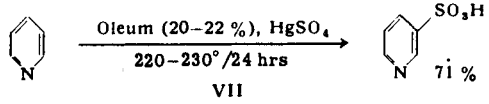
tion of pyridine. The following summary of a few important methods for substituting pyridine lays no claim regarding the rigorous validity of the classification according to the various mechanisms.

Electrophilic Substitution

In accordance with theoretical considerations, the electrophilic substitution of pyridine can in general only be accomplished under drastic conditions. The substituent then enters either position 3 or 5, or both simultaneously.

The nitration of pyridine at 300°, effected by adding a solution of the base in concentrated sulfuric acid to a molten mixture of the nitrates of sodium and potassium, yields but 4.5% of 3-nitropyridine, and 0.5% of 2-nitropyridine; if the reaction is carried out at higher temperatures, the proportions are altered in favor of 2-nitropyridine, and as much as 2.5% of the latter can be obtained (*5,6*).

The sulfonation of pyridine affords satisfactory yields. The method described by McElvain and Goese (*7,8*), in which pyridine is heated for 24 hr at 220–230° with 20% oleum and a little mercuric sulfate (*9*) catalyst, yields 71% of pyridine-3-sulfonic acid (VII).



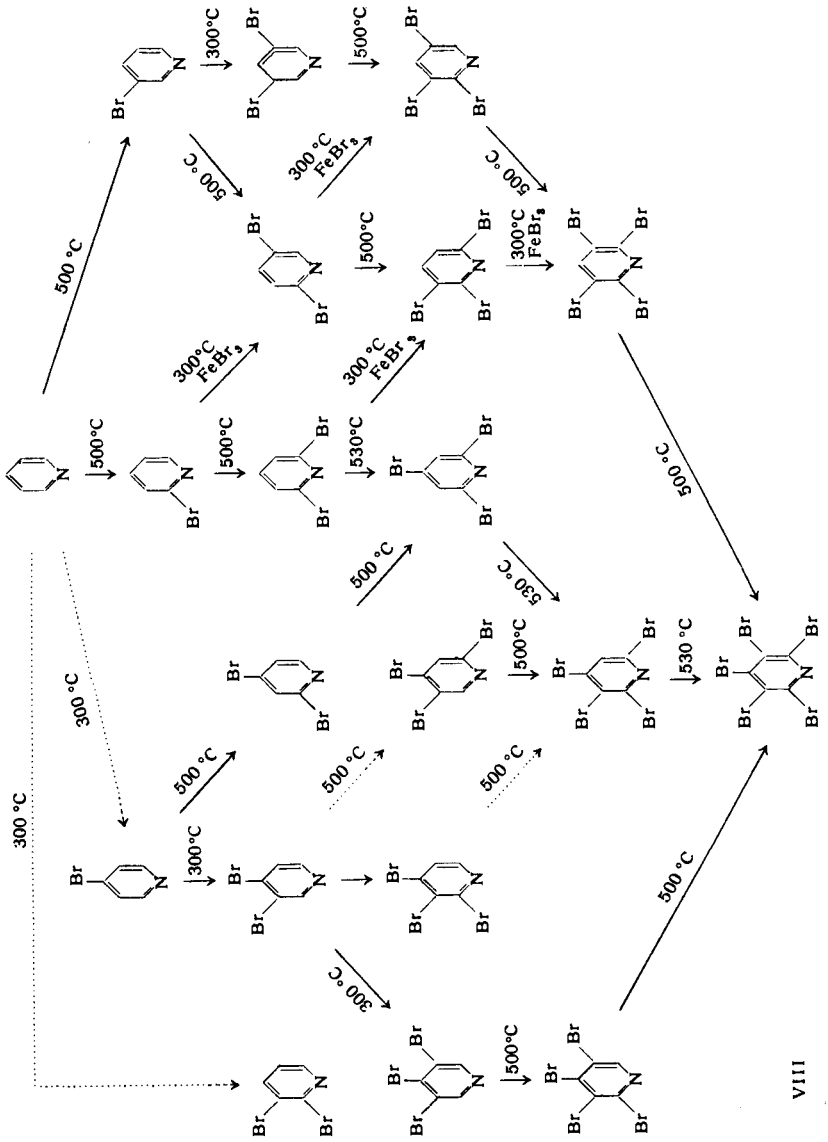
VII

The sulfonation of 2,6-di-*tert*-butylpyridine using SO_3 in liquid SO_2, gives a sulfonic acid in which the —SO_3H group is probably situated at position 4; pyridine and 2,6-lutidine merely form SO_3 addition compounds under these conditions (*10*) (see Appendix).

Pyridine forms an adduct with mercuric acetate (*11–14*); if the adduct is heated to 155° and water added, pyridyl-3-mercuric acetate is obtained in 50% yield (*13*).

The chlorination and bromination of pyridine have been investigated with extreme thoroughness by J. P. Wibaut and H. J. den Hertog (*15–18*).

The reactions are carried out in the gaseous phase between 200° and 500°, and in some cases a catalyst is added, e.g. the bromide of iron or copper. Whereas chiefly 3- and 3,5-halopyridines are obtained below 300° without catalyst, the 2-, 4-, and 6-positions are also attacked in the presence of a catalyst or at temperatures around 500°; this is probably attributable to a free radical mechanism (*19*). All 19 possible bromopyridines shown in reaction scheme VIII (*20*), have been prepared by means of gas-phase bromination (*16*).


500 °C
300 °C
500 °C
300 °C
FeBr3
500 °C
300 °C
FeBr3
500 °C
300 °C
FeBr3
500 °C
500 °C
530 °C
500 °C
500 °C
500 °C
300 °C
500 °C
300 °C
500 °C
500 °C
500 °C
530 °C
500 °C
VIII

Friedel-Crafts acylation, which has proved to be of such great significance in benzene chemistry, has not so far succeeded in the case of pyridine.

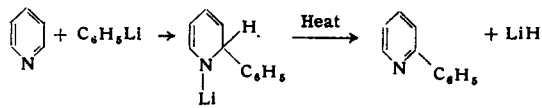
Nucleophilic Substitution

Nucleophilic substitution of the pyridine ring, which produces 2-, 4-, and 6-substituted derivatives (see formulae III–V), proceeds under far milder conditions. The best known and most important reaction of this type is the Tschitschibabin synthesis of 2-aminopyridine from pyridine and sodamide in toluene at 100–125° (*21*) or in xylene at 140–150° (*22, 23*). Small quantities of 4-aminopyridine and 2,6-diaminopyridine as well as 4,4′-dipyridyl and 2,2′-dipyridylamine are found among the by-products (*21, 22*). Since the 2-amino group in pyridine is easily replaced by other substituents, e.g. hydroxyl (*24–26*), fluorine (*25–28*), chlorine (*24–26*), bromine (*25, 29, 30*), and iodine (*25, 26, 29, 31*), this method is an extremely valuable aid in the preparation of pyridine derivatives (*32*).

2-Hydroxypyridine is formed when pyridine fumes are passed over potassium hydroxide powder at 300–320° (*33*).

Substituents may also be introduced into the 2- or 4-position of the pyridine ring by the use of Grignard reagents. 4-Benzylpyridine is obtained by shaking pyridine with benzylmagnesium chloride; dioxane may be used as the solvent (*34–36*). Bergstrom and McAllister (*37*) have reported the production of 2-alkyl- and 2-arylpyridines by the action of alkyl- or arylmagnesium halides, respectively, at 150°; N. Goetz-Luthy was, however, subsequently unable to obtain 2-ethylpyridine by this method (*38, 39*). 4-Allylpyridine is produced in low yield by the reaction between pyridine and allylmagnesium bromide (*40*).

The action of lithium alkyl or aryl on pyridine, described by Ziegler and Zeiser (*41*), is rather better suited to the introduction of alkyl or aryl substituents. The addition compound formed in the cold is decomposed on heating into LiH and 2-alkyl- or 2-arylpyridine (IX) (*42*).



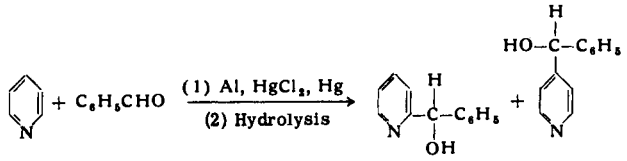
IX 40–49 %

The synthesis of alkylpyridines named after Ladenburg (*43*) is based on the migration of an alkyl group; this is accomplished by heating an N-alkylpyridinium salt, and leads mainly to 2- and 4-substitution. This reaction is nowadays only used for the preparation of benzylpyridines. When benzyl chloride or iodide is heated with pyridine to 250–270°, 2-

and 4-benzylpyridine are obtained (*44*); the yields can be improved by the use of a catalyst such as copper or CuCl (*45*). Dibenzylpyridines (*45, 46*) and 3-benzylpyridine (*47*) are among the by-products. Separation of the isomers is usually achieved via the picrates, in conjunction with fractional distillation (*48*).

The so-called Emmert reaction (*49, 50*) is an example of an anionic attack upon the pyridine ring; it has proved to be a valuable method for preparing 2-hydroxymethylpyridines [see also (*51, 52*)] and has recently been thoroughly investigated by Bachman and his collaborators (*53*). The method involves a heterogeneous bimolecular reduction in which 2- or 4-substituted pyridinecarbinols result from the action of magnesium or aluminum on pyridine and an aldehyde or ketone. The metal is activated by the addition of $HgCl_2$ and a few drops of mercury (*54*).

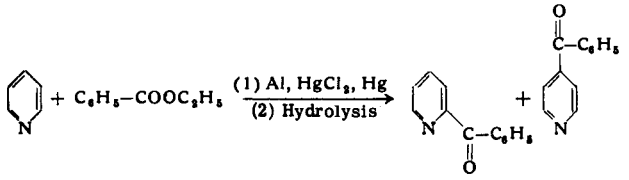
Whereas the aluminum method results in a mixture of 2- and 4-substituted products with the 2-isomer predominant (e.g., X) (*53*), the reduction with magnesium yields 2-hydroxymethylpyridines exclusively (*53*).



X 32 % 4 %

Dialkyl, diaryl, alkylaryl, and cycloalkyl ketones may be used as the carbonyl component; aldehydes usually react less readily (*53*). Besides pyridine, the reaction can also be carried out with 3-picoline (*49, 53, 55*) and 4-picoline (*53–55*); 2-substituted products are obtained. 2-Picoline is substituted in the 6-position but reacts poorly (*49, 51, 54, 55*) and 2,6-lutidine is not substituted at all (*49, 53*).

Bachman and Schisla (*56, 57*) recently extended this reaction when they succeeded in acylating pyridine and 4-picoline directly. These bases react with carboxylic acid derivatives in the presence of aluminum—in some cases also magnesium, beryllium, or sodium—activated by mercuric chloride and a little mercury, to form pyridyl ketones. Here too, the 2-isomer is the major product, with only a small quantity of the 4-substi-



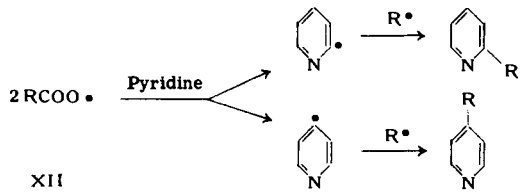
XI 24 % 6 %

tuted compound (e.g., XI) (*57*). Esters, N,N-dialkyl amides, and nitriles have been used as the acid component. The yields are generally not very high.

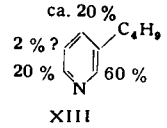
Free Radical Substitution

Varying amounts of 2-, 3-, and 4-substituted products may be obtained together when pyridine is subjected to free radical attack. The first reaction of this type was carried out by Möhlau and Berger (*58*) who were able to isolate 18% of 2-phenyl- and 3% of 4-phenylpyridine (as the picrates) from the decomposition of benzenediazonium chloride in pyridine. 3-Phenylpyridine was subsequently also identified among the reaction products; the exact proportions of the isomers were found to be 54% of 2-phenyl- and 23% each of 3- and 4-phenylpyridine (*59*). A number of other radical-forming substances was included in the investigation, and mixtures of isomers were obtained in every case (*60*). When diacyl peroxides are used, pyridine-N-oxide is probably formed (*61*).

Good yields of 4- and, especially, 2-alkylpyridines were obtained by St. Goldschmidt and M. Minsinger (*62*) in the decomposition of diacyl peroxides in pyridine (XII).



Even the action on butylpyridine of methyl radicals—formed from lead tetraacetate or red lead in glacial acetic acid at 100–110°—gives substitution of the 5-position to but a small extent (XIII) (*63*).



The above survey of a few important and interesting methods of substituting pyridine shows that the adaptation of the usual reactions to the production of 4-substituted pyridines is somewhat limited. Although these products are sometimes formed, the methods discussed here are of little preparative value; the yields are mostly poor and the separation of isomers obtained is often very difficult.

It should be noted that a number of total syntheses are known which lead to substituted pyridines, including 4-substituted compounds. Dis-

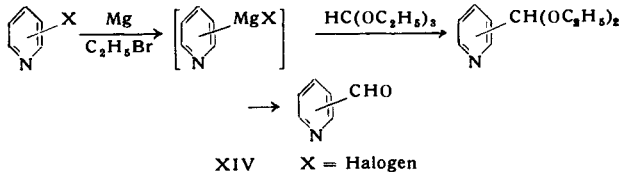
cussion of these methods, however, whose difficulty resides mostly in the procuring of starting materials, lies beyond the scope of this work.

In the following section reactions involving organometallic pyridine compounds are described. In order to give a complete picture of this class of compounds, reactions of 4-halopyridines are also discussed, even though the preparation of these substances is presented in a later section.

Syntheses Involving the Use of Organometallic Pyridine Compounds

Pyridylmagnesium Halides

Halopyridines do not react directly with magnesium to form organomagnesium compounds (*64*). It is only by using the "méthode de l'entraînement," i.e. by the simultaneous addition of ethyl bromide, that it is possible to obtain a compound from 2-bromopyridine and magnesium; this reacts as a Grignard reagent with aldehydes and ketones to form 2-hydroxymethylpyridines (*65, 66*). The structure of the organometallic compound is not known; it is probably a complex which then undergoes normal Grignard reactions (*67*). The same reaction can be effected with 3-halopyridine (*68, 69*), 4-halopyridine (*70*), and 2,6-dihalopyridine (*66*); besides the bromo derivatives, chloro- (*70*) and iodopyridines (*71*) also react. Apart from aldehydes and ketones (*65, 66, 68–70*), esters (*70, 71*), acid anhydrides (*69*), amides (*70*), nitriles (*71*), and CO_2 (*69*) may also be used as reactants. The action of orthoformic ester on pyridine-magnesium compounds results in the formation of pyridinealdehydes (*69, 70, 72*) (XIV).



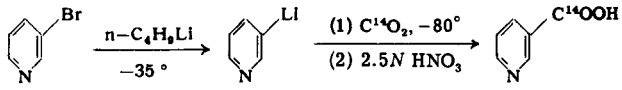
XIV X = Halogen

The commercial-scale preparation of pyridinealdehydes is, however, more readily accomplished by the vapor-phase oxidation of methylpyridines (*73*). A convenient laboratory method for synthesizing such aldehydes consists in oxidizing hydroxymethylpyridines with selenium dioxide (*74, 75*) or lead tetraacetate (*75a*).

The allyl group was similarly introduced into the pyridine ring by allowing 3-pyridylmagnesium compounds to react with allyl bromide (*76*).

Lithiumpyridines

The reaction between bromopyridines and butyllithium affords 2- (*77*), 3- (*77,78*), and 4-lithiumpyridines (*70*). These compounds react in a similar manner to the pyridylmagnesium complexes with ketones (*70, 77*), esters (*70,77*), nitriles (*70,77*), and carbon dioxide (*78*) to give the corresponding pyridine derivatives. Nicotinic acid (XV) (*79*), isonicotinic acid (*80*), and 4-butylpyridine-2-carboxylic acid (*81*) containing C^{14}-labelled carboxyl groups were prepared by this route.



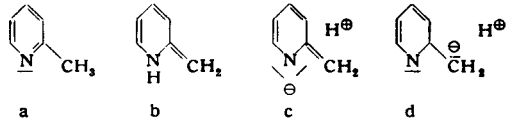
XV

Lithiumpyridines react with fluoroalkenes to give fluorinated alkylenepyridines with elimination of lithium fluoride (*82*). On heating lithium, sodium, or potassium with pyridine, alkali metal compounds of pyridine are formed (*83*). Thus, sodium may be dissolved in pyridine in the cold, and it is only on heating that the calculated amount of hydrogen is evolved; 36% of 2- and 54% of 4-pyridylsodium are obtained (*84*). The addition of bromine to the pyridylsodium solutions thus obtained yields the isomeric dipyridyls (*84*).

Reactivity of Substituents in the Pyridine Ring

The influence of the heteroatom in the pyridine nucleus manifests itself, as mentioned at the outset, by inducing a positive charge at positions 2, 4, and 6 (see structures III–V); the 3- and 5-positions are not thus affected. Since this influence also extends to the substituents at the particular positions, the 2-, 4-, and 6-substituted derivatives of pyridine differ markedly from the 3- or 5-substituted products. The differences in activity brought about by this effect are particularly well illustrated by the three isomeric monomethylpyridines.

Whereas 2- and 4-methylpyridine exhibit distinct proton activity of the methyl group, the latter is scarcely activated in 3-methylpyridine. Like 2- or 4-hydroxypyridine (*85*) and 2- or 4-aminopyridine (*86*), 2- and 4-picoline can therefore react in the pyridone form, e.g. XVIb, c

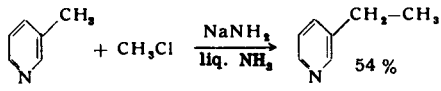


XVI

(*87*), or as an extreme form involving a carbanion structure, e.g. XVId (*88*).

Thus 2- and 4-methylpyridine can be condensed with benzaldehyde to give 2- and 4-styrylpyridine, respectively (*89, 90*), while 3-methylpyridine remains unaffected under the same conditions (*90*). The reactivity of the active methyl groups in positions 2 and 4 can be enhanced by quaternizing the nitrogen atom (*90*); 3-methylpyridine, however, cannot be condensed, even in the form of the quaternary compound (*90*). The SeO_2 oxidation of the picolines gives similar results. This oxidation, which can only be carried out on activated methyl or methylene groups (*91*), gives 2- or 4-pyridinecarboxylic acid from the corresponding picoline; 3-methylpyridine remains unattacked under the same conditions (*92, 93*). A more detailed investigation into the condensation (*90*) and SeO_2 oxidation of the picolines has revealed that the 4-methyl group is more strongly activated with respect to the oxidation than the 2-methyl group (*88*).

A certain mobility of the hydrogen atoms of the 3-methyl group is detectable, however. As recent experiments by Brown and Murphy (*94*) have shown, the side chain of 3-methylpyridine is readily alkylated by reaction with alkyl halides and sodamide in liquid ammonia (see e.g. XVII).



XVII

This reaction, originated by Tschitschibabin (*95*) and later improved by Bergstrom and his co-workers (*96*), was first carried out on 2- and 4-picoline only. Examination of the reactivity of dimethylpyridines (*97*) towards this alkylation, however, showed here too, the gradation in the reactivity (see, e.g., refs. *88*, *90*) of methyl groups previously noted, namely 4-CH_3 > 2-CH_3 > 3-CH_3.

Methods of Preparation of 4-Substituted Pyridine Derivatives

Substitution of the 4-position of the pyridine ring can be effected via N-substituted pyridines such as pyridinium salts and pyridine-N-oxides. Two fundamentally different types of pyridinium salts are found, each of which requires different treatment. The first kind possesses only *one* pyridine ring, with the nitrogen atom quaternized; under certain conditions a γ-pyridone structure can be formed. The 4-position thus activated

meets the requirement for substitution reactions with suitable entering groups. It is not always necessary to start from the actual pyridinium salt; this can just as well be produced during the reaction itself.

The second type of pyridinium salt contains *two* pyridine nuclei joined at one 4-position. In this instance the reactions resulting in the formation of pyridine derivatives proceed via the loss or fission of the quaternary ring.

Finally, in the case of pyridine-N-oxides, the presence of oxygen on the nitrogen atom sometimes brings about a condition which renders the molecule vulnerable to electrophilic attack at the 4-position.

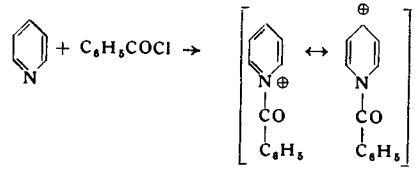
In the first type of pyridinium salts, a C—C bond can be formed at position 4; N-pyridyl-4-pyridinium salts and pyridine-N-oxides allow the introduction of functional groups, e.g. hydroxyl, amino, mercapto, and halogens, as well as the nitro group in the case of the N-oxide.

Reactions Using Pyridinium Salts

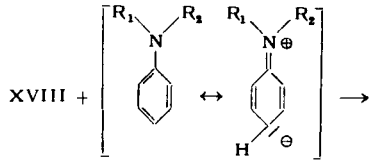
A number of alkyl- arylalkyl-, and acylpyridinium salts can be converted into dihydropyridine derivatives with a C—C bond in the 4-position; this conversion may be effected by either dimerization or reaction with suitable reactants. This procedure is not devoid of a certain preparative significance when it can be extended to include aromatic pyridines.

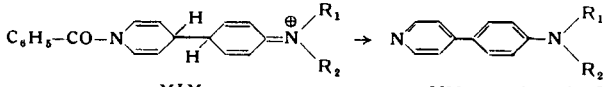
The reaction discovered by Koenigs and Ruppelt (*98*), between pyridine, benzoyl chloride, and dialkylanilines in the presence of "Naturkupfer C" results in 4-(*p*-dialkylaminophenyl)pyridines (XX) with the spontaneous elimination of the benzoyl fragment. The pyridinium salt appears here as a reactive intermediate (XVIII); it decomposes, following the substitution of the 4-position, into the pyridine derivative XX and benzaldehyde. The reaction course reproduced below is accepted as representative of this reaction, though McEwen and his collaborators (*99*) were unable in a subsequent investigation to isolate the hypothetical dihydropyridine intermediate XIX.

The synthesis of 4-alkylpyridines from pyridine and acid anhydrides in the presence of zinc dust, which also proceeds via an intermediate acylpyridinium salt, is both more important and more versatile. This method has its source in a reaction described by Dimroth and coworkers (*100*) between pyridine, acetic anhydride, and zinc dust, in which N-substitution (XXI) is followed by dimerization through the respective 4-positions of two pyridine nuclei to give a tetrahydropyridyl compound (XXIII). Heating with acetic anhydride converts this into a dehydro compound (XXIV) which can be oxidized (e.g. by atmospheric oxygen) to 4,4′-dipyridyl (XXV) (*100*).



XVIII





XIX XX $+ C_6H_5CHO$

R_1, R_2 = e.g. CH_3

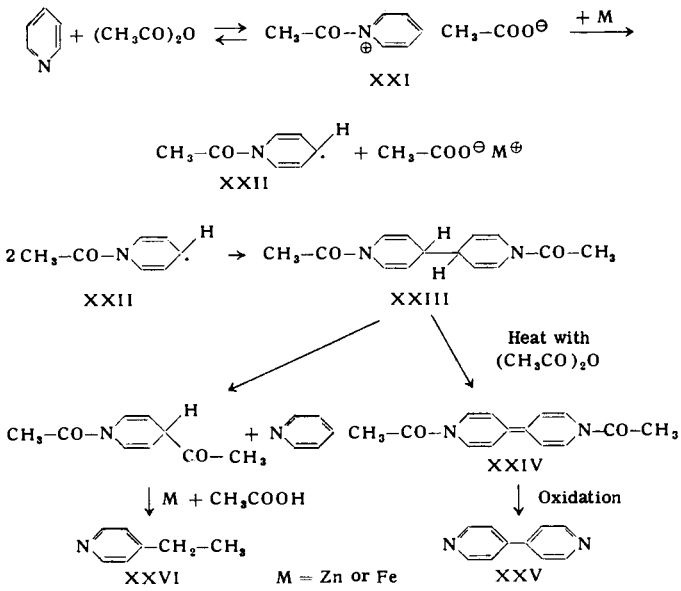
4-Ethylpyridine (XXVI) has been obtained by the addition of acetic acid and zinc dust to the reaction mixture and heating (*101–103*).

Small portions of zinc dust are added to a stirred mixture of pyridine and acetic anhydride maintained at 25° to 30°. The mixture is treated with glacial acetic acid and more zinc dust added; a short period of refluxing is followed by a further addition of zinc. Pyridine and 4-ethylpyridine can be steam-distilled after basification with 40% potassium hydroxide solution. Isolation from the distillate and purification by fractional distillation afford 4-ethylpyridine in 33–38% yield (*103*).

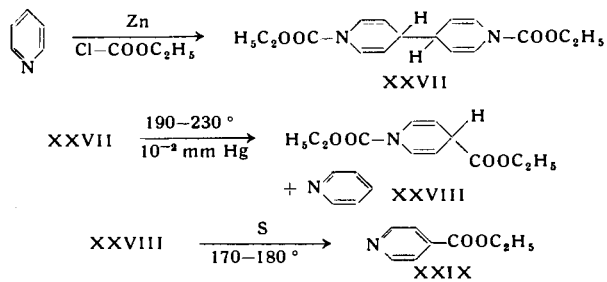
The use of the appropriate acids and anhydrides gives other 4-alkylpyridines (*104*), e.g. 4-propyl-, 4-butyl-, and 4-amylpyridine; 3-methyl-4-alkylpyridines can be prepared from 3-methylpyridine (*105*). The method fails, however, in the case of several 2-substituted pyridine derivatives (*106, 107*). In recent times replacement of zinc dust by iron powder has been recommended; this is said to attenuate the violence of the reaction (*108*).

The course of the reaction, elucidated by Wibaut and Arens (*102*), is reproduced in the scheme of Bachman and Schisla (*57*), who assume that the two pyridine nuclei become linked via a radical intermediate (XXII).

Substitution in the 4-position exclusively is also encountered in the action of benzaldehyde and *tert*-butyl peroxide on pyridine, yielding 4-(α-benzoxybenzyl)pyridine (*109*); an intermediate analogous to compound XXII is thought to take part in the reaction.



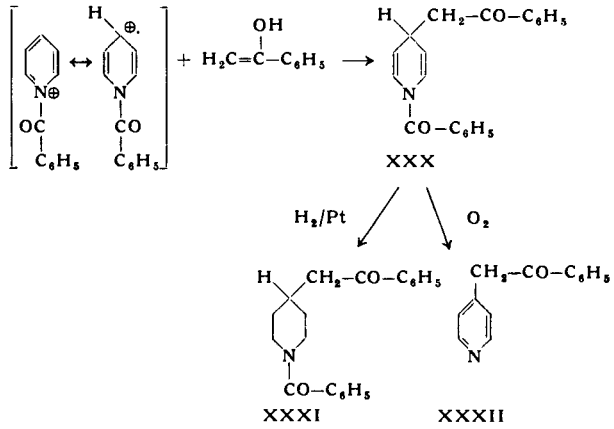
A method of synthesizing isonicotinic ester from pyridine, chloroformic ester, and zinc dust follows from the preparation of 4-alkylpyridines (*110*). When heated *in vacuo*, the N-substituted 4,4′-tetrahydrodipyridyl compound, XXVII, initially formed undergoes a rearrangement with loss of a pyridine ring to give compound XXVIII; this is converted into pyridine-4-carboxylic ester (XXIX) by warming with sulfur.



The first example of a reaction between a pyridinium salt and the activated methyl group of a ketone was the action of acetophenone on benzoylpyridinium chloride, discovered by Claisen and Haase (*111*). The course of the reaction was only elucidated in 1951 by Doering and McEwen (*112*), according to whom 1-benzoyl-4-phenacyl-1,4-dihydropyridine (XXX), and traces of the corresponding 2-phenacyl compound

are produced; propiophenone (*112*), cyclohexanone (*112*), and acenaphthenone (*112, 113*), react in a similar manner. These condensation products are split into their components by acids (*112*).

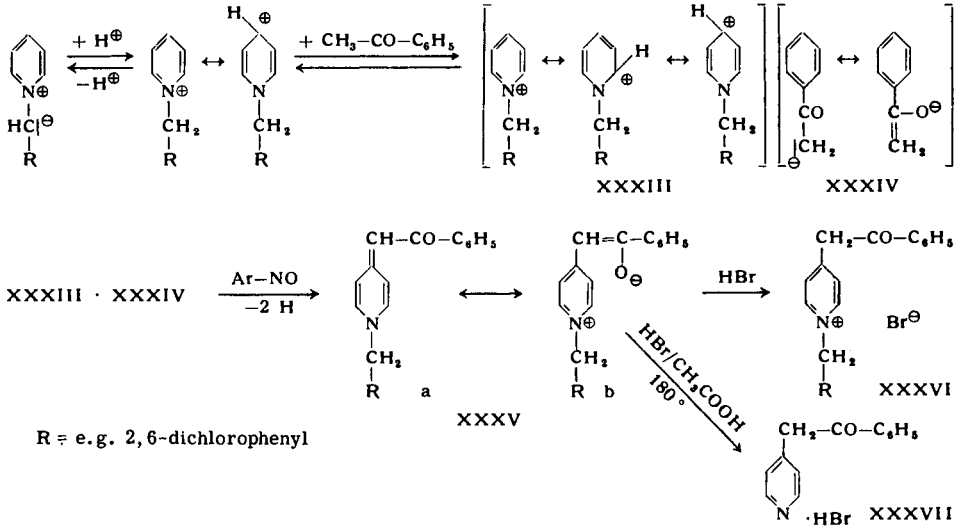
Catalytic hydrogenation of XXX on the other hand, results in the piperidine derivative XXXI, while oxidation by means of oxygen causes the loss of the N-benzoyl moiety to give 4-phenacylpyridine (XXXII) (*112*).



F. Kröhnke and co-workers have recently reported an interesting synthesis of 4-acylpyridines (*114, 115*). They obtained 4-ketonylidene-1,4-dihydropyridines (XXXV) by the action of oxidizing agents on pyridinium bases in the presence of methyl and methylene ketones. The pyridinium salt and ketone in alkaline solution first react to give adducts of the pyridinium cation and the ketone anion, both stabilized by resonance (XXXIII and XXXIV). A C—C bond is formed between the now positively charged 4-position of the pyridine ring and the reactive methylene group by the action of a dehydrogenating agent, usually *p*-nitrosodimethylaniline. The dehydro compound XXXV thus obtained yields a true pyridinium salt (XXXVI) with acid. Benzyl derivatives are generally used as the quaternizing component, as they can be removed by hydrobromic acid/glacial acetic acid at 180°, rendering 4-phenacylpyridines, e.g. XXXVII, readily accessible (*113*). The method is of some consequence due to the fact that it is also applicable to a variety of pyridine derivatives (*112, 113*).

According to Kröhnke (*114*), Wizinger and Mehta (*116*) also succeeded in linking the 4-position of the pyridine ring to the reactive methylene group by allowing pyridine methiodide and phenylmethyl-

pyrazolone or 1,3-diketohydrindene to react in alkaline solution; atmospheric oxygen acted as the dehydrogenating agent. The experiments using N-substituted nicotinamide derivatives also deserve mention; these investigations by Kröhnke showed that the 4-position of N-alkylnicotinamide is also strongly activated, and the 2- and 6-positions are not preferentially attacked (*114,115*).



Syntheses Using N-Pyridyl-4-pyridinium Salts

2-, 3-, and 4-Pyridylpyridinium salts are known; in these compounds the quaternary nitrogen atom of one pyridine nucleus is linked to the carbon atom in position 2, 3, or 4 of a second pyridine molecule. The halogens—especially chlorine—are the usual anions, though perchlorates are also known (*117,118*). Whereas the 2-pyridylpyridinium salts are monoacidic only, the 3- and 4-pyridylpyridinium salts generally contain a second molecule of acid, associated with the nitrogen of the tertiary ring (*117*).

The preparation of the 2- and 3-isomers can be effected by the oxidation of pyridine using aqueous potassium persulfate solution (*117*); in the case of N-pyridyl-4-pyridinium iodide, pyridine hydrochloride and iodine or iodine monochloride can also be used (*119*).

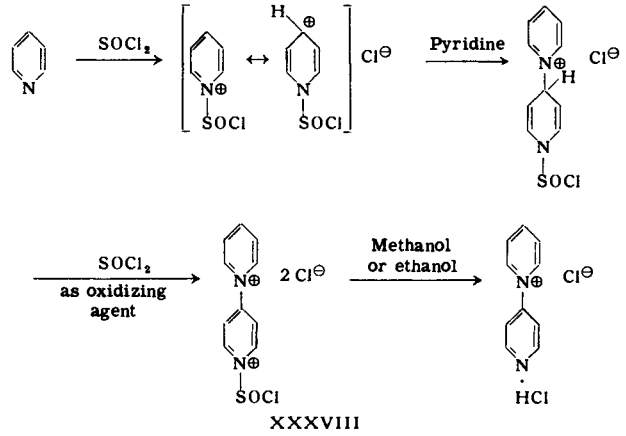
Only the preparation of the N-pyridyl-4-pyridinium salts is of interest, however, as the substitution of pyridine in positions 2 and 3 can be accomplished by simpler methods.

The best method for synthesizing N-pyridyl-4-pyridinium chloride hydrochloride has proved to be the action of thionyl chloride on pyridine, described by Koenigs and Greiner (*120*).

In this method, an excess of thionyl chloride is added to stirred, dry pyridine maintained at constant temperature. After being allowed to stand at room temperature for 3 days, the excess of thionyl chloride can be distilled under vacuum and the residue worked up with ethanol or methanol. Detailed instructions for the preparation of this important starting material will be found in the experimental section.

The mechanism of this reaction has not yet been fully elucidated. In support of Koenigs and Greiner (*120*), as well as Kröhnke (*121*), scheme XXXVIII can be proposed, according to which an acylpyridinium salt formed initially reacts with a second pyridine molecule to give a quaternary compound.

The dehydrogenation would thus be effected by the thionyl chloride; the oxidative action of this compound has been observed in other instances, and is attributed to the presence of ferric chloride (*122*). The thionyl chloride distilled from the reaction mixture always contains a large quantity of water-insoluble decomposition products, especially elementary sulfur.



XXXVIII

SCl_2 (*120d*) can be used instead of thionyl chloride, or alternatively, sulfur dioxide can be passed into a mixture of pyridine, phosphorus pentachloride, and benzene (*120d*). The reaction between pyridine and thionyl bromide yields N-pyridyl-4-pyridinium bromide hydrobromide (*120d*). Satisfactory yields of N-pyridyl-4-pyridinium salts are also obtained by the reaction between chlorine or bromine and pyridine in stoichiometric proportions (*123*). Catalysts such as aluminum, iron, or sul-

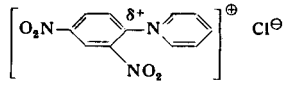
fur may be added to accelerate the reaction (*123*). N-Pyridyl-4-pyridinium bromide hydrobromide is also formed by the action of pyridine perbromide on pyridine (*123*).

Like pyridine, 3-methylpyridine (*124, 118*) also forms a 4-pyridylpyridinium salt. 2-Methylpyridine and 2-methyl-5-ethylpyridine, on the other hand, do not undergo this reaction (*118*).

The chlorides and bromides of N-pyridylpyridinium compounds are solid substances, readily soluble in water but dissolving with difficulty in typical organic solvents. When impure, they are strongly hygroscopic. Complete purification of the salts is wasteful; it is almost impossible to prepare a perfect, analytically pure sample (*125*). Thorough purification is not, however, normally essential for subsequent reactions.

N-Pyridyl-4-pyridinium salts can undergo both elimination and fission of the quaternary pyridine ring. Removal of the ring is effected by the action of nucleophilic reagents, which enter the tertiary pyridine ring at position 4. More strongly basic reagents, on the other hand, open the pyridine nucleus; glutaconic dialdehyde or its derivatives are produced together with 4-aminopyridine.

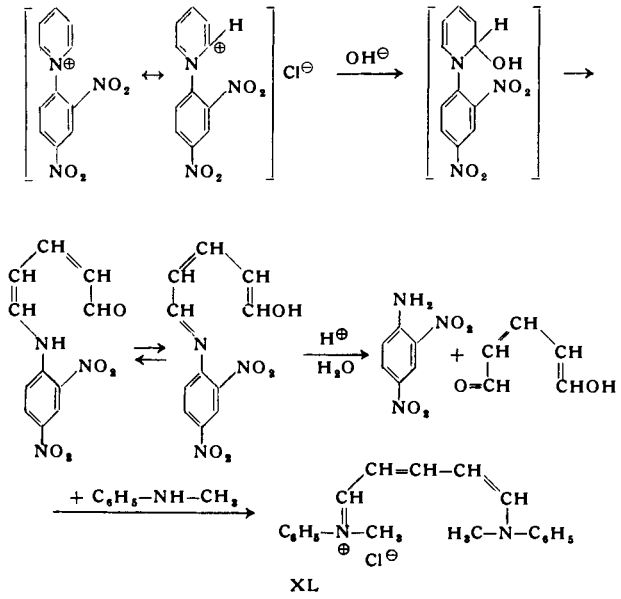
Both types of reaction are also known to occur in the case of 2,4-dinitrophenylpyridinium chloride (XXXIX) which was thoroughly examined by T. Zincke and his co-workers. In this compound, the presence of *o*- and *p*-nitro groups induces a powerful positive charge at the junction between the phenyl ring and the nitrogen atom (*127*). This position is thus rendered susceptible to nucleophilic substitution with the concomitant removal of the pyridine nucleus.



XXXIX

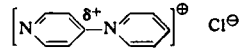
Because of the electron withdrawal in the direction of the benzene nucleus, the quaternary pyridine ring is further weakened, resulting finally—especially in the presence of a base—in the rupture of a C—N bond. Formation of a pseudo-base has not been proved, but seems none the less possible. In the well-known "Zincke fission" of 2,4-dinitrophenylpyridinium chloride (*128*), best effected by methylaniline, the anil of glutaconic dialdehyde is formed together with dinitroaniline (XL). Such derivatives of glutaconic dialdehyde have lately found application in an elegant synthesis of azulenes (*129*).

An effect similar to that of the two nitro groups in the dinitrophenyl moiety is produced by the tertiary nitrogen atom in 4-pyridylpyridinium chloride (XLI).



XL

Here also, an induced positive charge must be assumed at the point of junction; reactions similar to those displayed by the Zincke pyridinium salt can therefore be anticipated.

XLI 

Whereas the pyridinium salts containing but one pyridine ring, described above (pp. 63–67), react in the free 4-position of this ring, the reactive center of the pyridylpyridinium salts lies in the junction of the two rings. The fact that the latter offer no chance of entry in the 4-position to nucleophilic reagents is mostly due here, as in the case of 2,4-dinitrophenylpyridium chloride (*126, 128*) to the immediate fission to glutaconic dialdehyde, caused by the alkalinity of the medium (*120*).

If, on the other hand, an N-acylpyridinium salt is attacked by a nucleophilic reagent, reaction occurs at the acyl group, i.e., at the point of junction with the pyridine ring; the reaction frequently proceeds very vigorously, since the bond with the pyridine nitrogen is considerably more reactive in these salts than in the pyridylpyridinium salts or in the Zincke pyridinium salt (*130*). The only reactions considered here are those of acylpyridinium salts—or acyl halides in pyridine—with alcohols, phenols, and amines to give the corresponding acid derivatives, with water to give acid anhydrides and acids (*131*), and with hydrogen sulfide

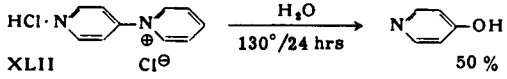
to give diacyl sulfides and thioacids (*131*). Even amides can be converted into triacylamines by the use of acylpyridinium salts (*132*).

The more important syntheses using N-pyridylpyridinium salts proceed via the loss of the quaternary ring, which regenerates pyridine hydrochloride. This method, therefore, allows the substitution of but half of the pyridine and recovery of the other half. This disadvantage is amply compensated for, however, by the low outlay and satisfactory yields usually associated with the reaction.

4-Hydroxypyridine and Pyridyl-4-ethers

4-Hydroxypyridine was first obtained by the decarboxylation of chelidamic acid (4-hydroxypyridine-2,6-dicarboxylic acid) (*133–135*). This acid is obtained by the condensation of diethyl oxalate and acetone in the presence of sodium ethoxide, and warming the chelidonic acid produced with ammonia [see e.g. refs. (*125, 136, 137*)]. In the diazotization of 4-aminopyridine in sulfuric acid solution, the 4-hydroxy compound is formed at temperatures as low as —15° (*138*).

The process, discovered by Koenigs and Greiner (*120*), of splitting N-pyridyl-4-pyridinium chloride hydrochloride with water at elevated temperatures (XLII) is superior to these methods (*125*).



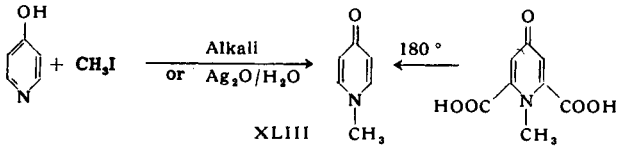
XLII 50 %

In the reaction of Koenigs and Greiner, the pyridinium salt is dissolved in a small quantity of water and heated at 150° (*120*) for 8 hr. There have, since their work, been many variations on these conditions; the method described by Bowden and Green affords good yields (*139*).

Water is distilled from an aqueous solution of N-pyridyl-4-pyridinium chloride hydrochloride until the internal temperature reaches 130°; the mixture is then heated under reflux for 24 hr. Water and sodium carbonate are added, the mixture evaporated to dryness under vacuum, and the 4-hydroxypyridine formed extracted with absolute alcohol. Treatment with animal charcoal and concentration give a pale yellow product, m.p. (after drying over P_2O_5) 120–130°; the yield amounts to approximately 50% (*139*). Following further purification, the m.p. of the anhydrous material rises to 147–151° (*125*).

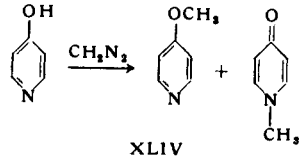
4-Hydroxypyridine forms a monohydrate, m.p. 66–67° (*120*), and is readily soluble in water. Attempts at alkylating the hydroxyl group soon revealed that the compound was not a true phenol of pyridine. By treating 4-hydroxypyridine with methyl iodide and alkali or moist silver oxide, Lieben and Haitinger (*140*) were thus merely able to convert it

into N-methyl-4-pyridone; the same product was obtained by heating N-methylchelidamic acid (XLIII).



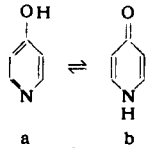
XLIII

Similarly, reaction with monochloroacetic acid yields N-carboxymethyl-4-pyridone, substitution occurring exclusively at the nitrogen atom of the pyridine nucleus (*141, 142*). The action of diazomethane on 4-hydroxypyridine results in the simultaneous formation of the corresponding N-methyl and O-methyl substitution products (XLIV) (*143*).



XLIV

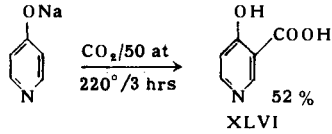
Arndt and Kalischek (*144*), on the other hand, obtained O-acyl derivatives exclusively by allowing 4-hydroxypyridine to react with acyl chlorides. It was only by investigation into their physical properties, especially the UV and IR spectra, that the structure of the 4- and 2-hydroxy derivatives of pyridine was elucidated: An example of true tautomerism was found to exist, with the so-called pyridone form (XLVB) strongly preferred; see, e.g., refs. (*85, 145, 146*).



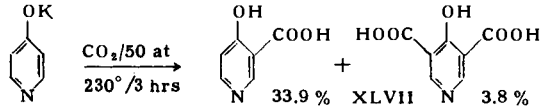
XLV

The introduction of the hydroxyl group into the pyridine nucleus increases the reactivity of positions 3 and 5 to an extraordinary degree. Nitration of 4-hydroxypyridine with nitric acid ($d = 1.52$) and oleum (70% SO_3) gives a 50–60% yield of 3-nitro-4-hydroxypyridine if the mixture is allowed to simmer gently for 2 hr; heating for 5 hr brings about the introduction of a second nitro group in the 5-position (*147, 148*). The nitration can even be effected at water-bath temperature, but requires in that case a longer reaction time (*149*). If 3-nitro-4-hydroxypyridine is heated with bromine in aqueous solution, 3-nitro-4-hydroxy-5-bromopyridine is readily formed (*147*).

The sodium or potassium salt of 4-hydroxypyridine can be carboxylated with carbon dioxide under pressure at elevated temperatures; in the case of the potassium salt, a small quantity of a dicarboxylic acid is also found (XLVI and XLVII) (*150*).

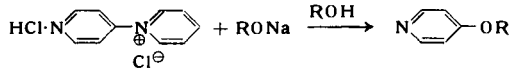


XLVI



XLVII

On account of the pyridone structure, pyridyl-4-ethers are not readily accessible via the alkylation of 4-hydroxypridine. They can be obtained by allowing 4-chloropyridine to react with alkoxides (*151, 152*) or phenoxides (*152*). The preparation of the ethers can, however, also be carried out directly from N-pyridyl-4-pyridinium salts by heating with alcohols (*118, 120, 153, 154*) or phenols (*118, 120, 154*); sufficient ethoxide or phenoxide is then usually added to an excess of the hydroxyl compound to neutralize half of the N-pyridylpyridinium chloride hydrochloride (XLVIII).



XLVIII

Few examples of the reaction with alcohols are known; phenols react rather more readily and do not necessitate the addition of phenoxides (*118, 120*), especially if N-pyridyl-4-pyridinium monochloride is used (*118*). A series of N-pyridyl-4-phenyl ethers with substituents in the pyridine ring has been prepared by this method (*118, 120, 154*).

4-Halopyridines

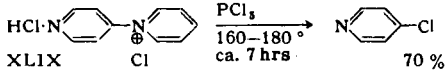
4-Chloropyridine was prepared as long ago as 1885 by heating anhydrous 4-hydroxypyridine with excess phosphorus trichloride at 150° (*151*). This method was retained until very recently, though yields were improved by using PCl_5 (*155*) or a mixture of PCl_5 and $POCl_3$ (*156*). 4-Bromopyridine is similarly formed by heating the hydroxy compound with phosphorus pentabromide at 110° (*157*). 4-Chloropyridine is also obtained by the diazotization of 4-aminopyridine; the nitroamine initially formed affords a high yield of the 4-chloro product by treatment with hydrochloric acid (*158*). The action of concentrated hydrobromic

acid and sodium nitrite on the 4-amino compound results in the formation of 4-bromopyridine (*157*).

Small quantities of 4-chloropyridine were detected by Koenigs and Greiner (*120*) in the thermal decomposition of N-pyridyl-4-pyridinium chloride hydrochloride. A patent specification by Haack (*159*) deals with the preparation of 4-chloro- and 4-bromopyridine by passing gaseous HCl or HBr into fused N-pyridyl-4-pyridinium salts at 220° to 250°. The yields reported are good, but could not subsequently be reproduced in the case of the chloro compound (*160*).

4-Chloro- and 4-bromopyridine are obtained directly from N-pyridyl-4-pyridinium chloride hydrochloride by fusing for some time with phosphorus pentachloride or pentabromide (*118, 161*); the pyridinium salt need not be particularly pure in this case.

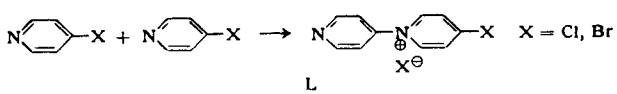
$AlCl_3$ can be used instead of PCl_5 in the preparation of 4-chloropyridine (*118*). The reaction mixture is cooled, ice water is added, followed by basification with caustic soda solution, and the mixture of pyridine and the 4-halopyridine separated by steam distillation. Fractional distillation through a Vigreux column yields 70% of 4-chloropyridine, b.p. 63–64°/50 mm (*61*) (XLIX).



XLIX 70 %

This method is equally applicable to the preparation of 3-methyl-4-chloropyridine, by heating the corresponding N-pyridylpyridinium salt with PCl_5 at approximately 180° (*118*).

4-Chloro- and 4-bromopyridine are colorless liquids with a pyridine-like odor, and can be distilled without decomposition under vacuum or at normal pressure. Both distillation and storage, however, require special precautions. Haitinger and Lieben (*151*) had early observed the formation of a solid decomposition product in 4-chloropyridine; the investigations of Wibaut and Broekman (*156*) showed this to be an N-pyridyl-4-pyridinium salt, thought to result from the combination of two or more molecules of the halopyridine, e.g., L.



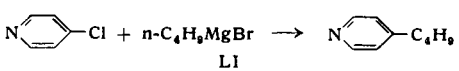
L

It has recently been established that the reaction occurs (*161*) only in the presence of traces of a strong acid or a quaternary pyridinium salt, e.g. N-methyl-4-chloropyridinium iodide. If acid formation is prevented by the addition of alkali, these halopyridines may be handled without

fear of decomposition. It is essential, therefore, that the walls of all apparatus used in the distillation or storage of 4-chloro- or 4-bromopyridine be covered with a thin layer of alkali by first rinsing with methanolic sodium or potassium hydroxide and drying (*161*). 4-Iodopyridine is obtained by heating 4-chloropyridine with hydriodic acid in a tube at 145° (*151*), or by treatment of 4-aminopyridine with sodium nitrite and potassium iodide in sulfuric acid solution (*162*). The compound melts at 100° with decomposition (*162*), and conversion into an N-pyridyl-4-pyridinium salt requires prolonged boiling with water (*163*). 4-Fluoropyridine, on the other hand, appears to be very unstable (*163*); until recently it had not proved possible to obtain it either from 4-aminopyridine by a diazo reaction (*164*), or by the replacement of the chlorine atom in 4-chloropyridine using potassium fluoride, with dimethylformamide as the solvent (*165*). Wibaut and Holmes-Kamminga (*165a*) have now succeeded in preparing 4-fluoropyridine from 4-aminopyridine by treatment with sodium nitrite in concentrated hydrofluoric acid.

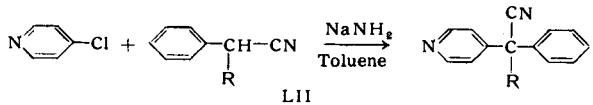
The halogen atom in 4-chloro- and 4-bromopyridine exhibits a certain reactivity, which enables these compounds to undergo a variety of reactions. The chlorine atom can thus be replaced by the amino group by heating with ammonia and zinc chloride at 220–230° for 4–5 hr (*166*); this method also renders possible the introduction of substituted amino groups into the 4-position of the pyridine ring (*161, 167, 168*). The formation of N-pyridyl-4-ethers from 4-chloropyridine and alkoxides or phenoxides has been referred to above. The kinetics of this reaction have been investigated by Chapman and Russel-Hill (*169*). The corresponding thioethers are obtained by replacing hydroxyl by mercapto compounds (*170*); N-pyridyl-4-sulfones are formed by allowing 4-halopyridine to react with the sodium salt of a sulfinic acid (*171*).

In contrast, 4-chloropyridine is not sufficiently reactive to be attacked by sodiomalonic ester (*172*), which will, however, react with 4-chloropyridine-2,6-dicarboxylic ester in toluene (*172*). Subsequent saponification and decarboxylation yield 4-methylpyridine; the use of substituted malonic esters renders other 4-alkylpyridines accessible (*172*). The latter are also formed by the reaction between alkylated barbituric acids and 4-bromo- or 4-chloropyridine, followed by the decomposition of the N-pyridyl-4-barbituric acid derivative with alkali (*173*). The action of aliphatic Grignard reagents on 4-chloropyridine results initially in the formation of a complex, which is decomposed on heating to give 4-alkylpyridines (*161*) (e.g., LI).



LI

Compounds of the benzyl cyanide type react with 4-chloropyridine in the presence of sodamide as hydrogen halide acceptors to give substituted 4-cyanomethylpyridines (LII) (*174*).



LII

The halogen atom in 4-chloropyridine can be replaced by a sulfonic acid group by boiling for 24 hr in aqueous sodium sulfite solution; the sodium salt of pyridine-4-sulfonic acid is obtained in 90% yield (*175*). Dry distillation of this salt with potassium cyanide gives a good yield of 4-cyanopyridine (*175*).

The halopyridines strongly resist the introduction of further substituents into the pyridine nucleus; nitration of 4-chloropyridine cannot be effected (*176*).

The use of 4-chloro- and 4-bromopyridine in the preparation of organometallic pyridine compounds has been discussed earlier.

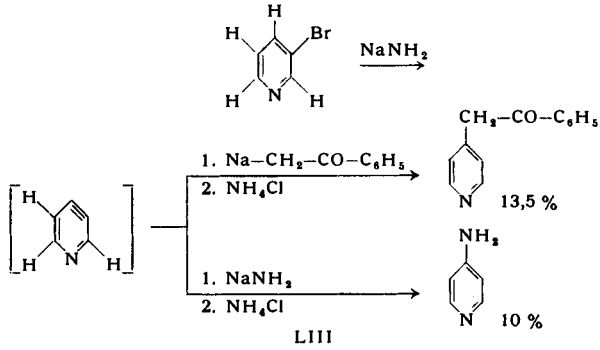
4-Aminopyridine and Substituted Pyridyl-4-amines

The first preparation of 4-aminopyridine, still used to a certain extent today, is based on the Hofmann degradation of pyridine-4-carboxylic acid amide (*138,177*). The introduction of the amino group into the 4-position of the pyridine ring can also be carried out by the reaction of 4-chloropyridine (*166*) or 4-bromopyridine (*157*) with ammonia. 4-Aminopyridine may be obtained in satisfactory yield from N-pyridyl-4-pyridinium chloride hydrochloride directly by heating the pyridinium salt for 8 hr at 150° with concentrated ammonium hydroxide solution. These directions by Koenigs and Greiner (*120*) were subsequently followed by J. P. Wibaut and his collaborators (*178*) who, in contrast to other workers (*179*), fully confirmed the usefulness of the method. An interesting modification is described by Albert (*180*).

According to this variation, a strong stream of ammonia is passed into a mixture of N-pyridyl-4-pyridinium chloride hydrochloride and phenol heated to 180–190°. After 3 hr the reaction mixture is worked up with the removal of the phenol by steam distillation, and the chloroform extraction of the concentrated basified residue. 4-Aminopyridine is thus obtained in 80% yield, and recrystallization from benzene gives a product of m.p. 158°.

Levine and Leake (*181*) have reported an unusual synthesis of 4-aminopyridine. If 3-bromopyridine is allowed to react with sodioacetophenone in the presence of sodamide and the product worked up with aqueous ammonium chloride solution, 4-amino- and 4-phenacylpyridine

are obtained. The authors assume that a dehydropyridine—"pyridyne"—is formed as intermediate, which then reacts at position 4 (LIII).



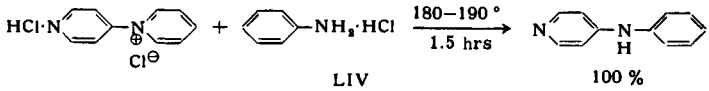
LIII

4-Aminopyridine is capable, like 4-hydroxypyridine, of forming tautomeric structures, though in this case the amino form is believed to predominate [see, e.g. refs. (*86, 145*)]. The action of methyl iodide on 4-aminopyridine nevertheless results in the formation of 1-methylpyridone-4-imide hydriodide (*182*) or 1-methyl-4-pyridoneimide (*183, 184*); in other words, substitution does not take place at the primary amino group, but at the pyridine nitrogen. The 4-amino compound can, however, be converted into pyridyl-4-carboxylic acid amides with acid derivatives (*120, 138*); similarly, e.g. 4-(*p*-aminophenylsulfonamido)pyridine, also known as 4-sulfapyridine, can be obtained from 4-aminopyridine and sulfanilic acid chloride (*185, 186*).

The diazotization of 4-aminopyridine, best effected by the slow addition of a mixture of nitric acid ($d = 1.4$) and nitrosylsulfuric acid, gives 4-nitraminopyridine and a solution of a diazonium salt which can be coupled with phenols and aromatic amines (*187*). 4-Nitraminopyridine also results from the action of nitric acid on a solution of the amine in sulfuric acid (*187*); the nitramino compound readily rearranges to 3-nitro-4-aminopyridine (*158*). Further nitration to 3,5-dinitro-4-aminopyridine is also possible (*158*). 4-Nitropyridine is obtained in 80% yield by the oxidation of 4-aminopyridine using fuming sulfuric acid and 30% oleum (*188*). The 4-nitro group is so reactive that it can be replaced by alkoxide or phenoxide groups, giving pyridyl-4-ethers (*189*). Reaction with ammonia yields 4-aminopyridine; with 50% caustic alkali 4-hydroxypyridine is obtained (*189*); the latter is also formed by allowing 4-nitropyridone to stand for prolonged periods with N-(4-pyridyl)pyridone-4 (*190*).

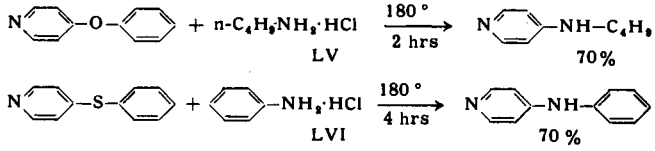
Since the alkylation of the primary amino group in 4-aminopyridine is rather difficult—it can be accomplished by passing the aminopyridine

with methanol over catalysts at elevated temperatures (*191*)—special methods are used to synthesize substituted 4-aminopyridines. 4-Alkylaminopyridines are obtained by allowing 4-chloropyridine to react with substituted amines (*167, 168*); if 4-chloropyridine-2,6-dicarboxylic acid is used instead, the reaction must be followed by decarboxylation (*182*). 4-Dimethylaminopyridine is formed by passing dimethylamine into a phenolic melt of 4-pyridylpyridinium chloride hydrochloride (*118*). If the latter is heated with a primary aromatic amine hydrochloride (which may also contain substituents in the phenyl ring), excellent yields of 4-phenylaminopyridines, e.g. LIV, are obtained (*192*).



LIV 100 %

The replacement of the pyridinium salt by 4-pyridyl phenyl ether extends the application possibilities of this method. Both aromatic and aliphatic primary and secondary amines can then be made to react; pyridine and morpholine can also be used (*192, 192a*) (see e.g. LV). Furthermore, 4-pyridyl 4-nitrophenyl ether and 4-pyridyl phenyl thioether can also be subjected to this aminolytic fission (*192*) (LVI).



LV 70 %

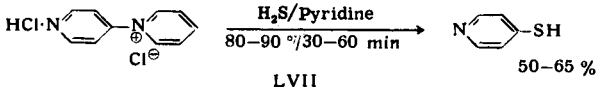
LVI 70 %

4-Mercaptopyridine and Pyridyl-4-thioethers

If equal parts by weight of 4-chloropyridine and potassium hydrosulfide are heated at 140° in aqueous alcoholic solution for 6 hr, a good yield of 4-mercaptopyridine is formed (*155*). This compound is also obtained by warming an intimate mixture of 4-hydroxypyridine and phosphorus pentasulfide to 60–70° (*193*).

Pyridine-4-thiol is readily obtained directly from N-pyridyl-4-pyridinium chloride hydrochloride (*118*) (LVII).

The pyridinium salt is suspended in a little pyridine, heated on a water bath to 80° to 90° and a strong stream of hydrogen sulfide passed in for 30 to 60 min. The yields lie between 50 and 65%, depending on the quality of the pyridinium salt used. Pure 4-mercaptopyridine has a m.p. of 186° (*118*).



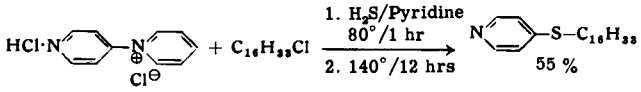
LVII 50–65 %

The reaction can be carried out in a similar manner using N-(3-methyl-4-pyridyl)-3-methylpyridinium chloride hydrochloride to give 3-methyl-4-mercaptopyridine, m.p. 159–160°, in 25% yield (*118*).

5-Nitropyridyl-2-pyridinium chloride can also be converted into the mercapto compound with hydrogen sulfide in the presence of pyridine; the 2-mercapto-5-nitropyridine formed in 80% yield is also formed by passing hydrogen sulfide into a mixture of 5-nitro-2-chloropyridine and pyridine (*194*).

Unlike 4-hydroxypyridine, 4-mercaptopyridine reacts with alkyl halides to give good yields of pyridyl-4-thioethers. In accordance with this fact, the UV spectrum of pyridine-4-thiol exhibits a band at 2350Å, ascribable to the SH form (*195*). 4-Pyridyl methyl sulfide hydriodide is obtained in quantitative yield from the mercaptan and methyl iodide in alcoholic solution; addition of alkali liberates the free base (*193*). Long-chain pyridyl-4-thioethers can also be obtained by this route (*118*).

A particularly facile preparation of 4-substituted aliphatic thioethers of pyridine consists in the initial treatment with hydrogen sulfide of a mixture of N-pyridyl-4-pyridinium chloride hydrochloride and alkyl halide in pyridine at ca. 80°, followed by heating in a tube for several hours at 110–150°. Depending on the solubility of its salt, the thioether can be either separated directly after the addition of water, or extracted with ether following basification (*118*) (LVIII).

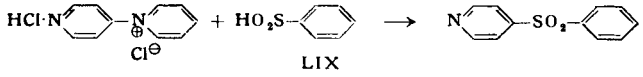


LVIII

Treatment of 4-mercaptopyridine with monochloroacetic acid and sodium bicarbonate in aqueous solution yields (pyridyl-4-mercapto)acetic acid (*193*), also formed from 4-chloropyridine and 2-mercaptoacetic acid (*196*). Application of the pyridine/H_2S method to monochloroacetic ester and N-pyridyl-4-pyridinium chloride hydrochloride gives the corresponding thioether directly (*118*). 4-Pyridyl phenyl thioether can be prepared from thiophenol by the action of both 4-chloropyridine (*170*) and N-pyridyl-4-pyridinium chloride hydrochloride (*118*).

4,4′-Dipyridyl disulfide is obtained by the oxidation of the thiol with iodine–potassium iodide solution in dilute sodium hydroxide (*155*), hydrogen peroxide and zinc oxide, or bromine in glacial acetic acid (*193*). The action of chlorine on 4-mercaptopyridine in dilute acetic acid produces 4-chloropyridine and 4,4′-dipyridyl sulfide (*193*); pyridyl-4-methyl sulfone is obtained by the oxidation of the corresponding thioether with 3% potassium permanganate solution (*193*). Sulfones also can be ob-

tained directly from pyridyl-4-pyridinium chloride hydrochloride and sulfinic acid, the reaction being carried out in alcohol (see, e.g. LIX) (*197*).



LIX

Pyridine-4-sulfonic acid may be obtained by the oxidation of 4-mercaptopyridine with perhydrol in 2 *N* sodium hydroxide solution (*193*) or nitric acid ($d = 1.2$) (*155*). Its preparation from 4-chloropyridine and aqueous sodium sulfite solution was mentioned earlier (*175*). Pyridine-4-sulfonic acid chloride is formed as a nonisolable compound by the action of chlorine on 4-mercaptopyridine in the presence of 30% hydrogen peroxide; reaction with amines gives the corresponding amides; the use of hydrazine hydrate in acetone results in the formation of pyridine-4-sulfonic acid hydrazide (*198, 199*).

Unlike the equivalent reaction using hydrogen sulfide, the action of hydrogen selenide on N-pyridyl-4-pyridinium chloride hydrochloride in pyridine at room temperature produces a mixture of 4,4′-dipyridyl selenide and 4,4′-dipyridyl diselenide (*118*).

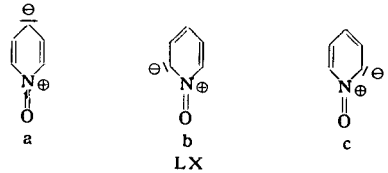
The Use of Pyridine-N-oxides in the Preparation of Substituted Pyridines

The method of preparing pyridine derivatives—especially those containing substituents in the 4-position—via the amine oxides is a relatively recent discovery. Studies in this field have been pursued in Japan particularly, where Ochiai and his co-workers have for the past 15 years carried out extensive investigations into the mechanism of the reactions undergone by the pyridine-N-oxides (*200*). Because of the war, it is only since 1950 that the publications of the Japanese school have made their way into the literature accessible to us. Unaware of this work, H. J. den Hertog, in Holland, and his collaborators (*201*), obtained similar results. A survey of the more important reactions of these amine oxides follows, special attention being accorded to preparative processes.

Theoretical Considerations Concerning the Mechanism of the Reactions of Pyridine-N-oxide

The presence of an oxygen atom linked to the pyridine nitrogen gives rise to a system possessing increased reasonance possibilities, and capable of undergoing a variety of reactions. The dipole moment of pyridine-N-oxide is significantly lower than that calculated from the moment of the amine oxide group and the moment of pyridine. This observation was explained by Linton (*202*) with the hypothesis that in its resonance

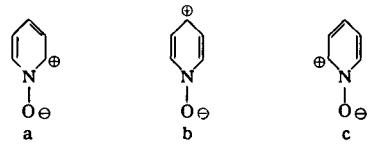
system pyridine-N-oxide can assume a number of extreme canonical structures which cannot be assumed by pyridine itself (LX).



a b c

LX

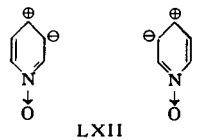
Ochiai (*200*) concluded from the existence of these canonical states that pyridine-N-oxide must be susceptible to substitution by electrophilic reagents and that these would enter in positions 2 and 4. As the electron distribution in pyridine-N-oxide calculated by Jaffé (*203*) showed, additional structures must be formulated in which the 2-, 4-, and 6-positions become positively charged (LXI).



a b c

LXI

The results of the investigations by Mosher and Welsh (*204*) have indicated that not all the reactions of pyridine-N-oxide can be explained by the above formulations, but rather by the participation of canonical structures of the type known in the case of pyridine itself (LXII).



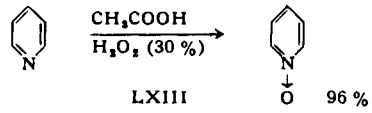
LXII

Preparation and Properties of Amine Oxides in the Pyridine Series

Amine oxides may be obtained from tertiary amines by the action of oxygen-releasing oxidizing agents. While it is possible to oxidize aliphatic amines under mild conditions, e.g. with 3% hydrogen peroxide, the formation of N-oxides from aromatic-heterocyclic amines like pyridine requires the use of more powerful agents. Pyridine-N-oxide was prepared as long ago as 1926 by Meisenheimer (*205*), by the action of perbenzoic acid on pyridine; the amine was purified via the picrate. Other organic peracids, like monoperphthalic acid (*160*) and peracetic acid (*206*) are suitable oxidizing agents. Pyridine-N-oxide is formed from glutaconic dialdehyde and hydroxylamine by ring closure (*207*).

The conversion of pyridines into amine oxides by means of hydrogen peroxide can only be accomplished if a carboxylic acid is added as

solvent. Picolinic acid N-oxide (*208*), isonicotinic acid N-oxide (*209*), and later nicotinic acid N-oxide (*210*) were thus obtained from the corresponding pyridinecarboxylic acid by using 30% hydrogen peroxide in glacial acetic acid. Ochiai (*200*) was the first, however, to recognize the general applicability of the acetic acid/perhydrol method to the preparation of N-oxides in the pyridine series (LXIII).



Other organic carboxylic acids can be used instead of glacial acetic, but anhydrous acetic acid has proved to be the most favorable solvent (*200*).

In order to prepare pyridine-N-oxide, pyridine dissolved in glacial acetic acid is heated for several hours at 70–80° with an excess of 30% H_2O_2; the solution is concentrated under vacuum and the basified residue extracted with chloroform. Purification is effected by distillation under reduced pressure.

The amine oxides of the pyridine homologs as well as of many other pyridine derivatives can be obtained, often in very good yields, according to these directions (*200*); the method does, however, fail in the case of, for example, 2-chloro-5-nitropyridine (*194*), and a number of other nitrogen-containing heterocycles (*211*).

Physical constants of some N-oxides in the pyridine series are given in Table 1.

Many N-oxides in the pyridine series are known today, and of these, particularly the N-oxides of pyridine itself and of its simple homologs possess great significance from the preparative point of view. The semipolar $N \rightarrow O$ bond confers a salt-like character upon these compounds; they are consequently readily soluble in water but dissolve with difficulty in organic solvents such as benzene and ether. The pyridine-N-oxides are, like quaternary pyridinium salts, frequently very hygroscopic. Their melting and boiling points are relatively high, and are always higher than the respective tertiary base. The amine oxides also react as bases and are capable of salt formation; picrates and picrolonates (*221*) can be used for identification. 4-Methylpyridine-N-oxide strongly differs in its physical properties from the N-oxides of pyridine and 2- and 3-methylpyridine. Its melting point is considerably higher and it can be recrystallized beautifully from acetone to give white, scarcely hygroscopic needles (*194*); the other oxides mentioned readily dissolve in this solvent.

This behavior allows the separation of mixtures of pyridine bases;

TABLE 1
Pyridine N-Oxides

Amine oxide	B.p. (°C/mm) or m.p. (°C)	M.p. of the picrate (°C)
Pyridine	138-140°/15 (*200*)	179.5° (*205*)
2-Methylpyridine	123-124°/15 (*212*)	125-126.5° (*212*)
3-Methylpyridine	146-149°/15 (*212*)	138-139° (*212*)
4-Methylpyridine	185-186° (*212*)	158.7-159.7°
2,4-Dimethylpyridine	148°/13 (*212*)	140 (*214*)
2,6-Dimethylpyridine	115-119°/18 (*212*)	127.5-129° (*213*)
2-Methyl-5-ethylpyridine	93°/0.2 (*215*)	–
2,4,6-Trimethylpyridine	135-139°/14 (*216*)	166-167° (*214*)
2-Benzylpyridine	99-100° (*216a*)	–
3-Benzylpyridine	66° (*216a*)	–
4-Benzylpyridine	104-105° (*216a*)	–
2-Hydroxypyridine	145-147° (*217*)	–
3-Hydroxypyridine	189-191° (*217*)	–
4-Hydroxypyridine	243-244° (*217*)	–
2-Aminopyridine	163-164° (*218*)	–
4-Aminopyridine	Hygroscopic crystals (*200*)	199-200° (*200*)
2-Chloropyridine	67-68.5° (*218*)	–
4-Chloropyridine	169.5° (*200*)	–
2-Hydroxymethylpyridine	143-143.5° (*212*)	–
3-Hydroxymethylpyridine	88-89° (*216a*)	–
4-Hydroxymethylpyridine	121-122° (*216a*)	–
2,6-Dihydroxymethylpyridine	136° (*216a*)	–
Pyridine-2-aldehyde (hydrate)	78-80° (*88*)	–
Pyridine-4-aldehyde	147° (*216a*)	–
Pyridine-2,6-dialdehyde	187-188° (*88*)	–
5-Methylpyridine-2-aldehyde	164.5-165.5° (*88*)	–
Pyridine-2-aldehyde-4-carboxylic acid	222-223° (*88*)	–
Pyridine-2-carboxylic acid	161° (*208, 213*)	–
Pyridine-2-carboxylic acid methyl ester	135-137°/0.6 (*219*)	–
Pyridine-3-carboxylic acid	249° (*210*)	–
Pyridine-3-carboxylic acid methyl ester	97° (*210*)	–
Pyridine-4-carboxylic acid	266° (*209*)	–
Pyridine-4-carboxylic acid methyl ester	118-119° (*220*)	–

these can be converted into mixtures of N-oxides and resolved into their components by distillation (*213, 219, 222*) or recrystallization (*219*). It is possible in this manner to separate the so-called β-picoline fraction without difficulty into 2,6-dimethylpyridine-N-oxide and 3-methylpyridine-N-oxide by fractional distillation. Crystallization of the residue from acetone yields pure 4-methylpyridine-N-oxide; reduction of the amine oxides gives the tertiary pyridine bases in a pure state (*219*).

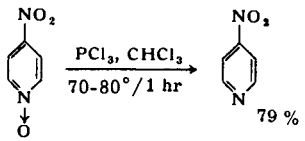
Reactions of N-Oxides in the Pyridine Series

Reduction of Pyridine-N-oxides

The amine oxides of the pyridine series are reduced with difficulty. Whereas the aliphatic and aliphatic-aromatic N-oxides are reduced to the corresponding tertiary amines by even mild reducing agents, the removal of the oxygen atom from the amine oxide group in the aromatic-heterocyclic series usually necessitates the use of powerful reagents. Good results were obtained in the catalytic hydrogenation with Raney nickel of N-oxides of pyridine and substituted pyridines in glacial acetic acid/acetic anhydride; the reaction proceeds at a rapid rate and the pyridine ring is unattacked (*219*). The use of platinum or palladium catalysts generally also requires the reaction to be carried out in acid solution (*200*), although some compounds, such as 3- and 4-methylpyridine-N-oxide are readily hydrogenated by PtO_2 in methanol (*223*). Nascent hydrogen—produced for example from iron in acetic acid solution—also reduces amine oxides to the original tertiary pyridine [see, e.g. refs. (*205, 219, 224–227*)]. This method allows the reduction of 2,6-dimethylpyridine-N-oxide, which is scarcely affected by catalytic hydrogenation (*219*).

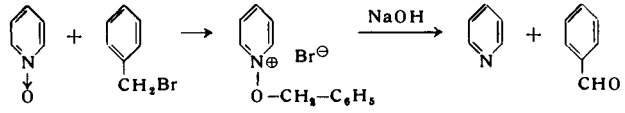
From a number of pyridine-N-oxides, the removal of the oxygen atom can be effected in liquid ammonia by both sodium (*228*) and sulfur (*229*). Benzenesulfenyl chloride and S_2Cl_2 are both suitable sulfur compounds for use in the reduction, and their action on pyridine-N-oxide gives pyridine in 80–85% yield (*230*). The loss of oxygen by heating does not occur below 140–210° in the case of pyridine-N-oxide and is assisted by the presence of zinc dust or copper powder; pyridine is formed together with another, unknown base (*231*). The same reaction can be carried out by warming the amine oxide in sulfuric acid with selenium dioxide (*232*).

While most of the above-mentioned methods cannot be applied when reducible substituents are present in the pyridine nucleus, a number of processes do exist which allow the selective reduction of the amine oxide group. 4-Nitropyridine can thus be prepared in 70–80% yield from 4-nitropyridine-N-oxide by the use of phosphorus trichloride in chloroform (LXIV) (*200, 233–235*); the chloride can also be replaced by the corresponding bromide (*236, 237*).



LXIV

Amine oxides react with alkyl halides to form O-alkyl compounds (*238*), which are split by alkali to give a tertiary amine and an aldehyde; this reaction, which is also undergone by pyridine-N-oxides (*200, 239*), can therefore be used to eliminate the N-oxide oxygen atom. Thus, pyridine-N-oxide and benzyl bromide initially form a quaternary compound, which is decomposed by sodium hydroxide solution to give pyridine and benzaldehyde (LXV) (*240*).



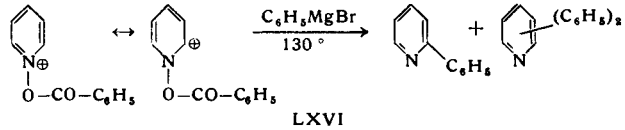
LXV

p-Toluenesulfonic acid methyl ester can similarly be used for the removal of the oxygen atom from the amine oxides of the pyridine series (*221*).

Substitution Reactions Accompanied by the Regeneration of the Tertiary Pyridines

A number of reactions are known, in which substitution of the pyridine nucleus is accompanied by the simultaneous reduction of the pyridine-N-oxide. Thus if pyridine-N-oxide is heated with sulfuryl chloride, 2- and 4-chloropyridine and a little pentachloropyridine are all obtained (*160*); the method, however, does not possess great significance due to the fact that separation of the isomers is fairly laborious. In a similar manner, phosphorus pentachloride yields 4-chloropyridine exclusively (*241*); phosphorus oxyhalides also reduce and halogenate simultaneously (*242–245*).

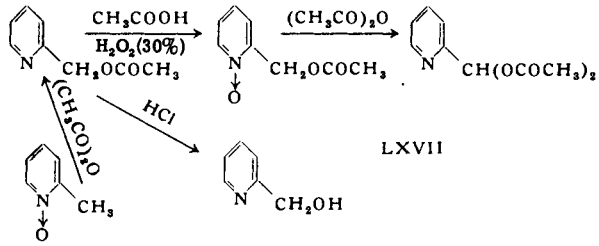
The action of phenylmagnesium bromide on pyridine-N-oxide results in the formation of 2-phenylpyridine with evolution of heat (*246, 247*); better yields are attained by the use of benzoyloxypyridinium chloride, obtained by allowing pyridine-N-oxide to react with benzoyl chloride (LXVI) (*248*).



LXVI

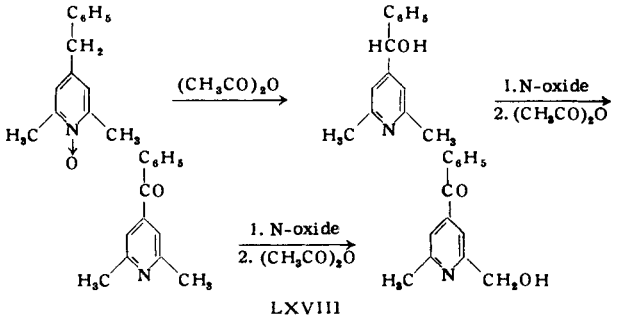
The reaction between acetic anhydride and the N-oxides of pyridine and its homologs has found widespread application. If pyridine-N-oxide is heated with acetic anhydride at 140–150°, 2-hydroxypyridine is formed in almost quantitative yield (*200, 249*); 2-hydroxy-3-methylpyridine is

analogously obtained from 3-methylpyridine-N-oxide (*212*). The introduction of a hydroxyl group into the side chain, on the other hand, is effected by treating 2- and 4-methylpyridine-N-oxide with acetic anhydride; the corresponding acetoxymethylpyridines are formed initially, and can be saponified by acids or alkalis to 2- and 4-hydroxymethylpyridine, respectively (*212,249–253*). If the acetoxymethylpyridine is again oxidized to the amine oxide and heated with the acid anhydride, the diacetate of pyridine-2-aldehyde is obtained (LXVII) (*212*).



LXVII

Carbinols of pyridine-N-oxide derivatives can also be prepared if the latter contain more than one methyl group (*212,254–257*). In this instance, the 2-position reacts in preference to the 4-position (*256*). If position 2 or 4 carries a longer side chain, the acetoxy group invariably enters the corresponding ring methylene group (*212,251,258–260*). After their conversion into the amine oxides, 2- and 4-benzyl derivatives of pyridine can be hydroxylated in the methylene group by heating with acetic anhydride (*255,261*). 2,6-Dimethyl-4-benzylpyridine-N-oxide first forms the 4-hydroxymethylpyridine; repetition of the reaction gives the 4-benzoyl derivative and substitution in a 2-methyl group only occurs after repeated treatment (*261*) (LXVIII).



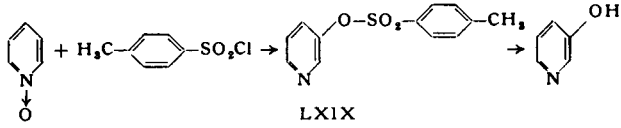
LXVIII

The mechanism of the N-oxide/acetic anhydride method has not yet been fully elucidated, though several theories have been postulated [see,

e.g. refs. (*252, 262*)]. The substitution does not always proceed uniformly, for even in the case of the 2- and 4-methyl derivatives, compounds hydroxylated in the pyridine ring are formed along with the carbinols (*212, 252–254, 256*).

According to an American patent (*263*) 2-hydroxypyridine-N-oxide is obtained by heating a mixture of pyridine, glacial acetic acid, perhydrol, and paraformaldehyde at 75–95°; analogous compounds are formed from 3-methyl and 3,5-dimethylpyridine.

On heating pyridine-N-oxide with *p*-toluenesulfonyl chloride, 3-(*p*-toluenesulfonyl)pyridine is formed and saponification of the latter yields 3-hydroxypyridine (LXIX) (*241, 264*). By-products are formed in this reaction, in which two pyridine rings are joined to one another (*265–267*). While 3-methyl pyridine-N-oxide allows the introduction of a hydroxyl group in the 5-position by this treatment (*268*), the action of tosyl chloride on 2-methylpyridine-N-oxide results in the formation of 2-chloromethylpyridine (*269*).

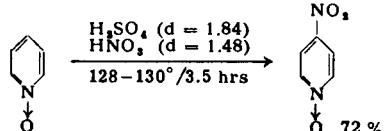


LXIX

ELECTROPHILIC SUBSTITUTION OF PYRIDINE-N-OXIDES

Nitration

The nitration of pyridine N-oxide was first carried out by Ochiai (*200*). By the action of concentrated nitric acid and concentrated sulfuric acid at 130° he obtained 4-nitropyridine-N-oxide in 72% yield (LXX). A very small quantity of 2-nitropyridine is also formed, which probably results from the corresponding N-oxide by loss of oxygen during the course of the reaction. Elevation of temperature causes a rise in the yield of 2-nitropyridine, and the reaction products then include 4-nitropyridine (*200*).



LXX

A shortened method has been reported by H. J. den Hertog and W. P. Combé (*225*). In this process pyridine is oxidized with glacial acetic acid and perhydrol, the mixture evaporated under vacuum and the

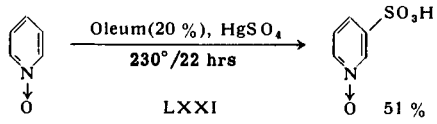
residue heated—without isolation of the N-oxide—with fuming nitric acid and sulfuric acid at 90° for 14 hr. The reaction mixture is then poured on to ice, neutralized, and extracted with ether, yielding over 90% of 4-nitropyridine-N-oxide.

The nitro group can also be introduced into position 4 in many derivatives of pyridine-N-oxide [see, e.g. refs. (*200, 221, 224–227, 237, 270–273*)]. If this position is already occupied, nitration does not occur (*194, 273*). The nitro group can, however, be introduced at other positions under the influence of substituents already present (*226, 227, 274–277*).

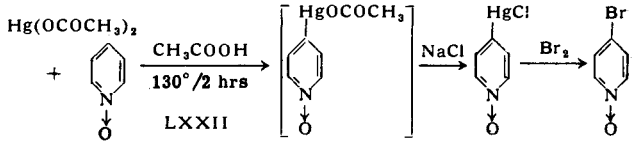
If benzoyl nitrate is allowed to stand with pyridine-N-oxide in chloroform for 4 days at room temperature, a very low yield of 3-nitropyridine-N-oxide is obtained (*278*).

Sulfonation—Electrophilic substitution

Surprisingly, the sulfonation of pyridine-N-oxide proceeds quite differently from the normal nitration. If the amine oxide is treated at 150° with 20% oleum in the presence of mercuric sulfate, the unchanged starting material is obtained in 60% yield, and no sulfonic acid is formed (*204*). It is only by using the conditions required for the sulfonation of pyridine itself, namely heating with 20% oleum and mercuric sulfate for 22 hr at 230°, that a sulfonic acid is formed; it is, however, found to be pyridine-3-sulfonic acid N-oxide (LXXI) (*204*).



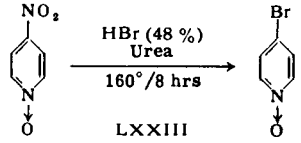
Conversely, reaction with mercuric acetate gives the 4-substituted pyridine-mercury compound, which was isolated as 4-(chloromercuri)-pyridine-N-oxide following the addition of saturated salt solution (LXXII) (*279*). Treatment of LXXII with bromine yields 4-bromopyridine-N-oxide (*279*). According to van Ammers and den Hertog (*280*), on the other hand, substitution occurs in the 2- or 2- and 6-positions, not position 4.



Other electrophilic reactions, e.g. bromination, chlorosulfonation, and Friedel-Crafts reactions have as little effect on pyridine-N-oxide as they have on pyridine itself (*204*).

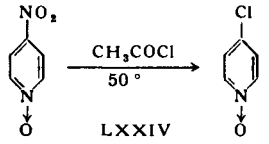
Reactions Using 4-Nitropyridine-N-oxides

The nitro group in the 4-position of pyridine-N-oxide is distinguished by an extraordinary reactivity, with the result that numerous 4-substituted pyridine derivatives can be prepared using this nitro compound. 4-Nitropyridine-N-oxide itself is a stable substance; recrystallization from acetone or water yields yellow crystals, m.p. 159° (*200*). Mere warming with aqueous alkali or with hydrohalic acids causes a replacement of the nitro group. If 4-nitropyridine-N-oxide is warmed with dilute sodium hydroxide solution, a vigorous reaction ensues but no uniform product is formed. 4,4′-Azopyridine-N-oxide (*281*) and 4,4′-azopyridine were isolated from the reaction mixture (*225*). Besides these, 4-hydroxypyridine is probably also formed (*225*); it becomes the main product on the addition of hydrogen peroxide to the sodium hydroxide solution (*282*). If 4-nitropyridine-N-oxide is heated with ammonia, 4,4′-azopyridinedi-N-oxide and a small quantity of 4-aminopyridine-N-oxide are produced (*283*). Prolonged warming with hydrobromic or hydrochloric acid yields mainly 4-bromopyridine-N-oxide (LXXIII) (*284*) [see also ref. (*225*)] and 4-chloropyridine-N-oxide, respectively (*225*).



LXXIII

A particularly good method for synthesizing 4-chloro- or 4-bromopyridine-N-oxide is based on the reaction between the nitro derivative and acetyl chloride or bromide; an excess of the acid halide is used and the reaction is carried out at 50° (LXXIV) (*200, 285*).

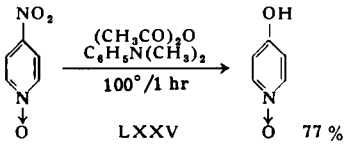


LXXIV 92 %

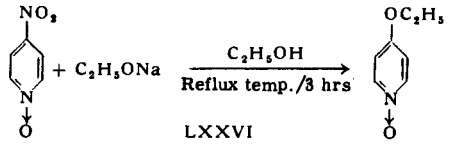
The action of phosphorus oxychloride on 4-nitropyridine-N-oxide gives 4-chloropyridine-N-oxide as the major product if a temperature of 70° is maintained; at 100°, 2,4-dichloropyridine is formed (*200, 285*).

The preparation of 4-hydroxypyridine-N-oxide is accomplished by warming 4-nitropyridine-N-oxide with acetic anhydride and dimethylaniline on a water bath (LXXV) (*200*); [see also ref. (*237*)].

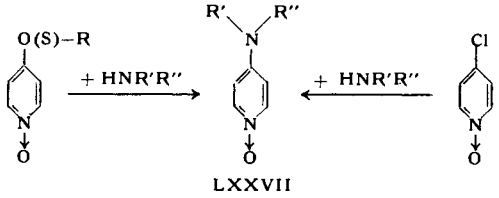
Pyridyl-4-ether-N-oxides and the corresponding thioether-N-oxides are obtained with equal ease by allowing the nitro compound to react



with alkoxides or phenoxides and thiophenoxides, respectively (*200, 225, 283, 286*). A 70% yield of 4-ethoxypyridine-N-oxide is obtained by this route (LXXVI) (*225*). The reagents mentioned also cause ready ether formation with 4-chloropyridine-N-oxide (*200, 286*).

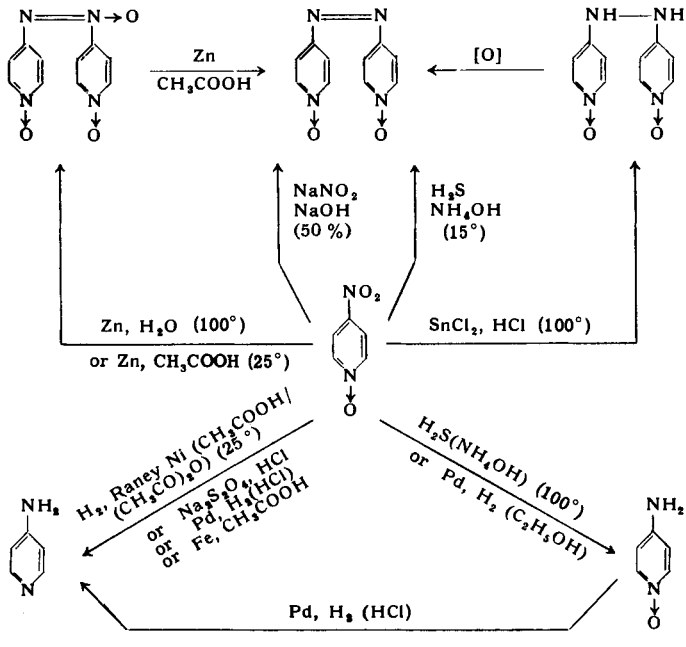


Catalytic hydrogenation of 4-benzyloxypyridine-N-oxide with palladium-charcoal in methanol gives 4-hydroxypyridine-N-oxide with elimination of toluene (*200*). As in pyridine itself, the phenoxy and thiophenoxy groups in the 4-position of pyridine-N-oxide exhibit a high reactivity and can be replaced by heating with primary or secondary amines, thus allowing the introduction of the amino group in this position (LXXVII) (*200, 286*). The same reaction also occurs with 4-chloropyridine-N-oxide (LXXVII) (*200, 286*), though not without the danger of removing the N-oxide function (*221*).



On prolonged standing with thiourea, 4-chloropyridine-N-oxide affords an 80% yield of pyridyl-4-isothiouronium chloride N-oxide and hydrolysis of the latter with cold sodium hydroxide solution results in the formation of 4-mercaptopyridine-N-oxide (*287*) [see also ref. (*200*)]. The salt obtained by allowing this mercaptan to react with mercuric acetate possesses high bacteriostatic activity (*194*). If the isothiouronium salt is evaporated down with ammonia on a water bath, 4,4'-dipyridyl sulfide N-oxide is obtained (*287*); this compound is also formed in small quantities by the action of hydrogen sulfide on 4-nitropyridine-N-oxide

in the presence of pyridine (*194*). These reactions are illustrated in reaction scheme LXXVIII (*200*).



LXXVIII

The reduction of 4-nitropyridine-N-oxide with phosphorus trichloride has been referred to above; in this reaction the nitro group remains unaffected. If this process is combined with the action of acetyl chloride, 4-chloropyridine is obtained (*175*). Most of the reduction methods described above (pp. 84–85) can be applied directly to 4-substituted pyridine-N-oxides obtained from 4-nitropyridine-N-oxide. Under the action of reducing agents, the behavior of 4-nitropyridine-N-oxide resembles that of nitrobenzene inasmuch as azo, azoxy, and hydrazo compounds are formed in addition to 4-aminopyridine-N-oxide; 4-aminopyridine is only produced in acid solution (LXXVIII) (*200, 288*).

4-Aminopyridine-N-oxide, unlike 4-aminopyridine, is readily diazotized (*200*). The diazonium salt can be coupled, yielding azo dyes (*200*). Furthermore, the diazo group can be replaced by a halogen, a nitrile, and a thiocyano group (*200*).

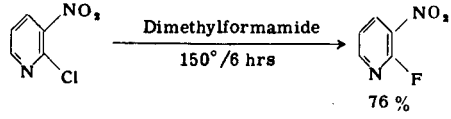
The reactions depicted in this section also apply to many substituted pyridine-N-oxides. Since they offer nothing of a particularly novel character, however, these methods are not discussed.

Appendix

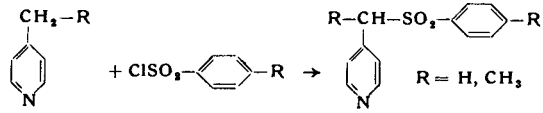
Tertiary Pyridines and Pyridinium Salts

The sulfonation of 2,6-di-*tert*-butylpyridine using SO_3 in liquid SO_2 does not yield the corresponding 4-pyridinesulfonic acid as previously thought (*10*), but 2,6-di-*tert*-butyl-3-pyridinesulfonic acid; this was recently proved with the aid of nuclear magnetic resonance spectra (*289*).

2-Chloropyridine is obtained in 65–80% yield in the chlorination of pyridine with chlorine and sulfur dioxide at 340–370° (*290*). No halogen exchange is undergone by either 2-chloropyridine, 2-chloropyridine-N-oxide, 2-chloropyridine hydrochloride, or 2-bromopyridine when heated with potassium fluoride in dimethylformamide; 2-chloro-3-nitro- and 2-chloro-5-nitropyridine, on the other hand, give the corresponding fluoro compounds by this treatment (*291*).

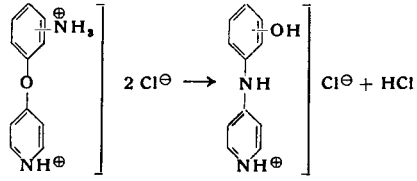


Földi (*292*) has recently described an interesting reaction between 4-alkylpyridines and benzene- or *p*-toluenesulfonyl chloride. Loss of a proton results in the linking of the arylsulfonyl group to the C atom attached to position 4 of the alkylpyridine.



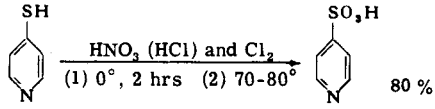
The investigation by Wibaut and Broekman (*293*) into the polymerization of 4-chloropyridine revealed that substances possessing the properties of pyridyl-4-chloropyridinium chlorides are formed; rapid hydrolysis affords 4-hydroxypyridine and N-(4′-pyridyl)-4-pyridone.

Jerchel and Jakob (*294*) have recently reported an interesting rearrangement undergone by pyridyl aminophenyl ethers. If the dihydrochlorides of the 4-pyridyl aminophenyl ethers containing the NH_2 group in position 2, 3, or 4 of the benzene nucleus, are warmed, good yields of the corresponding pyridyl-4-hydroxyphenylamines are obtained.



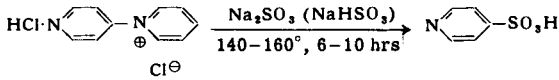
2-Pyridyl aminophenyl ethers also undergo this reaction (*294*).

Further investigation into the action of nitric acid on 4-mercaptopyridine has shown that the main product is the dinitrate of di-4-pyridyl disulfide (*295, 296*), not 4-pyridinesulfonic acid (*155*). The desired sulfonic acid is obtained from 4-pyridinethiol, nitric acid, and chlorine, or nitric acid, hydrochloric acid, and chlorine (*295*).



80 %

Further preparations of 4-pyridinesulfonic acid are based on the oxidation of 4-pyridinethiol with hydrogen peroxide in glacial acetic acid (*296*), the oxidation of the barium salt with H_2O_2 (*297*), the treatment of 4-chloropyridine with sodium sulfite (*275, 295, 297*) or the action of sodium bisulfite on 4-hydroxypyridine (*297*). According to Evans and Brown (*297*), the best method of preparing 4-pyridinesulfonic acid consists in the decomposition of 4-pyridylpyridinium chloride hydrochloride with sodium sulfite or bisulfite (*298*).



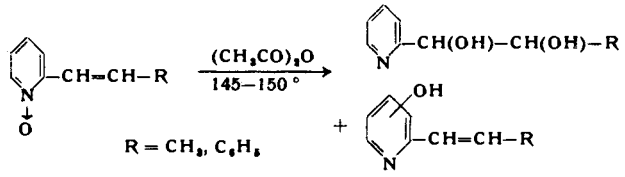
4-Pyridinesulfonyl chloride is obtained from 4-mercaptopyridine and chlorine in concentrated hydrochloric acid at 0° (*299*). It is not isolated, but allowed to react directly with various bases.

Pyridine-N-oxides

Evans and associates (*300*) have recently proposed the use of a mixture of trifluoroacetic acid and H_2O_2 (30%) in the preparation of pyridine-N-oxides from bases that are not readily oxidized; they succeeded in obtaining 2,6-dibromopyridine-N-oxide in 70% yield by means of this method.

The catalytic reduction of pyridine-N-oxides with Raney nickel and hydrogen does not take place in the presence of glacial acetic acid/acetic anhydride exclusively (*219*), but also in methanol; even then the addition of glacial acetic acid is advisable (*301*). According to the investigations of Howard and Olszewski (*302*), the N-oxide oxygen can be eliminated with triphenylphosphine at elevated temperatures. In contrast to the above, aromatic amine oxides in boiling glacial acetic acid were found to be stable to triethyl- or triphenylphosphine (*303*). Removal of the oxygen from pyridine-N-oxides is also brought about by sulfur and its compounds at temperatures of 115–150° (*304*).

The action of acetic anhydride on pyridine-N-oxides has been repeatedly investigated recently. 2-Styrylpyridine-N-oxide and 2-propenylpyridine-N-oxide are hydroxylated by acetic anhydride both at the ethylenic linkage and in the pyridine nucleus (*305*).

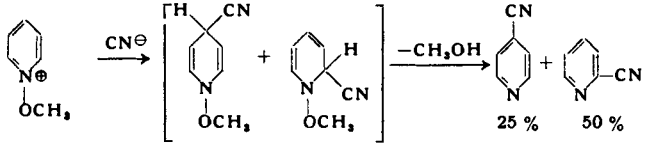


3-Chloro-, 3-bromo-, and 3-fluoropyridine-N-oxide react with acetic anhydride to give the corresponding 2-acetoxy-3-halopyridines (*306*). The acetic anhydride method was also invoked in the synthesis of 3- and 6-alkylpicolinic acid, 5-methylpicolinic acid (*307*) and pyridinealdehyde-N-oxides (*308, 309*).

Papers by both Furukawa (*310*) and Traynelis and Martello (*311*) deal with the question of the mechanism of this reaction.

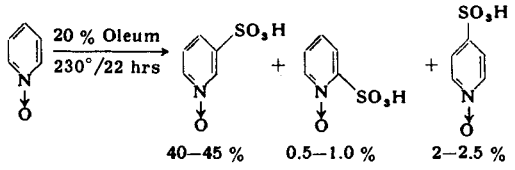
The replacement of acetic anhydride by trifluoroacetic anhydride is recommended, as the latter reacts even at 40° and is more readily saponified (*312*). The reaction between 2-picoline-N-oxide and ketene in the presence of catalytic quantities of H_2SO_4 results in the formation of 2-acetoxypicoline, which is obtained from the same N-oxide by the action of acetic anhydride (*313*).

A recently discovered reaction between pyridine-N-oxides and potassium cyanide is not without interest. The action of alkyl halides or dimethyl sulfate on pyridine-N-oxide yields quaternary compounds which can be converted by potassium cyanide into 2- and 4-cyanopyridine at room temperature (*314, 315*).



Picoline- and lutidine-N-oxides also undergo this reaction (*314, 315*).

In a detailed study of the sulfonation of pyridine-N-oxide, M. van



Ammers and H. J. den Hertog (*316*) detected small quantities of isomers in addition to the main product, 3-pyridinesulfonic acid N-oxide; 45% of the pyridine-N-oxide subjected to the reaction remained unchanged.

Experimental

N-(2,6-Dichlorobenzyl)-4-phenacyl-1,4-dihydropyridine (*114, 115*). N-(2,6-Dichlorobenzyl)pyridinium bromide (*114*) (6.38 gm) in methanol (25 ml) is treated with acetophenone (5 ml) and *p*-nitrosodimethylaniline (1.8 gm) in a closed round-bottomed flask fitted with in- and outlet tubes. Nitrogen is passed into the solution—which is maintained at 20°—until the air in the flask is expelled, and sodium hydroxide solution (2 *N*, 20 ml) added. A red coloration develops after a few minutes and the solution becomes slightly warm. After cooling, crystallization is induced by scratching and completed by the addition of water (25 ml). After 3 hr the crystals are filtered and washed with water and a little alcohol, yielding the crude product (5.4 gm, 76%).

4-Phenacylpyridine (*114, 115*). The compound described above (3.56 gm) is heated with hydrobromic acid (66%, 3 ml) in a tube for 1 hr at 180°. After cooling, the 4-phenacylpyridine hydrobromide formed may be freed from 2,6-dichlorobenzyl bromide by filtering and washing with ether followed by acetone. The aqueous fraction of the filtrate is evaporated under reduced pressure on a water bath; crystallization, initiated by scratching in the presence of a little methanol, is completed by the addition of ether. The total yield of hydrobromide amounts to 2.6 gm (93%). 4-Phenacylpyridine, liberated from the salt by alkali, is recrystallized from petroleum ether or acetone and has a m.p. of 115° (*115*).

N-Pyridyl-4-pyridinium chloride hydrochloride (*120, 161*). Dry pyridine (300 ml) is vigorously stirred with thionyl chloride (technical grade, 900 gm) in a 1 liter three-necked flask fitted with a dropping funnel, stirrer, and reflux condenser protected by a calcium chloride tube. An internal temperature of 20° is easily maintained by external cooling with flowing water and a controlled dropping rate. After the addition of $SOCl_2$ is completed the mixture is allowed to stand for 3 days at room temperature. The excess of thionyl chloride is removed by vacuum distillation, the temperature of the water bath being gradually raised to 100°; this temperature is maintained for 2 hr following the complete removal of thionyl chloride. The solid residue left in the flask is converted into a homogeneous crystalline mass by boiling with absolute methanol (200 ml), cooled to 0°, and filtered. The crude product, washed with a little alcohol and dried at 110°, has a m.p. of 145–148° and the yield is 260 gm (60%). Further purification is effected by dis-

solving the crude product in a little hot 2 *N* hydrochloric acid, filtering, and treating the filtrate repeatedly with animal charcoal. Evaporation under vacuum and addition of alcohol cause the separation of off-white crystals; after cooling these are filtered, washed with alcohol, and dried. Recrystallization from methanol affords colorless needles, m.p. 151°.

4-Pyridyl 4-nitrophenyl ether (*118*). A mixture of N-pyridyl-4-pyridinium chloride hydrochloride (10 gm) and *p*-nitrophenol (6.6 gm) is heated at 160–165° in an oil bath, forming a clear melt within a few minutes. On cooling, this is treated with 10% sodium carbonate solution, filtered, and the filtration residue washed with sodium hydroxide solution and water. Recrystallization from aqueous alcohol gives needles (4.5 gm, 47%), m.p. 128°.

4-Chloropyridine (*118, 161*). N-Pyridyl-4-pyridinium chloride hydrochloride (200 gm, crude product) is thoroughly ground to a powder, intimately mixed with phosphorus pentachloride (180 gm) and heated to 160° in an oil bath, in a 500-ml flask equipped with an air condenser. As the internal temperature rises to 165–170°, a dark, mobile melt is formed. The reaction mixture is maintained at a bath temperature of 180° for a further 6 hr. Ice water is carefully added through the condenser, accompanied by efficient cooling, until a clear solution is obtained; the solution is transferred to a larger flask and basified with sodium hydroxide solution, the operation being carried out with vigorous stirring and careful cooling. 4-Chloropyridine and pyridine come over together when the mixture is steam-distilled, and are separated by the addition of potassium carbonate. The aqueous phase is extracted with ether; the ethereal extracts are used to dissolve the previously separated bases. After drying with KOH, the product is distilled in the apparatus shown in Fig. 1. The apparatus must first be thoroughly rinsed with alcoholic potassium hydroxide and dried. After removal of the solvent at normal pressure, pyridine comes over first at 57–59°/100 mm, followed by 4-chloropyridine at 63–64°/50 mm. The yield of 4-chloropyridine amounts to 72 gm (73%).

4-Phenylaminopyridine (*192*). N-Pyridyl-4-pyridinium chloride hydrochloride (2.3 gm) and aniline hydrochloride (2.6 gm) are heated at 180° for 90 min, dissolved in water on cooling and warmed with animal charcoal. A large excess of sodium hydroxide is added and the mixture brought to the boil; crystals separated on cooling which are filtered and recrystallized from methanol/water to give 4-phenylaminopyridine, m.p. 172°, in quantitative yield.

4-n-Butylaminopyridine (*192*). 4-Pyridyl phenyl ether (*120*) (2.6 gm) and *n*-butylamine hydrochloride (4.9 gm) are heated at 180° for 2 hr, and at 200° for the last 5 min. The mixture is freed from unreacted starting material by dissolving the cooled melt in water, rendering the

solution alkaline with sodium hydroxide solution and steam-distilling. On cooling, the amine produced crystallizes out from the oily residue. The crude product obtained by filtration is dried and recrystallized from petroleum ether (b.p. 40–70°) yielding colorless needles of 4-*n*-butylaminopyridine (1.6 gm, 70%), m.p. 65°.

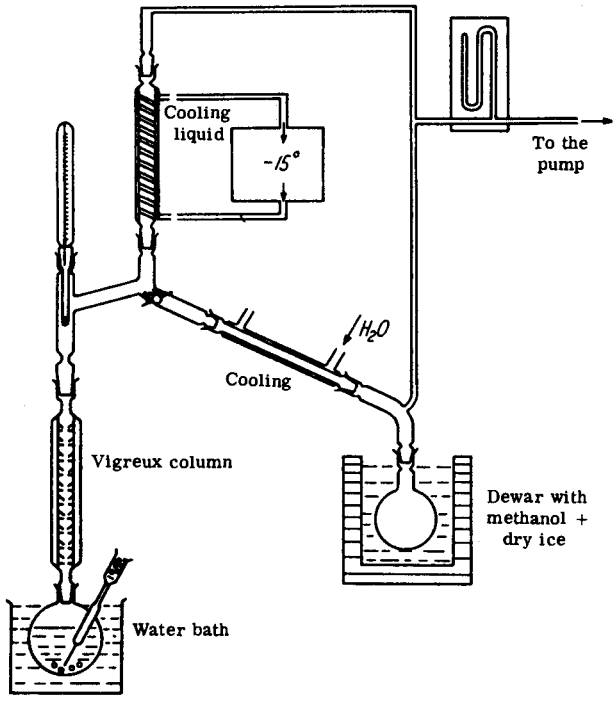


Fig. 1. Apparatus for the distillation of 4-chloropyridine

4-Pyridyl n-cetyl thioether (*118*). Hydrogen sulfide is passed for 2 hr into a suspension of N-pyridyl-4-pyridinium chloride hydrochloride (15 gm) in pyridine (15 ml) maintained at approximately 70°, forming a clear solution. *n*-Cetyl chloride (20 gm) is added, the mixture heated in a tube for 12 hr at 145° and the product dissolved in warm water (150 ml). After the addition of HCl (2 *N*, 20 ml) and cooling, the scarcely soluble hydrochloride of the thioether can be largely freed from water and pyridine by filtration. The moist product is suspended in water, treated with sodium hydroxide solution (2 *N*) and vigorously stirred at 50° for 15 min. A semisolid, reddish mass forms on cooling which can be brought into solution with hot methanol/ethanol; treatment with animal charcoal yields white flakes (11 gm, 52%), m.p. 52°.

Pyridine-N-oxide (*200*). A mixture of pyridine (40 gm), glacial acetic acid (100 ml), and hydrogen peroxide (50 ml) is heated at 70–80° for 8 hr; after 3 hr, more perhydrol (35 ml) is added. The solution is then evaporated under vacuum to half its volume, diluted with water (100 ml), and evaporated under vacuum as far as possible. Small portions of anhydrous sodium carbonate are added until a solid crystalline mass is obtained, when the amine oxide can be extracted by shaking with chloroform (ca. 300 ml). After standing for several hours at room temperature the undissolved salt is filtered off, the filtrate dried with Na_2SO_4 and the solvent evaporated. Pyridine-N-oxide (40–45 gm, 85–95%) distils at 138–140°/15 mm.

Purification of 4-methylpyridine via 4-methylpyridine-N-oxide (*219*). (a) 4-Methylpyridine (23 gm), glacial acetic acid (120 ml), and perhydrol (40 ml) are treated as described above. The residue left after removal of the chloroform can in this case be recrystallized from a large quantity of acetone, yielding white needles of 4-methylpyridine-N-oxide (21.6 gm. 80%), m.p. 186–186.5°.

(b) The amine oxide (20 gm) is dissolved in glacial acetic acid (60 ml) and acetic anhydride (10 ml); Raney nickel (1 gm) is added and the mixture hydrogenated with vigorous stirring at room temperature. When the uptake of hydrogen has stopped the major portion of the catalyst is removed by filtration; the filtrate, to which conc. HCl (20 ml) has been added, is evaporated at 80° at the water pump to a sirupy consistency. Addition of dilute sodium hydroxide solution causes precipitation of nickel hydroxide. The free base is steam-distilled, separated with NaOH, and dried for several days with solid NaOH. The last traces of the base may be extracted from the aqueous layer with ether. Distillation of the combined portions of the base yields pure 4-methylpyridine (39.2 gm, 84%), b.p. 144–145°/760 mm.

4-Nitropyridine-N-oxide (*200*). Pyridine-N-oxide (10 gm) is dissolved in a mixture of nitric acid (12 gm, $d = 1.48$) and conc. sulfuric acid (30 ml) and warmed at 128–130° for 3 to 4 hr in an oil bath. On cooling, the reaction mixture is poured on to ice and neutralized by the addition of small portions of solid sodium carbonate. As a crystalline precipitate separates out, the mixture is filtered and the solid washed with ice water. The filtrate is basified with cooling and shaken with chloroform, yielding a further crop of the nitro compound which is isolated by evaporation of the solvent. Recrystallization of the combined products from acetone or water gives yellow crystals of 4-nitropyridine-N-oxide (10.6 gm, 72%), m.p. 159°.

4-Chloropyridine-N-oxide (*200*). 4-Nitropyridine-N-oxide (8 gm) is added portionwise to acetyl chloride (40 ml) placed in a flask equipped

with a reflux condenser. After gentle initial warming, a vigorous reaction ensues. The mixture is heated at 50° for half an hour, during which time a crystalline mass is formed. This is carefully dissolved in water, basified with sodium hydroxide solution and extracted with chloroform. The solution of the base is dried with sodium carbonate and the solvent evaporated; recrystallization of the residue from acetone yields white needles of 4-chloropyridine-N-oxide (4.0 gm, 55%) m.p. 169.5° with decomposition. Higher yields are reported in smaller-scale reactions (*200*).

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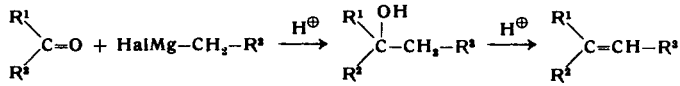
Carbonyl-Olefin Transformation Using Triphenylphosphinemethylenes. The Wittig Reaction

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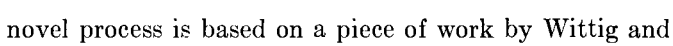
Introduction

The usual procedure followed in the conversion of a C=O into a C=C bond (carbonyl-olefin transformation) consists of adding a Grignard reagent to the carbonyl and eliminating a molecule of water from the carbinol intermediate thus formed.

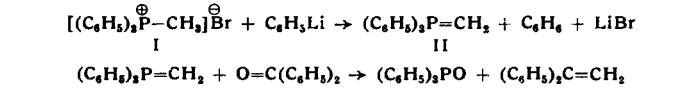


This classical method does not, however, permit the uniform conversion of aliphatic aldehydes or ketones into olefins with the double bond in a definite and unambiguous location. In the case of secondary and tertiary aliphatic alcohols, water elimination can proceed in two or three directions.

In such cases the method worked out by Wittig (*1*), utilizing triphenylphosphinemethylenes (*2*) is applied to advantage. These derivatives of pentavalent phosphorus are capable of exchanging their methylene group with the double-bonded oxygen of a carbonyl group.



This novel process is based on a piece of work by Wittig and Geissler (3), who succeeded in 1953 in effecting the following reactions:



Triphenylmethylphosphonium bromide (I), readily accessible from triphenylphosphine and methyl bromide, is treated with phenyllithium, thus forming triphenylphosphinemethylene (II). Reaction between the latter and benzophenone results in an almost quantitative yield of 1,1-diphenylethylene and triphenylphosphine oxide.

Wittig and associates (*4, 5*) showed furthermore that other phosphinealkylenes and carbonyl compounds undergo this exchange reaction and that good yields of the olefins are usually obtained. They consequently proposed (*4*) the general use of triphenylphosphinemethylenes in the

carbonyl-olefin transformation. Under the name of Wittig reaction the method rapidly found its way into laboratory practice and now forms an integral part of the preparative organic chemist's stock in trade.

Its merit lies primarily in the fact that the double bond always appears at the position originally occupied by the carbonyl group. On the whole, this rule also seems to hold for α,β-unsaturated carbonyl compounds, in which 1,4-addition can theoretically also take place. In only two cases thus far have products been isolated which could have resulted from the 1,4-addition of an ylene to a $>C{=}C{-}\overset{\overset{O}{\|}}{C}$ system (cf. below).

The fact that the exchange is effected under alkaline conditions and proceeds in the cold or at a slightly raised temperature is of prime preparative significance. It is by virtue of this behavior that the process offers access to sensitive olefins such as carotenoids, vitamin A, methylene-steroids, and the like, which can otherwise not be synthesized without difficulty if at all. It may be said that it is in this field, namely the chemistry of natural products, that the Wittig reaction is most able to provide a fresh approach.

Triphenylphosphinemethylenes

According to Wittig and his co-workers (*4, 5*), the preparation of the reagents is effected by the action of one equivalent of a strong base B^- (phenyllithium, sodium ethoxide, etc.) on a triphenylalkylphosphonium halide in a suitable solvent (see the General Experimental section, below). The base abstracts a proton from the salt, and the equilibrium set up results in the formation of the triphenylphosphinemethylene.

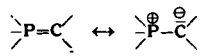
$$(C_6H_5)_3\overset{\oplus}{P}{-}CHR^1R^2 + |\overset{\ominus}{B} \rightleftharpoons \underset{\text{Ylide III}}{(C_6H_5)_3\overset{\oplus}{P}{-}\overset{\ominus}{C}R^1R^2} + BH$$

$$\updownarrow$$

$$\underset{\text{Ylene IV}}{(C_6H_5)_3P{=}CR^1R^2}$$

The process is due to the proton-releasing action of the positively charged central atom, which can stabilize a negative charge on the neighboring carbon atom by inductive and mesomeric action. Mesomeric because phosphorus, being an element of the second period, is capable of expanding its valency shell to accommodate ten electrons by incorporation from the *d*-level (*6*); the free electron pair can thus be in relatively close proximity to the phosphorus atom in the case of P—C bond formation. The triphenylphosphinemethylenes must accordingly be conceived in terms of resonance hybrids of two extreme mesomeric structures, namely the ylide form III and the ylene form IV.

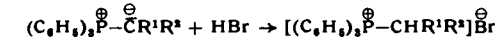
Besides theoretical considerations, kinetic studies by Doering and Hoffmann (7) also support the existence of the



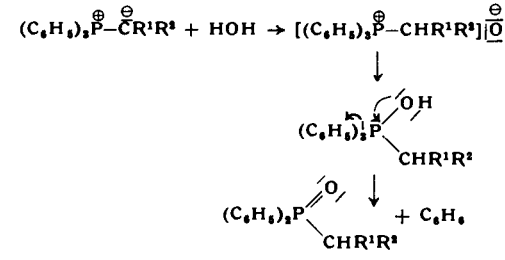
system. During ylide formation, tetramethylphosphonium iodide parts with a proton approximately 10^5 times more rapidly than tetramethylammonium iodide although the repulsive Coulomb forces are much weaker in the case of the phosphonium salt than the ammonium salt, due to the greater distances in the former (P—C, 1.87Å compared with N—C, 1.47Å). The increased ease of formation of the phosphorus ylide may be attributed to the ylene–ylide mesomerism, which can even be noticed by a lowering of energy in the transition state of the deprotonization.

The semipolar ylide structure III confers a nucleophilic character upon the triphenylphosphinemethylenes and explains why these will react with the C=O group (see the section Mechanism of the Wittig reaction) or add polar groups.

With hydrohalic acids, for example, the reverse of the formative reaction takes place, and the starting materials are obtained,

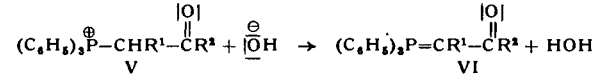


and in a similar manner the action of water yields the hydroxides.

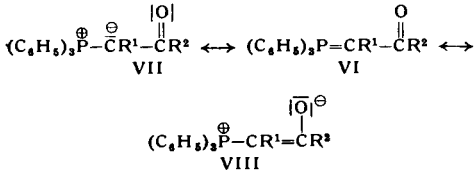


Although the hydrolysis as such is a reversible reaction which should therefore establish an equilibrium, it proceeds practically in one direction only; this is due to the fact that the phosphonium hydroxides formed are mostly unstable and decompose irreversibly to diphenylalkylphosphine oxide and benzene (and partially to triphenylphosphine oxide and alkane) (*8*). This is the reason why precautions must be taken to exclude moisture from reactions involving triphenylphosphinemethylenes, and why hydroxyl ions are in general not suited to the elimination of hydrogen halide.

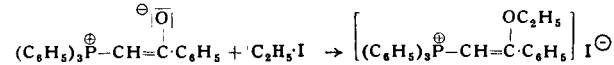
Exceptions are found in the triphenylacylphosphonium salts (V) which are rapidly and quantitatively converted into the triphenylphosphineacylmethylenes (VI) by the action of caustic soda or potash (*9, 10*).



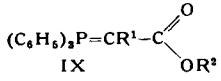
These triphenylphosphineacylmethylenes are crystalline, colorless substances; they are largely inert towards water and are not hydrolyzed unless boiled. Their stability may be due to mesomerism of extreme structures, VI, VII, and VIII, in which both the phosphorus atom and the C=O group lay claim to the lone pair.



Their behavior corresponds to structure VIII during alkylation which, according to Ramirez and Dershowitz (*10*), attacks the oxygen atom exclusively.

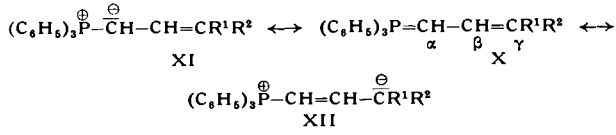


The phosphineacylmethylenes are capable of adding to carbonyl groups in spite of this resonance stability (*10*). Some representatives of the group, namely triphenylphosphinecarbalkoxymethylenes of structure IX,

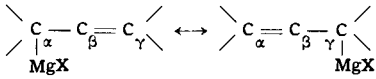


have commanded pronounced preparative interest. They proved to be a valuable aid to O. Isler and his collaborators in the synthesis of polyenoic carboxylic esters of the carotenoid series (cf. below).

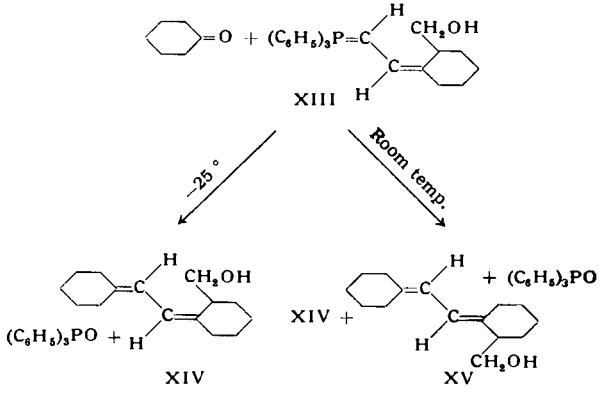
The ylides of type X, obtained from substituted triphenylallylphosphium salts, are also very readily condensed in spite of their capacity for resonance; these compounds possess great preparative significance.



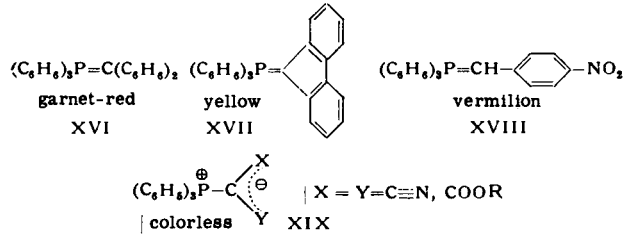
As far as investigation has revealed to date, they react at the α-carbon atom exclusively; a certain nucleophilic reactivity would however be predicted for the γ-carbon atom on the basis of structure XII. The phosphorus ylenes are therefore distinguished from the related allylmagnesium halides in this respect, as the latter are known from experience to be capable of reacting at both ends of the three-carbon system.



The mesomeric relationship XI $\leftrightarrow$ X $\leftrightarrow$ XII and its associated delocalization of π-electrons manifests itself under certain conditions at room temperature in the more or less rapid *cis* $\rightleftharpoons$ *trans* isomerization at the $C_\beta{=}C_\gamma$ bond. By allowing the ylene XIII to react with cyclohexanone in tetrahydrofuran at —25°, Harrison and Lythgoe (*11*) obtained the expected *cis*-diene XIV almost exclusively; at higher temperatures, however, considerable quantities of the *trans* isomer XV also made their appearance.

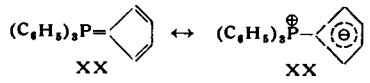


If the methylene carbon atom is linked to another unsaturated substituent, i.e., one capable of resonance, phosphorus ylenes are produced which are in general inert to aldehydes and ketones. Examples are found in triphenylphosphinediphenylmethylene (XVI) (*12*), fluorenylene



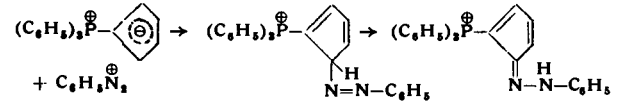
(XVII) (*13*), *p*-nitrobenzylene (XVIII) (*14*), and the compound of formula XIX examined by Horner and Oedinger (*15*). According to the UV absorption spectrum, the negative charge in XIX is completely distributed over the two CN or COOR groups.

Triphenylphosphinecyclopentadienylide (XX) (*16*) ranks as an oddity among phosphorus ylenes, inasmuch as a quasi-aromatic system, namely the cyclopentadienyl anion, is linked to the phosphorus atom.



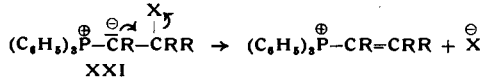
XX XX

Compound XX no longer reacts with the carbonyl group, even under forcing conditions; reaction does occur with the more strongly electrophilic phenyldiazonium ion which adds rather astonishingly, not to the ylide-carbon atom, but to the 2-position (*16*).



Briefly it may be said that the behavior of the phosphorus ylenes is not determined by the ylene-ylide mesomerism alone, but depends in the last resort also on the nature of the substituent on the α-carbon atom. Specifically, the reactivity decreases with increasing participation by the doublet in other resonance areas.

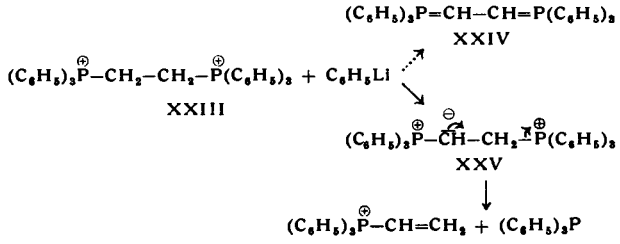
Like the increased stability, the pronounced tendency exhibited by some phosphorus ylenes towards decomposition is associated with certain requirements. In general, systems of type XXI appear to be unstable



XXI

when X represents a group of facile anionic mobility, such as onium-, alkoxy, halogen, and the like. In such cases the molecule can undergo β-elimination.

As an example, Wittig and Stilz (*17*) report that the action of phenyl-



XXIII XXIV XXV

lithium on the bisphosphonium salt XXIII—readily accessible from 1,2-dibromoethane and triphenylphosphine—in ether yields, not the desired bifunctional ylene XXIV, but triphenylphosphine and triphenylvinylphosphonium bromide, presumably via the intermediate XXV.

Triphenylphosphine is also readily eliminated from the ylide XXVI, the vinylog of XXV (*18*); the electrons of the central double bond participate in this elimination.

$$\underset{\text{XXVI}}{(C_6H_5)_3\overset{\oplus}{P}-\overset{\ominus}{C}H-CH=CH-CH_2-\overset{\oplus}{P}(C_6H_5)_3} \rightarrow$$

$$(C_6H_5)_3P + (C_6H_5)_3\overset{\oplus}{P}-CH=CH-CH=CH_2$$

In contrast, the conversion of trimethylene- (*19*) and tetramethylene-bis(triphenylphosphonium) dibromide, (XXVII) and (XXVIII), respectively, into the corresponding diylenes XXIX and XXX presents no difficulty.

$$(C_6H_5)_3\overset{\oplus}{P}-CH_2-(CH_2)_n-CH_2-\overset{\oplus}{P}(C_6H_5)_3$$

XXVII n = 1
XXVIII n = 2

$$(C_6H_5)_3P=CH-(CH_2)_n-CH=P(C_6H_5)_3$$

XXIX n = 1
XXX n = 2

By-products are, however, formed in the reactions between the tetramethylene derivative XXVIII and organolithium compounds in ether (*20*) and the use of alcohol containing sodium ethoxide as proton acceptor is recommended.

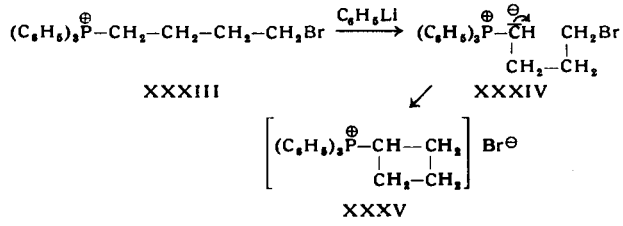
Bifunctional phosphonium salts containing several central double bonds or a central triple bond do not appear to have been investigated so far. It seems, however, reasonable to predict that the monoylenes formed in the first stage will exhibit an increased stability compared to XXV.

The stability of alkoxy-substituted phosphorus ylenes was also found to depend on the position of the substituent (*19*); whereas XXXI is stable and a useful agent in the carbonyl–olefin conversion, XXXII with its methoxy group β to the phosphorus atom could not be obtained.

$$\underset{\text{XXXI}}{(C_6H_5)_3\overset{\oplus}{P}-\overset{\ominus}{C}H-CH_2-CH_2-OC_2H_5} \qquad \underset{\text{XXXII}}{(C_6H_5)_3\overset{\oplus}{P}-\overset{\ominus}{C}H-CH_2-OCH_3}$$

Mondon (*20*) observed recently that on storage the decomposition of an ylene may sometimes result in cyclic products. The reaction between XXXIII and phenyllithium in ether yields a deep-red ylide XXXIV which is slowly converted into a new phosphonium salt; the latter prob-

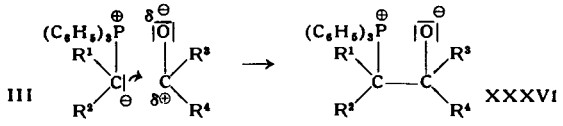
ably possesses a triphenylcyclobutylphosphonium bromide structure (XXXV).



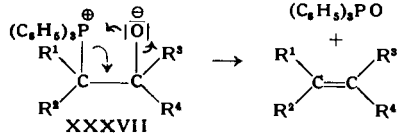
When such unstable examples are encountered in practice, it is best to effect their condensation with the carbonyl component as soon as possible, preferably the moment they are formed. The alkoxide method is the most suitable of the many techniques available. It is readily modified so that the aldehyde or ketone is already present in the reaction mixture during ylide formation.

Mechanism of the Wittig Reaction

Wittig and Schöllkopf (*4*) interpret the mechanism of the olefin-forming step by postulating that the phosphorus ylene first adds to the polarized carbonyl group as the mesomeric ylide form III, with the production of a phosphonium betaine XXXVI.

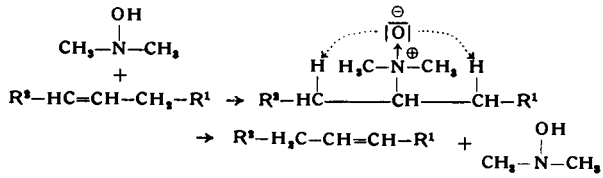


Satisfying the tendency of phosphorus to coordinate with oxygen, one of the latter's free doublets now becomes shared with the central atom and initiates the decomposition to phosphine oxide and olefin. A synchronous electron shift presumably occurs within the four-membered transition state XXXVII, resulting in stereospecific elimination.

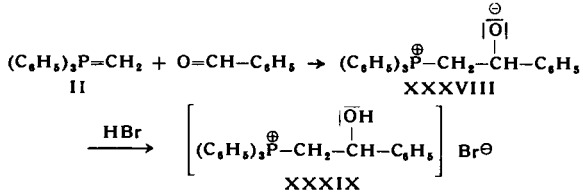


This view of the course taken by the phosphine oxide elimination sets the pattern for other *cis*-eliminations, long used in preparative work, e.g. the Chugaev reaction or the pyrolysis of amine oxides. Whereas these reactions generally result in a mixture of two isomeric olefins, as

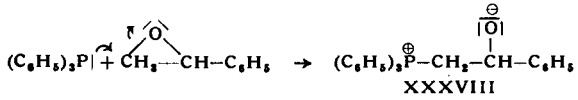
indicated schematically in the case of an amine oxide pyrolysis, the phosphine oxide elimination proceeds naturally in only one direction.



The formation of a zwitterion, XXXVI, in the first stage of the ylide-carbonyl addition was proved when benzaldehyde was allowed to react with triphenylphosphinemethylene (II). Compound XXXVIII, which does not decompose below 60–65°, was isolated and characterized as the hydrobromide (XXXIX) (*21*).

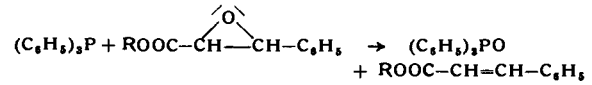


Wittig and Haag (*5*) also prepared the betaine XXXVIII by a different route, starting from styrene oxide and triphenylphosphine.

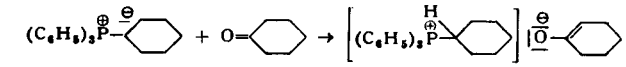


XXXVIII is, however, not stable under the forcing conditions required to open the oxide ring (150°) and decomposes to styrene and triphenylphosphine oxide.

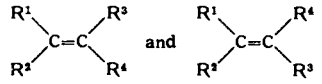
A method of deoxidizing olefin oxides is based on this reaction. Phenylglycidic ester, for example, can be reduced to cinnamic ester in 82% yield in this manner.



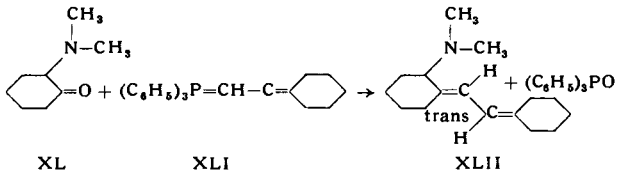
It may be mentioned in this connection that sterically hindered ylides can react with enolizable ketones to give enolates instead of adding to the C=O group. This secondary reaction occasionally becomes the main reaction, as in the case of triphenylphosphinecyclohexylene with cyclohexanone (*21*):



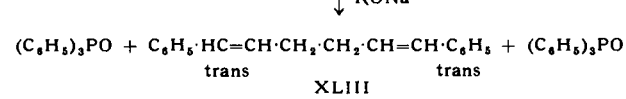
If the ylide and carbonyl compound are unsymmetrically substituted ($R_1 \neq R_2$; $R_3 \neq R_4$), a mixture of two *cis-trans* isomeric olefins is normally obtained.



The *trans*-alkene (with the two largest substituents *trans* to one another) usually predominates. In some instances only the *trans* isomer is formed, especially when it is energetically strongly favored on steric grounds. One example of this situation is encountered in the reaction between 2-(dimethylamino)cyclohexanone (XL) and the ylide XLI which results almost exclusively in XLII due to the effect of the bulky dimethylamino group (*22*).



Similarly, the reaction between tetramethylenebis(triphenylphosphonium) dibromide (XXVIII) and two moles of benzaldehyde in the presence of alcoholic sodium ethoxide yields the *trans,trans*-1,6-diphenyl-1,5-hexadiene (XLIII) (*20*).



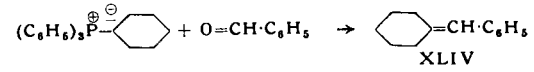
No systematic investigation has so far been undertaken regarding the stereochemistry of the Wittig reaction; nor has it definitely been established whether alteration of the reaction conditions affects the ratio of *cis* to *trans* olefin.

Reactions with Individual Carbonyl Compounds

With Aromatic Aldehydes

The reactions between the phosphorus ylenes and benzaldehyde itself usually proceed smoothly and present no peculiarities. Unlike the case

of benzophenone even sterically hindered ylides add in this case, e.g., triphenylphosphinecyclohexylene and the aldehyde afford benzylidenecyclohexane (XLIV) in 71% yield (*21*).



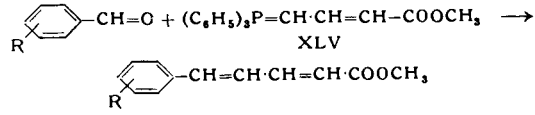
XLIV

(In this and further formulae in this chapter the triphenylphosphine oxide is omitted).

As anticipated, reactions involving unsymmetrically substituted ylides result in a mixture of *cis* and *trans* isomeric olefins (*4*).

$$(C_6H_5)_3P{=}CH{-}C_6H_5 + O{=}CH{-}C_6H_5 \rightarrow \underset{\text{70\% trans, 30\% cis-Stilbene}}{C_6H_5CH{=}CH{-}C_6H_5}$$

Bohlmann (*23*) allowed benzaldehydes containing substituents in the ring to react with the ylide XLV obtainable from γ-bromocrotonic ester



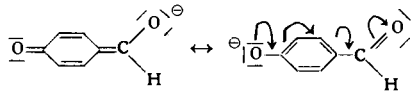
XLV

and compared the yields with those obtained by a Reformatsky synthesis. The findings are reproduced in Table 1.

TABLE 1
Comparison of Wittig and Reformatsky Reactions

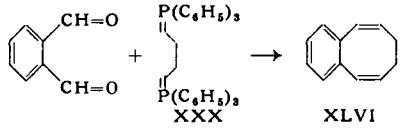
R·C$_6$H$_4$·(CH=CH)$_2$·COOCH$_3$ R=	Yields %	
	Wittig	Reformatsky
p—OCH$_3$	48	40
p—OH	3	6
o—OH	25	25
p—Cl	35	5
p—N(CH$_3$)$_2$	25	15
o, *m*, *p*-Trimethoxy	35	90
p—OCH$_3$, *m*—OAc	50	33
o, *o'*, *p*-Trimethyl	46	55
m-Nitro	40	-

According to Table 1, the Wittig reaction is preferable in most instances, particularly when nitro, chloro, and hydroxyl functions are present in the benzaldehyde molecule. It is noteworthy that even the free *o*-hydroxy compounds allow the conversion to the olefin. The poor yield obtained with *p*-hydroxybenzaldehyde may be attributable to the positive mesomeric effect exerted by the phenoxide oxygen; this so powerfully



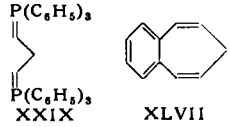
deactivates the aldehyde group that only a small proportion of the ylide molecules—namely those which dispose of the necessary activation energy—are capable of addition. As the author emphasizes, the Wittig reaction is simpler from the experimental point of view than the Reformatsky synthesis.

o-Phthalic dialdehyde undergoes this conversion in a similar manner to benzaldehyde, though here the process may be slightly more troublesome. According to Wittig and associates (*24*, *25*), the reaction between the aldehyde and the diylene XXX affords an 18% yield of the thus far unknown 1,2-benzo-1,3,7-cycloöctatriene (XLVI).



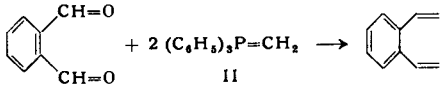
XXX XLVI

The synthesis of 1,2-benzo-1,3,5-cycloheptatriene (XLVII) from XXIX proceeds along identical lines.



XXIX XLVII

The simple preparation of *o*-divinylbenzene is also worth noting (*25*).



General procedure. Sodium (0.23 gm) is dissolved in absolute methanol (10 ml) and the triphenylphosphonium salt (4.3 gm) obtained from methyl γ-bromocrotonate added with stirring. After 15 min 0.01 mole of the aldehyde is added, and stirring continued for a further 15 min. The reaction mixture is then cooled to −10°. (The reactions are practically completed after 5 min). Crystallization of the products frequently occurs during this cooling period. Soluble esters are extracted with ether after diluting with water.

o-Divinylbenzene (*25*). Sodium amide (0.06 mole) in liquid ammonia (300 ml) is mixed with triphenylmethylphosphonium bromide (0.055

mole) and the ammonia evaporated. The residue is boiled under reflux with ether (200 ml). *o*-Phthalic dialdehyde (0.028 mole) in ether (100 ml) is stirred into the orange-yellow solution of the triphenylphosphinemethylene over a period of 15 min and the mixture boiled for 2 hr. Filtration, concentration of the filtrate to a volume of 50 ml and renewed filtration of triphenylphosphine oxide afford *o*-divinylbenzene (2.7 gm, 75%), b.p. 75–78°/14 mm, from the filtrate.

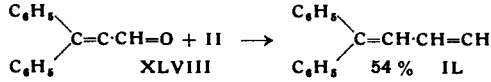
With Aldehydes Containing One Double Bond

So far as investigation to date has revealed, the reaction between α,β-unsaturated aldehydes and the phosphorus ylenes proceeds "normally," i.e. in the sense of 1,2-addition.

Wittig and Schöllkopf (*4*) found that the action of cinnamic aldehyde on triphenylphosphinemethylene (II) results in the exclusive formation of 1-phenyl-1,3-butadiene.

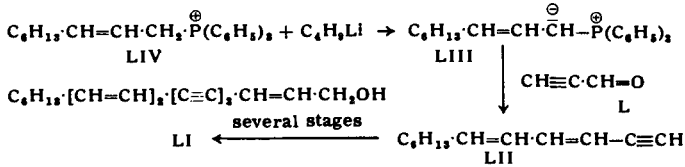
$$\underset{}{C_6H_5{\cdot}CH{=}CH{\cdot}CH{=}O} + \underset{II}{(C_6H_5)_3P{=}CH_2} \rightarrow C_6H_5{\cdot}CH{=}CH{\cdot}CH{=}CH_2$$

The action of β-phenylcinnamic aldehyde (XLVIII) on II also proceeds normally, yielding the previously unknown, extremely readily polymerized 1,1-diphenyl-1,3-butadiene (IL) (*19*).



The carbonyl–olefin conversion undergone by propargyl aldehyde (L) was investigated by Bohlmann and his co-workers with a view to synthesizing naturally occurring polyacetylenic compounds. Two of the experiments are illustrated here.

Dodeca-3,5-dien-1-yne (LII), required as an intermediate in the synthesis of enanthetol (*25a*) (LI), was obtained in 43% yield (*26*).



The unsaturated ylide LIII is prepared from triphenylnonenylphosphonium bromide (LIV) and butyllithium in ether.

Bohlmann and Herbst (*27*) obtained hepta-3,5-dien-1-yne (LV) in good yield by the action of triphenylphosphinepropenylmethylene (LVI) on propargyl aldehyde.

$$\underset{\text{LVI}}{(C_6H_5)_3P{=}CH{\cdot}CH{=}CH{\cdot}CH_3} + CH{\equiv}C{\cdot}CH{=}O \rightarrow \underset{\text{LV}}{CH{\equiv}C{\cdot}CH{=}CH{\cdot}CH{=}CH{\cdot}CH_3}$$

In the synthesis of anacylin (LVII), a diacetylenic compound isolated from Anacylus pyrethrum, Bohlmann and Inhoffen (*28*) condensed fumaraldehyde carboxylic ester (LVIII) with the phosphorus ylide LIX to give the polyenynoic carboxylic ester LX.

$$\underset{\text{LIX}}{H_7C_3{\cdot}[C{\equiv}C]_2{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{\ominus}{C}H{-}\overset{\oplus}{P}(C_6H_5)_3} + \underset{\text{LVIII}}{O{=}CH{-}CH{=}CH{-}COOR} \rightarrow$$

$$\underset{\text{LX}}{H_7C_3{\cdot}[C{\equiv}C]_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH{=}CH{\cdot}CH{=}CH{-}COOR} \xrightarrow{\text{several stages}}$$

$$\underset{\text{LVII}}{H_7C_3{\cdot}[C{\equiv}C]_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH{=}CH{\cdot}CH{=}CH{-}\overset{O}{\overset{\|}{C}}{-}NH{-}CH_2{\cdot}CH\begin{matrix}CH_3\\CH_3\end{matrix}}$$

This ester LX, which was obtained in satisfactory yield, was saponified, converted into the chloride, and then into the isobutylamide with isobutylamine; the amide corresponded to the natural anacylin in every respect. In the condensation LIX + LVIII → LX, it was found expedient to add the ylide solution to a solution of the aldehyde; if this is not done, the ester carbonyl also reacts.

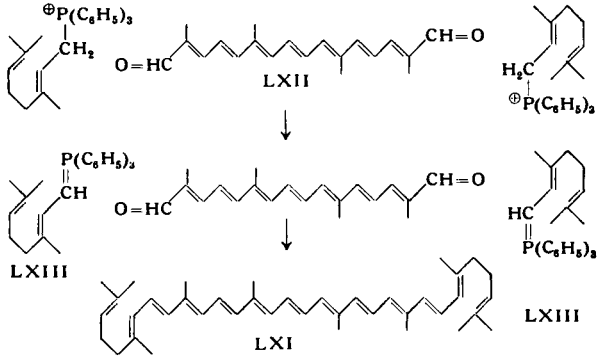
Dodeca-3,5-dien-1-yne (*26*) (*LII*). Triphenylnon-2-enylphosphonium bromide (LIV) (3.8 gm) is allowed to react with butyllithium (95% of the theoretical amount) in absolute ether. The solution, initially deep red, acquires an orange color after 2 hr. Propargyl aldehyde (L) (1 ml) is then added with stirring. The white slurry is stirred for a further 2 hr and filtered; the filtrate is washed with water, dilute HCl, and again with water, and the residue distilled from a bulb tube. Dodeca-1,3-dien-1-yne (43%), b.p. 50°/0.05 mm, is obtained.

Methyl tetradeca-2,4-diene-8,10-diynoate (*LX*) (*28*). The corresponding phosphonium salt (22 gm) is carefully dried and ground, suspended in ether (200 ml), and treated with the equivalent amount of butyllithium in ether with stirring. The formation of the ylide is complete after 1 hr and the red solution is transferred with nitrogen into a stirred solution of the aldehyde LVII (4.7 gm). A gray precipitate appears immediately. The reaction solution is boiled for 2 hr and the precipitated phosphine oxide/salt mixture filtered off. The ethereal solution is washed, the ether evaporated, and the residue chromatographed on alumina. Elution with petroleum ether–ether (10:1) yields the ester LX (5 gm).

With Aldehydes Containing Several Double Bonds

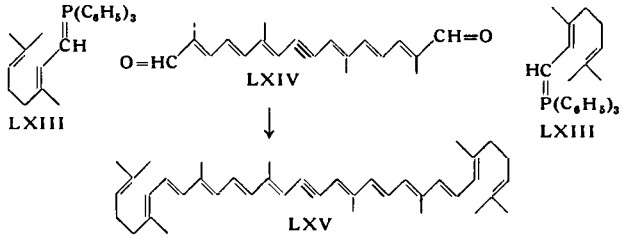
All the experiments to date involving polyunsaturated aldehydes have shown that these undergo the olefin transformation with satisfactory yields. The Wittig reaction therefore provides a welcome opening for the synthesis of sensitive polyenes.

Good examples of the usefulness of the reaction in the carotenoid field are given by O. Isler and his collaborators. Lycopene (LXI), for instance, was synthesized from crocetin dialdehyde (LXII) by condensing both ends of the molecule with the ylene LXIII, obtained from triphenylgeranylphosphonium bromide and phenyllithium (*29*).



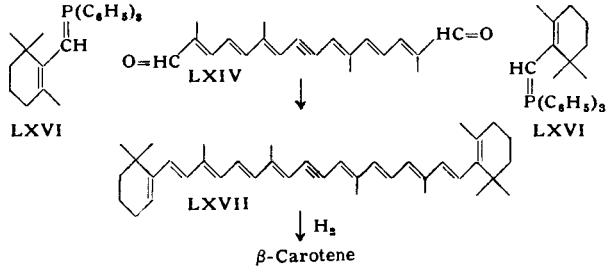
A single recrystallization yielded the pure dyestuff which proved to be identical with the naturally occurring all-*trans*-lycopene in melting point, mixed melting point, and IR spectrum. The two new double bonds are accordingly formed in the *trans*-configuration.

From 8,8′-dehydrocrocetin dialdehyde (LXIV), and LXIII, the authors obtained 15,15′-dehydrolycopene (LXV) in an analogous manner.

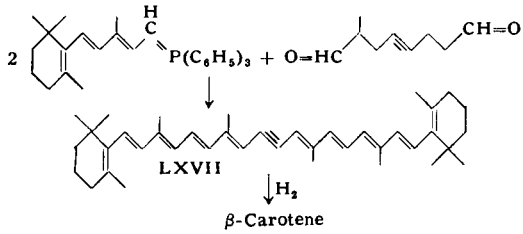


β-Carotene was synthesized by the same route as lycopene: The condensation of LXIV and the ylene LXVI obtained from β-cyclogeranyltriphenylphosphonium bromide first yielded 15,15′-dehydro-β-carotene

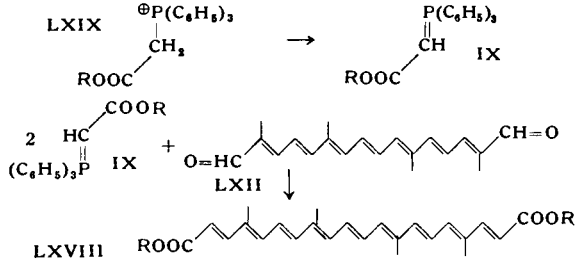
(LXVII), which was converted into β-carotene by catalytic hydrogenation (*29*).



β-Carotene was also synthesized by Pommer (*30*) who followed the scheme $C_{15} + C_{10} + C_{15} = C_{40}$.



In order to effect the synthesis of a number of diesters, LXVIII, of norbixin (*31a*), Isler and his co-workers (*31*) joined crocetin dialdehyde (LXII) to two moles of a triphenylcarbalkoxymethylene of structure IX.



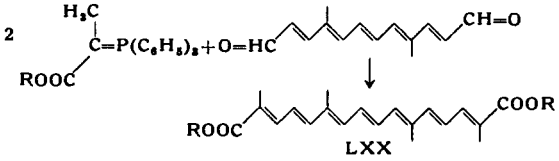
The elimination of hydrogen halide from the triphenylcarbalkoxymethylphosphonium salt (LXIX) can be effected in either alcoholic solution with sodium ethoxide or aqueous solution with sodium hydroxide.

If the reaction is carried out in aqueous solution, the water-insoluble ylides are isolated as described in the foregoing directions and purified by recrystallization from acetic ester-petroleum ether. Condensation with the aldehyde is then effected by boiling in benzene (Method *a*).

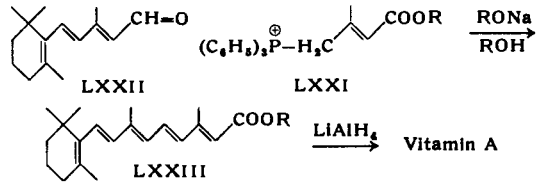
If, on the other hand, the hydrogen halide is eliminated with sodium methoxide in methanol, the ylides remain in solution and are allowed to react with LXII directly without being isolated (Method *b*). One example is given for each method.

Diesters (LXX) of crocetin (a C_{20}-dicarboxylic acid present in saffron as the digentiobiose ester) have been synthesized in a similar manner. As shown in the scheme, the synthesis follows the principle $C_3 + C_{14} + C_3 = C_{20}$ (*31*).

The dimethyl, diethyl, and dicetyl esters of both carboxylic acids have been prepared.



A new route to vitamin A has been reported by Pommer (*32*).



γ-Bromo-β-methylcrotonic ester was added to triphenylphosphine to give the phosphonium salt LXXI, which is in turn condensed with β-ionylideneacetaldehyde (LXXII) in the presence of alcoholic sodium ethoxide to form vitamin A ester (LXXIII). LXXIII was then reduced to vitamin A itself with lithium aluminum hydride.

Lycopene (*29*). A stirred suspension of triphenylgeranylphosphonium bromide (100 gm) in absolute ether (1 liter) is treated with a 1 *N* solution of ethereal phenyllithium (200 ml). After stirring for 1 hr, a solution of crocetin dialdehyde (20 gm) in anhydrous methylene dichloride (500 ml) is added to the deep-red ylene solution over a period of 5 min. Stirring is continued for another 15 min at 30° and 5 hr at the reflux temperature. Methanol (600 ml) is added all at once to the warm solution which is then cooled to 10° with stirring. The crystalline slurry is filtered under CO_2. The crude lycopene is dissolved in acid-free methylene dichloride (300 ml) at a maximum temperature of 40°, and reprecipitated with methanol (500 ml). Yield 25 gm, m.p. 172–173°.

Methyl bixin (*LXVIII, R=CH₃*) *according to Method a* (*31*). Crocetin dialdehyde (LXII) (1.5 gm) and triphenylphosphinecarbomethoxy-

methylene (IX, R=CH_3) (4.5 gm) are heated for 6 hr under nitrogen in dry benzene (50 ml). On slow cooling, methyl bixin (ca. 1.2 gm) crystallizes. Concentration of the filtrate yields a further 0.8 gm. After recrystallization the product melts at 203°.

Norbixin diethyl ester (LXVIII, R=C_2H_5) according to Method b (31). The stirred clear solution of carbethoxymethyltriphenylphosphonium bromide (LXIX, R=C_2H_5) in dry methylene dichloride (300 ml) is treated in an atmosphere of nitrogen with a 2 *N* solution of sodium methoxide (75 ml); the solution becomes very turbid. After stirring for one-half hour, a solution of crocetin dialdehyde (19 gm) in methylene dichloride (300 ml) is added over a period of 5 min and the mixture boiled under reflux for 5 hr. After cooling, the precipitated triphenylphosphine oxide is filtered off; the filtrate is washed with water, dried, and filtered through a column of alumina (1 kg). Elution with methylene dichloride yields norbixin diethyl ester (22 gm), m.p. 189–190°.

With Aldehydes Containing Double and Triple Bonds

A Wittig reaction was used by Bohlmann and Viehe (*33*) in the synthesis of cicutol (LXXIV), isolated from water hemlock.

$$C_6H_5\cdot CH{=}CH\cdot CH_2\cdot \overset{\oplus}{P}(C_6H_5)_3 + C_6H_5Li \longrightarrow$$
LXXV

$$C_6H_5\cdot CH{=}CH\cdot \overset{\ominus}{C}H{-}\overset{\oplus}{P}(C_6H_5)_3$$
LXXVI

$$\text{LXXVI} + OCH\cdot CH{=}CH\cdot C{\equiv}CH \longrightarrow$$
LXXVII

$$C_6H_5\cdot CH{=}CH\cdot \underset{\text{trans}}{\overset{\text{cis}}{CH{=}CH}}\cdot CH{=}CH\cdot C{\equiv}CH$$
LXXVIII

$$\text{LXXVIII} + HOCH_2\cdot CH_2\cdot C{\equiv}CH \longrightarrow$$
LXXIX

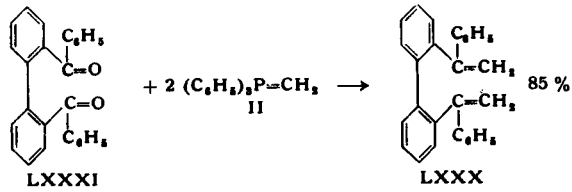
$$C_6H_5\cdot CH{=}CH\cdot \underset{\text{trans}}{\overset{\text{cis}}{CH{=}CH}}\cdot CH{=}CH(C{\equiv}C)_2\cdot CH_2\cdot CH_2OH$$
LXXIV

Compound LXXV reacts with butyllithium in ether to give a deep-red ylide LXXVI; the action of the latter on pent-2-en-4-yn-1-al (LXXVII) resulted in a 60% yield of dodeca-3,5,7-trien-1-yne (LXXVIII). The oxidative crossed dimerization of this polyenyne with the carbinol LXXIX formed a mixture of three hydrocarbons, from which all-*trans*-cicutol could be separated chromatographically. Small quantities of a liquid compound, presumably 10-*cis*-cicutol, were obtained from the *trans*-cicutol mother liquors.

With Aromatic Ketones

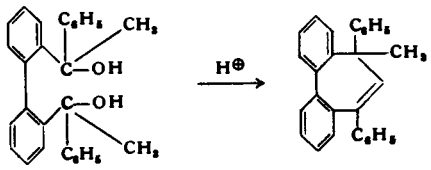
Wittig reactions with benzophenone and the majority of its ring-substituted derivatives are of minor preparative importance, since these ketones usually undergo the olefin transformation readily via the Grignard method. Use of the phosphinealkylene process is only made in exceptional cases.

One such special case is presented by the synthesis of *o,o'*-distyryldiphenyl (LXXX) (*34*).



LXXXI LXXX

This synthesis is of significance in that when the glycol, LXXXII, obtained from LXXXI and two moles of methylmagnesium halide, is dehydrated, a cyclic hydrocarbon is formed and not compound LXXX (*34*).

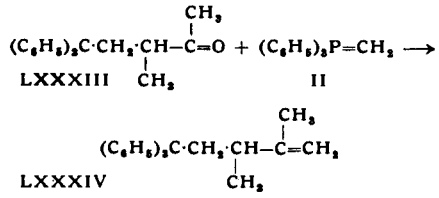


LXXXII

The discovery by Wittig and his co-workers (*4,5*) that *p*-nitrobenzophenone also undergoes the exchange reaction is worth noting. The action of the ketone on triphenylphosphinemethylene (II) yields *p*-nitrodiphenylethylene (60%), and on triphenylphosphinebenzylene, *p*-nitrostilbene. Whereas the nitro group thus remains largely unaffected during these exchange reactions, this is not so in the case of a Grignard reaction.

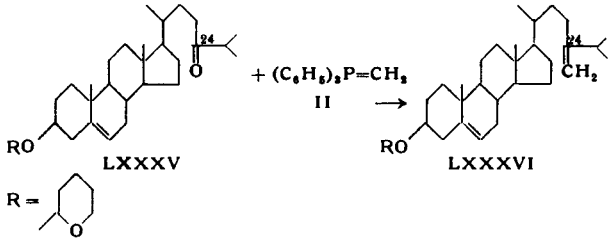
With Aliphatic Ketones

The first aliphatic ketone examined by Wittig and Schöllkopf (*4*) was 3-methyl-1,1,1-triphenyl-4-pentanone (LXXXIII); it was found to react readily with II to give 71% of 3,4-dimethyl-1,1,1-triphenyl-4-pentene (LXXXIV).



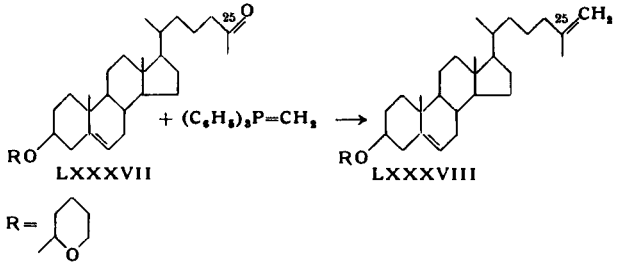
The observation that in branched ketones the double bond is also invariably formed at the position of the original C=O group, was later repeatedly confirmed.

Bergmann and Dusza (*35*) allowed II to react with 24-oxocholesterol (LXXXV) and obtained 24-methylenecholesterol (LXXXVI).

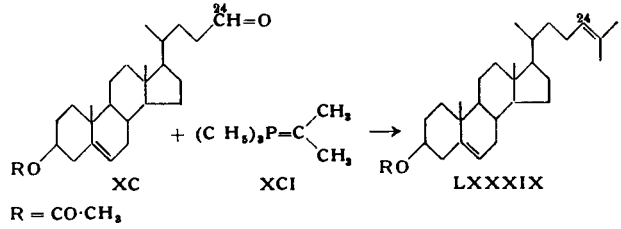


This methylene compound, thus obtained pure for the first time, was found to be identical with a sterol isolated from sponges and sea anemones, so-called chalinasterol, whose structure was a matter of controversy.

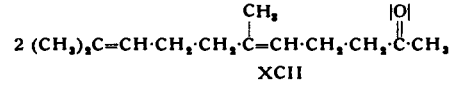
25-Oxonorcholesterol (LXXXVII) was also subjected to a Wittig reaction recently; a very good yield of 25-dehydrocholesterol (LXXXVIII), which cannot be prepared by classical methods, was obtained (*36*).

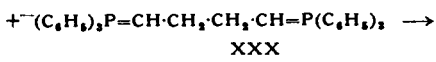


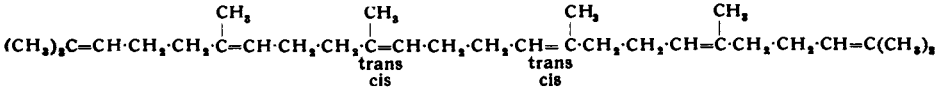
The 24-dehydro compound LXXXIX required for comparison purposes was also prepared by the Wittig method, from 3β-acetoxy-5-cholenaldehyde (XC) and triphenylphosphinedimethylmethylene (XCI) (*37*).



Reference should finally be made to a synthesis of squalene, which was recently devised in three different laboratories almost simultaneously (*38, 39, 40*). This is effected by allowing two equivalents of geranylacetone (XCII) to react with one mole of the bifunctional ylene XXX.







Using pure *trans*-geranylacetone, Dicker and Whiting (*39*) were able to isolate a 12.5% yield of pure all-*trans*-squalene, indistinguishable from the natural terpene, from the crude reaction product (25% of the theoretical total yield) via the thiourea complex.

A comparable yield was obtained by Mondon (*40*), who effected the condensation by means of sodium ethoxide in ethanol.

24-Dehydrocholesterol (*LXXXIX*) (*37*). Triphenylisopropylphosphonium bromide (3.08 gm) is suspended in ether (25 ml) and shaken overnight with a solution of butyllithium (0.62 *N*, 12.9 ml, 8 mmoles) in a pressure bottle. 3β-Acetoxy-5-cholenaldehyde (XC) (840 mg) is added, the mixture shaken for a further hour at room temperature and maintained at 65° for 6 hr. Filtration, washing of the filtrate with water, drying, and chromatography yielded 24-dehydrocholesteryl acetate (205 mg).

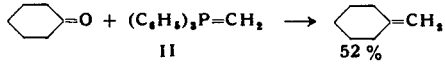
Squalene [*according to the method of Mondon* (*40*)]. A solution of sodium (0.92 gm) in ethanol (50 ml) and geranylacetone (8.15 gm) are added to a solution of tetramethylenebis(triphenylphosphonium) dibromide (XXVIII) (14.5 gm) in ethanol (75 ml). The mixture is allowed to stand for 5 days under nitrogen at room temperature. The alcohol is evaporated and the residue extracted with petroleum ether, benzene, and chloroform in that order. The insoluble residue consists of sodium

bromide. The petroleum ether extracts are washed with water, dried, and concentrated until copious crystallization results. After storage in the refrigerator, triphenylphosphine oxide (4.03 gm) is filtered off. On evaporation, the filtrate yields an oil (8.4 gm) which is dissolved in pentane and purified chromatographically. Squalene (2.12 gm, 26%), present as a mixture of isomers, b.p. 155–175°/0.04 mm, can be obtained from the main fraction, eluted with pentane. This fraction contains all-*trans*-squalene (0.4 gm) which is isolated via the thiourea complex.

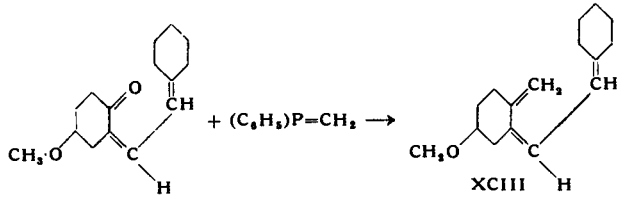
With Alicyclic Ketones

In no other sphere did the Wittig reaction become indispensable as rapidly as in the alicyclic ketone field. It represents the only method available for converting a cyclic ketone into the corresponding olefin containing an exocyclic double bond. As is well known, the Grignard method yields almost exclusively the endocyclic unsaturated isomers.

According to Wittig and Schöllkopf (*4*), cyclohexanone reacts with triphenylphosphinemethylene (II) to give methylenecyclohexane (free from isomers) and with triphenylphosphinebenzylidene to give the corresponding benzylidenecyclohexane (XLIV).



This route was followed by Milas and his collaborators (*41*) in model reactions effected with a view to synthesizing vitamin D_2, when they obtained the triene XCIII possessing a double bond system typical of calciferol.

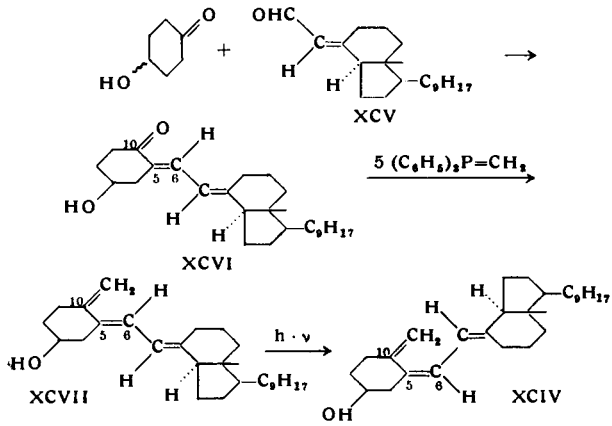


Harrison and Lythgoe (*42*) obtained a simpler model of vitamin D.

Inhoffen and co-workers (*43*) have recently described a synthesis of vitamin D_2 (XCIV) in which the exocyclic methylene group at C_{10} is introduced by the Wittig method.

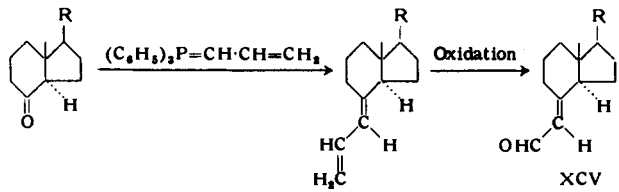
The C_{21}-aldehyde (XCV) (a degradation product of vitamin D_2) is first condensed with *p*-hydroxycyclohexanone to give the hydroxytrienone XCVI. The 3β-isomer of the latter, separated chromatographically from the epimeric mixture, is converted into the 5,6-*trans*-vitamin D_2 (XCVII) by heating in the presence of a fivefold excess of II in ether.

The *trans*-vitamin, obtained in 50% yield, is finally converted into calciferol (XCIV) by photoisomerization.



Harrison and Lythgoe (*42*) also obtained vitamin D_2 (as a mixture of the C_3-epimers), by subjecting the *cis*-isomer of the triene XCVI to a Wittig reaction and using tetrahydrofuran as the solvent.

According to Inhoffen and associates (*44*), the C_{21}-aldehyde XCV mentioned above, can also be prepared by means of the phosphinealkylene method.

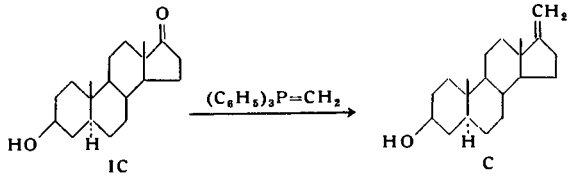


It is worth noting that in spite of the alkalinity of the reaction medium, the *trans* structure of the C/D ring system is retained.

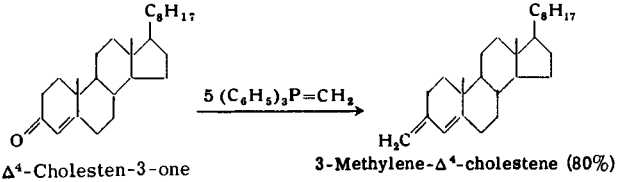
These examples show that the Wittig reaction solved a fundamental problem of the chemistry of vitamin D, namely the introduction of a methylene group at C_{10}. The formation of the 5,6-double bond possessing the correct configuration (*cis*) has so far proved unsuccessful. In corresponding experiments, H. H. Inhoffen and other workers invariably obtained the *trans*-isomers.

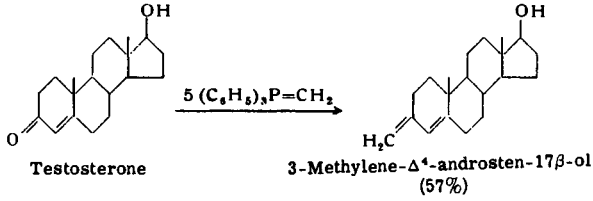
Sondheimer and Mechoulam (*45*) described the carbonyl–olefin conversion undergone by a total of thirteen steroidal ketones, including some with OH and C=C functions. The yields varied between 30 and 70%; an excess of ylide appears to exert a favorable effect on the yield.

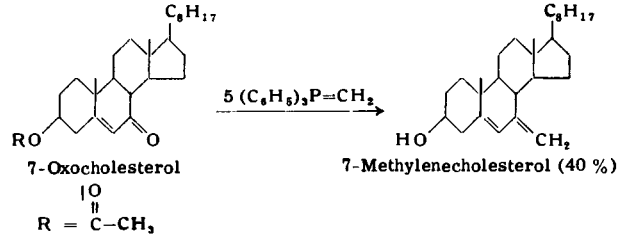
As an example, if androstan-3β-ol-17-one (IC) is allowed to react with triphenylphosphinemethylene, the yield of 17-methyleneandrostan-3β-ol (C) rises from 32% with three equivalent of the phosphinealkylene to 58% in the presence of five equivalents of the reactant.



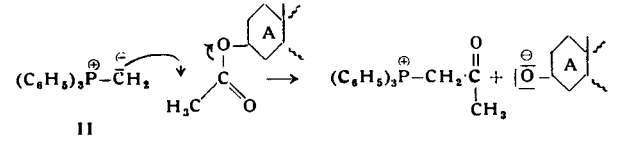
The Wittig reaction is also applicable to unsaturated steroidal ketones.



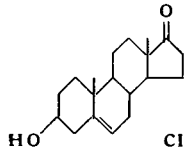




When 7-oxocholesterol was subjected to the reaction as the acetate, the acetyl group was eliminated by the ylide during the course of the reaction.

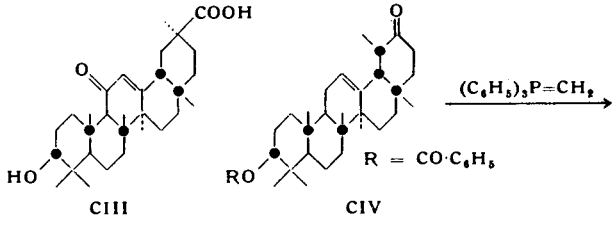


The authors also examined the effect on the yield of a group protecting the hydroxyl function. Thus they investigated the action of three equivalents of II on (a) Δ^5-androsten-3β-ol-17-one (CI), (b) its acetate, and (c) its tetrahydropyranyl ether. The yields were: (a) 36%; (b) 27%; and (c) 44%. Although the tetrahydropyranyl ether affords the highest yield, the use of the free ketol is recommended on the grounds that the formation and fission of the ether is associated with a greater loss of material.



CI

A more recent study (*46*) of the stereochemical relationships in the triterpene series deals with the synthesis of α-amyrin (CII) from glycyrrhetic acid (CIII), a derivative of β-amyrin of known configuration. The ketone CIV obtained from CIII is allowed to react with II during the course of the synthesis and the methylene compound CV selectively reduced to α-amyrin.



Methylenecyclohexane (*4*). Cyclohexanone (9.8 gm, 0.1 mole) is added to a solution of triphenylphosphinemethylene (0.1 mole) (prepared from triphenylmethylphosphonium bromide and butyllithium; cf. below) in absolute ether (200 ml); a white precipitate forms instantaneously. After allowing the mixture to stand for 3 hr at 65°, the precipitate is removed by centrifuging and repeatedly washed with ether. The ethereal layer is washed with water, the solvent evaporated and the

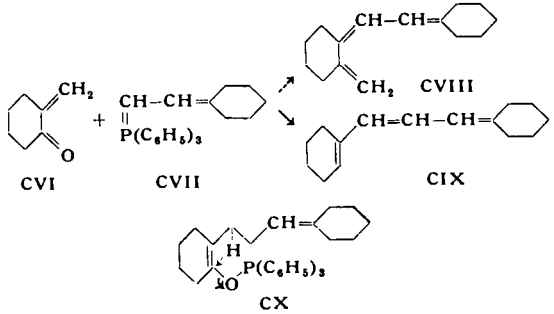
residual oil fractionated through a Vigreux column 30 cm high, yielding methylenecyclohexane (5.4 gm, 52%), b.p. 100–103°/744 mm.

3β-5,6-trans-Vitamin D_2 (XCVII) (*43*). Butyllithium (0.00563 mole) is diluted with absolute ether to a volume of 15 ml, the stirred mixture treated with triphenylmethylphosphonium bromide (2.7 gm) and stirring continued for some time at room temperature. The mixture is then cooled in ice, the 3β-hydroxytrienone (XCVI) (450 mg) added, and stirring at room temperature resumed. After simmering for 3 hr in an oil bath, the mixture is worked up with ether, sodium chloride, and distilled water, and the crude product chromatographed on alumina (45 gm). Elution with petroleum ether–ether (8:2) first yields the phosphine oxide and this is followed by petroleum ether–ether (7:3), when 3β-5,6-*trans*-vitamin D_2 is obtained. Yield 44.6%.

Olefin conversion of steroidal ketones with triphenylphosphinemethylene (*45*). An ethereal solution of butyllithium (1 *N*, 9 ml) is added to a stirred suspension of triphenylmethylphosphonium bromide (3.57 gm) in absolute ether (50 ml). The mixture is shaken for 2 hr, a solution of the ketone in ether (50–100 ml) added and shaking continued for a further 4 hr. The mixture is allowed to stand overnight, the ether distilled off, and tetrahydrofuran added. It is then boiled under reflux for 6 hr, cooled, diluted with water, and extracted with ether. The extracts are washed with water (or dilute acid), dried, and concentrated. The methylenesteroid is isolated from the residue by crystallization or chromatography.

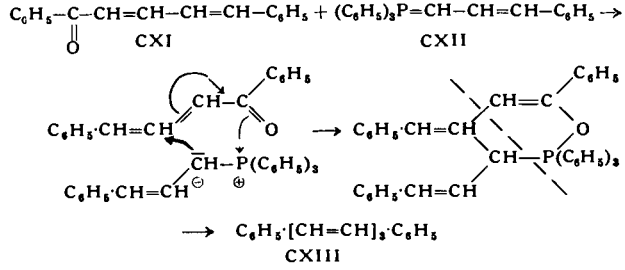
With Unsaturated Ketones

Whereas unsaturated aldehydes react normally throughout with the phosphorus ylenes, unsaturated ketones are obviously capable of undergoing 1,4-addition. Inhoffen and collaborators (*22*) for example, found that the reaction between 1-methylene-2-cyclohexanone (CVI) and the ylene CVII resulted in the formation of CIX, not CVIII. They assume



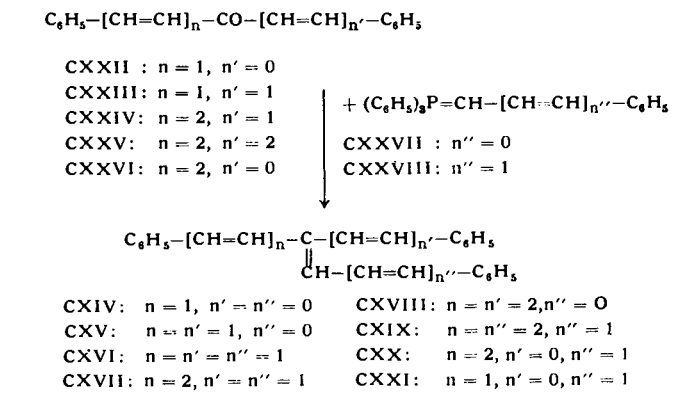
a 1,4-addition accompanied by the simultaneous migration of a hydrogen atom and discuss the transition state CX.

Bohlmann (*47*) allowed the cross-conjugated ketone CXI to react with CXII in boiling tetrahydrofuran and isolated both the normal reaction product and 1,6-diphenyl-1,3,5-hexatriene (CXIII); the formation of the latter can also be explained as the basis of a 1,4-addition.



In general, however, most of the carbonyl–olefin transformations undergone by these compounds do proceed normally, as already shown by the examples given in the preceding section from the steroid series and 9,10-secosteroids.

Bohlmann (*47*) synthesized a number of cross-conjugated hydrocarbons (CXIV–CXXI) by the action of the phosphorus ylenes, CXXVII and CXXVIII, on the ketones CXXII–CXXVI.



The yields are good throughout; the ketone CXXVI is the only exception and undergoes some 1,4-addition. The pure compounds are partially obtained directly from the crude reaction products by crystallization.

Preparation of hydrocarbons CXIV–CXXI. Butyllithium (0.05 mole) is added to a stirred suspension of the phosphonium salt (0.06 mole) in

absolute ether (50 ml). After 30 min the ketone (0.05 mole) in tetrahydrofuran (10 ml) is added and stirring continued for a further hour. The mixture is filtered through a layer of alumina and the filtrate washed with dilute sulfuric acid and with water. The products are isolated from the ether solution residues by crystallization or chromatography.

With Isocyanates and Ketenes

Staudinger and Meyer (*48*) described as early as 1919 the reaction between triphenylphosphinediphenylmethylene (XVI) with phenyl isocyanate to give the phenylimine of diphenylketene.

$$\underset{\text{XVI}}{(C_6H_5)_3P{=}C(C_6H_5)_2} + O{=}C{=}N{-}C_6H_5 \rightarrow (C_6H_5)_2C{=}C{=}N{-}C_6H_5$$

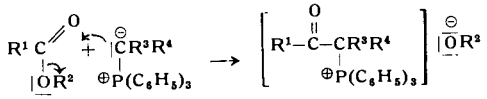
Other isocyanates do not appear to have been investigated.

Lüscher (*49,50*) found that XVI can also exchange its methylene group for the carbonyl oxygen of diphenylketene, but only under forcing conditions.

$$\underset{\text{XVI}}{(C_6H_5)_3P{=}C(C_6H_5)_2} + O{=}C{=}C(C_6H_5)_2 \xrightarrow{140\,^\circ} (C_6H_5)_3PO + \underset{\text{Tetraphenylallene}}{(C_6H_5)_2C{=}C{=}C(C_6H_5)_2}$$

With Ester Groups

In the form of carbanions, the phosphorus ylides are capable of adding to the C=O of a COOR function; an alkoxide anion is eliminated in the process and the triphenylacylphosphonium salts are obtained.



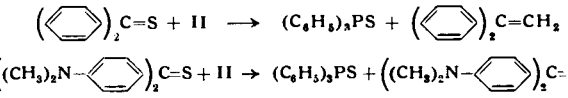
The normal C=O group, especially that of an aldehyde, reacts more rapidly than an ester carbonyl, so that under suitable reaction conditions (inverse addition, cooling) keto- and aldehydo-esters can selectively be converted.

Other Reactions

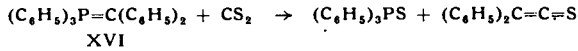
With Thiocarbonyl Compounds

Thiobenzophenone and thio-Michler's ketone resemble the corresponding ketones in their behavior and react with triphenylphosphinemethyl-

ene (II) to give 1,1-diphenylethylene and bis(*p*-dimethylaminophenyl)-ethylene, respectively, together with triphenylphosphine sulfide (*19*).

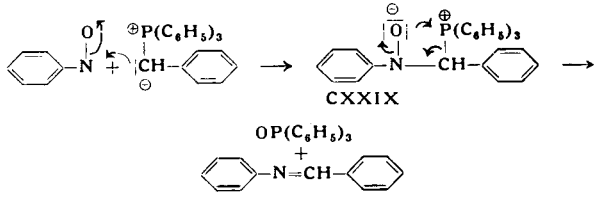


The same scheme is followed by the reaction, discovered by Staudinger (*48*), between the diphenylmethylene XVI and carbon disulfide.

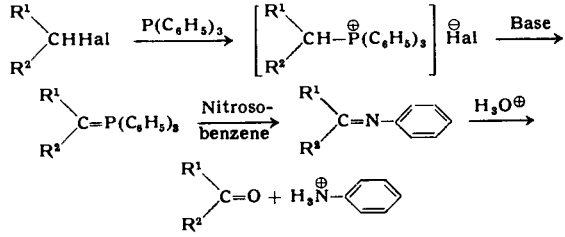


With Nitroso Compounds

Like the carbonyl function, the N=O group in nitroso compounds possesses some electrophilic character and is capable of adding triphenylphosphinealkylenes. Thus nitrosobenzene reacts with triphenylphosphinebenzylene to give the betaine CXXIX, which decomposes spontaneously at room temperature to benzalaniline and triphenylphosphine oxide (*21*).



A number of other phosphinealkylenes undergo this condensation with nitrosobenzene. Since the Schiff bases formed can readily be hydrolyzed to aldehydes and ketones, the reaction sequence



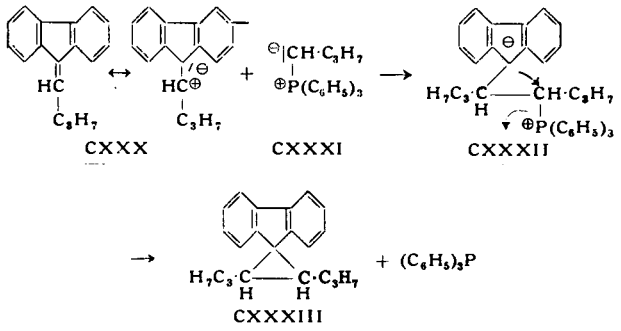
represents a novel synthesis of carbonyl compounds (*51*).

Citral (*51*). Geranyltriphenylphosphonium bromide (70 gm) is dissolved in dimethylformamide (100 gm) and treated with a methanolic solution of sodium methoxide (27 gm, 30%) at 10° in the absence of air. The dark-red ylene is immediately formed. Nitrosobenzene (15 gm) is carefully added portionwise to the stirred, ice-cooled mixture. An exo-

thermic reaction ensues, and the red color of the ylide disappears. After 30 min stirring the dark-brown solution is treated with phosphoric acid (200 gm, 10%) and steam-distilled. The distillate is extracted with petroleum ether and the organic layer washed and dried over Na_2SO_4, yielding citral (16.5 gm), b.p. 104–105°/13 mm.

With the Carbon-Carbon Double Bond

The readily polarized C=C bond of 9-*n*-butylidenefluorene (CXXX) is capable of adding triphenylphosphinepropylmethylene (CXXXI). The zwitterion (CXXXII) initially produced is stabilized by the elimination of triphenylphosphine to give spiro (2,3-di-*n*-propylcyclopropane-1,9′-fluorene) (CXXXIII) (*52*).



The identical product is obtained if fluorenone is allowed to react with three equivalents of CXXXI. A normal carbonyl-olefin transformation obviously occurs first and gives CXXX, which then reacts further with the excess of phosphinemethylene present to give CXXXIII.

General Experimental

Preparation of the Phosphonium Salts

The triphenylalkylphosphonium salts are prepared from triphenylphosphine and the primary or secondary alkyl halide according to the equation

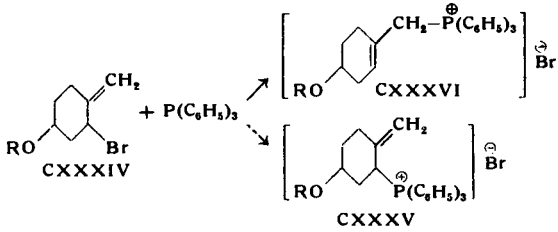
$$(C_6H_5)_3P + R^1R^2CH{-}Hal \rightarrow [(C_6H_5)_3\overset{\oplus}{P}{-}CHR^1R^2]\ \overset{\ominus}{Hal}$$

As usual, the alkyl iodides react more rapidly than the bromides and chlorides. The bromides are generally used, as these are more readily prepared than the iodides. The rate of reaction also depends on the nature of the alkyl group; methyl, benzyl, and allyl halides react rapidly, as do compounds in which the halogen is activated by the presence of a

C=O or COOR group in the immediate vicinity. In such a case it suffices to allow the components to stand in benzene or ether (with warming if necessary) until the salt has separated quantitatively.

In obstinate cases, more highly polar solvents (nitromethane, nitrobenzene, dimethylformamide) are used; alternatively, the quaternization is effected in the molten state (if necessary in a bomb tube) at 100–200°. The preparation of bisphosphonium salts in particular demands such forcing conditions. It has been found empirically that the use of benzene as the solvent results in the formation of the mono-salts only.

It should be noted that allyl bromides may sometimes undergo an allylic rearrangement during the course of the quaternization. Thus, by allowing 1-bromo-2-methylene-5-alkoxycyclohexane (CXXXIV) to react with triphenylphosphine, Inhoffen and his co-workers (*53*) obtained, instead of the anticipated phosphonium salt CXXXV, its allylic isomer CXXXVI.



For the purification of the salts, it usually suffices if they are thoroughly washed with benzene. Crystallization from higher alcohols (with or without the addition of tetrahydrofuran) yields purer products; these are also obtained by reprecipitation with ether, acetone, or acetic ester from a solution of the crude product in chloroform, methanol, ethanol, or some other good solvent. Some salts are hygroscopic or tend to occlude the solvent (chloroform); they must consequently be thoroughly dried *in vacuo* before being utilized in the transformation.

Triphenylmethylphosphonium bromide (*4*). Methyl bromide (50 gm) is added to a solution of triphenylphosphine (100 gm) in benzene at −10° in a pressure bottle. The mixture is allowed to stand for 2 days at room temperature and the precipitated salt filtered. Washing with benzene purifies it sufficiently for use in the conversion. Yield, 101 gm, m.p. 227–229°.

Triphenylcarbomethoxymethylphosphonium bromide (*31*). Methyl bromoacetate (144 gm) is added dropwise to a stirred solution of triphenylphosphine (262 gm) in benzene (1200 ml) over a period of 30 min, when a temperature rise of 30–40° is observed. The mixture is stirred overnight and the triphenylcarbomethoxymethylphosphonium bromide

filtered and washed with petroleum ether and benzene and dried *in vacuo* at 50°. Yield 345 gm, m.p. 163°.

Tetramethylenebis(triphenylphosphonium) dibromide (25). Triphenylphosphine (500 gm, 1.91 mole) and 1,4-dibromobutane (185 gm, 0.85 mole) are warmed to 200°, and then slowly heated to 250° with stirring. The mixture solidifies into a crystalline mass which is maintained at the same temperature for a further 30 min. On cooling it is dissolved in boiling chloroform, filtered, and treated with acetone until crystallization commences. The cold crystalline bisphosphonium salt is filtered and dried in high vacuum at 110°. Yield 570 gm, m.p. 292–294°.

Triphenylethylphosphonium bromide. Triphenylphosphine (78 gm, 0.3 mole) and ethyl bromide (44 gm, 0.4 mole) are heated in a bomb tube at 120° for 15 hr. The crude triphenylethylphosphonium bromide is extracted with boiling benzene and recrystallized from water. Yield, 90%, m.p. 203–204°.

Preparation of Triphenylphosphinemethylenes* and Their Use in the Carbonyl–Olefin Transformation

The reagents are generally not isolated, but allowed to react *in situ* with the carbonyl compound; the manner of preparation of the ylide will therefore determine the over-all reaction procedure.

The Organometallic Method

In this method phenyl- or butyllithium act as the proton acceptor and diethyl ether or tetrahydrofuran as the solvent. For small-scale operations it is found expedient to carry out the reaction in a Schlenk tube (Fig. 1) which can be sealed and warmed in a water bath if necessary.

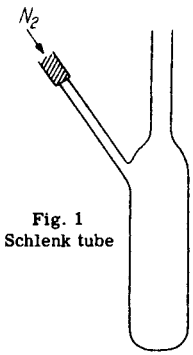


Fig. 1
Schlenk tube

If larger quantities are to be reacted or no warming is required, an ordinary three-necked flask may be used, equipped with stirrer, dropping funnel, reflux condenser, and gas inlet tube for passing nitrogen.

* See Table 2, page 145.

One equivalent of a (usually) ethereal solution of phenyl- or butyllithium is slowly added to a vigorously stirred or shaken suspension of the dried and powdered phosphonium salt in ether or tetrahydrofuran. As a rule the ylide is formed immediately and a red or orange coloration appears as the salt goes into solution.

The carbonyl compound to be converted is added to the solution or suspension of the ylide prepared as above, resulting in the usually sudden precipitation of the betaine (XXXVI). The elimination of the phosphine oxide frequently proceeds in the cold, especially if the formation of a conjugated double bond results. In some cases it is, however, necessary to raise the temperature to the boiling point of the solvent or to 60–70°. The fission of the betaine is accomplished more rapidly in tetrahydrofuran than in ether.

During the course of the reaction the triphenylphosphine oxide is precipitated as an almost insoluble adduct together with one mole of lithium halide and can be filtered off. The olefin is isolated from the filtrate in the usual manner. Since the granular crystalline adduct mentioned above differs from the curdy precipitate of the betaine, the progress of the reaction can, after some experience, be assessed from the altered appearance of the precipitate.

In the event of the carbonyl compound's containing one or more hydroxyl groups, a corresponding (three- to fivefold) excess of the ylide must be used if the hydroxyl groups are not first etherified with dihydropyran or acetylated. In the latter case, it should be noted that the ester carbonyl is also capable of reacting with the ylide.

G. Wittig and his collaborators (*25*) have recently proposed a modification of the organometallic method. This consists in synthesizing the ylide with sodium amide in liquid ammonia, and the subsequent replacement of the latter by ether or tetrahydrofuran. Experimental details will be found on p. 122. The preparation of the bis-ylene XXX from tetramethylenebis(triphenylphosphonium) dibromide (XXVIII) is described here.

Phosphorus ylene from triphenylgeranylphosphonium bromide (*29*). An ethereal solution of phenyllithium (200 ml, 1 *N*) is added over a period of 10 min to a stirred suspension of triphenylgeranylphosphonium bromide (110 gm) in absolute ether (1 liter). A deep-red solution of the ylide is obtained after stirring for 1 hr.

Triphenylphosphinemethylene (*4*), $(C_6H_5)_3P{=}CH_2$ (*II*). Ether (150 ml) and an ethereal solution of butyllithium, (40 ml, 1 *N*) are placed in a Schlenk tube; finely ground triphenylmethylphosphonium bromide (14.3 gm) is slowly added to the agitated solution and the tube shaken for 3 hr. A yellow-orange coloration develops as the triphenylphosphinemethyl-

ene goes into solution, leaving but a small residue of undissolved salt on the bottom. In some instances the product separates as pale yellow crystals.

Triphenylphosphinevinylmethylene (*4*), $(C_6H_5)_3P{=}CH{-}CH{=}CH_2$. An ethereal solution of phenyllithium (16.5 ml, 1.23 *N*) is slowly added to a shaken suspension of allyltriphenylphosphonium bromide (7.7 gm, 0.02 mole) in absolute ether (120 ml). The deep-red color of the ylide appears immediately and the salt goes rapidly into solution.

Tetramethylenebis(triphenylphosphinemethylene). Sodium (3.12 gm) is dissolved portionwise in liquid ammonia (ca. 300 ml) containing a few grains of ferric nitrate, the operation being carried out under nitrogen. The bisphosphonium salt (44.4 gm, 0.06 mole) is added to the colorless suspension of sodium amide (0.135 mole), when the bis-ylene (XXX) separates out as a yellow precipitate. Ether (300 ml) is added and the ammonia evaporated through a mercury valve, the last traces being removed by warming in a stream of nitrogen. The residue consists of an orange-red solution containing a yellow solid. The carbonyl compound to be converted is added to the vigorously stirred suspension of the bis-ylene.

The Alkoxide Method

This process, which is used to an ever-increasing degree due to its simplicity, utilizes sodium methoxide or ethoxide as the proton acceptor, and the corresponding alcohol as the solvent. One equivalent of an alcoholic solution of the sodium alkoxide is added to a solution of the phosphonium salt and carbonyl compound in methanol or ethanol. The operation can of course be carried out in the reverse order, and the components added to a solution of one equivalent of sodium in alcohol.

The alkoxide anion abstracts a proton from the salt, and the triphenylphosphinemethylene is formed in the solution according to

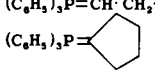
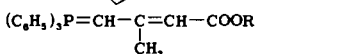
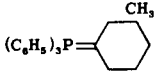
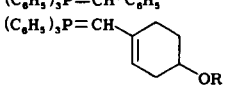
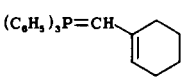
$$R^1R^2CH{-}\overset{\oplus}{P}(C_6H_5)_3 + |\overset{\ominus}{\underline{O}}{-}R' \overset{HOR'}{\rightleftharpoons} R^1R^2C{=}P(C_6H_5)_3 + HOR'$$

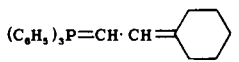
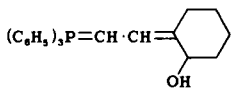
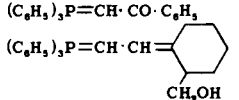
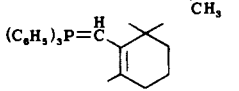
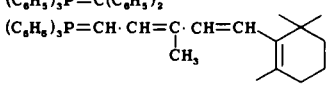
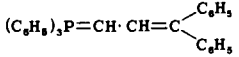
The product reacts with the carbonyl compound present, and is generated from the phosphonium salt at a rate proportional to its disappearance. In the case of somewhat insoluble carbonyl compounds, the alcohol is advantageously diluted with a suitable solvent, such as methylene dichloride or dimethylformamide. The latter is of course only suited for conversions involving relatively unreactive (unsaturated) ylides, which are no longer capable of attacking the amide function.

The rate of reaction depends primarily on the reactivity of the C=O group and the nature of the olefin produced; polyenes with conjugated

TABLE 2

List of Triphenylphosphinemethylenes

C atoms in the methylene moiety		Literature references
	Monofunctional ylenes	
C_1	$(C_6H_5)_3P{=}CH_2$	(4)
C_2	$(C_6H_5)_3P{=}CH\cdot CH_3$	(54, 55)
	$(C_6H_5)_3P{=}CH\cdot COOR$	(5, 31)
	$(C_6H_5)_3P{=}CH{-}CN$	(62)
	$(C_6H_5)_3P{=}CH{-}CONH_2$	(62)
C_3	$(C_6H_5)_3P{=}C(CH_3)_2$	(37, 55)
	$(C_6H_5)_3P{=}CH\cdot CH{=}CH_2$	(4)
	$(C_6H_5)_3P{=}CH\cdot COOR$ (CH$_3$)	(31)
	$(C_6H_5)_3P{=}CH\cdot CO\cdot CH_3$	(10)
	$(C_6H_5)_3P{=}CH\cdot CH_2\cdot CH_2\cdot OR$	(19)
C_4	$(C_6H_5)_3P{=}CH\cdot CH_2\cdot CH_2\cdot CH_3$	(52)
	$(C_6H_5)_3P{=}CH\cdot CH{=}CH\cdot CH_3$	(56)
	$(C_6H_5)_3P{=}CH\cdot CH{=}CH\cdot COOR$	(23)
	$(C_6H_5)_3P{=}CH\cdot CH_2\cdot CH_2\cdot CH_2Br$	(20)
C_5		(21)
		(32)
C_6	$(C_6H_5)_3P{=}CH\cdot (CH{=}CH)_2\cdot CH_3$	(56)
	$(C_6H_5)_3P{=}CH\cdot C(CH_3){=}CH\cdot C{\equiv}CH$	(57)
		(21)
C_7	$(C_6H_5)_3P{=}CH\cdot (CH_2)_4\cdot CH{=}CH_2$	(58)
	$(C_6H_5)_3P{=}CH\cdot C_6H_5$	(5)
		(53)
		(22)
	$(C_6H_5)_3P{=}CH\cdot CH{=}CH\cdot C_4H_9$	(33)

C atoms in the methylene moiety		Literature references
	Monofunctional ylenes (cont'd)	
C_6		(22, 42)
		(11)
	$(C_6H_5)_3P{=}CH\cdot CO\cdot C_6H_5$	(10)
C_9		(11)
	$(C_6H_5)_3P{=}CH\cdot CH{=}CH\cdot C_6H_5$	(47)
	$(C_6H_5)_3P{=}CH\cdot CH{=}CH\cdot (CH_2)_4\cdot CH{=}CH_2$	(58)
	$(C_6H_5)_3P{=}CH\cdot CH{=}CH\cdot C_6H_{13}$	(26)
C_{10}	$(C_6H_5)_3P{=}CH\cdot CH{=}CH\cdot (C{\equiv}C)_2\cdot CH{=}CH\cdot CH_3$	(59)
	$(C_6H_5)_3P{=}CH\cdot CH_2\cdot CH_2\cdot (C{\equiv}C)_2\cdot C_2H_7$	(28)
	$(C_6H_5)_3P{=}CH\cdot CH{=}C(CH_3)\cdot CH_2\cdot CH{=}C(CH_3)_2$	(29)
		(29)
C_{11}	$(C_6H_5)_3P{=}CH\cdot CH{=}CH\cdot (C{\equiv}C)_2\cdot C(CH_3)_3$	(61)
	$(C_6H_5)_3P{=}CH\cdot (CH{=}CH)_2\cdot C_6H_{13}$	(56)
C_{13}	$(C_6H_5)_3P{=}CH\cdot CH{=}CH)_2\cdot C{\equiv}C\cdot C_6H_5$	(60)
	$(C_6H_5)_3P{=}C(C_6H_5)_2$	(12)
C_{15}		(30)
		(18)
	Bifunctional ylenes	
C_3	$(C_6H_5)_3P{=}CH\cdot CH_2\cdot CH{=}P(C_6H_5)_3$	(19)
C_4	$(C_6H_5)_3P{=}CH\cdot CH_2\cdot CH_2\cdot CH{=}P(C_6H_5)_3$	(20, 25)

double bonds are usually formed extremely rapidly, even at low temperatures. Since the base becomes used up during the course of the reaction, the latter's progress may be followed acidimetrically.

The work-up is determined by the properties of the product. If it is not readily soluble in alcohol, it may be isolated by freezing out. Alternatively, the solvent is evaporated under vacuum and the residue, which still contains triphenylphosphine oxide and sodium halide, separated by distillation, crystallization, or chromatography. Readily soluble olefins are best extracted with cold low-boiling petroleum ether, in which the phosphine oxide is practically insoluble.

The alkoxide method allows the conversion of carbonyl compounds containing nitro, chloro, hydroxyl, and carboxylic ester functions to be effected without the application of special protective measures.

Preparation of Triphenylphosphineacyl- and Triphenylphosphinecarbalkoxymethylenes

As mentioned above, these phosphorus ylenes (VI or IX) occupy a special position inasmuch as they are inert towards water and hydroxyl ions. They are precipitated in crystalline form from an aqueous solution of their triphenylacyl- or triphenylcarbalkoxyphosphonium salts by the addition of alkali. Isler and his co-workers (*31*) recommend crystallization from acetic ester/petroleum ether for purification. They may be condensed with aldehydes by boiling in benzene (*31*), tetrahydrofuran (*10*), dioxane or some other inert solvent.

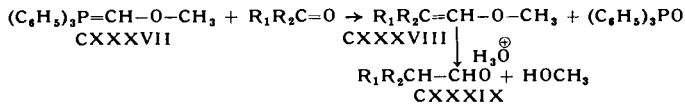
Triphenylphosphinecarbomethoxymethylene, $(C_6H_5)_3P \cdot CH \cdot COOH$ (*31*). Sodium hydroxide solution is added to a stirred solution of triphenylcarbomethoxymethylphosphonium bromide (LXIX, R=CH_3) (ca. 40 gm) in water (approximately 1 liter) until the mixture gives an alkaline reaction to phenolphthalein. The precipitated solid is filtered off, washed with water, dried over clay, and recrystallized from hot acetic ester by the addition of low-boiling petroleum ether. Colorless prisms are obtained, m.p. 162–163°.

The triphenylacylphosphonium salts can of course be made to react in alcohol according to the process mentioned earlier, with alkoxide or hydroxyl ions acting as the condensing agent.

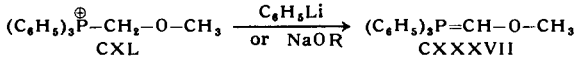
Appendix

A novel synthesis of aldehydes, devised simultaneously by Wittig (*63*) and Levine (*64*), deserves special mention; this allows the conversion of a carbonyl compound into an aldehyde possessing one more carbon atom. In this process, triphenylphosphinemethoxymethylene (CXXXVII) is allowed to react with a carbonyl compound to give an

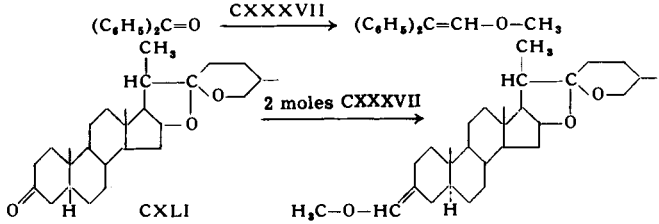
enol ether (CXXXVIII) which is then saponified to the desired aldehyde, CXXXIX.



The phosphinemethoxymethylene (CXXXVII), a deep-red compound, is obtained by a method described in the General Experimental section from triphenylmethoxymethylphosphonium chloride (CXL) and ethereal phenyllithium or alcoholic sodium alkoxide.



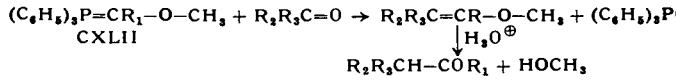
The yield of enol ether depends on the nature of the carbonyl compound. In the case of both benzophenone (*63*) and 5α,22β,25-D-spirostan-3-one (CXLI) (Tigogenone), for example, it amounts to approximately 85%.



In other instances, e.g. with benzaldehyde or acetophenone, yields of 40–50% were obtained.

As an example, the preparation of 1,1-diphenylvinyl methyl ether, $(C_6H_5)_2C{=}CH{-}O{-}CH_3$, is described below.

Ketones may be synthesized in a similar manner when CXXXVII is replaced by its derivatives substituted in the methylidyne group (CXLII).



This idea suggests itself by the fact that a large number of α-haloethers, required as starting material together with triphenylphosphine for the preparation of CXLII, are fairly readily accessible (*65*).

Triphenylmethoxymethylphosphonium chloride (*CXL*) (*63*). Chloromethyl ether (16.1 gm) is added to a solution of triphenylphosphine (52.4 gm, 0.2 mole) in absolute benzene (100 ml) and the mixture

heated for 60 hr at 50°. The thick, crystalline mass is filtered off, washed with ether, dissolved in chloroform and reprecipitated with acetic ester. The solid is washed with ether and dried overnight under high vacuum at 80°, yielding triphenylmethoxymethylphosphonium chloride (57 gm, 83%) m.p. 201–202°.

1,1-Diphenylvinyl methyl ether (63). A solution of phenyllithium (19.6 ml, 1.02 *N*) is added under nitrogen to a suspension of triphenylmethoxymethylphosphonium chloride (6.84 gm, 0.02 mole) in absolute ether (65 ml) contained in a Schlenk tube. On gentle warming, the mixture first becomes orange-red, and then dark red. After several minutes, a solution of benzophenone (3.64 gm, 0.02 mole) in ether (40 ml) is added portionwise, and the mixture starts to boil. A gray-brown precipitate separates, leaving the supernatant solution an orange-yellow color. After 2 hr the precipitate is filtered, washed with ether, and the ethereal solution washed with water and dried over potassium carbonate. The ether is evaporated and the residue distilled through a Vigreux column, b.p. 102–103°/high vacuum, yielding 1,1-diphenylvinyl methyl ether (3.45 gm, 82%), m.p. 38°.

Acknowledgment

I thank Prof. Dr. Dr. h. c. G. Wittig for numerous discussions and for making available unpublished material.

References

(1) G. Wittig, *Experientia* **12,** 41 (1956); *Angew. Chem.* **68,** 505 (1956).
(2) The nomenclature used here is due to H. Staudinger and J. Meyer, the discoverers of this class of compounds. A more recent proposal [*Chem. Eng. News* **30,** 1415 (1952)], prefers to regard these compounds as derivatives of the hypothetical phosphorane, PH_5, and to name them accordingly. Triphenylphosphinemethylene $(C_6H_5)_3P = CH_2$, would thus be designated as triphenylmethylenephosphorane or methylenetriphenylphosphorane.
(3) G. Wittig and G. Geissler, *Ann. Chem. Liebigs* **580,** 44 (1953).
(4) G. Wittig and U. Schöllkopf, *Chem. Ber.* **87,** 1318 (1954).
(5) G. Wittig and W. Haag, *Chem. Ber.* **88,** 1654 (1955).
(6) The preparation by G. Wittig and M. Rieber of pentaphenylphosphorus proves that phosphorus is capable of forming a ten-electron system [*Ann. Chem. Liebigs* **562,** 187 (1949)].
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(10) F. Ramirez and S. Dershowitz, *J. Org. Chem.* **22,** 41 (1957).
(11) I. T. Harrison and B. Lythgoe, *J. Chem. Soc.* p. 843 (1958).
(12) XVI was prepared by H. Staudinger and J. Meyer as far back as 1919 by the pyrolysis of triphenylphosphinebenzophenoneazine:
$$(C_6H_5)_3P{=}N{-}N{=}C(C_6H_5)_2 \rightarrow (C_6H_5)_3P{=}C(C_6H_5)_2 + N_2$$
[*Helv. Chim. Acta* **2,** 635 (1919)]. Other triphenylphosphinemethylenes can

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N-Bromosuccinimide, Its Properties and Reactions The Course of Substitution*

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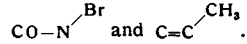
Introduction

The outstanding brominating ability of N-bromosuccinimide is due to four fundamental properties:

1. An almost nonpolar N—Br bond, allowing homolytic fission to give a Br atom.

2. Good agreement between the NBr—CO bond distance in N-bromosuccinimide and the C=C distance in olefins and aromatic compounds.

3. Similarity between the valency angles in



4. Planar structure of the N-bromosuccinimide molecule as a prerequisite for an exchange reaction at the surface of the N-bromosuccinimide crystal lattice.

In the case of allylic bromination in a heterogeneous system, N-bromosuccinimide acts in a free radical surface reaction. The course of the N-bromosuccinimide reaction can be substantially influenced by physical and chemical means:

1. The N-bromosuccinimide reaction can be catalyzed thermally, by UV light or the use of free radical generators (dibenzoyl peroxide, azoisobutyronitrile, and redox systems), and retarded or inhibited by free radical traps (quinone, oxygen, nitroso compounds, iodine, etc.). Activators considerably shorten the reaction times and suppress the formation of by-products.

2. The allylic bromination is activated by increasing the N-bromosuccinimide surface area (N-bromosuccinimide on neutral SiO_2).

3. Allylic bromination is associated with the surface of the N-bromosuccinimide crystals. N-Bromosuccinimide in solution no longer brominates in the allyl position, but adds bromine to the double bond.

4. If the standard conditions are adhered to, the "N-bromosuccinimide side reactions" are the subsequent reactions undergone by the thermolabile primary products, which can be stabilized by the elimination of HBr following a possible allylic rearrangement.

* No. XV in a series of studies dealing with the course of substitution (*1, 2*).

It was found possible to widen the applicability of N-bromosuccinimide as brominating agent to several classes of compounds, and to extend it to include new ones. The following rules may be derived from the data available:

1. Straight or branched-chain olefins with terminal or intermediate double bonds can be monobrominated only at an allyl position.

2. An olefinic double bond is capable of activating up to four allyl positions with respect to bromination by N-bromosuccinimide.

3. In the case of mono- and bicyclic olefins, the second bromine is introduced in the other, as yet free, allyl position in the same ring system.

4. In methylated aromatic compounds, a maximum of two hydrogen atoms in any one methyl group can be replaced by bromine under the action of N-bromosuccinimide, less if that group is sterically hindered.

5. The bromination is rendered more difficult if: (a) N-bromosuccinimide dissolves in the substance to be brominated; (b) the allyl position is screened by bulky substituents; (c) the angle between the double bond and the allyl position deviates widely from 120°; or (d) the allyl position is polarized by NO_2, CN, SO_2, or C≡C.

6. Tertiary aliphatic amines and ethers are brominated in the vicinity of the heteroatom. The highly reactive primary products are hydrolyzed into aldehydes and secondary amines or alcohols, respectively.

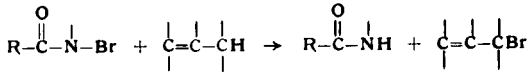
7. Mixed aliphatic–aromatic amines and ethers are selectively brominated in good yield in the *p*-position. In the case of tertiary aromatic amines, the bromine enters in the *p*-position; aromatic ethers and thioethers are not attacked by N-bromosuccinimide.

8. The ratio of ring: side chain bromination in heterocycles can be controlled by the presence or absence of free radical activators.

9. The activating effect of various substituents on N-bromosuccinimide allylic bromination is discussed.

General Discussion

Wohl (*3*) was the first to observe the interchangeability of the bromine atom of N-bromoacetamide with the hydrogen in an allyl position.



In the course of the last 15 years, however, it is N-bromosuccinimide (I),

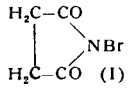


TABLE 1

N-Br Compounds and Their Suitability in the Bromination of Cyclohexene (7)

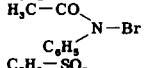
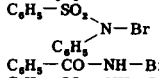
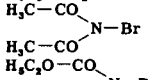
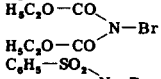
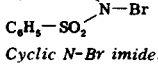
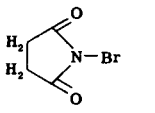
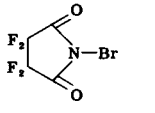
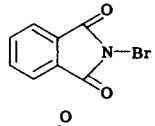
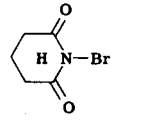
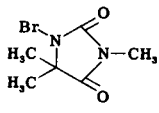
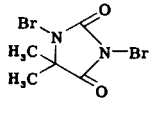
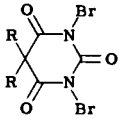
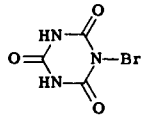
N-Halo compound	Br (%)	Type of reaction[a]			Remarks, literature refs.
		Allylic substitution	Addition to C=C	1:1 Adduct	
N-Br amides and open-chain imides		A	B	C	
$H_3C-CO-NH-Br$	58.0	++	++	–	(*3, 9, 68*)
$ClCH_2-CO-NH-Br$	46.5	+	+	–	(*9*)
$F_3C-CO-NH-Br$	46.5	–	++	+	(*9*)
$H_5C_2O-CO-NH-Br$	47.6	–	–	–	Could not be prepared (*2*)
	37.4	+	+++	?	(*4*)
	32.0	(+)	(+++)	(+)	Analogous to the N-Cl compound (*4, 98*)
$C_6H_5-CO-NH-Br$	40.0	(+)	(+++)	?	No accurate data (*4*)
$C_6H_5-SO_2-NH-Br$	33.9	(+)	(+++)	(+)	No accurate data (*4, 98*)
	44.5	–	+++	–	Could not be isolated (*2, 68*)
	33.3	–	+++	–	Could not be isolated (*2*)
	21.3	(+)	(+++)	(+)	(*4*)
Cyclic N-Br imides					
	44.9	+++	(+)	–	(*2, 4, 5, 8, 12, 13, 21, 22, 23, 25, 47, 63, 68, 118*)
	32.0	–	+++	–	(*107*)
	35.4	++	++	–	(*4*)
	41.6	(–)	?	?	No accurate data (*4*)
	36.2	+++	?	?	(*136*)
	56.0	+++	(+)	?	(*118*)

TABLE 1 (*continued*)

N-Halo compound	Br (%)	Type of reaction[a]			Remarks, literature refs.
		Allylic substitution	Addition to C=C	1:1 Adduct	
Cyclic N-Br imides (cont'd)					
	46.8	(+)	(++)	?	(*4*)
	38.5	–	+++	?	The tri-N-Br deriv. could not be prepared (*2, 4, 95*)
Trisubstituted bromomethanes					
$(CH_3)_3CBr$	58.3	–	–	–	C–Br too stable (*2*)
$(C_6H_5)_3CBr$	24.4	–	–	–	
$(H_5C_2OCO)_3CBr$	25.7	+	(+)	–	(*2*)
$(NC)_3CBr$	47.0	?	?	?	Preparation difficult
$(Cl_3C)_3CBr$	17.9	–	(–)	+	C–Br too unstable (*124*)
$(NO_2)_3CBr$	34.8	–	(–)	+	

[a] Brominating ability: – None 0%; + Low 10 – 20%; ++ Fair ca. 50%; +++ Good to very good 50 – 100%

introduced by Ziegler and his co-workers (*4*), which has become of indispensable assistance to the preparative organic chemist (*4a*). Djerassi (*5*) and Waugh (*6*) presented comprehensive reviews of N-bromosuccinimide and its reactions in 1948 and 1951, respectively. Since that time, however, an abundance of fresh observations have been made and these are collected here together with some of the older material. We were concerned less with giving a complete survey of the literature than with presenting the more important reaction characteristics.

Preparation and Brominating Properties of Other N-Bromoimides

In his fundamental work on new methods of halogenation, K. Ziegler synthesized a large number of N-halogen compounds which he examined for their ability to substitute in the allyl position (*4*).

Table 1 gives a survey of these and more recent futile efforts at discovering a brominating agent more effective than N-bromosuccinimide (*2*).

No N-chloro, N-iodo, N-nitro (*8*), or N-cyano compound has so far been found useful in allylic substitiution.

Reasons for the Unique Characteristics of N-Bromosuccinimide

The ability of bromoamides to substitute in the allyl position depends basically on the nature of the mono- or dicarboxylic acid from which the

amide is derived. In the bromoamides of strong acids the tendency to release positive bromine is increased, with a concurrent disappearance of the allylic substitution ability.

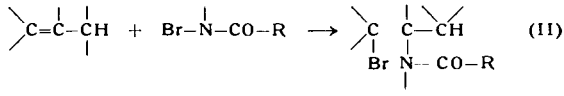
This connection is illustrated by a comparison between Tables 1 and 2.

TABLE 2

Dependence of the Polarity of the N-Br Bond on the Acidity of the Mono- and Dicarboxylic Acids

Mono- and dicarboxylic acids	Dissociation constant, k		Acidity of amide and imide	Type of N-Br bond
	Stage I	Stage II		
Trichloroacetic acid	$1.3 \cdot 10^{-2}$	–	Strong	Strongly polar
1,2-Tetrafluorosuccinic acid	?	?		
1,2-Dibromosuccinic acid	$3.4 \cdot 10^{-2}$	$1.6 \cdot 10^{-3}$		
Phthalic acid	$1.0 \cdot 10^{-3}$	$4.7 \cdot 10^{-6}$	Medium	Fairly polar
Glutaric acid	$4.5 \cdot 10^{-3}$	$3.8 \cdot 10^{-6}$		
Acetic acid	$1.8 \cdot 10^{-5}$	–		
Benzoic acid	$6.8 \cdot 10^{-5}$	–		
Succinic acid	$6.4 \cdot 10^{-5}$	$3.3 \cdot 10^{-6}$	Fair	Hardly polar
Hexahydrophthalic acid	$4.6 \cdot 10^{-5}$	$1.7 \cdot 10^{-7}$		
Diethylbarbituric acid	$3.7 \cdot 10^{-8}$	–		

The tendency of the bromoamide to add to the olefinic double bond rises with increasing polarity of the N—Br bond. 1,1-Adducts (II) of this type have in some cases been isolated (*4, 9*); they are particularly readily formed from the polar N-bromosulfonamides or imides (*4, 10*).



(II)

Unlike in compounds of this type, the N—Br bond in N-bromosuccinimide possesses but a small dipole moment; it is almost nonpolar (*11*).

This property is a result of the weak acidity of succinic acid and is an important cause of the largely nonpolar, i.e. free radical, nature of the bromine transfer (*5, 12–14*).

As seen in Table 3, the dipole moment of the N–halogen bond is significantly larger in both N-chlorosuccinimide and N-iodosuccinimide.

The exceptional ability of N-bromosuccinimide to brominate in the allyl position is very likely due to its spatial arrangement: It has a planar structure (*15*), the N—C distance in the amide group is 1.3Å like the C—C distance of an olefinic double bond and the

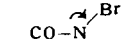


TABLE 3
Dipole Moments of N-Halosuccinimides

	Dipole moment of the haloimide	Dipole moment of the N-X bond, calculated for	
		Trigonal arrangement	Pyramidal arrangement
N-Chlorosuccinimide	2.86	1.04	1.4
N-Bromosuccinimide	2.10	0.30	0.4
N-Iodosuccinimide	0.97	0.80	1.5

angle approximates closely to that of



This body of common structural characteristics is the reason why the bromine is placed in ideal spatial proximity to the allyl hydrogen following the initial adsorption of the olefinic double bond into the vicinity of the amide, thus facilitating the exchange. These considerations are supported by the following observations:

1. N-Bromosulfonamides or imides are poor halogen-carriers for effecting substitution in the allyl position. Apart from the increased polarity of the N—Br bond, the N—SO_2 distance (1.75Å) differs by more than 0.4Å from that of the C=C double bond.

2. The close agreement of the angular relationship no longer holds in the case of derivatives of cyclobutane, cyclopropane, and acetylene. N-Bromosuccinimide accordingly attacks cyclobutene only with difficulty (*16*), cyclopropane derivatives with concomitant ring-opening (*17*), and 1-hexyne (*2*) and tetrolic ester (*18*) not at all. As anticipated, cyclopentane derivatives are very readily brominated.

The spatial arrangement of the substance to be brominated also exerts a definite influence on the course of the reaction. Thus the action of N-bromosuccinimide on isopropylbenzene results almost exclusively in ring-bromination, even if free radical activators are used (*19*); 1,2-dimethylnaphthalene can only be converted into 1-ω-bromomethyl-2-ω-dibromomethylnaphthalene (*2,20*) and durene into a heptabromo compound (*20*). 9,10-Di(ω-bromomethyl)phenanthrene and ω,ω,ω′,ω′-tetrabromo-*p*-xylene, on the other hand, are stable to N-bromosuccinimide but can be substituted further by bromine (*2*).

N-Bromosuccinimide Activators

In his basic work on N-bromosuccinimide Ziegler (*4*) developed a number of ideas concerning its mechanism of action; it is only more recently, however, that observations have been reported by different

TABLE 4
Effect of Activators

Activating agent	Reaction[g] Time	Temp. (°C)	Yield (%)	Activating agent	Reaction[g] Time	Temp. (°C)	Yield (%)
	Monobromination				*Dibromination*[a]		
UV[a]	4 hr	25	>25	UV[c]	5 hr	25	30
none[b]	1 hr	80	~50	UV + Azoisobutyronitrile[c,d]	3 hr	25	30
SiO_2[a,e]	45 min	80	~50	none	2 hr	80	~50
Dibenzoyl peroxide[d]	30 min	80	>50	SiO_2[e]	1.5 hr	80	~50
Azoisobutyronitrile[d]	10 min	80	75	Dibenzoyl peroxide[d]	30 min	80	>50
				tert-Butyl hydroperoxide[d]	30 min	80	>50
				Azoisobutyronitrile[d]	15 min	80	>50
				tert-Butyl hydroperoxide + Co^{2+}[f]	10 min	80	~70
				tert-Butyl hydroperoxide + Cu^{2+}[f]	7 min	80	~70

[a] See ref. (*2*).

[b] See ref. (*4*).

[c] UV = Irradiation in a quartz vessel by a Hanau S 81 quartz lamp.

[d] Dibenzoyl peroxide, Azoisobutyronitrile, *tert*-Butyl hydroperoxide } 1/100 mole calculated with respect to N-bromosuccinimide.

[e] SiO_2 = N-Bromosuccinimide on a SiO_2 carrier in the molecular proportion 1:2-4.

[f] Co^{2+} and Cu^{2+} = Heavy metal salts (laurates) as partners in the redox catalysis.

[g] Reaction time: Measured from the start of the reaction (excluding the induction period) until the N-bromosuccinimide is quantitatively converted. Reaction temperature: Room temperature or boiling CCl_4. The yields quoted refer to an average of reproducible yields. In the case of 3,6-dibromocyclohexene in particular they are much higher, but its isolation frequently presents difficulties on account of its ready solubility. In contradiction to ref. (*4*) cyclohexene can be dibrominated directly. The dibromide is also formed in yields of over 30% from the monobromide within 10 minutes at 80°.

authors (*2, 12–14, 21–24*) which suggest a free radical mechanism for the allylic bromination. Under special conditions N-bromosuccinimide appears nevertheless to be capable of reacting in polar form, adding bromine directly to the double bond or introducing it directly into the ring in the case of aromatic compounds (*2, 13, 22, 24–27*).

A number of systems which promote allylic substitution will now be discussed.

Karrer (*21*) and Schmid (*27*) were the first to observe the accelerating effect of homolytically dissociating dibenzoyl peroxide on the allylic bromination. Other free-radical–generating substances, such as azoisobutyronitrile (*14*) also promote allylic substitution. The two redox systems, *tert*-butyl hydroperoxide and cobaltous or cupric laurate have been found particularly effective, and produce free radicals even at low temperatures (*2*). The relatively high dissociation temperature (30° above the boiling point of CCl_4) of dibenzoyl peroxide has a rather detrimental effect; the reactions with N-bromosuccinimide then frequently set in spontaneously and can only be controlled with difficulty. Its use is nevertheless advisable in the case of sensitive alkylaromatic compounds or substances not readily brominated (*20*). Azoisobutyronitrile is suited to the bromination of sensitive olefins on account of its relatively low dissociation temperature. The above-mentioned redox systems are more effective still and their use results in even and rapid reactions. Classical free radical generators like hexaphenylethane and tetraphenylhydrazine are not suitable (*2*). The free radical nature of the N-bromosuccinimide reaction is confirmed by the inhibiting effect of substances such as iodine, quinones, oxygen (*28*), nitrosobenzene, picric acid, etc. (*14*), which also act as radical traps in other free radical reactions. Many reactions with N-bromosuccinimide proceed purely thermally however (*4*), though it is still questionable whether traces of peroxide are not active. UV light also activates the reaction between N-bromosuccinimide and olefins (*28, 29*) and already initiates a reaction at 25° (*2*). Photoactivation alone is unfavorable from a preparative point of view, however, on account of the long reaction time and the formation of by-products. It is not surprising in this connection that telomers are also formed in this reaction with N-bromosuccinimide in CCl_4 (*2*). Table 4 gives a qualitative survey of the action of a few activators.

The use of free radical activators results in the bromination of cyclohexane (*14*) and the incorporation of benzene in the form of a phenyl group attached to the nitrogen of the succinimide (*16*).

Allylic Bromination by N-Bromosuccinimide—A Free Radical Surface Reaction

As has long been known, CCl_4 is a particularly suitable reaction medium for allylic brominations (*4*). This is somewhat surprising, inas-

much as N-bromosuccinimide is only slightly soluble in CCl_4. In fact, the disappearance of the dense N-bromosuccinimide from the bottom of the flask and the appearance of the lighter succinimide on the surface is considered a reliable criterion for the completion of the reaction (*4*). This state of affairs and general considerations concerning the probability of independent free radicals existing in solution have prompted us to investigate the effect of the N-bromosuccinimide surface area on the rate of reaction with cyclohexene. If, for example, N-bromosuccinimide is put on an "inert" carrier such as neutral kieselguhr (Merck) (alumina, CaO, MgO, etc. were unsuitable), with the proportion of N-bromosuccinimide: SiO_2 = 1:2–4, a moderate increase in the rate of both the mono- and dibromination of cyclohexene is observed (see Table 4). This process is unfavorable from the preparative point of view, however, due to the large quantities of SiO_2 and considerable volume of solvent required, with the consequent dilution of the reactants. Reduction of the surface—effected, e.g., by growing larger crystal aggregates by recrystallizing from water—manifests itself in a lowered activity (*2*). This loss in activity cannot be made good by pulverization. The method of preparation proposed by Ziegler (*4*) has the advantage of developing a large surface area, which then results in increased activity. If the surface of N-bromosuccinimide is reduced to zero by solution in a suitable polar solvent such as tetrachloroethane or nitromethane, the allylic bromina-

TABLE 5

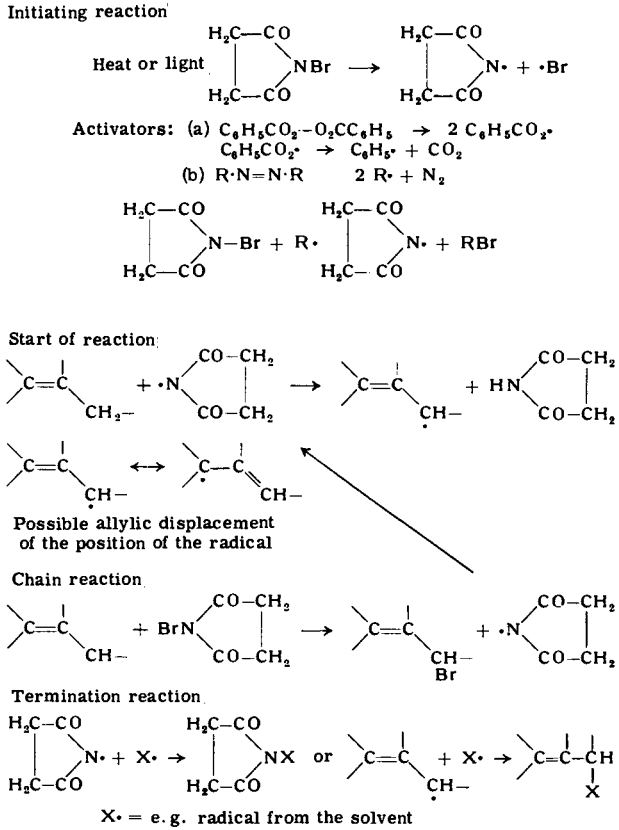
Influence of the Solubility of N-Bromosuccinimide on the Course of the Reaction

Solvent	Dipole moment μ (in debye units)	Solubility	Remarks
CCl_4	0.00	Almost insol.	Ideal reaction medium (*2*, *4*)
	0.00	Hardly sol. at b.p.	Suitable in the presence of reactive partners
	0.00	Slightly sol. at b.p.	
$Cl_2C{=}CHCl$	0.94	Partially sol., depending on b.p.	Usable, but with strong reservations (*2*, *13*, *42*, *61*)
$BrCH_2CH_2Br$	1.03		
$CHCl_3$	1.10		
CH_2Cl_2	1.57		
C_6H_5Cl	1.69		
$Cl_2CHCHCl_2$	1.90	Completely soluble, partly at room temp.	Completely unsuited to allylic bromination (*2*). N-Bromosuccinimide reacts like Br_2
	2.23		
CH_3CN	3.40		
CH_3NO_2	3.54		
$C_6H_5NO_2$	3.95		

tion activity disappears (*2*) and the addition of bromine to the double bond becomes the main reaction (*2*).

Table 5 shows the effect of the dielectric constant of the solvent on the allylic bromination. The list of solvents is restricted to those with which N-bromosuccinimide will not react even on heating.

The results of the three preceding sections are represented in the following reaction scheme. It must, however, be stated explicitly that in contrast to previous formulations (*5, 12–14*), the allylic bromination in nonpolar solvents takes place at the crystal surface of N-bromosuccinimide and that independent free radicals do not come into operation. It is therefore a free radical chain reaction which occurs at the crystal lattice; the exchange of material may be controlled by the rate of diffusion of the substrate to and from the surface.



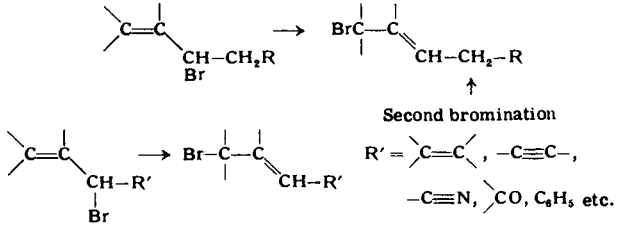
An attempt at formulating a possible three-dimensional free radical chain reaction in the crystal surface was hazarded by E. H. Winkelmann

(*2*) in his dissertation. More definite assertions are not possible, however, until more is known of the crystal structure of N-bromosuccinimide. It may nevertheless be assumed that the shifting of the reaction to the crystal lattice surface and the consequent lack of solvation considerably reduce the energy of activation. The allylic bromination with N-bromosuccinimide also deserves special attention as a model for many enzyme reactions.

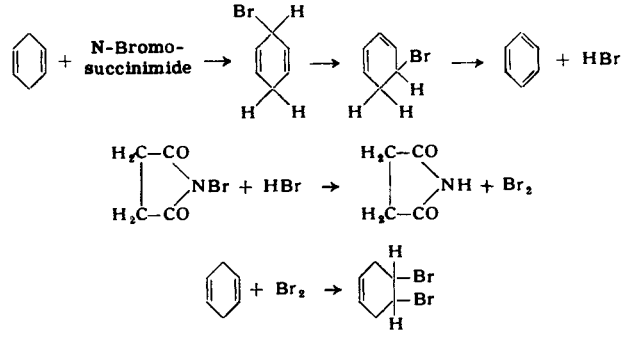
Side Reactions of N-Bromosuccinimide

In heterogeneous N-bromosuccinimide reactions, rearrangement of the "allyl bromides" formed gives rise to two types of secondary reaction.

The first type consists of an allylic rearrangement (*30, 31*) accelerated by the tendency to conjugate with possible neighboring multiple bonds. Olefins containing terminal double bonds and diolefins with isolated double bonds are particularly vulnerable to this effect (*2, 13, 22, 32, 34, 35*). The introduction of a second bromine atom following an allylic rearrangement is greatly facilitated by the presence of an excess of N-bromosuccinimide.



The second type of side reaction consists in the elimination of hydrogen bromide from the rearranged "allyl bromides." This elimination occurs the more readily if further conjugation of double bonds or aromatization results (*2, 13, 22, 30, 33–37*). The HBr formed abstracts bromine



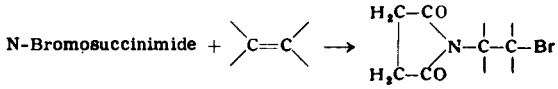
from N-bromosuccinimide (*38*) and the halogen immediately adds to the alkene produced or the as yet unreacted starting olefin. If the temperature of the HBr elimination is not substantially higher than that of the allyl bromide formation, this reaction proceeds quantitatively; two end products invariably result: the higher olefin or aromatic compound and the bromine-addition compound (ratio 1:1).

The two side reactions are very frequently encountered; low reaction temperatures and effective activation keep them in check but cannot obviate them entirely (*2*, *39*, *40*).

Further Reactions of N-Bromosuccinimide

Depending on the reaction medium and the nature of the substrate, a series of reactions have been discovered which may be classified into four groups.

Formation of 1:1 Adducts



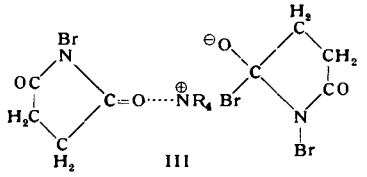
From the findings of Lumbroso (*11*), it is hardly surprising that this addition takes place chiefly in polar media, in which the N—Br bond reacts in the polarized form.

Addition of Bromine to the Olefinic Double Bond

This addition (which sometimes occurs to the extent of quantitative N-bromosuccinimide conversion) may be caused by a series of reaction conditions and reactants.

Reactions in fused N-bromosuccinimide (*4*) involve partial autobromination.

Solutions of N-bromosuccinimide in polar solvents react "abnormally" in the sense of bromine addition to the olefinic double bond. No definite assertion can as yet be made regarding the mechanism of this reaction. Bromine also adds to the olefinic double bond in the presence of alumina, activated charcoal (*2*), and sulfur powder (*26*). The addition of bromine



can be initiated by small quantities of alkyl halides (*22*) or quaternary ammonium salts (*13*). A well-defined N-bromosuccinimide-salt adduct III was isolated. Lewis acids also catalyze the addition of bromine via intermediates of possible composition IV (*25*).

Bromine is liberated from N-bromosuccinimide by water (present in not absolutely anhydrous solvents) (*41*), aliphatic alcohols (present as stabilizers in chloroform) (*42*), *o*- and *p*-dihydroxyphenols (present as stabilizers and polymerization inhibitors) (*22*), and strong acids (*25, 38, 43, 44*); the bromine thus liberated then adds to double bonds.

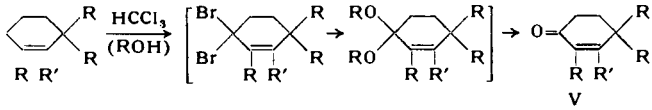
If N-bromosuccinimide is allowed to react with olefins in the presence of an adequate amount of water, bromohydrins are formed (*41, 45*).

Cyanoacetic acid undergoes decarboxylation and dibromination (*46*).

$$NC{-}CH_2{-}CO_2H \rightarrow NC{-}CHBr_2 + CO_2$$

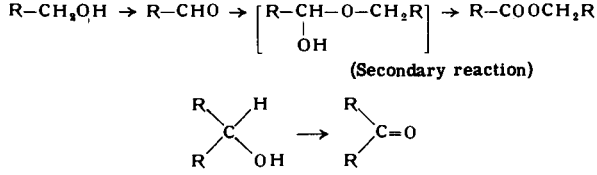
Oxidation Reactions with N-Bromosuccinimide

In the carotenoid series, the action of N-bromosuccinimide on alcohol-containing chloroform solutions yields ketones, e.g., V (*42*).



V

Primary and secondary (not tertiary) alcohols are oxidized to the aldehydes (acetals and esters) and ketones (*47–55*).



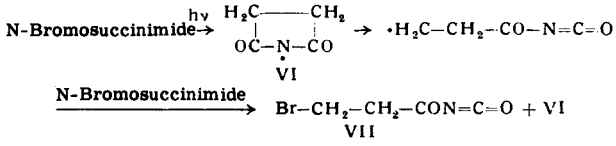
The formation of brominated ketones (by elementary bromine from N-bromosuccinimide + HBr) is avoided by effecting the reaction in the presence of $CaCO_3$ or pyridine (*56*).

The following are oxidized in the same manner: α-hydroxycarboxylic acids (*50, 54*), α-hydroxycarboxylic esters (*52*), α-aminocarboxylic acids (*48, 55*), mercaptans and thiophenols (*57*), *tert* amines to *sec* amines + aldehyde (*2, 58*) (oxidative dealkylation), ketoximes (*59*), hydrazines and hydrazones (*54*), formazans to tetrazolium salts (*60*). Malic acid, tartaric acid, citric acid, etc. are converted into aldehydes and ketones, while polyhydroxy alcohols (glycol, glycerol, and hexitols) are quantitatively decomposed to carbon dioxide and water (*57*).

Photolysis of N-Bromosuccinimide

Exposure of a solution of N-bromosuccinimide in chloroform to light in the presence of allyl halides results in the unexpected transformation into its isocyanic acid derivative, VII (*61,62*).

J. C. Martin and P. D. Bartlett propose the following plausible scheme for the reaction:



The part played by the allyl halide is as yet not understood.

Survey of the Reactivity of N-Bromosuccinimide

Although an impressive collection of empirical material has been gathered since the introduction of N-bromosuccinimide in preparative organic chemistry, its synthetic possibilities are by no means exhausted. An attempt is now made to sketch a general picture of the use of this reagent and to draw attention to existing gaps.

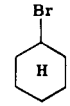
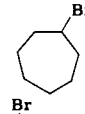
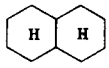
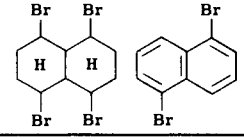
Aliphatic and Alicyclic Hydrocarbons

Until recently, nothing was known regarding the action of N-bromosuccinimide on saturated aliphatic hydrocarbons. Alicyclic hydrocarbons such as cyclohexane and decalin undergo bromination in the presence of free radical initiators. Cyclohexane is converted into the monobromide, and decalin into 1,4,5,8-tetrabromo-9,10-octalin via 9-bromodecalin and 9,10-octalin (*2,33*). (See Table 6.)

Mono- and Diolefins

This class of compounds was thoroughly investigated by Ziegler, so that we ourselves merely undertook orienting and complementary experiments. Ziegler also discovered the first regularities and drew up the first rules governing the ability of N-bromosuccinimide to brominate mono- and diolefins. According to this, methylene groups in the allyl position are more readily brominated by N-bromosuccinimide than are methyl groups, and these more readily than methylidyne groups. The difference between the last two groups is usually not very great. This order of succession largely loses its validity, however, if activators are used. Straight-chain and branched olefins can only be monobrominated in one allyl position by N-bromosuccinimide, irrespective of the location of the double bond (terminal or intermediary). Thus allyl bromide, for ex-

TABLE 6
Reactions of N-Bromosuccinimide with Aliphatic and Alicyclic Hydrocarbons

Starting compound	Moles of *N*-bromo-succinimide	Reaction type [a] / Reaction time	Stable end product isolated	Yield (%)	Lit. ref.
$CH_3-CH_2-C(CH_3)_2-Br$	1 Dibenzoyl peroxide	A	$CH_3-CH(Br)-C(CH_3)_2-Br$	20	(*3,63*)
	1 Azoisobutyronitrile	A 20 min		48	(*14,63*)
	1 Dibenzoyl peroxide	A		30	(*63*)
	4 Dibenzoyl peroxide	A/C 20 min		14/9	(*33,63*)

[a] A = Allylic bromination. C = Elimination of HBr and secondary reactions.

ample, cannot be brominated further (*53*). On the other hand, one double bond renders up to a maximum of 4 allyl positions vulnerable to attack by N-bromosuccinimide, as could be shown in the case of tetramethylethylene and 9,10-octalin. HBr can be eliminated thermally or with bases (N-dimethylaniline, quinoline, alkali acetate, etc.) from most allylic-brominated olefins. Ziegler recognized and developed this method of preparing conjugated dienes (*4*). The elimination of HBr from cyclic olefins proceeds even more readily. Trienes, however, are difficult to obtain by this route (*4*).

Certain diolefins exhibit peculiar behavior under the action of N-bromosuccinimide. Thus diallyl (*32,34*) and 2,3-dimethylbutadiene (*2,64*) undergo bromination in only one allyl position, accompanied by a partial allylic rearrangement. The action of 2 moles of N-bromosuccinimide on diallyl results in a double allylic rearrangement to give 1,6-dibromo-2,4-hexadiene (*32,34*) while with 2,3-dimethylbutadiene an abnormal reaction results, yielding 1,4-dibromo-2,3-dimethyl-2-butene (*2,64*).

Alicyclic Olefins

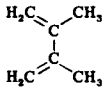
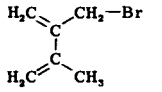
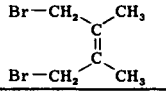
This class of compounds was also thoroughly examined. The readily accessible cyclohexene served as a good test substance in the investigations first of Ziegler (*4*) and subsequently of others (*10, 14, 33, 65–68*),

TABLE 7

Reactions of N-Bromosuccinimide with Olefins

Starting compound (Ph = Phenyl)	Moles of N-bromo-succinimide	Reaction type[a] / Reaction time	Stable end product isolated	Yield (%)	Lit. ref.
$H_2C{=}CH{-}CH_2{-}C_3H_7$	1 Azoisobutyronitrile	A/B 30 min	$H_2C(Br){-}CH{=}CH{-}CH_2{-}C_2H_5$	30	(2, 13)
			$H_2C{=}CH{-}CH(Br){-}C_3H_7$		
	2 Azoisobutyronitrile	B 15 min	$H_2C(Br){-}CH{=}CH{-}CH(Br){-}C_2H_5$	50	
$H_2C{=}CH{-}CH_2{-}C_5H_{11}$	1	A/B ?	$H_2C(Br){-}CH{=}CH{-}CH_2{-}C_4H_9$	44	(4, 82)
			$H_2C{=}CH{-}CH(Br){-}C_5H_{11}$	17	
	2	B ?	$H_2C(Br){-}CH{=}CH{-}CH(Br){-}C_4H_9$	?	
$CH_3{-}CH{=}CH{-}CH_2{-}C_3H_7$	1 Benzoyl peroxide	A 2 hr	$CH_3{-}CH{=}CH{-}CH(Br){-}C_3H_7$	76	(102)
$H_2C{=}C(CH_3){-}CH_2{-}C(CH_3)_2{-}CH_3$	1	A 5 hr	$[H_2C{=}C(H_3C,Br){-}CH{-}C(CH_3)_2{-}CH_3]$	68	(4)
$(H_3C)_2C{=}CH{-}CH_3$	1	A 16 hr	$(H_3C)_2C{=}CH{-}CH_2{-}Br$	40	(4)
$(H_3C)_2C{=}CH{-}CH_2{-}C_2H_5$	1	A 10 min	$(H_3C)_2C{=}CH{-}CH(Br){-}C_2H_5$	40	(4)
$Ph{-}CH{=}CH{-}CH_3$	1	A 16 hr	$Ph{-}CH{=}CH{-}CH_2{-}Br$	75	(4)
$Ph{-}CH_2{-}CH{=}CH_2$	1 Benzoyl peroxide	A/B 2 hr	$Ph{-}CH{=}CH{-}CH_2{-}Br$	50	(13, 84)
	1	A ?	$Ph{-}CH(Br){-}CH{=}CH_2$	10	
$Ph{-}C(CH_3){=}CH_2$	–	–	$Ph{-}C(H_2CBr){=}CH_2$ $Ph{-}C(H_3C,Br){=}CH$	75/25	(120)
$(Ph)_2C{=}CH{-}CH_3$	1	A 18 hr	$(Ph)_2C{=}CH{-}CH_2{-}Br$	86	(4)
$H_2C{=}CH{-}CH_2{-}Br$	1	–	No reaction	–	(61)
$Ph{-}CH{=}CH_2$	1	–	No reaction	–	(4, 68, 88, 109)
$H_2C{=}CH{-}CH_2$ / $H_2C{=}CH{-}CH_2$	1 Benzoyl peroxide UV	A 8 hr	$H_2C(Br){-}CH{=}CH{-}CH_2$ / $H_2C{=}CH{-}CH_2$	-/45	(32)
			$H_2C{=}CH{-}CH(Br){-}CH_2$ / $H_2C{=}CH{-}CH_2$	70/10	(34, 83)
	2 Benzoyl peroxide UV	B 6 hr	$H_2C(Br){-}CH{=}CH$ / $H_2C(Br){-}CH{=}CH$	52	(32)

TABLE 7 (*continued*)

Starting compound (Ph = Phenyl)	Moles of N-bromo-succinimide	Reaction type [a] / Reaction time	Stable end product isolated	Yield (%)	Lit. ref.
	1	A 3 hr		20	(*2, 4, 64*)
	2	B 2 hr		40	(*64*)

[a] A = Allylic substitution. B = Allylic bromination and allylic rearrangement.

e.g. in the comparison of the reactivity of various bromoamides (*2, 4*) or of the effect of activators (*2, 14, 33*). The same rules apply to the cycloölefins as to the olefins; methylene groups react more readily than methyl groups. Ziegler's idea (*4*) of the different resistances shown by various intermediate adducts (N-bromosuccinimide + cyclohexene, and N-bromosuccinimide + 3-bromo-1-cyclohexene) and the consequent difference in the rate of the second bromination is not substantiated (*2*). Mono-, di-, and tetrabromination with N-bromosuccinimide in the absence of activators proceed at approximately the same rate. The second bromination invariably occurs in the same ring, namely in the second, as yet free, allyl position. Only in the event of the latter's being occupied are other allyl positions in different rings brominated (cf. 9,10-octalin) (*2*).

Cyclic olefins can be dibrominated in one allyl position by N-bromosuccinimide.

These products are thermolabile, however, and cannot be isolated as they undergo an allylic rearrangement and HBr elimination to give stable end products (e.g. cyclohexene forms *m*- and *p*-dibromobenzene) (*2, 33*). Polybromination of cyclohexene clearly proceeds only as far as 3,6-dibromo-1-cyclohexene (*2*). Tetralin gave the extremely thermolabile 1,1,4,4-tetrabromide which was isolated and is readily aromatized to 1,4-dibromonaphthalene via a double HBr elimination (*2*). 1,4,5,8-Tetrabromo-9,10-octalin strongly resists the entry of more bromine but does finally yield 1,5-dibromonaphthalene (*2, 33*). Inspection of models reveals that steric factors are responsible for this reduced reactivity.

The reasons for the increased difficulties in introducing bromine into cyclobutene and methylenecyclobutane (*16*) have been discussed earlier; cyclic diolefins also exhibit an unusual behavior towards N-bromosuccinimide. 1,3-Cyclohexadiene is not attacked by N-bromosuccinimide (*2, 4*), while 1,4-cyclohexadiene is monobrominated (*40*); the secondary reactions mentioned earlier follow immediately, however, resulting in the

TABLE 8

Reactions of N-Bromosuccinimide with Cyclic Olefins

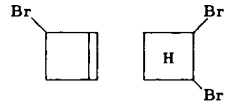
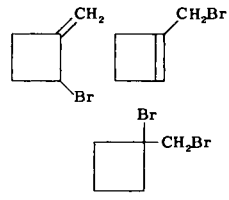
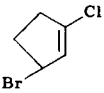
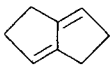
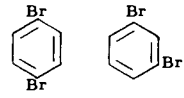
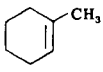
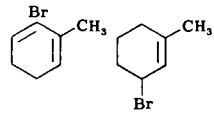
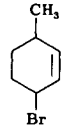
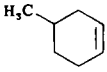
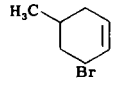
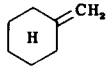
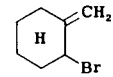
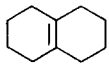
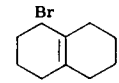
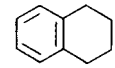
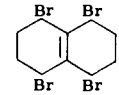
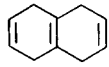
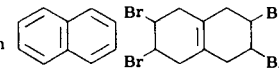
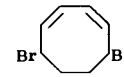
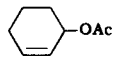
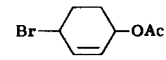
Starting compound	Moles of N-bromo-succinimide	Reaction type / Reaction time	Stable end product isolated	Yield (%)	Lit. ref.
	1 Dibenzoyl peroxide	A/C 6 hr		1/67	(*16*)
	1 Dibenzoyl peroxide	A/B/C 6 hr		14/2 57	(*16*)
	1	A ?		?	(*115*)
	2 Dibenzoyl peroxide	? 3 hr	Dibromide	?	(*110*)
	1 Azoisobutyronitrile	A 10 min		75	(*2, 4, 9, 14, 65, 66, 68*)
	4 Azoisobutyronitrile	A/C 10 min		10/30	(*2, 33*)
	1	A		–	–
	1	A		–	(*115*)
	1	A		–	(*115*)
	1	A		–	(*115*)

TABLE 8(*continued*)

Starting compound	Moles of N-bromo-succinimide	Reaction type / Reaction time	Stable end product isolated	Yield (%)	Lit. ref.
	1	A		-	(*115*)
	1	A 5 min		80	(*2*)
	2	C 5 min		50	(*2, 33*)
	4 Dibenzoyl peroxide	A 5 min		>30	(*2, 33*)
	1	C		?	(*4*)
	?	?		?	(*108*)
	1	C 6 hr	 	1:1	(*40*)
	2	C 6 hr	 	30/20	(*10*)
	2 Dibenzoyl peroxide	C 5 min		1:1	(*2*)
	1 Dibenzoyl peroxide	A 1 hr		57	(*69*)
	2 Dibenzoyl peroxide	B 1 hr		34	(*69*)
	1	A 30 min		58	(*4*)

formation of equal amounts of benzene and 4,5-dibromo-1-cyclohexene. Isotetralin is correspondingly converted into naphthalene and 2,3,6,7-tetrabromo-9,10-octalin (*2*). 1,5-Cycloöctadiene behaves analogously to diallyl; it undergoes a double allylic rearrangement to give 1,4-dibromo-5,7-cycloöctadiene (*69*). Cycloöctatetraene behaves like an aromatic compound and does not react with N-bromosuccinimide in the absence of activators (*2*).

Mono- and Polycyclic Aromatic Compounds

The field of aromatic and alkylaromatic compounds may be regarded as closed.

N-Bromosuccinimide does not attack benzene; it brominates naphthalene in position 1, and anthracene and phenanthrene in position 9. In methylated or more highly alkylated aromatic compounds the CH_3 or CH_2 group, respectively, corresponds to the allyl position. This "benzyl position" is generally more strongly activated by the aromatic nucleus than most other allyl positions. In this class of compounds N-bromosuccinimide also reacts more readily with CH_2 groups than with CH_3 or CH groups. Here also, the differences in activity are effaced by the use of activators. Thus, under the action of N-bromosuccinimide, toluene, and 1- and 2-methylnaphthalene will admit up to two bromine atoms in the methyl group before side reactions are observed. Unlike bromine, N-bromosuccinimide does not succeed in perbrominating the methyl group.

If an alkyl group is activated by several phenyl rings, the bromination proceeds particularly readily; this is illustrated by reactions with diphenyl- and triphenylmethane and fluorene. If longer alkyl chains are present, as found in the case of 2-ethylnaphthalene, the bromides readily undergo HBr elimination to form a double bond.

In *o*-, *m*-, and *p*-dimethyl(alkyl)aromatic compounds, one to four atoms of bromine may be introduced depending on the choice of reaction conditions; formation of even-numbered bromides (especially in *o*-alkyl side chains) is favored.

N-Bromosuccinimide only introduces one bromine atom into sterically unfavorable positions; thus only a dibromide, tribromide, and heptabromide are produced by 9,10-dimethylphenanthrene, 1,2-dimethylnaphthalene, and durene, respectively. Further bromination is not possible, even under forcing conditions (*2*, *20*). These findings are in excellent agreement with steric hindrance effects, revealed by inspection of molecular models. The steric hindrance associated with polybrominated *o*-dimethyl aromatic compounds is also manifested in a shift of certain bands in the IR spectrum (*2*). Compared to *o*-xylene, benzocyclobutene

TABLE 9
Reactions of N-Bromosuccinimide with Mono- and Polycyclic Aromatic Compounds

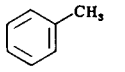
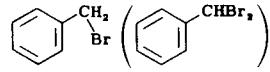
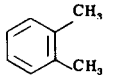
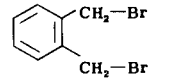
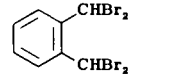
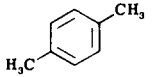
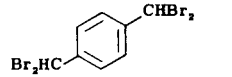
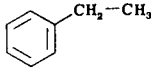
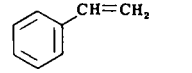
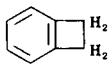
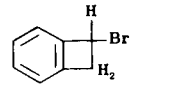
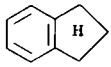
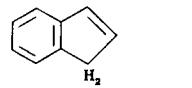
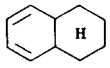
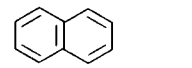
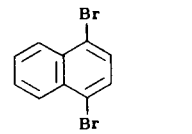
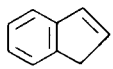
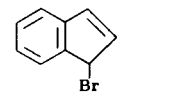
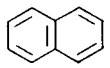
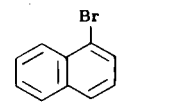
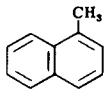
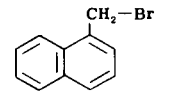
Starting compound	Moles of N-bromo-succinimide	Reaction type / Reaction time	Stable end product isolated	Yield (%)	Lit. ref.
	1 Azoisobutyronitrile	A 30 min		66	(*21, 25*)
	2 Dibenzoyl peroxide	A 10 min		> 50	(*113, 128, 19, 2*)
	4 Dibenzoyl peroxide	A		50	
	4 Dibenzoyl peroxide	A		?	
	1 Dibenzoyl peroxide	A/C		?	(*19, 72*)
	1 Dibenzoyl peroxide	A 15 min		50	(*2, 70, 71*)
	1 Azoisobutyronitrile	A/C 10 min		50	(*2*)
	2 Dibenzoyl peroxide	A/C 5 min		75	(*2, 33, 39*)
	4 Dibenzoyl peroxide	A/C 15 min		50	(*2*)
	1 Dibenzoyl peroxide	A 24 hr		< 40	(*2, 73*)
	1	A 6 hr		77	(*73*)
	1 Dibenzoyl peroxide	A 30 min		90	(*89*)

TABLE 9 (*continued*)

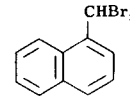
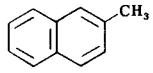
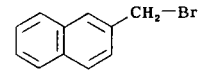
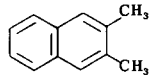
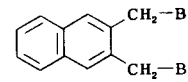
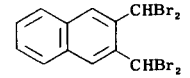
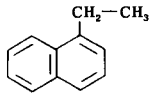
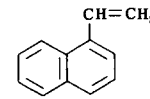
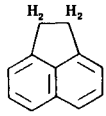
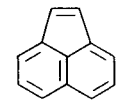
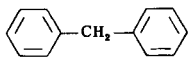
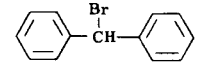
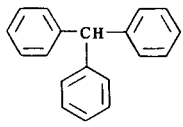
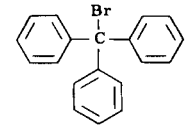
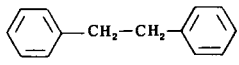
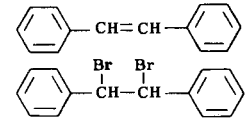
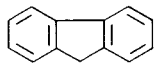
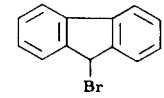
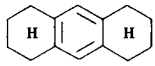
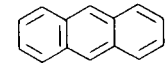
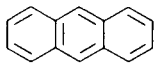
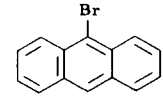
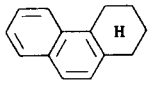
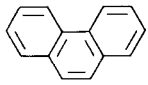
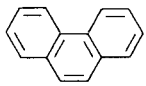
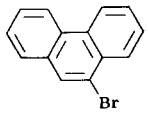
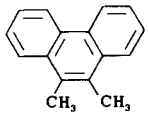
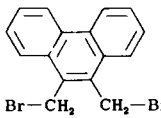
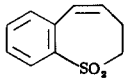
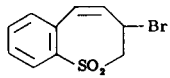
Starting compound	Moles of N-bromo-succinimide	Reaction type / Reaction time	Stable end product isolated	Yield (%)	Lit. ref.
	2 Dibenzoyl peroxide	A 45 min		80	(*2*)
	1	A 6 hr		80	(*89, 94*)
	2 Dibenzoyl peroxide	A 5 min		64	(*2, 20, 105, 128*)
	4 Dibenzoyl peroxide	A 1 hr		72	(*2, 20*)
	1	A/C 30 min		73	(*89*)
	1 Dibenzoyl peroxide	A/C 5 min		20	(*33, 73, 101*)
	1	A 1 hr		81	(*73*)
	1	A 5 min		62	(*73*)
	1 Dibenzoyl peroxide	C 5 min		56/10	(*33, 39, 73, 101*)
	1	A 3 hr		61	(*91, 99*)
	4 Dibenzoyl peroxide	A/C I/III		69	(*33*)
	1	A		58	(*73*)

TABLE 9 (*continued*)

Starting compound	Moles of N-bromo-succinimide	Reaction type / Reaction time	Stable end product isolated	Yield (%)	Lit. ref.
	2 Dibenzoyl peroxide	A/C I/III		79	(*33*)
	1	A 5 hr		46	(*73*)
	2 Dibenzoyl peroxide	A 5 min		68	(*2*)
	? Dibenzoyl peroxide	A		?	(*126*)

is only slightly less readily monobrominated by N-bromosuccinimide (*2, 70, 71*). The ability to undergo bromination increases sharply from indane to tetralin and 9,10-dihydroanthracene, but so does the thermolability of the bromides obtained. Tetralin yields a reasonably stable dibromide, but the tetrabromide decomposes appreciably to 1,4-dibromonaphthalene at room temperature. No intermediate can be isolated in the case of 9,10-dihydroanthracene; a 9-bromo- or 9,10-dibromoanthracene is obtained, depending on the proportion of N-bromosuccinimide (2 or 3 moles).

The elimination of HBr from thermolabile bromides and consequent aromatization was developed into a synthetic method (*2*) by Barnes (*33, 72*) and others. Thus the monobromides of dibenzyl and acenaphthene (obtained by the action of N-bromosuccinimide) lose HBr to form stilbene and acenaphthylene. If the bromination is carried out with two or more moles of N-bromosuccinimide, the secondary reactions initiated by the HBr elimination also become predominant in this system, and two end-products result.

Indene and propenylbenzene form exceptions in that they only undergo bromination by N-bromosuccinimide with extreme difficulty. 1,2- and 1,4-Dihydronaphthalene react readily with 2 moles of N-bromosuccinimide. The thermolabile monobromides, however, undergo HBr elimination to give equal quantities of naphthalene and 3,4- or 2,3-dibromotetralin, respectively (*39*).

TABLE 10
Reactions of N-Bromosuccinimide with Alcohols, Phenols, and Mercaptans

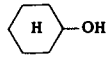
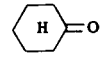
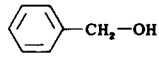
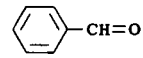
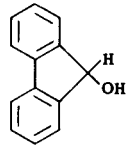
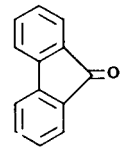
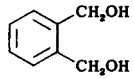
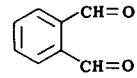
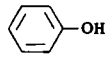
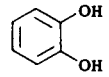
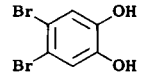
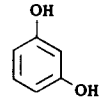
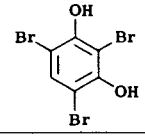
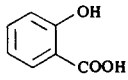
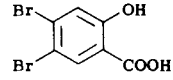
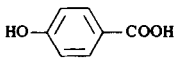
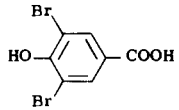
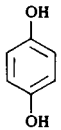
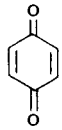
Starting compound	Moles of N-bromo-succinimide	Reaction type / Reaction time	Stable end product isolated	Yield (%)	Lit. ref.
CH_3OH	–		$HCOOCH_3$	45	
C_2H_5OH	–	Oxidation	$CH_3CHO/CH_3COOC_2H_5$	15/25	(*49*, *53*, *55a*, *56*)
n-C_3H_7OH	–		$C_2H_5CHO/C_2H_5COOC_3H_7$	6/39	
iso-C_3H_7OH	–		CH_3COCH_3	97	
1-Butanol	1	Oxidation	Ester	44	(*55a*)
3-Methyl-1-butanol	1	Oxidation	Ester	43	(*55a*)
1-Heptanol	1	Oxidation	Ester	55[a]	(*55a*)
1-Octanol	1	Oxidation	Ester	57	(*55a*)
Cetyl alcohol	2	Oxidation	Ester	37[b]	(*55a*)
β-Phenylethyl alcohol	1	Oxidation	Ester	30	(*55a*)
Furfuryl alcohol	1	Oxidation	Aldehyde	8.3	(*55a*)
β-Pyridyl carbinol	1	Oxidation	Aldehyde	6.3[b]	(*55a*)
2-Octanol	1	Oxidation	Ketone	56	(*55a*)
α-Phenylethyl alcohol	1	Oxidation	Ketone	80	(*55a*)
Benzoin	1	Oxidation	Ketone	52	(*55a*)
Benzaldehyde	1	Oxidation	Acid	50[b]	(*55a*)
	–	Oxidation		61	(*55a*, *56*)
$CH_2{=}CH{-}CH_2{-}OH$	–	?	$CH_2{=}CH{-}CH{=}O$	?	(*3*)
	1	Oxidation		70–80	(*3*, *47*, *49*, *55a*)
$Ph_2CH{-}OH$	–		$Ph_2C{=}O$	77	(*55a*)
	–	–		89	
	–	–		22	(*47*, *51*, *54*)
	–	A 12 hr		?	(*3*)
	2	A 1 hr		65	(*22*, *57*)
	3	15 min		92	

TABLE 10 (*continued*)

Starting compound	Moles of N-bromo-succinimide	Reaction type / Reaction time	Stable end product isolated	Yield (%)	Lit. ref.
	2	A 30 min		50	(22, 50, 54, 57)
	2	A 1.5 hr		76	
	2 (H_2O)	Oxidation ?		?	
Ph—SH	1	Oxidation	Ph—S—S—Ph		

[a] In diethyl ether only 13% is obtained, but in CCl_4 in the absence of pyridine, the yield is 68%; with 2 moles of N-bromosuccinimide in the absence of pyridine, 91% of ester is formed.

[b] In the absence of pyridine.

Alcohols, Phenols, and Mercaptans

The oxidation of primary and secondary alcohols has already been discussed above (p. 163). Primary dehydrogenation results in the formation of aldehydes, and a second dehydrogenation via the hemiacetal finally yields esters. Secondary alcohols give rise to ketones. Phenols are preferentially substituted in the *p*-position, hydroquinone is dehydrogenated to quinone and mercaptans are converted into disulfides.

Ethers and Thioethers

Aliphatic ethers and thioethers most probably exchange α-hydrogen for bromine. Phenyl alkyl ethers, phenyl esters and resistant thiophenyl alkyl ethers undergo ring bromination. Diphenyl ether, diphenyl sulfide, and diphenylene oxide are stable to N-bromosuccinimide. No scheme allowing the generalization of the reactions of ethers and thioethers with N-bromosuccinimide will be possible until a larger number of examples and exact knowledge of the structure of the primary reaction products are available. The same requirements apply to sulfoxides and sulfones.

Aliphatic and Aromatic Amines

Nothing was known hitherto concerning the reactions between N-bromosuccinimide and tertiary aliphatic amines in an anhydrous medium.

TABLE 11
Reactions of N-Bromosuccinimide with Ethers and Thioethers

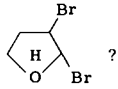
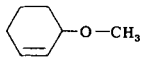
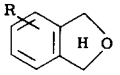
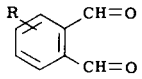
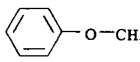
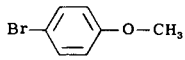
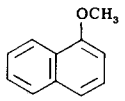
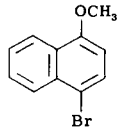
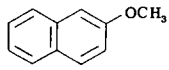
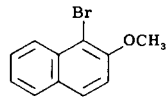
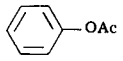
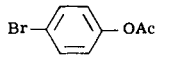
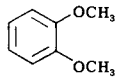
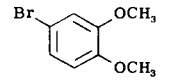
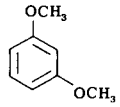
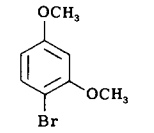
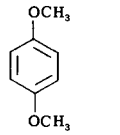
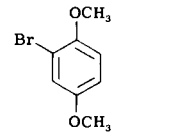
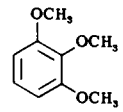
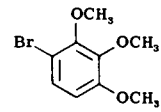
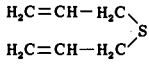
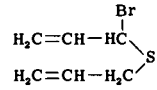
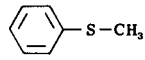
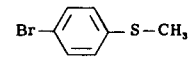
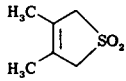
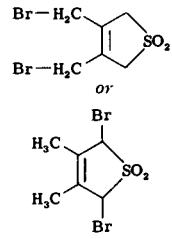
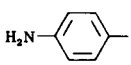
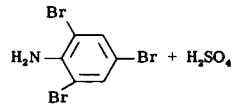
Starting compound	Moles of N-bromo-succinimide	Reaction type / Reaction time	Stable end product isolated	Yield (%)	Lit. ref.
	1	? / 1 hr	 ?	50	(2)
	1		?	?	(4)
Ph—CH_2—O—CH_2—Ph	1 Dibenzoyl peroxide/UV	A / ?	PhCH=O	-	(117)
	1	A / ?		-	(85)
	1	A / 16 hr		32	(73)
	1	A / 15 min		79	(73)
	1	A / 15 min		94	(73)
Ph—CH_2—O—CH_3 / Ph—CH_2—O—Ph	1 Dibenzoyl peroxide/UV	A / ?	PhCH=O / PhCH=O + PhOH	- / -	(117)
	1	A / ?		37	(73)
	1	A / 6 hr		62	(73)
	1	A / 6 hr		82	(73)
	1	A / 12 hr		73	(73)

TABLE 11 (*continued*)

Starting compound	Moles of N-bromo-succinimide	Reaction type / Reaction time	Stable end product isolated	Yield (%)	Lit. ref.
	1	A ?		-	(*92*)
	1	A 10 hr		-	(*41*)
	1	A ?		-	(*73*)
	2 Azoisobuty-ronitrile	A 5 min	 *or*	25	(*2,41*)
	3 (H_2O)	B/ Oxidation 15 min	 + H_2SO_4	95	(*57*)

After the conclusion of our own investigations into this subject (*2*), a study by Dunstan and Henbest (*58*) appeared. They observed an oxidative dealkylation to the aldehyde and secondary amine in aqueous dioxane via the intermediate enamine step. The authors suggest the following empirical equation to account for the reaction:

$$(R\text{-}CH_2)_3N + \text{N-Bromo-succinimide} \longrightarrow \text{Unknown colored intermediate} \longrightarrow$$
$$RCHO + (RCH_2)_2NH\cdot HBr + HN(COCH_2)_2$$

If the addition of water is omitted, the highly reactive α-bromoamines react with the tertiary amine present, accompanied by resinification (*2*). It is only in the case of tribenzylamine that a subsequent hydrolysis eliminates a benzyl fragment quantitatively as benzaldehyde (*2,58*).

Of the mixed substituted aliphatic-aromatic amines, only N-dimethylaniline and acetanilide were investigated (*73*). It could be shown that a series of tertiary aromatic amines can be brominated in the *p*-position in frequently excellent yields and with high selectivity (*2*). Substitution

TABLE 12

Reactions of N-Bromosuccinimide with N Compounds

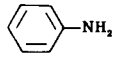
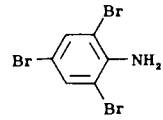
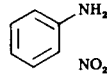
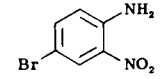
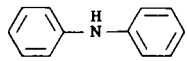
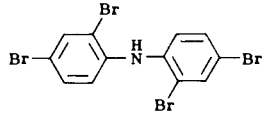
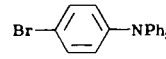
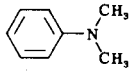
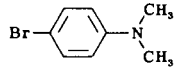
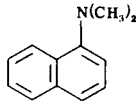
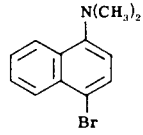
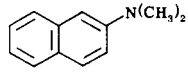
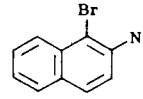
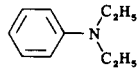
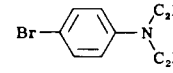
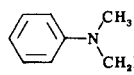
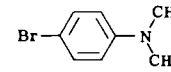
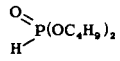
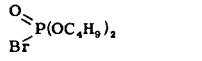
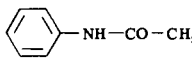
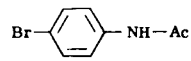
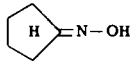
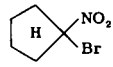
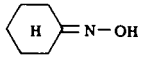
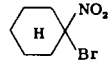
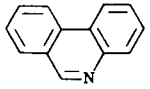
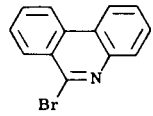
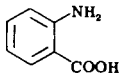
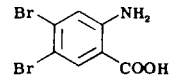
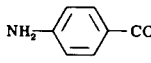
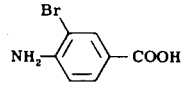
Starting compound	Moles of N-bromo-succinimide	Reaction type[a] / Reaction time	Stable end product isolated	Yield (%)	Lit. ref.
$(C_2H_5)_3N$	1	A 1 hr	$CH_3CH{=}O + (C_2H_5)_2NH$	?	(*2*)
	3 (H_2O)	A 15 min		93	(*57, 81*)
	1	A 2.5 hr		90	(*57*)
	4	A 2 hr		60	(*57*)
Ph_3N	1	A 3 hr		50	(*2, 57*)
$PhCH_2NH_2$	–	?	PhCN + PhCHO	34/31	(*47*)
$(PhCH_2)_3N$	1	A 30 min	$PhCHO + (PhCH_2)_2NH$	90/90	(*2*)
	1	A 15 min		70	(*73*)
	1	?		?	(*2*)
	1	?		?	
	1	?		?	
	1	A 5 min		85	
$(C_6H_5)_3P$	1	-	Adduct	-	
	1	–		-	(*129*)
	1	A 1 hr		99	(*57, 73*)

TABLE 12 (*continued*)

Starting compound	Moles of N-bromo-succinimide	Reaction type[a] / Reaction time	Stable end product isolated	Yield (%)	Lit. ref.
$Ph-NH-NH_2$	1	?	$Ph-NH-NH-Ph$	87	(*54*)
$Ph_2-CH=N-NH_2$	1	?	$Ph_2C=N-N=CPh_2$	90	(*54*)
	1 (H_2O)	Oxidation 15 min		72	(*59*)
	1 (H_2O)	Oxidation 15 min		80	(*59*)
	1	A 40 hr		?	(*100*)
	2	A 1 hr		90	(*50*, *54*)
	2	A 2 hr		80	

[a] A = Allylic bromination.

in the *p*-position also proceeds quantitatively in the case of dibenzylaniline with its two active methylene groups. No oxidative dealkylation has thus far been observed in this type of compound where the ratio amine: N-bromosuccinimide was 1:1 (*2*). Triphenylamine also reacts with N-bromosuccinimide in the normal manner, unlike quaternary salts such as dimethylethyl- or benzylanilinium bromide which do not (*2*). The N-bromosuccinimide may therefore initially attack the electron pair of the nitrogen atom. Triphenylphosphine also combines with N-bromosuccinimide to give labile, salt-like adducts; these have so far not been isolated in a pure state (*2*).

Heterocycles

Only reactions with compounds of simple structure are known and we restricted ourselves to orientation experiments. Pyridine, the three isomeric picolines, quinoline, isoquinoline, quinaldine, and lepidine remain unattacked by N-bromosuccinimide (in CCl_4, in the absence of activators), even after prolonged boiling. N-Bromosuccinimide does partially go into solution, but separates again unchanged on cooling.

According to Hasegawa (*74*) bromination of the methyl groups is possible if dibenzoyl peroxide is used as activator. The highly reactive bromomethyl compounds can only be isolated as the picrates. The

N-oxides of the heterocycles mentioned above are similarly only brominated in the methyl groups by N-bromosuccinimide, with the assistance of free radical activators (*2*, *74*).

The directing effect of free radical activators is particularly evident in the reaction of N-bromosuccinimide with 2- and 3-methylfuran and the corresponding thiophenes (*75*, *76*). Depending on the reaction conditions, bromine is introduced either in the side chain or in the ring; in the latter case, it invariably occupies the position adjacent to the heteroatom. The action of N-bromosuccinimide on indole, 2,3-benzofuran, and 2,3-benzothiophene results in the exclusive bromination of the β-position. The reaction probably proceeds via transient free radicals (*77*) bound to the crystal surface of the N-bromosuccinimide. The reaction scheme which we believe to be correct corresponds fully, if one changes the substrate accordingly, to the scheme which we had proposed for the reaction of chlorine and pseudohalogens with compounds containing heteroatoms. Observations also have been made concerning pyrimidines (*78*), uracils (*79*), thiazoles, imidazoles (*80*), and coumarins (*75*). Carbazole behaves like an aromatic amine in this reaction and is brominated in the position *para* to the nitrogen. Acridine reacts with N-bromosuccinimide in the *meso*-position; both a 9-bromoacridine and an N-bromosuccinimide–acridine adduct are formed (*21*, *27*).

Effect of Substituents on the Ability to Undergo Bromination

In this connection, the susceptibility to attack by N-bromosuccinimide of CH_2 groups in the general grouping X—CH_2—R (R=H or alkyl) is of particular interest. The experimental data available to date allow no more than a qualitative gradation of activities for N-bromosuccinimide in the absence of activators. The differences in activity within the series are frequently insignificant and are strongly dependent on the over-all constitution. This series loses all validity in the presence of free radical initiators (*2*).

$$X = CH_3 < C{=}C < C_6H_5 < R_2N$$
$$< RO < SO < (RO)_2CH < CO$$

CO stands for aldehydes, ketones, carboxylic esters, and lactones. Its activating effect surpasses all those substituents which lack a prerequisite for favorable adsorption on the N-bromosuccinimide crystal lattice, such as: $-\overset{\oplus}{N}R_3$, $=SO_2$, $-C{\equiv}C-$, $-CN$, and $-NO_2$. Since these substituents strongly acidify CH bonds by their inductive and mesomeric effects, compounds of this type are resistant to N-bromosuccinimide but are readily attacked by elementary bromine. Awareness of these facts may be important with regard to selective bromination by N-bromosuccinimide.

TABLE 13
Reactions of N-Bromosuccinimide with Heterocycles

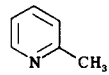
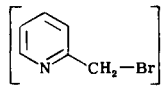
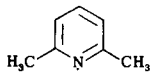
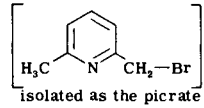
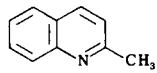
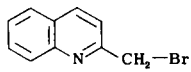
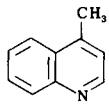
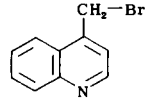
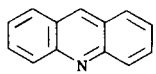
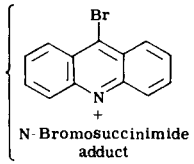
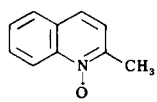
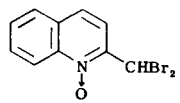
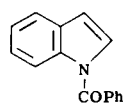
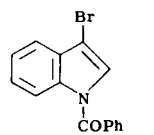
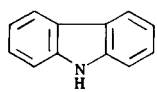
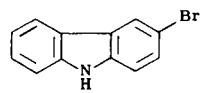
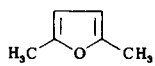
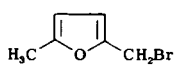
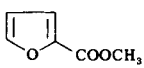
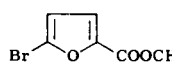
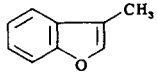
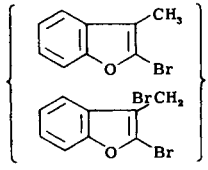
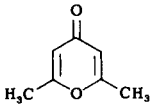
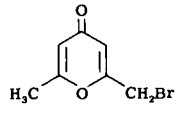
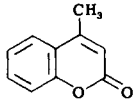
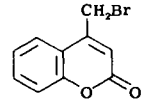
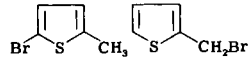
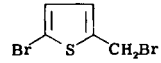
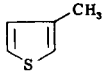
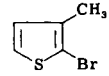
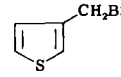
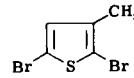
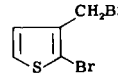
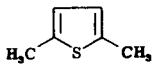
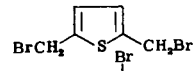
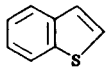
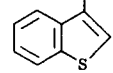
Starting compound	Moles of N-bromo-succinimide	Reaction type[a] / Reaction time	Stable end product isolated	Yield (%)	Lit. ref.
	1	?	2,4-Ring bromination	-	(*73*)
	1 Dibenzoyl peroxide/ UV	A 3 hr	 isolated as the picrate	-	(*2, 74*)
	1 Dibenzoyl peroxide/ UV	A ?	 isolated as the picrate	-	(*74*)
	1 Dibenzoyl peroxide	A ?		-	(*103*)
	1 Dibenzoyl peroxide	A ?		-	(*74*)
	1 Dibenzoyl peroxide	A 5 hr	 N-Bromosuccinimide adduct	-	(*21, 27*)
	2 Dibenzoyl peroxide	A 5 min		22	(*104*)
	1	?			(*73*)
	1 Dibenzoyl peroxide	A 7 min		55	(*27*)
	1	A ?		-	(*75*)
	1 Dibenzoyl peroxide	?		15	(*130*)

TABLE 13 (*continued*)

Starting compound	Moles of N-bromo-succinimide	Reaction type[a] / Reaction time	Stable end product isolated	Yield (%)	Lit. ref.
	1 Dibenzoyl peroxide	A 2 hr		–	(*97*)
	1	A 30 min		–	(*75, 87, 111*)
	1	?		–	(*114*)
	1	24 hr		77	(*75*)
	1	5 hr		66/24	(*76, 96*)
	1 Dibenzoyl peroxide	5 hr		16/84	
	2	5 hr		–	
	1	5 hr		90	
	1 Dibenzoyl peroxide	5 hr		90	
	2	5 hr		–	
	2 Dibenzoyl peroxide	5 hr		–	
	2	A 5 min		37	(*75*)
	1	? 36 hr			

[a] A = Allylic bromination.

TABLE 14

Reactions of N-Bromosuccinimide with Aldehydes and Ketones

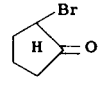
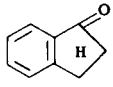
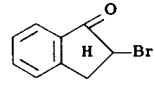
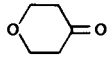
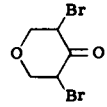
Starting compound	Moles of N-bromo-succinimide	Reaction type / Reaction time	Stable end product isolated	Yield (%)	Lit. ref.
$CH_3CH(OC_2H_5)_2$	1	A	$CH_3C(Br)(OC_2H_5)_2$	57	(*112*)
$H_2C=C(OC_2H_5)_2$		2.5 hr	$BrH_2CCOOC_2H_5 + H_2C=CH_2$	44	(*121*)
$PhCH(OC_2H_5)_2$	1	A	$PhCOOC_2H_5 + C_2H_5Br$	–	(*112*)
CH_2COCH_3	1	A	CH_3COCH_2Br	–	(*2, 56*)
$C_2H_5COC_2H_5$	1	A	$C_2H_5COCHBrCH_3$	–	(*2*)
	1	A 5 min		–	(*2*)
	1	A 5 min		–	(*21, 122, 127*)
	1	A 8 min		90	(*2*)
$CH_3COCH=CHCH_3$	1		$BrCH_2COCH=CHCH_3$	–	(*90*)
$CH_3COCH=C(CH_3)_2$	1	–	$BrCH_2COCH=C(CH_3)_2$	–	(*90*)
$CH_3COCH=CHPh$	1 Dibenzoyl peroxide	18 hr	$CH_3COCHBr-CHBrPh$	46	(*22, 119, 125*)
$CH_3COCH=C(CH_3)Ph$	1 Dibenzoyl peroxide	48 hr	$CH_3COCHBr-CBr(CH_3)Ph$	57	
$CH_3COCH=CPh_2$	1 Dibenzoyl peroxide	–	$CH_3COCHBr-CBrPh_2$	–	
$CH_3COCH_2CH_2CH=C(CH_3)_2$	1	–	$CH_3COCHBrCH_2CH=C(CH_3)_2$	–	(*90*)
$PhCH_2COCH_2Ph$	1	A	$PhCHBrCOCH_2Ph$	–	(*2*)
$PhCOCH_3$	1		$PhCOCH_2Br$	–	
$PhCH_2COCH_3$	1		$PhCHBrCOCH_3$	–	
$CH_3COCH_2COCH_3$	1	A	$CH_3COCHBrCOCH_3$	–	(*2*)
$CH_3COCH_2CH_2COCH_3$	1		$CH_3COCHBrCH_2COCH_3$	–	
$CH_3COCOCH_3$	1		$CH_3COCOCH_2Br$	–	

TABLE 14 (*continued*)

Starting compound	Moles of N-bromo-succinimide	Reaction type / Reaction time	Stable end product isolated	Yield (%)	Lit. ref.
PhCOCHPh (OH)	1	Oxidation	PhCOCOPh	95	(*54*)
	2	A 25 min		50	(*123*)

Experimental

N-Bromosuccinimide. Succinimide (50 gm) is dissolved in a cold solution of caustic soda "Merck" (20 gm) in water (100 ml) (*a*), finely ground ice (100 gm) is added (*b*), and bromine (27 ml) poured into the vigorously stirred solution all at once (*c*). N-Bromosuccinimide separates immediately as a thick crystalline mass. Stirring is continued for a further 10 min and the solid is thoroughly filtered. Any free bromine left is removed by stirring the crystals into a paste with a little water in a mortar and then the mixture is again thoroughly filtered; the operation is repeated up to 3 times. The N-bromosuccinimide should now be pure white and the washings completely free from bromine (*d*). The product is dried in the desiccator, first over technical caustic soda then over P_2O_5 (*e*). Yield: approximately 70 gm (75–80%), m.p. 174–175° (with decomposition); usually 98% with an active bromine content of 44.9% (*f*).

Notes: N-Bromosuccinimide is best prepared in a steep-walled, wide-necked flask fitted with a mechanical stirrer.

(*a*) Commercial succinimide, m.p. 125–126°, can be used without further purification. The succinimide recovered from N-bromosuccinimide reactions must first be recrystallized from twice its weight of alcohol, to which a little animal charcoal has been added.

(*b*) Additional external cooling by means of ice is indispensable in larger-scale preparations.

(*c*) The quantity of bromine required is added in one portion directly from the measuring cylinder. Vigorous stirring is essential during this addition.

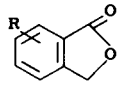
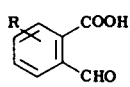
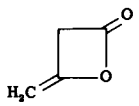
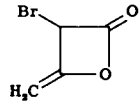
(*d*) Free bromine is only slowly and usually incompletely washed out of the Büchner funnel.

TABLE 15

Reactions of N-Bromosuccinimide with Acids, Esters, Lactones and Their Derivatives

Starting compound	Moles of N-bromo-succinimide	Reaction type / Reaction time	Stable end product isolated	Yield (%)	Lit. ref.
$CH_2{=}CH{-}CH_2{-}COOH$	1 Dibenzoyl peroxide	8 hr	$CH_2(Br){-}CH(Br){-}CH_2{-}COOH$	68	(*43*)
$PhCH_2COOH$	1 (H_2O)	A/ Oxidation 30 min	PhCHO	72	(*50, 54*)
$CH_2(OH)COOH$	1 (H_2O)	Oxidation	CH_2O	-	(*50, 54*)
$CH_3CH(OH)COOH$			CH_3CHO	-	
$PhCH(OH)COOH$			PhCHO	-	
$Ph_2C(OH)COOH$			PhCOPh	90	
$CH_3CH(NH_2)COOH$	1 (H_2O)	Oxidation	CH_3COOH	50	(*48, 50*)
$C_4H_9CH(NH_2)COOH$			C_4H_9CHO	-	
$PhCH(NH_2)COOH$			PhCHO	40	
$NCCH_2COOH$	2 (H_2O)	A 15 min	$NCCHBr_2 + CO_2$	75	(*46*)
$CH_3COOC_2H_5$	1	A	$BrCH_2COOC_2H_5$	-	(*2*)
$C_2H_5COOC_2H_5$	1	A	$CH_3CH(Br)COOC_2H_5$	42	(*63*)
$C_{11}H_{22}COOCH_3$	1	A 12 hr	$C_{10}H_{20}CH(Br)COOCH_3$	40	(*63*)
$CH_2{=}CHCOOC_2H_5$	1	?	$CH_2(Br){-}CH(Br)COOC_2H_5$	25	(*22*)
$CH_3CH{=}CHCOOCH_3$	1 Dibenzoyl peroxide	A 5 min	$BrCH_2CH{=}CHCOOCH_3$	86	(*22*)
$CH_3CH{=}CHCOOC_2H_5$	1	A 6 hr	$BrCH_2CH{=}CHCOOC_2H_5$	82	(*4, 18*)
$(H_3C)_2C{=}CHCOOC_2H_5$	1	A 8 min	$BrH_2C(H_3C)C{=}CHCOOC_2H_5$	80	(*4*)
$(H_3C)_2CH{-}CH{=}CHCOOC_2H_5$	1 Dibenzoyl peroxide	A	$(H_3C)_2C(Br){-}CH{=}CHCOOC_2H_5$	67	(*27*)
$CH_3[CH{=}CH]_2COOCH_3$	1 Dibenzoyl peroxide	A 15 min	$CH_2(Br)[CH{=}CH]_2COOCH_3$	65	(*106*)

TABLE 15 (*continued*)

Starting compound	Moles of N-bromo-succinimide	Reaction type / Reaction time	Stable end product isolated	Yield (%)	Lit. ref.
Oleic acid ester Erucic acid ester	1 Dibenzoyl peroxide	A/C	Dienes (?)	40	(*116*)
$CH_3CH(OH)COOC_2H_5$	1	Oxidation A 5-8 hr	$CH_3COCOOC_2H_5$	64	(*52, 56*)
$C_2H_5CH(OH)COOC_2H_5$			$CH_3CH(Br)COCOOC_2H_5$	66	
$PhCH(OH)COOC_2H_5$			$PhCOCOOC_2H_5$	79	
$PhCH_2CH(OH)COOC_2H_5$			$PhCH(Br)COCOOC_2H_5$	71	
$CH_3COCH_2COOC_2H_5$	1	A	$CH_3COCH(Br)COOC_2H_5$	–	(*2*)
$CH_3COCH_2CH_2COOC_2H_5$	1	A	$CH_3COCH(Br)CH_2COOC_2H_5$	–	(*2*)
$NCCH_2COOC_2H_5$	1	A	No reaction	–	(*2*)
$CH_2[COOC_2H_5]_2$	Dibenzoyl peroxide	A	$BrCH[COOC_2H_5]_2$	–	(*63*)
$(CH_2)_4(COOCH_3)_2$	Dibenzoyl peroxide	A 12 hr	1-Bromo derivative	30	(*49, 63*)
$H_3C-C(=CH-COOC_2H_5)-COOC_2H_5$	1 Dibenzoyl peroxide	A 1 hr	$Br-CH_2-C(=CH-COOC_2H_5)-COOC_2H_5$	68	(*93*)
	1	–		–	(*85*)
	1	A		43	(*86*)

(*e*) N-Bromosuccinimide dries more rapidly in the drying oven or pistol at a maximum temperature of 50°.

(*f*) Pure N-bromosuccinimide, free from NaBr, m.p. 176–177°, is obtained by recrystallization from 10 times its quantity of water at a maximum temperature of 75–80°. Crude N-bromosuccinimide is dissolved portionwise in water warmed to 75–80°; insoluble particles are immediately filtered off and the solution cooled in ice. Some decomposition is unavoidable at this stage (*2, 4, 22*). N-Bromosuccinimide can, however, be recrystallized without decomposition from nitromethane (*2*). Recrystallized N-bromosuccinimide, even in finely ground form, possesses a lower activity than the product prepared according to the earlier directions.

TABLE 16

Reactions of N-Bromosuccinimide with Nitriles, Nitro Compounds and Derivatives of Acetylene

Starting compound	Moles of N-bromo-succinimide	Reaction type / Reaction time	Stable end product isolated	Yield (%)	Lit. ref.
CH_3CH_2CN	1 Dibenzoyl peroxide	24 hr	$CH_3\underset{Br}{C}HCN$	40	(*26*)
$(CH_3)_2CHCN$	1 Dibenzoyl peroxide	A 1.5 hr	$(CH_3)_2\overset{Br}{C}CN$	80	(*26*)
C_4H_9CN	1 Dibenzoyl peroxide	A 3 hr	$C_3H_7\underset{Br}{C}HCN$	76	(*26*)
			$C_2H_9\underset{Br}{C}HCH_2CN$	24	(*26*)
$C_5H_{11}CN$	1	A 1.5 hr	$C_4H_9\underset{Br}{C}HCN$	63	(*26*)
			$CH_3\underset{Br}{C}HCH_2CH_2CH_2CN$	37	(*26*)
	1 Dibenzoyl peroxide	A 30 min	1- and 4-Bromo derivatives	30/70	(*26*)
$H_2C{=}CHCH_2CN$	1 Dibenzoyl peroxide	B/C 2 hr	$Br{-}CH_2CH{=}CHCN$	13	(*22, 35*)
			$CH_2(\underset{Br}{C}H)CH_2CN$	21-37	(*22, 35*)
			+ N-Bromosuccinimide adduct	2	(*22, 35*)
$CH_3CH{=}CHCN$	1 Dibenzoyl peroxide	A 15 min	$Br{-}CH_2CH{=}CHCN$	40-80	(*22, 35*)
$CH_3{-}C_6H_4{-}NO_2$	1	A 12 hr	$Br{-}CH_2{-}C_6H_4{-}NO_2$	50	(*73*)
$CH_3C{\equiv}CCOOC_2H_5$	1 Dibenzoyl peroxide/UV	1 hr	$CH_3C(\underset{Br}{)}{=}C(\underset{Br}{)}COOC_2H_5$	12	(*18*)

N-Bromosuccinimide in a heterogeneous phase (Allylic bromination). The reactants (*a*), e.g., the olefin or alkylaromatic compound, are dissolved in CCl_4 (*b*) placed in a large round-bottomed flask, with ground joints, equipped with an efficient reflux condenser (*c*); the required quantity of N-bromosuccinimide (*d*) and an activator (*e*) are added and the flask is slowly heated on a bath to the b.p. of CCl_4 (approximately 80°) (*f*). The bromination frequently commences when the boiling point is reached. The reaction is usually exothermic (*g*) so that no further heating is required. In fact, a short period of cooling in ice-water is often necessary (*h*). If the reaction is slow in starting, the temperature is maintained at 80° for a few minutes (*i*). The reaction is usually complete after several minutes, irrespective of its scale (*j*). The termination of the reaction and the quantitative consumption of the N-bromosuc-

cinimide can be observed by the fact that all the lighter succinimide formed has risen to the surface of the liquid (*k*). Heating may be continued for several minutes unless the compounds concerned are very thermolabile. Succinimide is filtered off from the product (*l*), washed with a little CCl_4, and the solvent removed from the filtrate *in vacuo* (*m*). The residue is then fractionated under vacuum or recrystallized, depending on the product obtained; thermolabile compounds are allowed to react further directly.

(*a*) The reactants are heated to boiling with occasional shaking (not stirring). Especially reactive compounds are best added dropwise to a stirred suspension of N-bromosuccinimide in CCl_4 at room temperature. Heat-sensitive or readily polymerized substances are added dropwise to a suspension of N-bromosuccinimide in boiling carbon tetrachloride containing dissolved activators. Long periods in contact with the reaction mixture are thus avoided. The most favorable conditions for any particular reaction are best first ascertained in a test-tube experiment. The reactants must be absolutely anhydrous in order that side reactions and poor yields be avoided. Olefins are often advantageously distilled over metallic sodium and it is expedient to dry the N-bromosuccinimide over P_2O_5 in the desiccator. Reactions between N-bromosuccinimide and alkylaromatic compounds are mostly less sensitive. These recommendations apply equally to reactions involving but a few milligrams and to those involving several hundred grams.

(*b*) CCl_4 is the most suitable reaction medium for allylic brominations; hot benzene dissolves small quantities of N-bromosuccinimide, and side reactions consequently result. All the bromination reactions of olefins and alkylaromatic compounds utilized CCl_4, and in those of amines and ethers benzene was used (*2*). Technical CCl_4 was refluxed for one day over P_2O_5 and distilled through a fractionating column. In reactions containing N-bromosuccinimide and CCl_4 in the ratio 1:4 the optimum proportions of substrate to CCl_4 varied from 1:10 to 1:20. Reactive olefins are converted with higher, more inert substrates, in lower dilution. Liquid reactants may also be brominated in the absence of solvent.

(*c*) Volatile olefins may be converted: 1. by using two efficient condensers connected in series; 2. in a sealed glass tube; or 3. by UV irradiation at as low a temperature as possible.

(*d*) N-Bromosuccinimide was almost invariably used in the form in which it is produced by the Ziegler method. The use of recrystallized N-bromosuccinimide is only advisable in special cases, and a decline in activity must be taken into consideration. This can be compensated for by the addition of activators.

(*e*) Specially reactive substrates can be made to react with N-bromo-

succinimide alone, but the addition of activators is advantageous in many instances. Their presence assists the ready initiation of the reaction and its completion within a reasonable period, with the consequent absence of side reactions. Azoisobutyronitrile and dibenzoyl peroxide have both proved valuable free radical activators, the former particularly in the bromination of olefins, the latter for alkylaromatic compounds. Irradiation by UV light is usually favorable. The activators are added in the ratio N-bromosuccinimide:azoisobutyronitrile = 100:1 to 1000:1, and N-bromosuccinimide:dibenzoyl peroxide = 100:1; they are either dissolved in a little chloroform or added directly as the solid. In the latter case, the activator is intimately mixed but not ground with the N-bromosuccinimide. Redox catalysts e.g., tertiary butyl hydroperoxide and copper laurate, are even more efficacious, since they already yield free radicals at room temperature. Minimal quantities of redox catalyst are used, e.g. 3–4 drops of a 60% solution of *tert*-butyl hydroperoxide in methyl phthalate are added to the preparation in the cold; the heavy metal laurate (1–2 drops of a concentrated chloroform solution) is only added at ca.70°. Under these conditions the reactions start immediately and proceed evenly.

The simultaneous utilization of various catalysts can, but need not, be successful. Addition of polymerization inhibitors should be avoided, as they usually alter or retard the course of the reaction. A more rapid rate of reaction is mostly favorable, since the occurrence of side reactions is thus suppressed.

(*f*) When somewhat unreactive compounds are to be brominated, the reaction vessel is placed in a water or oil bath preheated to 80°. Long periods of induction are thereby avoided.

(*g*) Many N-bromosuccinimide reactions are extremely exothermic. In larger-scale work it is advisable to carry out preliminary experiments and to have ice-water at hand.

(*h*) It is detrimental to cool the mixture too strongly, since the reaction is then brought to a complete standstill. A uniform, even rate of reaction, similar to that sought in Grignard reactions, is most suitable.

(*i*) If the reaction is slow in starting, the addition of more activator is advisable.

(*j*) When N-bromosuccinimide reactions require longer than one hour at 80°, side reactions must be expected, especially in the case of olefins. N-Bromosuccinimide reactions which continue for 12 hr or more are futile.

(*k*) In order to ascertain whether the N-bromosuccinimide has quantitatively been converted into succinimide, heating is interrupted for a moment to enable the latter compound to rise to the surface of the

liquid. In cases of high substrate concentration dilution with a little CCl_4 must be effected so that the ascent of the succinimide may be observed. The succinimide must be completely free from bromine and may not liberate iodine. Recrystallization from ethanol renders it suitable for the preparation of more N-bromosuccinimide.

In the work-up of reactions yielding polybrominated products (especially from alkylaromatic compounds), the succinimide must be filtered off from the hot solution; if this is not done the polybromides crystallize out and these are then difficult to separate from the succinimide.

(*l*) If volatile halides are produced, the solvent must be distilled through an efficient column. Solutions of sensitive substances are evaporated *in vacuo* under nitrogen. Thermolabile compounds must be freed from the solvent under a good vacuum at as low a temperature as possible.

Bromination of mixed aliphatic–aromatic amines and ethers (*2,73*). The compound to be brominated is dissolved in 4 to 6 times its quantity of benzene or carbon tetrachloride, and an equimolar amount of N-bromosuccinimide [prepared according to the method of Ziegler (*4*)] added in small portions to the well-stirred solution maintained at 20–30° (ice-water cooling). An exothermic reaction usually ensues, and yellow to red colorations sometimes appear. The reaction commences immediately and proceeds quantitatively. Stirring is continued for a short time after completion and the regenerated succinimide filtered or extracted with water. The clear, colorless solution is evaporated and the residue purified by distillation or crystallization.

Oxidation reactions with N-bromosuccinimide (*50,55a,56*). Vigorously stirred equimolar quantities of the compound to be oxidized and dry N-bromosuccinimide [prepared according to ref. (*4*)] are boiled under reflux with pyridine (1.05 mole, calculated with respect to the weight of N-bromosuccinimide used) in the absence of moisture, in a five- to tenfold quantity of absolute benzene or carbon tetrachloride until all the N-bromosuccinimide has been converted. Reaction times vary from a few minutes to several hours. On cooling, water (100 ml) is added and stirring at room temperature continued for 1 hr. Insoluble material is filtered off and the organic layer separated and shaken with dilute hydrochloric acid, sodium bicarbonate solution (10%), and water. The products are worked up as described under "Allylic bromination."

Appendix

A few months after the first publication of this review, a paper appeared by Dauben and McCoy (*131*), entitled "N-Bromosuccinimide 1. Allylic Bromination: A General Survey of Reaction Variables." Apart

from known information, this study contains a series of very interesting new observations which are reproduced here.

These authors also used cyclohexene in carbon tetrachloride as their test substance. They found that N-bromosuccinimide dried in air reacts 1.5 times more rapidly than that dried over phosphorus pentoxide. It is conclusively shown that the peroxide content of the cyclohexene exerts a decisive effect on the reaction rate. Cyclohexene which has been exposed to the air for 20 days reacts 4 to 5 times more rapidly with N-bromosuccinimide than the freshly distilled material. It is striking that beyond a certain concentration of peroxide no further acceleration of the reaction is observed. This effect, which the authors do not attempt to explain, we attribute to the diffusion-controlled saturation of the N-bromosuccinimide surface by the activator. We see therein a confirmation of our assumption that the allylic bromination by N-bromosuccinimide is a free radical surface reaction. The startling result accordingly follows that pure alkenes do not react with N-bromosuccinimide or only do so slowly, while contaminated alkenes react more rapidly. The higher or lower peroxide content of the substrate to be brominated may also be responsible for a series of irregularities found in the literature.

In a further line of investigation, the effect of oxygen, light, and hydroperoxide on the formation of 3-bromo-, 3,6-dibromo- and 1,2-dibromocyclohexene is studied.

New activators and inhibitors of the N-bromosuccinimide reaction were discovered by the determination of the relative reactivity (ratio of reaction times in the presence to reaction times in the absence of modifiers). The following order was drawn up for the activators.

(*a*) For hydroperoxide-free cyclohexene: azobisisobutyronitrile > dibenzoyl peroxide > tetralyl hydroperoxide > cyclohexenyl hydroperoxide > di-*tert*-butyl peroxide > triethylamine > pyridine > bromine (atomic).

(*b*) For hydroperoxide-containing cyclohexene (0.022 mole): triethylamine > azobisisobutyronitrile > pyridine > dibenzoyl peroxide > bromine (atomic) > tetralyl hydroperoxide > di-*tert*-butyl peroxide.

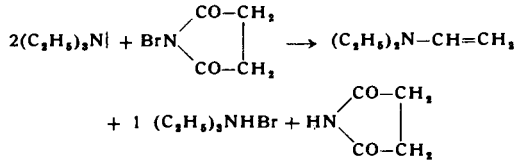
The acceleration caused by the activators (except tertiary aliphatic amines and pyridine) is proportional to the half-life period of their decomposition into free radicals (*132*). A combination of different activators causes no additional acceleration. We see in this further confirmation of our conception of the mechanism of allylic bromination, namely that it proceeds via a free radical surface reaction.

For the inhibitors, the following order applies in the case of hydroperoxide-containing cyclohexene: bromanil > picric acid > 1,3,5-trinitrobenzene > iodine > *m*-dinitrobenzene > hydroquinone.

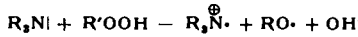
Oxygen and sulfur also exert a retarding effect. The large difference between bromine as activator and iodine as inhibitor is attributed to the difference in the strength of the bonds between these halogens and the succinimidyl radical (*14, 133, 134*). The presence of small quantities of water, low aliphatic alcohols, and hydrohalic acids exerts but a weak effect on the course of the reaction and its products.

Higher concentrations of tertiary aliphatic amines (*13, 135*), the corresponding quaternary ammonium salts (*13*), and alkali halides (*22, 24*) suppress the allylic substitution in favor of the addition of bromine to the carbon–carbon double bond; this effect results from the polarizing influence they exert on N-bromosuccinimide.

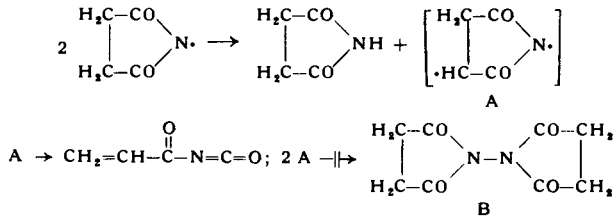
The possible reasons for the powerful activation of the allylic bromination by small quantities of tertiary aliphatic amines are discussed and comparisons with similar reactions made (*77*). In the absence of olefins, the redox reaction between N-bromosuccinimide and tertiary aliphatic amines may proceed according to the following equation (*58*):



The accelerating effect exerted by small quantities of tertiary aliphatic amines is only observed if these are added directly to the N-bromosuccinimide–cyclohexene system. If N-bromosuccinimide is allowed to react with aliphatic amines first and cyclohexene added subsequently, the allylic bromination is not accelerated but impaired by increased addition of bromine to the double bond. The following reaction scheme represents an attempt at explaining the additional activation of the tertiary amines by hydroperoxides.



The course of the N-bromosuccinimide allylic bromination is discussed, and the possibilities considered may, in certain circumstances, proceed simultaneously. The rate-determining step is assumed to be the abstraction of the allyl hydrogen atom and its transfer to the succinimidyl radical, which is assumed to be the maintaining factor of the chain reaction. The termination of the chain reaction may be due to: (*a*) a reaction between the succinimidyl radical and other radicals (e.g. those produced by the solvent), and (b) the disproportionation of two succinimidyl radicals according to the following scheme.



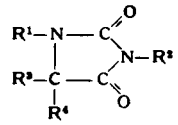
The formation of β-bromo- and α,β-dibromopropionyl isocyanate (*61,62*) during the irradiation of N-bromosuccinimide in boiling carbon tetrachloride is invoked in support of this hypothesis. No dimerization to disuccinimidyl (B) has thus far been observed.

To the synthetic chemist the following points are of interest: The allylic bromination depends on the origin of the olefin; small quantities of hydroperoxides accelerate the reaction. The same effect is obtained (in the case of a hydroperoxide-containing substrate) by the addition of small quantities of tertiary aliphatic amines. Acceleration and inhibition or retardation are fully compatible with the idea of a free radical reaction at the surface of the N-bromosuccinimide.

Allylic Brominations with N-Bromohydantoins

The suitability of N-bromohydantoins for allylic bromination was thoroughly investigated by Orazi and Corral and their collaborators in the Argentine (*136*).

The following hydantoin derivatives were examined:



	R^1	R^2	R^3	R^4	A	B	C
I	H	Br	CH_3	CH_3	62	–	–
II	Br	Br	CH_3	CH_3	64	87	0
III	Br	CH_3	CH_3	CH_3	66	84	22
IV	Br	CH_3	CH_3	C_2H_5	–	–	–
V	Br	Br	CH_3	$CH(CH_3)_2$	–	88	–
VI	Br	Br	C_6H_5	C_6H_5	92	–	–

The dibromohydantoin II is more active than the monobromo derivative I. It affords better yields and reacts more rapidly. Compounds IV and V have the advantage of higher solubility in carbon tetrachloride over N-bromosuccinimide and the hydantoin derivative II. Compound V

is particularly recommended for preparative work. The yields obtained in allylic brominations with compounds I to V correspond to those obtained with N-bromosuccinimide. Column A shows the yields of 3-bromo-1-cyclohexene from cyclohexene (N-bromosuccinimide affords 84–87%), column B the yields of the 3-brominated 1,1-diphenyl-1-propene (isolated as the pyridinium bromide; N-bromosuccinimide gives 89%), and column C shows the yields of cinnamyl bromide from 1-phenyl-1-propene (N-bromosuccinimide affords 66%).

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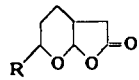
The Acyllactone Rearrangement; A Method for the Preparation of Heterocyclic Ring Systems (*1*, *2*)

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Introduction

Cyclic derivatives of carboxylic acids, such as lactones, thiolactones, or lactams can be converted by partial reduction into heterocycles of the same ring size. Lactones thus form cyclohemiacetals or diols, which can be cyclized by the addition of acid. This process presents certain preparative difficulties however, and is not much investigated from the point of view of its general applicability. Furthermore, the unsubstituted heterocycles thus obtained offer few possibilities of building up a second ring system at a definite position. In the course of our investigations into



I

the gentian bitter principle, gentiopicrin, it became necessary to synthesize bicyclic hemiacetallactones (I) in order to confirm the proposed constitution (*3*). During the course of this work, we discovered a rearrangement reaction characteristic of α-acyllactones, in which di- and tetrahydrofuran or pyran derivatives are readily obtained by the proton-catalyzed alcoholysis of substituted γ- or δ-lactones. We designated this reaction the α-hydroxyalkylidenelactone rearrangement.

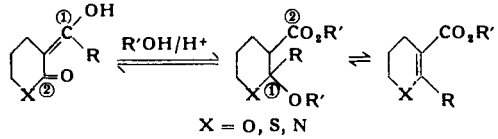
Lactones with other α-acyl esters, e.g., α-hydroxymethylenearyl or α-oximino can also be converted. β-Acyllactones are also capable of undergoing a rearrangement (see p. 218). We should therefore prefer to name the reaction more generally and briefly the acyllactone rearrangement. Further investigation showed that the reaction can also be effected in an aqueous medium; heterocyclic acids or their decarboxylation products are then produced. Inspection of the literature revealed that the rearrangement in H_2O/H^+ had successfully been applied to synthetic work on many previous occasions. All the reactions can be included under the common heading of acyllactone rearrangement and, depending on the constitution of the acyl compound and on the rearrangement medium, they can be classified according to definite reaction sequences. In this review, we hope to give a survey of the work to date and the results

obtained, and to show the limitations in the application of the acyllactone rearrangement.

Preparative Methods

Preparation of the α-Acyl Derivatives

The rearrangement proceeds according to the general scheme



X = O, S, N

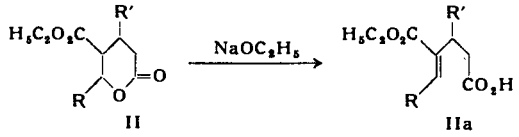
and is to be regarded as a sequence of equilibrium reactions (*4,5*). The α-acyllactones, -lactams and -thiolactones required as starting materials can be prepared in the following ways.

By Ester Condensation

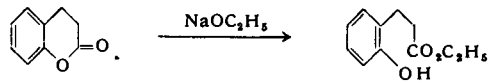
Lactones or thiolactones, being internal esters, can be condensed with esters in the presence of an equimolar quantity of a base. The mixed ester condensation thus constitutes a general practical method for the preparation of α-acyllactones, in which the α-acyl group can be varied within wide limits. Since many lactones are sensitive to bases and are converted into their open-chain isomers, the success of the reaction frequently depends on the condensing base employed. The following are among the condensing agents which can be used: powdered sodium or potassium, sodium ethoxide, sodium hydride, sodium amide, diisopropylaminomagnesium bromide, triphenylmethylsodium, sodium methylanilide, etc. (*4, 6–12*).

Stable mono- and bicyclic γ- and δ-lactones condense with oxalic or formic ester, and give yields of up to 80% when powdered sodium is used as the condensing agent (*13*). Condensations with ethyl acetate give better yields with sodium hydride (*9*), as the autocondensation of ethyl acetate in the presence of sodium to give acetoacetic ester reduces the yield of α-acetyllactone.

γ-Carbethoxy-δ-lactones (II) isomerize to α-ethylideneglutaric acid half-esters (IIa) in the presence of sodium ethoxide; dihydrocoumarin (III) yields α,β-dihydrocoumaric ester (IIIa).



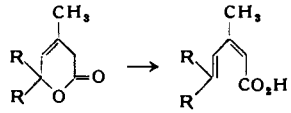
II IIa



III IIIa

The condensation of these lactones with ethyl formate or ethyl oxalate can nevertheless be accomplished by the use of Grignard bases such as diisopropylaminomagnesium bromide (*10*, *13*).

β,γ- or α,β-Unsaturated δ-hydroxypentenoic acid lactones, e.g., IV, do not condense with esters, but isomerize under the influence of basic condensing agents to give substituted sorbic acids (*10*).



IV V

The unstable thiolactones are also best condensed by means of Grignard bases (*14–16*). Ruzicka (*17*) and Späth (*18*) have reported on the condensation of lactams and both quinolinecarboxylic ester and nicotinic ester by the use of sodium ethoxide. Table 1 shows the yields of α-ethoxalyl-N-methylpyrrolidone obtained under constant working conditions, and their dependence on the condensing base utilized (*11*, *12*).

The preparation of α-acetyllactams by ester condensation has thus far been unsuccessful. The activation of the α-position is weaker in the

TABLE 1

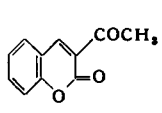
Dependence of the Yield of α-Ethoxalyl-N-methylpyrrolidone on the Condensing Agent

Condensing agent	Yield of α-Ethoxalyl-N-methyl-pyrrolidone (%)
Diisopropylamino-Mg-Br	0
Sodium ethoxide	5.7
$NaNH_2$	6.1
Powdered sodium	4.8
$(C_6H_5)_3Na$	11.1
$(C_6H_5NHCH_3)$ (Na)	21.1
Potassium	45.6
NaH	70.0

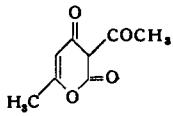
case of lactams than it is in that of lactones, with the result that the condensation does not proceed as readily. The α-acylcarboxylic acid derivatives exhibit a higher ring stability compared to the unsubstituted parent substances, i.e., the lactones, thiolactones, and lactams (*15*).

By Direct Synthesis

Ring closure is especially effective for the one-step preparation of α-acetyllactones. Thus, according to Lacey (*19*), various substituted α-acetyl-γ- and -δ-lactones are obtained from α- or β-hydroxyaldehydes or -ketones with diketene, e.g., α-acetylcoumarin (VI) from salicylaldehyde and diketene.

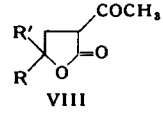


VI

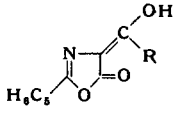


VII

α-Acetyllactones are similarly formed by the reaction between substituted propargyl alcohols and diketene (*19*). Dehydroacetic acid (VII) is obtained by the condensation of acetoacetic ester (*20*) or diketene (*21*). According to Knunjanz (*22*), α-acetyl-γ-lactones (VIII) can be prepared from ethylene, propylene, or butylene (*23*) oxides and acetoacetic ester. α-Acyllactones containing nitrogen in the ring are also formed by a simple ring closure. 4-Hydroxyalkylideneoxazolin-5-one (IX) can be prepared from sodium hippurate and acetic anhydride (*24*) or orthoformic ester (*25*) in this manner.



VIII

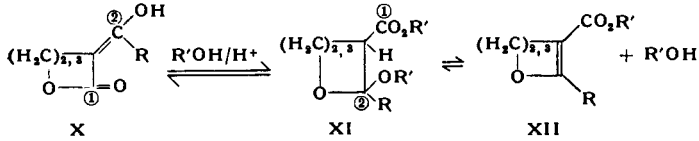


IX

Methods of Rearrangement

In Alcohol/H⁺

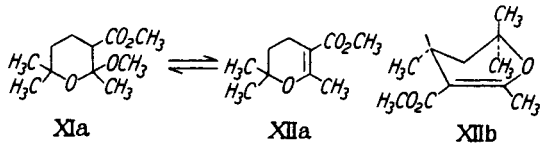
Lactones which are readily opened by alcoholysis, e.g. mono- and bicyclic α-acyl-δ-lactones, rearrange even at room temperature. In order to effect the reaction, the α-acyllactone is dissolved in 5–10 times its quantity of absolute alcohol to which 3–6% of hydrochloric or other acid has been added, and the solution allowed to stand for one or two days. The acid is then neutralized with saturated potassium carbonate or bicarbonate solution and the rearrangement product extracted with



X XI XII

ether. Yields of 80–95% are obtained throughout. More stable acyllactones, e.g. α-acyl-γ-lactones, are rearranged in boiling alcohol/H^+.

As shown in examples X, XI, and XII, heterocyclic carboxylic esters (XI) in equilibrium with the dihydrofuran or pyran form, XII, can thus be prepared from α-acyllactones. The R group in the α-acyl grouping appears in the rearrangement product XI at position 2, while the R′ group contained in the rearrangement solvent becomes linked to position 2 via the oxygen atom and to position 3 in the ester grouping. Distillation of the rearrangement product XI in the presence of catalytic amounts of polyphosphoric or sulfuric acid yields the pure dihydro compound XII via R′OH elimination. The preparation of the pure tetrahydrofuran or pyran compound XI is best achieved by effecting the rearrangement in higher alcohols, since the mixtures of dihydro and tetrahydro forms obtained are then more readily separated by distillation (see Experimental section). The rearrangement, consisting of a sequence of equilibrium reactions, is reversible. If the ester XII is dissolved in 30% perchloric acid and 2,4-dinitrophenylhydrazine added, the 2,4-dinitrophenylhydrazone of the α-acyl compound X is obtained. The composition of the mixture of XI and XII resulting from the rearrangement is affected by both the ring size and the substitution. In the case of the six-membered α-hydroxymethylene- and α-ethoxalyllactones the proportion of dihydro product XII lies between 10 and 20%, while with the corresponding five-membered lactones it is 1–5%. If, as in the rearrangement of the α-acetyl-γ- and δ-lactones, the product contains a methyl group in position 2, the proportion of dihydro product rises appreciably and lies between 40 and 60%. In the pyrancarboxylic esters XIa, an additional methyl group in the C_6-position causes a further displacement in the equilibrium, to 90% of XIIa. This phenomenon can be accounted for by the steric hindrance resulting from the



XIa XIIa XIIb

reciprocal effect of the two axial 2,6-methyl groups. The unsaturated dihydropyran XIIa, which exists in the strainless half-chair conformation XIIb, is formed by the elimination of methanol (*9*).

In Aqueous Acid

If the rearrangement is carried out in concentrated hydrochloric acid, the acyl compound is dissolved in the acid—which contains added

acetic acid or dioxane in the case of more insoluble compounds—and the solution allowed to stand at room temperature or in the refrigerator (0°). In rearrangements involving decarboxylation the equilibrium is shifted in favor of the rearrangement product by the crystallization of the heterocyclic carboxylic acid or the evolution of CO_2. The isolation of soluble rearrangement products is accomplished by neutralizing the solution with alkali carbonate and extracting with ether.

Rearrangement of stable acyllactones in dilute acids (e.g., 2 *N* HCl, 2 *N* H_2SO_4, 2 *N* $HClO_4$) is effected by heating under reflux, when decarboxylation usually occurs. This can be avoided in some cases by working at room temperature or by cooling in ice.

Special Methods

The rearrangement of α,β-unsaturated α-acyl-γ-lactones to furan-3-carboxylic acids is carried out in acetic acid/HCl or acetic acid/H_2SO_4 (*19*). The double bond migrates to the β,γ-position during the reaction. BF_3 etherate or $AlCl_3$ can also be used (*19*).

In the rearrangement of acyl-γ-lactams by hydrolysis with concentrated HCl, the ring closure to the pyrrolidine presents some difficulty. It can be accomplished by the hydrogenation of the carbonyl of the acyl group followed by iodination of the hydroxyl group and elimination of HI (see pp. 211–213).

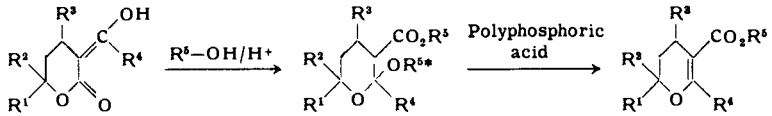
α-Acyloxazolin-5-ones can be opened by alcoholysis, and only ring-close to the oxazole-4-carboxylic ester after heating with $SOCl_2$ or a mixture of H_2SO_4 and acetic anhydride (*26*).

The method of Cornforth represents a special variant of the rearrangement process; according to this modification, the sodium salts of oxazole-4-carboxylic acids are obtained by heating the sodium salts of the hydroxyalkylideneoxazolin-5-ones (see p. 213). The rearrangement of some nitrogen heterocycles is favored by the presence of strong alkali hydroxides (*27–29*) (see p. 214).

Special Reactions

Rearrangement of α-Acyl-δ-lactones

The preparation of alkyl-substituted α-acyl-δ-lactones presents no difficulty. The ester condensations with formic, oxalic, and acetic ester proceed in good yield when powdered sodium or sodium hydride is used as the condensing agent. Table 2 shows a number of rearrangement products (XIVa to XIVl) and the yields obtained. The corresponding dihydropyran compounds XVa to XVl are readily obtained by distillation with polyphosphoric acid.



XIII (a–l) XIV (a–l) XV (a–l)

γ-Carbethoxy-δ-caprolactones isomerize to α-ethylidenеglutaric esters when the condensation with powdered sodium or sodium ethoxide is attempted (*10*). The ester condensation can nevertheless be accomplished by the use of strongly basic condensing agents such as sodium amide,

TABLE 2

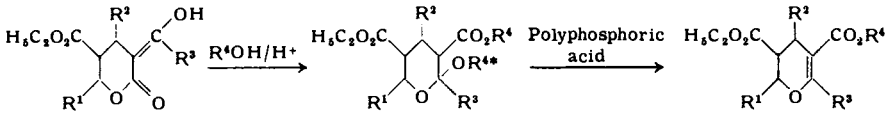
Products of the Rearrangement of Alkyl-Substituted α-Acyl-δ-lactones

	XIII				XIV [a]			XV		
	R^1	R^2	R^3	R^4	R^5	Yield (%)	B. p. (°C/mm Hg)	Yield (%)	B. p. (°C/mm Hg)	Lit. ref.
a	CH_3	H	H	H	CH_3	80	43–44°/0.05	88	91°/11	(*7*)
b	CH_3	CH_3	CH_3	H	CH_3	79	50–51°/0.05	92	104–105°/12	(*7*)
c	CH_3	H	CH_3	H	CH_3	58	56–57°/2	82	91–92°/12	(*6*)
d	H	H	CH_3	H	CH_3	48	38–40°/0.2	56	53°/1.5	(*30*)
e	$CH(CH_3)_2$	H	H	H	CH_3	67	58–59°/0.01	90	57°/0.03	(*31*)
f	CH_3	H	H	$CO_2C_2H_5$	CH_3 $R^{5a} = H$	66	Mp 90°	90	95°/0.03	(*32*)
g	CH_3	CH_3	CH_3	$CO_2C_2H_5$	CH_3	85	74°/0.01	96	79°/0.01	(*32*)
h	CH_3	H	CH_3	$CO_2C_2H_5$	C_2H_5 $R^{5a} = H$	73	103–104°/1	–	–	(*32*)
i	H	H	CH_3	$CO_2C_2H_5$	C_2H_5 $R^{5a} = H$	73	87–88°/0.2	77	92°/0.2	(*30*)
j	CH_3	H	H	CH_3	CH_3	80 [b]	41–44°/0.05	87	92°/12	(*9*)
k	H	H	H	CH_3	CH_3	80 [b]	45–46°/0.04	88	97°/12	(*9*)
l	CH_3	H	CH_3	CH_3	CH_3	70 [b]	42–45°/0.1	85	86°/10	(*8*)

[a] When not indicated otherwise, $R^{5a} = R^5$.

[b] Mixed with XV.

sodium hydride, and especially diisopropylaminomagnesium bromide (*10, 33*). The rearrangement of the α-acyl-γ-carbethoxylactones in ethanol/H^+ gives good yields of dihydropyran-3,5-di- and 2,3,5-tricarboxylic esters (Table 3).



XVI (a–c) XVII (a–c) XVIII (a–c)

The formation of stable cyclohemiacetals of type XIX during the rearrangement of primary and secondary α-ethoxalyl-δ-lactones is not without interest. The structural evidence was adduced by degradation

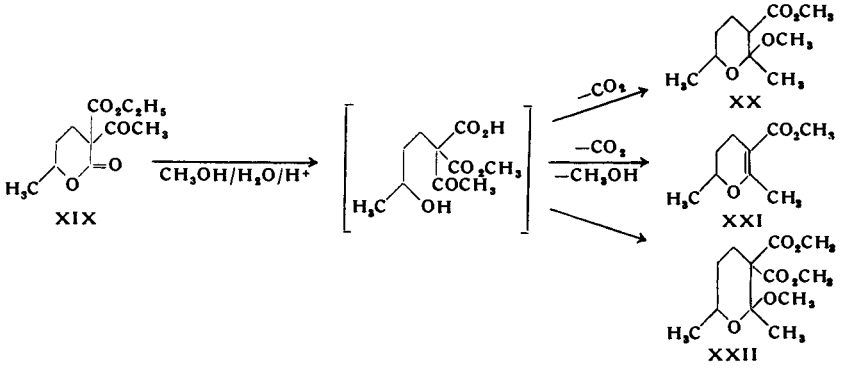
TABLE 3

Products of the Rearrangement of α-Acyl-γ-carbethoxy-δ-lactones

	XVI			XVII[a]			XVIII		
	R^1	R^2	R^3	R^4	Yield (%)	B.p. (°C/mm Hg)	Yield (%)	B.p. (°C/mm Hg)	Lit. ref.
a	CH_3	H	H	C_2H_5	78	95°/0.05	88	86°/0.05	(*10*)
b	CH_3	H	$CO_2C_2H_5$	C_2H_5 R^{4a} = H	71	125–126°/0.01	90	124°/0.02	(*10*)
c	CH_3	CH_3	H	C_2H_5	50	58–59°/0.01	70	65–67°/0.01	(*33*)

[a] When not indicated otherwise R^{4a} = R^4.

reactions (*32*). The formation of the 2-hydroxy compounds can be explained by solvolysis and steric hindrance (see the section on ring opening of α-acyl-δ-lactones).



An exceptional reaction course is followed during the rearrangement of compound XIX (*9*). Apart from the normal rearrangement product XXII, the decarboxylation products XX and XXI can also be isolated. The reaction can be explained by the formation of a methanetricarboxylic acid-type intermediate and the latter's subsequent decarboxylation (*9*).

Rearrangement of α-Acyl-γ-lactones

Good yields of α-acyl-γ-lactones are obtained via ester condensation by the use of powdered sodium. α-Acetyl-γ-lactones can also be prepared according to the method described by Knunjanz (*22, 9, 23*). The rearrangement in methanol or ethanol/H^+ results in the formation of 2-alkoxytetrahydrofurans, which are readily converted into the corresponding dihydrofuran derivatives by the elimination of alcohol (Table 4).

α-Benzoylbutyrolactone (XXVI) rearranges in an analogous manner, yielding 2-phenyl-substituted tetrahydro or dihydrofuran derivatives (XXVIIa and b) (*34*).

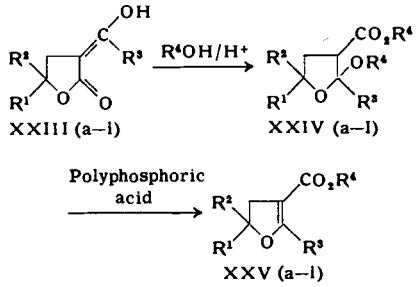
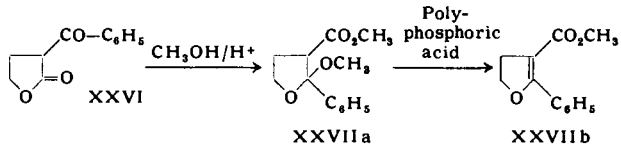


TABLE 4

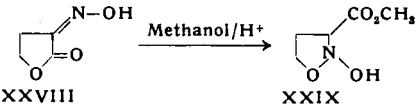
Products of the Rearrangement of α-Acyl-γ- lactones

	XXIII			XXIV[a]			XXV		
	R^1	R^2	R^3	R^4	Yield (%)	B. p. (°C/mm Hg)	Yield (%)	B. p. (°C/mm Hg)	Lit. ref.
a	H	H	H	CH_3	82	85–86°/13	79	70°/10	(*4*)
b	H	H	$CO_2C_2H_5$	CH_3	54	72–73°/0.03	88	75°/0.02	(*32*)
c	H	H	CH_3	CH_3	40[a]	74–77°/12	93	72–73°/11	(*9*)
d	CH_3	H	H	CH_3	60	84°/9	81	75°/9	(*30*)
e	CH_3	H	CH_2CH_3	CH_3	71	66°/0.01	–	–	(*9*)
f	CH_3	H	CH_3	CH_3	43[a]	75–78°/11	92	76°/11	(*32*)
g	CH_3	CH_3	H	CH_3	64	84–85°/9	86	75–76°/9	(*30*)
h	CH_3	CH_3	$CO_2C_2H_5$	C_2H_5	61	76–78°/0.01	91	74°/0.1	(*30*)
i	CH_3	CH_3	CH_3	CH_3	70[a]	36–41°/0.2	90	81–82°/12	(*30*)

[a] Mixed with XXVI.

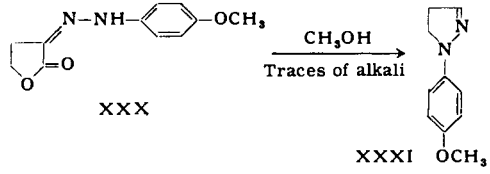


α-Oximino-γ-butyrolactone (XXVIII), obtainable from α-aceto-γ-butyrolactone and ethyl nitrite (*35*), can be rearranged in methanol/H^+ to give 2-hydroxy-3-carbomethoxyisoxazolidine (XXIX) (*34*).



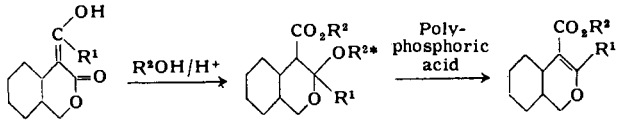
α-Hydroxymethylene-γ-butyrolactone couples with diazotized *p*-methoxyaniline at pH 7. Deformylation yields the azo compound or its tautomeric form, the *p*-methoxyphenylhydrazone XXX; the latter is re-

arranged and decarboxylated in boiling methanol containing traces of alkali, to give the pyrazoline derivative XXXI (*27*). An analogous rearrangement to the pyridazine system is known in the case of a δ-lactone hydrazone (*35a*).



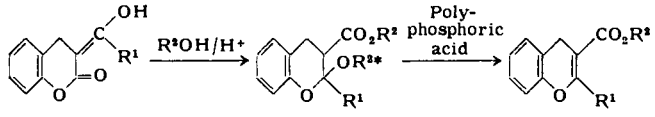
Rearrangement of Bicyclic α-Acyl-γ- and -δ-lactones

Bicyclic δ-lactones, which possess the same skeleton as the ant poison iridomyrmecin (*36*), can be condensed with esters in the presence of powdered sodium (*8*). The rearrangement in methanol or ethanol/H^+ of the α-acyllactones (XXXII) which are formed results in good yields of hexahydroisochroman (XXXIII) or hexahydroisochromene derivatives (XXXIV) (*8*).



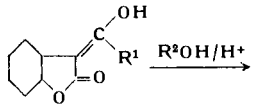
XXXIIa, b	XXXIIIa, b		XXXIVa, b
a: $R^1 = H$	$R^2 = R^{2*} = CH_3$	Yield 67%	Yield 91%
b: $R^1 = CO_2C_2H_5$	$R^2 = C_2H_5$, $R^{2*} = H$	Yield 95%	Yield 68%

Ester condensations of dihydrocoumarin and formic or oxalic ester can be effected by diisopropylaminomagnesium bromide; the use of sodium or sodium ethoxide results mainly in the formation of *o*-dihydrocoumaric ester. The rearrangement of the acyl compounds, XXXVa, b, yields derivatives of chroman (XXXVI) or chromene (XXXVII) (*8*).

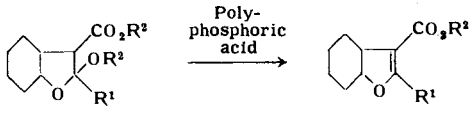


XXXVa, b	XXXVIa, b		XXXVIIa, b
a: $R^1 = H$	$R^2 = R^{2*} = CH_3$	Yield 84%	Yield 71%
$R^1 = CO_2C_2H_5$	$R^2 = C_2H_5$, $R^{2*} = H$	Yield 88%	Yield 75%

Bicyclic α-acyl-γ-lactones (XXXVIII) are readily prepared via an ester condensation in the presence of sodium. Rearrangement in methanol or ethanol/H^+ yields derivatives of hexahydrocoumaran (XXXIX) or hexahydrocoumarone (XL) (*8*).



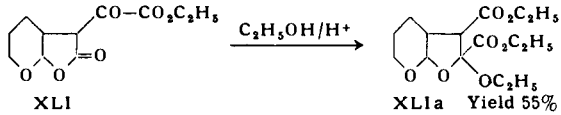
XXXVIIIa, b
a: $R^1 = H$
b: $R^1 = CO_2C_2H_5$



XXXIXa, b
$R^2 = CH_3$ Yield 81%
$R^2 = C_2H_5$ Yield 78%

XLa, b
Yield 92%
Yield 80%

Ester condensations with hemiacetallactones afford only small yields. The α-ethoxalyllactone XLI rearranges to the diketal XLIa in ethanol/H^+ (*8*).



XLI

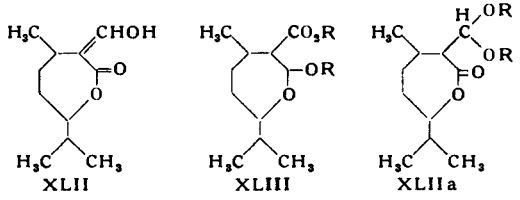
XLIa Yield 55%

Rearrangement of Macrocyclic α-Acyllactones

The acylation by ester condensation of macrocyclic lactones from ϵ-caprolactone upwards has thus far not been accomplished in satisfactory yield. The fundamental difficulty resides in the strong tendency shown by these lactones to polymerize in the presence of traces of soluble alkali. Thus ϵ-caprolactone could only be acylated to the extent of 1–2% by formic ester/sodium. Ester condensations using heptanolide (7-hydroxyheptanolactone) raised the yield to 10–15%; the major products are polymers such as di-, tetra-, or heptameric lactones (*37*). Grignard bases are completely useless as condensing agents. Alkyl-substituted lactones show in general a lower tendency to undergo polymerization. Thus, while say, δ-valerolactone cannot be subjected to ester condensation on account of the immediate onset of polymerization, α-acyl-δ-caprolactones are formed in good yield. Even β-methyl-ϵ-isopropyl-ϵ-caprolactone (mentholide) however, affords yields of only 2–5% of acyllactone by the ester condensation with sodium, potassium, or Grignard bases (*38*). Ring stabilization by alkyl substitution is no longer adequate in the case of ϵ-lactones. According to the investigations of Huisgen and Ott (*39*), a *cis* to *trans* change in configuration occurs in lactones of medium ring size. The *trans*-lactones, from approximately

nonalide onwards, again display an increased stability; this is evidenced by the hydrolysis constants, for example, which are of the same order as the constants of open-chain *trans*-esters. Ester condensations should therefore proceed more favorably again from nonalide upwards. In condensation experiments with 15,1-hexadecanolide, however, no acyl product could be detected (*40*). Compared to the γ- and δ-lactones, the macrocyclic *trans*-lactones manifestly occupy a special position in chemical reactions; also, they are hardly comparable to the homologous open-chain esters in their chemical behavior [cf. their behavior during Friedel-Crafts reaction (*41*)].

If the crude condensation products of mentholide containing 2–5% of the acyl compound XLII are dissolved in methanol/H^+, the enol reaction with $FeCl_3$ and the UV absorption band at 240 mμ due to the acyl compound both disappear after a certain time. This can be explained by either a rearrangement to XLIII or the formation of the acetal XLIIa. No well-defined products have thus far been isolated in pure form.



Rearrangement of α-Acyl-γ- and -δ-thiolactones

In the ester condensation of γ- and δ-thiolactones, the best yields are obtained by the use of diisopropylaminomagnesium bromide or sodium hydride as condensing agent (*8, 14–16*). In contrast to the oxygen homologs, no 2-alkoxytetrahydro compounds are formed during the rearrangement; instead, the elimination of alcohol results in the immediate formation of the 2-alkoxydihydro compounds. The elimination of alcohol is promoted by the pronounced participation of the free electron pairs of sulfur in the mesomeric system (cf. the section on optical measurements). α-Acyl-γ-thiolactones (XLIV) and α-acyl-δ-thiolactones (XLVI) yield 4,5-dihydrothiophene-3-carboxylic esters or -2,3-dicarboxylic esters (XLV, Table 5) and 5,6-dihydrothiopyran-3-carboxylic

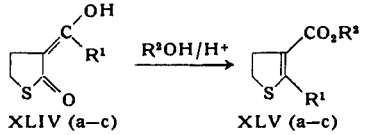
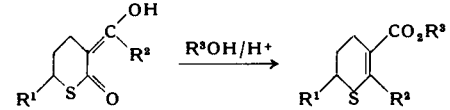


TABLE 5
Products of the Rearrangement of α-Acyl-γ-thiolactones

	XLIV	XLV		
	R^1	R^2	Yield (%)	B. p. (°C/mm Hg)
a	H	CH_3	84	43-46°/0.5
b	CH_3	CH_3	73	52-54°/0.5
c	$CO_2C_2H_5$	C_2H_5	86	96-98°/0.05

esters or -2,3-dicarboxylic esters (XLVII, Table 6), respectively. The corresponding acids are obtained by the alkaline saponification of the



(XLVI (a–f)) XLVII (a–f)

esters. Unlike the dihydrofuran-3-carboxylic acids, the dihydrothiophene-3-carboxylic acids are not readily decarboxylated; nor is it possible to add methanol to the double bond under normal conditions (*14*).

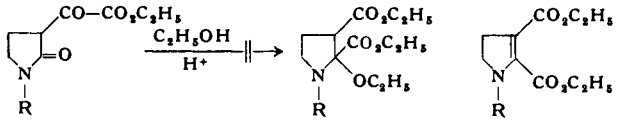
TABLE 6
Products of the Rearrangement of α-Acyl-δ-thiolactones

	XLVI		XLVII			
	R^1	R^2	R^3	Yield (%)	B. p. (°C/mm Hg)	Lit. ref.
a	H	H	CH_3	82	64-66°/0.15	(*15*)
b	H	CH_3	CH_3	91	65-67°/0.4	(*15*)
c	H	$CO_2C_2H_5$	C_2H_5	83	119-120°/0.3	(*15*)
d	CH_3	H	C_2H_5	80	63°/0.2	(*16*)
e	CH_3	CH_3	CH_3	81	103°/0.1	(*16*)
f	CH_3	$CO_2C_2H_5$	C_2H_5	78	58°/0.01	(*16*)

Rearrangement of α-Acyllactams

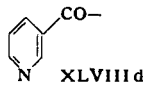
In order to avoid the N-acylation of lactams during the course of the ester condensation, it is best to effect the reaction on N-alkylated or N-arylated lactams. The difficulties encountered during the condensation of lactams have been referred to earlier. The solvolysis of the amide linkage is an essential prerequisite in the rearrangement of α-ethoxalyl-N-methyl-γ-butyrolactam (*11*) in alcohol/H^+. Ring stabilization of the cyclic carboxylic acid derivatives generally results from the acylation (see the section on optical measurements). α-Acyllactones are less susceptible to hydrolysis than are the unsubstituted lactones. Since lactams are more resistant to alcoholysis than lactones, it follows that α-acyllac-

tams are particularly stable to proton-catalyzed alcoholysis. Thus no change worth mentioning is observed in the α-acyl-γ-lactams (XLVIII) even after heating for 180 hr in ethanol containing 5% HCl. Though it is true that the UV absorption band at 301 mμ due to the acyl bond is diminished by 50–60% on boiling in absolute methanol/H_2SO_4, no pyrrolidinecarboxylic esters (XLVIIIa) or pyrroline derivatives of type XLVIIIb could be isolated (*11*).



XLVIII XLVIIIa ($R = CH_3$; C_6H_5) XLVIIIb

The amide linkage in γ-lactams is weakened by acylation with a strongly electronegative acyl group, such as the nicotinyl group (XLVIIId).



XLVIIId

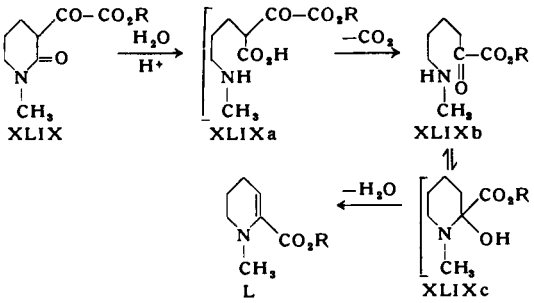
The fission of the α-nicotinyl-γ-lactams and their simultaneous decarboxylation is thus rendered possible by heating with concentrated HCl in a bomb tube. The ring-opened compound can be cyclized to the pyrrolidine (see p. 222). As in the case of the corresponding lactones, the δ-lactams are also opened solvolytically more readily than are the γ-lactams. Thus α-ethoxalyl-N-methyl-2-piperidone (XLIX) can be rearranged in boiling absolute ethanol/14%HCl (*42*); decarboxylation yields 2-carbethoxy-N-methyltetrahydropyridine (L) (*42, 43*).

The rearrangement to L involves the loss of one molecule of CO_2. In order to explain the course of the reaction, it must be assumed that the lactam ring is partially opened hydrolytically by the water present, as a result of the equilibrium due to the high concentration of HCl in the reaction medium.

$$C_2H_5OH + HCl \rightleftharpoons C_2H_5Cl + H_2O$$

This results in the formation of a β-ketoacid (XLIXa) which has a low stability like oxalacetic acid, and is decarboxylated to give the aminoketone XLIXb or hemiaminal XLIXc. Elimination of water stabilizes the latter as the tetrahydropyridinecarboxylic ester L.

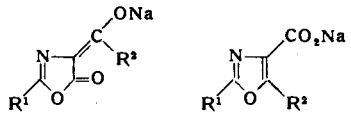
We have reported earlier on similar conditions of decarboxylation and esterification (*5*) (see also sections on Rearrangement of α-Acyl-δ-lactones and Rearrangement in Aqueous Mineral Acid). Other rearrange-



ments undergone by α-acyllactams in boiling hydrochloric acid are also described in the section on rearrangement in mineral acid.

Rearrangement of 4-Acyloxazolin-5-ones

The process used by Cornforth for the synthesis of oxazolecarboxylic acids (*44, 45*) may be regarded as an original variant of the α-acyllactone rearrangement. When the sodium salts of the 4-hydroxyalkylideneoxazolin-5-ones (LI) are heated, the sodium salts of the 5-alkyloxazole-4-carboxylic acids (LII) are obtained. This method has been applied to various oxazoline derivatives (*44, 46*) (see Table 7).



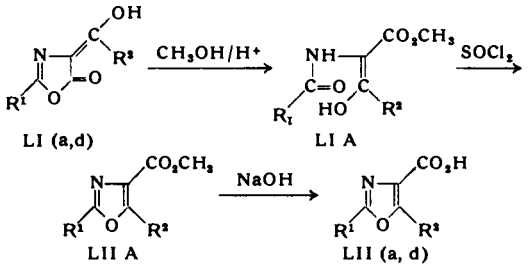
The rearrangement of oxazolones in alcoholic hydrochloric acid gives no satisfactory results. Only 2-benzyl-4-hydroxymethyleneoxazolin-5-one (LIb) rearranges in small yield in methanol/ethereal hydrochloric acid. The ester thus formed can be saponified with NaOH to give 2-benzyl-

TABLE 7

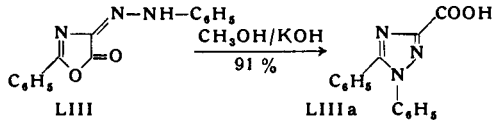
Yields of 5-Alkyloxazole-4- carboxylic Acids (LII) Resulting from the Rearrangement of 4-Hydroxyalkylideneoxazolin-5-ones (LI) by the Method of Cornforth

	R^1	R^2	Yield (%)
a	C_6H_5	H	78
b	C_6H_5—CH_2	H	29
c	C_6H_5—CH=CH	H	63
d	C_6H_5	CH_3	67
e	C_6H_5—CH=CH	CH_3	42
f	*n*-C_5H_{11}	H	–
g	C_3H_7—CH=CH	H	–

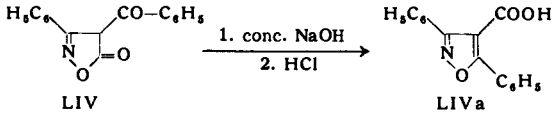
oxazole-4-carboxylic acid (LIIb) (*47*). Alcoholytic ring opening of the oxazolones (LI) causes the stabilization of the enolic γ-OH group as an acid amide group. With the exception of 2-benzyloxazolone, LIb, no ring closure of this ketoester (LIA) in methanol/H^+ to the oxazole-4-carboxylic ester (LIIA) could be observed (*26*). The cyclization of the open-chain acylaminoacetoacetic ester (LIA) can, however, be accomplished by heating with thionyl chloride or H_2SO_4/Ac_2O. Saponification of the oxazolecarboxylic esters (LIIA) with NaOH yields the oxazolecarboxylic acids (LII) (*26*).



The 4-phenylazo-2-phenyloxazolones can be rearranged in similar manner to the α-phenylazo-γ-lactones (XXX). Heating of LIII in methanol/20% KOH affords a high yield of 1,5-diphenyl-3-carboxy-1,2,4-triazole (LIIIa) (*28*). Tetrazolecarboxylic acids were obtained from 4-phenylazo-1,2,3-triazolones in corresponding manner (*47a*).



Isoxazolecarboxylic acids are also accessible via the acyllactone rearrangement. Thus treatment of 3-phenyl-4-benzoylisoxazol-5-one (LIV) with concentrated NaOH yields 3,5-diphenylisoxazole-4-carboxylic acid (LIVa) (*29*). Phenylfurazancarboxylic acids are formed from 3-aryl-4-oximinoisoxazol-5-ones in an analogous manner (*47b, 47c*).



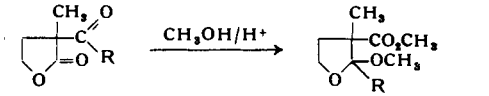
Rearrangement of α-Substituted α-Acyllactones

SUBSTITUTION BY MEANS OF ALKYL HALIDE

α-Hydroxyalkylidene-γ-lactones possess an additional acidic CH group in the α-position. The α-methylated lactones are obtained by heat-

ing under reflux with an excess of methyl iodide in absolute acetone (*48*). The method of Marshall and Cannon (benzene/dimethylformamide) also affords good yields (*49*).

The substitution of the α-hydrogen atom fixes the α-alkyl-α-acyllactones LV in the keto form, and no enol reaction with $FeCl_3$ is consequently observed. If LV (a–c) are heated for approximately 24 hr in absolute methanol containing 3% HCl, the tetrahydrofurancarboxylic esters LVI are obtained.



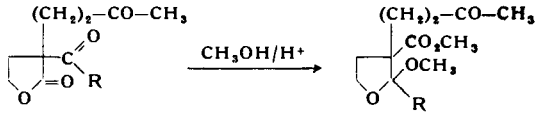
LV (a–c) LVI (a–c) (Yield 70%)

a: R = H b: R = CH_3 c: R = $CO_2C_2H_5$

These examples show that even nonenolizable α-acyllactones can be rearranged.

Substitution via the Michael Addition

α-Acyllactones can react as α-substituted β-dicarbonyl compounds by a Michael addition with α,β-unsaturated carbonyl compounds such as methyl vinyl ketone. The substituted α-acyl-γ-lactones LVII (a–b) thus obtained rearrange to the tetrahydrofurancarboxylic esters LVIII (a–b) in methanol/H^+ (*27*).

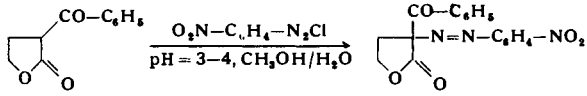


LVII (a, b) LVIII (a, b)

a: R = H b: R = $CO_2C_2H_5$

Substitution by Coupling with Diazonium Salts

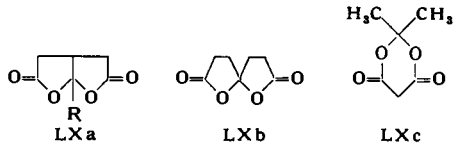
α-Acyllactones couple with diazonium salts in an aqueous medium. The acyl group is usually eliminated, and the azo compound is stabilized as the α-hydrazone of the corresponding lactone. In some instances, however, the azo compound can be isolated. Thus the azo compound LIX is obtained by coupling α-benzoylbutyrolactone (XXVI) with *p*-nitroanilinediazonium chloride (*49a*).



XXVI LIX (60 %)

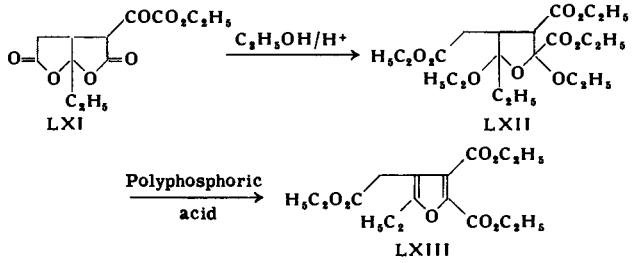
Rearrangement of Special Acyllactones

The rearrangement of dilactones of type LXa (*50*), LXb (*51*), LXc (*52*) offers interesting synthetic possibilities.



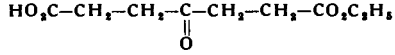
LXa LXb LXc

Ester condensations do not proceed uniformly with these unstable lactones. The use of NaH as condensing agent affords the best yields, and the monoacyllactones (e.g. LXI) are formed (*53*). Rearrangement of LXI in ethanol/H^+ results in the formation of a tetrahydrofuran ester lactone LXII, which is converted into the dihydrofuran derivative LXIII by distillation with polyphosphoric acid (*53*).



LXI LXII LXIII

The condensation accompanied by the alcoholytic fission of the lactone ring of the spirolactone LXb with formic ester and sodium yields approximately 80% of the γ-ketopimelic acid half-ester LXIV, and only a small quantity of α-acyllactone which is difficult to separate from the by-products (*53*).



LXIV

Rearrangement in Aqueous Mineral Acids

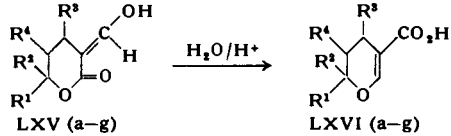
α-Acyllactones

The α-acyllactone rearrangement essentially also proceeds in water/H^+. The rearrangement of acyllactones in both absolute alcohol/H^+ and water/H^+ involves the solvolytic fission of the lactone ring; the former case results in the *trans*-esterification of the lactonecarboxyl group, the

latter in the formation of the heterocyclic 3-carboxylic acid. This crystallizes out, so that the equilibrium is displaced in the direction of the rearrangement product. If the open-chain intermediate or the carboxylic acid readily loses CO_2, various decarboxylation products dependent on the acid concentration are obtained.

The rearrangement can usually be effected extremely simply. If α-hydroxymethylene-δ-lactones (LXVa–g) are dissolved in concentrated hydrochloric acid at 25°, the corresponding dihydropyran-3-carboxylic acids (LXVIa–g) are precipitated after some time as colorless crystals in yields of 80–90%.

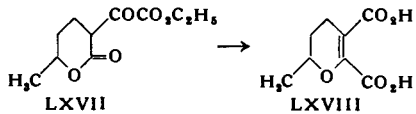
The ester group in the α-hydroxymethylene-γ-carbethoxy-δ-lactones LXVf and g remains unsaponified, and the half-esters LXVIf and g can be isolated.



LXV (a–g) LXVI (a–g)

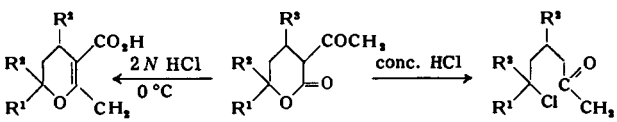
a: $R^1 = CH_3$, $R^2 = R^3 = R^4 = H$
b: $R^1 = CH(CH_3)_2$, $R^2 = R^3 = R^4 = H$
c: $R^1 = R^2 = R^3 = R^4 = H$
d: $R^1 = R^2 = R^3 = CH_3$, $R^4 = H$
e: $R^1 = R^2 = R^4 = H$, $R^3 = CH_3$
f: $R^1 = CH_3$, $R^2 = R^3 = H$, $R^4 = CO_2C_2H_5$
g: $R^1 = R^2 = CH_3$, $R^3 = H$, $R^4 = CO_2C_2H_5$

Rearrangement of α-ethoxalyl-δ-caprolactone (LXVII) in concentrated hydrochloric acid yields the 6-methyl-5,6-dihydro-4H-pyran-2,3-dicarboxylic acid (LXVIII) or its half-ester (*5*).



LXVII LXVIII

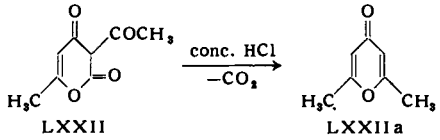
α-Acetyl-δ-lactones (LXIXa,b) dissolved in concentrated hydrochloric acid are decarboxylated even at room temperature and δ-chloroketones (LXXa,b) can be isolated. The rearrangement to the carboxylic acids LXXIa,b can, however, be accomplished in ice-cooled dilute hydrochloric acid.



LXXI (a, b) LXIX (a, b) LXX (a, b)

a: $R^1 = CH_3$, $R^2 = R^3 = H$ b: $R^1 = R^2 = R^3 = CH_3$

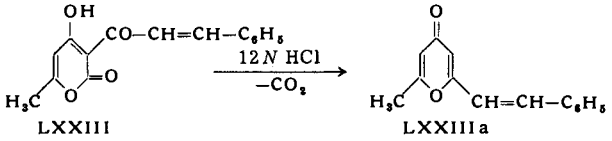
The long-known conversion of dehydroacetic acid (LXXII) in concentrated hydrochloric acid into 2,6-dimethyl-γ-pyrone (LXXIIa) (*54*), is also an example of an acyllactone rearrangement in H_2O/H^+.



LXXII LXXIIa

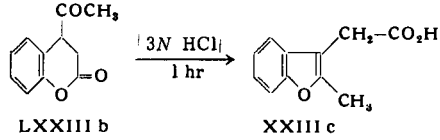
This rearrangement is also undergone in ethanol/H^+. The course of the reaction is explained below.

The conversion, discovered by Wiley, of 3-cinnamoyl-4-hydroxy-6-methyl-2-pyrone (LXXIII) into the γ-pyrone derivative LXXIIIa is an example of the rearrangement of lactones containing unusual acyl groups (*55*).



LXXIII LXXIIIa

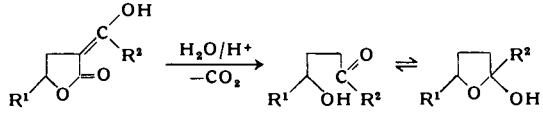
The rearrangement of a β-acyl-δ-lactone is described by Lawson (*55a*). If 4-acetyl-3,4-dihydrocoumarin (LXXIIIb) is heated for 1 hr in 3 *N* hydrochloric acid, 2-methylbenzofuran-3-acetic acid (LXXIIIc) is formed.



LXXIII b XXIII c

No further examples of the rearrangement undergone by β-acyllactones are available as yet, due to the difficulties encountered in the preparation of these compounds.

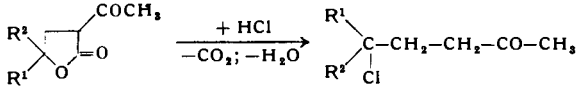
The rearrangement of α-hydroxyalkylidene-γ-lactones (LXXIV) yields only small quantities of dihydrofuran-3-carboxylic acids, as these are very readily decarboxylated in aqueous mineral acids. γ-Hydroxyketones (LXXIVa) are obtained instead, and these can be identified as their 2,4-dinitrophenylhydrazones (*5, 22*).



LXXIV LXXIVa

$R^1 = H, CH_3$ $R^2 = H, CO_2C_2H_5$

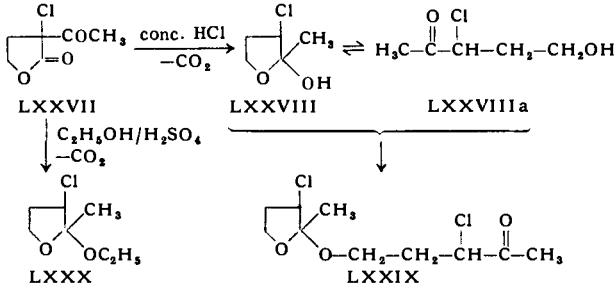
α-Acetyl-γ-lactones (LXXVa–c) are decarboxylated in concentrated hydrochloric acid at room temperature (*5*), resulting in good yields of γ-chloroketones (LXXVIa–c).



LXXV (a–c) LXXVI (a–c)

a: $R^1 = R^2 = H$ b: $R^1 = CH_3$, $R^2 = H$ c: $R^1 = R^2 = CH_3$

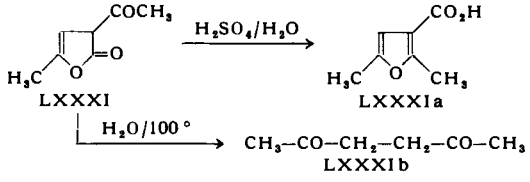
α-Substituted α-acyllactones will also undergo a rearrangement in aqueous acids. If α-chloro-α-acetylbutyrolactone (LXXVII) is heated with conc. HCl, loss of CO_2 results in the formation of a hemiketal LXXVIII in equilibrium with the open-chain chloroketoalcohol, LXXVIIIa (*56*). Stevens (*57*) was able to show that the hemiketal, LXXVIII, partially condenses with the alcohol LXXVIIIa to give the ketal LXXIX. A patent specification by Klingenfuss (*58*) describes a "saponification" of compound LXXVII, effected by warming in ethanol/H_2SO_4 at 50°, to the ketal LXXX. The formation of the 2-alkoxytetra-



LXXVII LXXVIII LXXVIIIa LXXX LXXIX

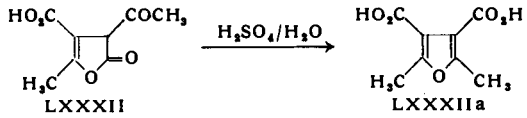
hydrofurans is in agreement with the results obtained in the rearrangement of other α-acyl-γ-lactones (see above).

Furan-3-carboxylic acids are less readily decarboxylated than dihydrofuran-3-carboxylic acids. β,γ-Unsaturated α-acyllactones can consequently readily be converted into furancarboxylic acids by means of aqueous acid, as illustrated by the trouble-free conversion of α-acetylangelica lactone (LXXXI) into pyrotritaric acid (LXXXIa). Vigorous reaction conditions will, however, also cause decarboxylation to acetonylacetone (LXXXIb) in this instance (*59*).



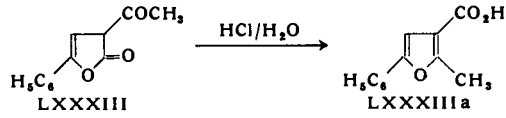
LXXXI LXXXIa LXXXIb

The isocarbopyrotritaric acid (LXXXII) yields a furandicarboxylic acid LXXXIIa (carbopyrotritaric acid) (*60*).



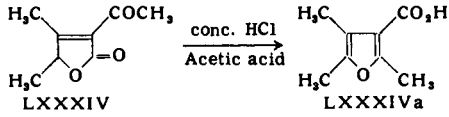
LXXXII LXXXIIa

A similar reaction is undergone by 3-acetyl-5-phenyl-3H-2-furanone (LXXXIII), which is rearranged to 2-methyl-5-phenylfuran-3-carboxylic acid (LXXXIIIa) (*61*).

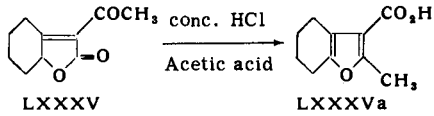


LXXXIII LXXXIIIa

α,β-Unsaturated α-acetyllactones also rearrange in yields of over 90% to furan-3-carboxylic acids, as shown by examples LXXXIV–LXXXIVa and LXXXV–LXXXVa (*62*).

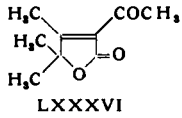


LXXXIV LXXXIVa



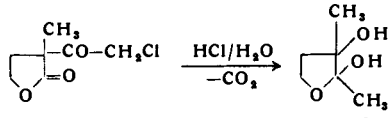
LXXXV LXXXVa

In this reaction, the double bond is displaced into the β,γ-position. If the γ-position in the α-acyllactone is blocked by a tertiary grouping, as e.g., in 2,2,3-trimethyl-4-acetyl-5-furanone (LXXXVI), no furancarboxylic acid can be formed (*8*).



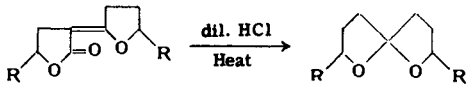
LXXXVI

The formation of the dihydroxyfuran LXXXVIII from the α-chloroacetyl-α-methyl-γ-butyrolactone LXXXVII (*63*) demands a special reaction mechanism (see the section on optical measurements). Essentially, however, this is also an example of an acyllactone rearrangement.



LXXXVII LXXXVIII

An interesting reaction undergone by the "dibutolactones" [α-(2-tetrahydrofurylidene)-γ-hydroxybutyrolactones, LXXXIX] was reported by Fittig as long ago as 1892 (*64*). On heating in dil. HCl they yield spiro compounds of the type XC by decarboxylation. Fittig called this class of compounds "oxetones."

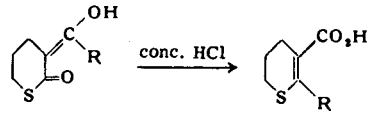


LXXXIX R = H, CH_3, C_2H_5 XC

Dibutolactone may be considered as an α-acyllactone stabilized in the enol form. The formation of the oxetones is thus also an example of an acyllactone rearrangement.

α-Acylthiolactones

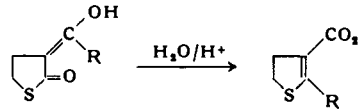
The action of conc. HCl on the α-hydroxyalkylidene-δ-thiolactones, XCI, results in the formation of the dihydrothiopyrancarboxylic acids XCII; these thus become readily accessible via this simple reaction (*65*). The rearrangement of α-acetyl-δ-thiolactone is completed after only a few minutes. The dicarboxylic acid XCIIc is present in the reaction mixture as the anhydride.



XCI (a–c)
a: R = H b: R = CH_3
c: R = $CO_2C_2H_5$

XCII (a–c)
a: R = H b: R = CH_3
c: R = CO_2H

Of the α-acyl-γ-thiolactones, only the α-ethoxalyl compound, XCIIIc, rearranges in good yield. In the case of the α-hydroxymethylene- and α-acetylthiolactones XCIIIa and b, the yield of dihydrothiophenecarboxylic acids is reduced by a retrogressive ester condensation (acid cleavage) and partial decarboxylation (ketonic cleavage). Compounds XCIVa–b are obtained more easily by rearrangement in alcohol/H^+ followed by the saponification of the esters.

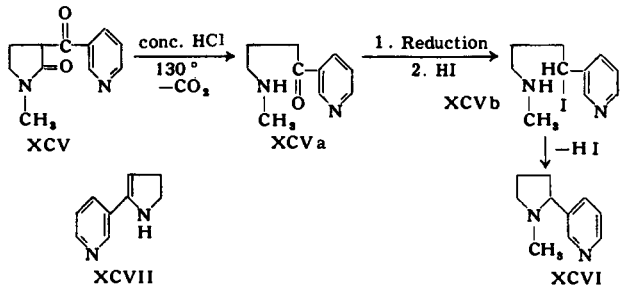


XCIII (a–c)
a: R = H b: R = CH_3
c: R = $CO_2C_2H_5$

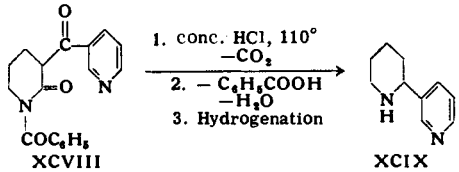
XCIV (a–c)
a: R = H b: R = CH_3
c: R = COOH

α-ACYLLACTAMS

The hydrolytic ring opening of α-acyllactams can be effected either by heating with conc. HCl in a bomb tube at 130° or by boiling under reflux, when decarboxylation takes place. Various examples of this reaction are described in the literature (*66*). Späth and Bretschneider applied this method to the synthesis of nicotine (*18*). The recyclization to the heterocycle is however not always achieved under the conditions of the rearrangement. This can then be effected via an indirect method: N-methylpyrrolidone is condensed with nicotinic ester to the α-acyllactam XCV, which is hydrolyzed to XCVa with HCl in a bomb tube. The carbonyl group is reduced and the alcohol formed converted into the alkyl iodide XCVb, which then cyclizes to DL-nicotine (XCVI) with the elimination of HI.

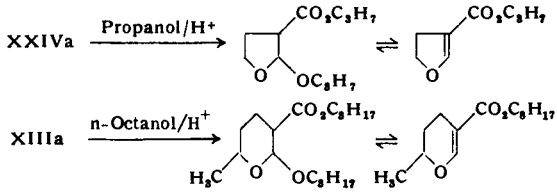


The synthesis of myosmine (XCVII) proceeds along similar lines (*67*). In this instance, ring opening, debenzoylation, and recyclization occur when α-nicotinyl-N-benzoyl-2-pyrrolidone is heated in conc. HCl; the detour via the iodide consequently becomes superfluous. α-Acylpiperidones can also be opened in boiling conc. HCl. The fission is then accompanied by the simultaneous rearrangement to the tetrahydropyridine; this reaction also agrees with the scheme of the acyllactone rearrangement accompanied by the loss of CO_2 and H_2O. The tetrahydropyridine ring is readily hydrogenated to piperidine. The synthesis of DL-anabasine (XCVIII → XCIX) is an example of this type of rearrangement (*68*). In the meantime, the rearrangement of various α-acyl-N-methylpiperidones to the corresponding piperideine derivatives was also accomplished (*13*).

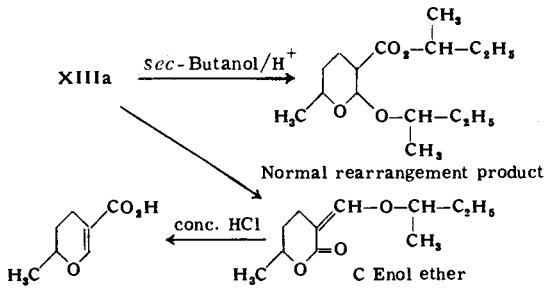


Rearrangement in Higher Alcohols

α-Acyllactones can essentially also be rearranged in the presence of higher alcohols (*69*). α-Hydroxymethylenelactones (XXIVa or XIIIa)

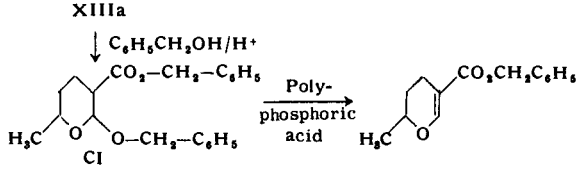


thus yield the corresponding tetrahydro- and dihydrofuran- or pyran-carboxylic esters, respectively, of propanol to *n*-octanol.



Besides the normal products the rearrangement in *sec*-butanol also results in the partial formation of the enol ether, C, which rearranges to dihydropyran-3-carboxylic acid in conc. HCl.

Rearrangement in benzyl alcohol gives 2-benzyloxytetrahydropyran-3-carboxylic acid benzyl esters (CI) (*69*).



Enol Content of the α-Acyllactones

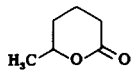
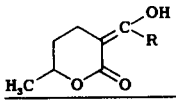
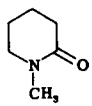
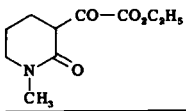
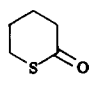
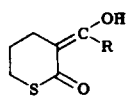
The degree of enolization of acyllactones has recently been reported (*30, 70*). The reason for the large differences in the enol content of individual acyllactones may be attributed to steric effects, and is not solely conditioned by the branching of the α-substituents (*71*) or the alcohol components (*72*). No relationship could be determined between the enolizing tendency and the course of the rearrangement.

Optical Measurements of α-Acyllactones, -thiolactones, and -lactams and Their Rearrangement Products

UV Spectra

Together with the enol reaction with $FeCl_3$, UV absorption measurements have proved valuable in the detection and especially the quantitative determination of α-acylcyclocarboxylic acid derivatives. The UV spectra of all the α-acyl compounds which we have synthesized are given in the original papers (*2*). The increase in mesomerism due to the introduction of the acyl groups into the lactones, thiolactones, and lactams results in a bathochromic shift of the main maxima in the UV range (*73*). The shifts associated with the formyl, acetyl, and ethoxalyl groups amount to approximately 30–40, 50–60, and 65–75 mμ, respectively. A number of examples are shown in Table 8.

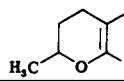
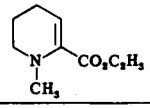
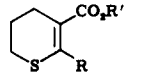
TABLE 8
Position of the UV Absorption Maximum and Extinction Coefficient of a Few α-Acyl-δ-cyclocarboxylic Acid Derivatives (in CH_3OH)

Compound		R	λ_{max} (mμ)	log ε
	–	–	212	1.78
	a	H	252	3.99
	b	CH_3	266	3.97
	c	CO_2CH_5	284	3.91
	–	–	206	3.75
	–	–	282	3.98
	–	–	237	3.61
	a	H	275	4.00
	b	CH_3	299	3.90
	c	$CO_2C_2H_5$	312	3.79

UV absorption is also used to advantage in the quantitative determination of the dihydropyrans or dihydrofurans, which are formed in equilibrium with the tetrahydro compounds during the rearrangement.

Table 9 shows a few examples of the position of the absorption maxima of the dihydropyrancarboxylic esters and their S and N homologs.

TABLE 9
Position of the UV Absorption Maximum and Extinction Coefficient of a Few 5,6-Dihydro-4H-pyran-3-carboxylic Acid Esters and the Corresponding Thiopyran and Pyridine Derivatives

Compound		R	λ_{max} (mμ)	log ε
	a	H	240	4.13
	b	CH_3	248	4.10
	c	$CO_2C_2H_5$	245	3.93
	-	-	273	3.50
	a	H	281	4.15
	b	CH_3	281	4.21
	c	$CO_2C_2H_5$	289	4.05

The bathochromic shift undergone by the maxima of the dihydrothiopyrancarboxylic esters is explained by the greater contribution to the mesomeric system made by the electron pairs of sulfur compared to those of oxygen or nitrogen (*14, 15*). The increased ring-stability of the α-acyllactones compared to the unsubstituted lactones is demonstrated by kinetic measurements. Whereas, e.g. the band at 237 mμ in unsubstituted δ-thiolactone in methanol/NaOH at room temperature disappears within one minute as a result of ring fission, about ⅓ of the original amount of α-acyl-δ-thiolactone is still unchanged after 7 hr under the same conditions. [See refs. (*14, 15*).]

IR Spectra

The IR spectra of weakly enolized α-acyllactones possess two characteristic separate C=O bands (lactone and acylcarbonyl group, respectively) and a C=C double bond band around 1650 cm^{-1} which is attributable to the enol constituent. A few examples are given in Table 10.

TABLE 10
IR Absorption Maxima of a Few α-Acyl-γ-lactones

Compound	C=O (Lactone) (cm^{-1})	C=O (Acyl) (cm^{-1})	C=C (Enol) (cm^{-1})	Remarks
α-Acetyl-γ-butyrolactone	1766	1720	1650	Film
α-Acetyl-γ,γ-dimethyl-γ-butyrolactone	1763	1720	1650	Film
α-Ethoxalyl-γ-butyrolactone	1750	1710[a]	1650	in CCl_4

[a] CO Frequency of the $COOC_2H_5$ group.

In the case of α-acyl compounds with a high enol content, the band due to the acyl C=O group disappears, while the position of the lactone carbonyl band is shifted to lower frequencies, as is invariably observed with α,β-unsaturated esters and lactones. We have recently reported on the position of the frequency of endocyclically unsaturated lactones (74). As a result of chelation, the enolic OH band is similarly displaced and coincides in part with the CH_2 valency vibrations (Table 11).

TABLE 11

IR Absorption Maxima of Strongly Enolized α-Acyl-δ-lactones

Compound	O—H (Enol) (cm^{-1})	C=O (Lactone) (cm^{-1})	C=C (cm^{-1})
α-Hydroxymethylene-δ-caprolactone	2750	1680	1615
α-Hydroxymethylene-β-methyl-δ-caprolactone	2750	1665	1615

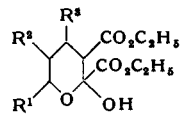
The carbonyl bands of the γ- and δ-thiolactones, 1705 and 1665 cm^{-1}, respectively, are shifted by about 70 cm^{-1} towards lower frequencies compared to the γ- and δ-lactones (1774 and 1735 cm^{-1}, respectively); those of the α-ethoxalylthiolactones are located approximately 30 cm^{-1} lower still (Table 12).

TABLE 12

IR Absorption Maxima of Thiolactones and α-Ethoxalylthiolactones

Compound	C=O ($COOC_2H_5$ group) (cm^{-1})	C=O (Lactone) (cm^{-1})	C=C (Enol) (cm^{-1})
γ-Thiobutyrolactone	–	1705	–
δ-Thiovalerolactone	–	1665	–
α-Ethoxalyl-γ-thiobutyrolactone	1725	1682	1625
α-Ethoxalyl-δ-thiovalerolactone	1730	1638	1590

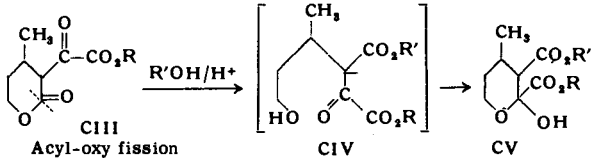
The 2-hydroxypyrans (CIV), both in KBr and chloroform solution, exhibit a sharp OH band in the IR at 3425 or 3460 cm^{-1}, respectively. Even in the solid state no OH association occurs, which points to steric hindrance of the OH group. This explains why no ketalization of the 2-hydroxypyrans CIV is observed during the rearrangement of primary and secondary α-ethoxalyl-δ-lactones.



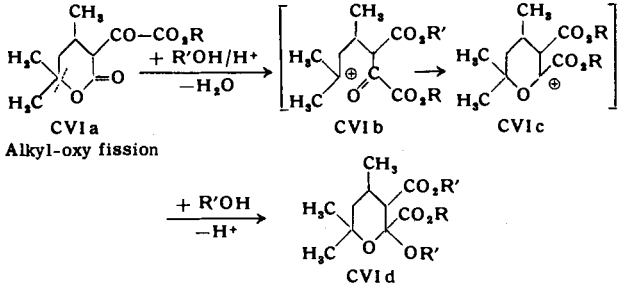
CII

Ring-Opening Mechanism of the α-Acyl-δ-lactones

Whereas rearrangement of primary and secondary α-ethoxalyl-δ-caprolactones (CIII) in absolute alcohol/HCl results in the formation of 2-hydroxytetrahydropyran derivatives (CV), the tertiary α-ethoxalyl-β,δ-dimethyl-δ-caprolactone (CVIa) yields a 2-methoxytetrahydropyran derivative CVId (see section on rearrangement of α-acyl-δ-lactones, particularly Table 2). This difference in reaction course can be explained by the different mechanisms of alcoholysis undergone by the lactones (*30*).



While primary and secondary α-acyllactones are opened by acyl-oxy fission, the opening of tertiary lactones is effected by alkyl-oxy fission. The strongly electrophilic carbonium ion, CVIC, formed in the latter case can stabilize itself with alcohol to the 2-alkoxytetrahydropyran, CVId.



The acyl-oxy fission mechanism, on the other hand, converts CIII into a 2-hydroxy product, CV; ketal formation of the latter to a 2-methoxy compound cannot take place as a result of steric hindrance (IR spectra, molecular models) due to the presence of the neighboring bulky carbethoxy groups (*30*).

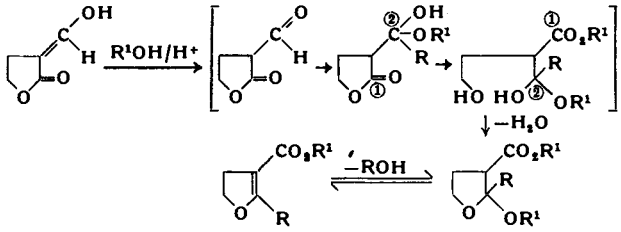
In the planar tetrahydrofuran ring, a 2-hydroxy group is no longer sterically hindered. Rearrangement of the ethoxalyl-γ-lactones consequently yields 2-methoxytetrahydrofurans exclusively. Nothing more can be concluded here from the rearrangement products concerning the ring-opening mechanism.

Mechanism of the Rearrangement

No common reaction mechanism can be established experimentally, nor can this be expected when so many equilibria are possible. Examples of possible rearrangement mechanisms are given in the following sections.

In Alcohol/H^+

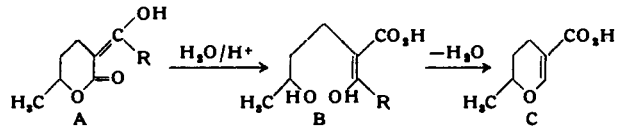
If α-hydroxymethylene-γ-lactones are dissolved in methanol, the absorption at 240 mμ due to the acyllactone drops to an equilibrium value. This phenomenon can be explained by the formation of a hemiacetal. Wislicenus determined the reduction in enol content of formylphenylacetic ester per unit time by titration according to the method of K. H. Meyer and isolated the hemiacetal formed (*75*). We consequently assume the following reaction stages:

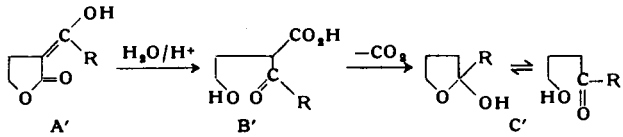


Whether the formation of the hemiacetal or hemiketal occurs before or after the transesterification of the lactone cannot be determined. It is more probable that the hemiacetal formation initiates the rearrangement, since this increases the resonance stabilization of the acyllactone ring, thus facilitating its alcoholysis.

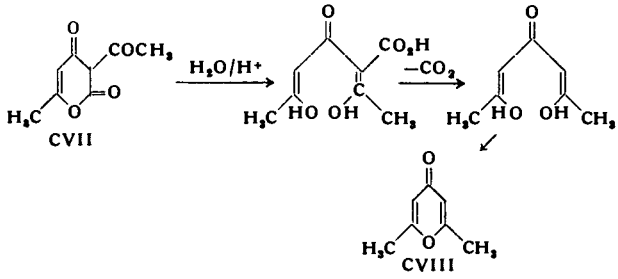
In H_2O/H^+

The lactone ring A is opened by hydrolysis in aqueous acid. This results in the formation of a β-keto-γ- or δ-hydroxyacid B which either stabilizes itself as the heterocyclic carboxylic acid C or is decarboxylated to the ketoalcohols C′. In high concentrations of HCl, the OH group can be replaced by chlorine.



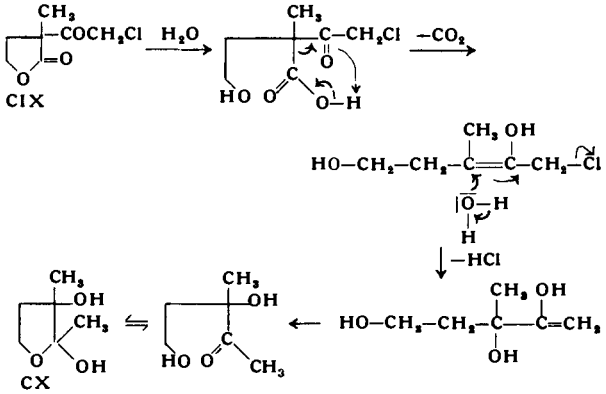


In the case of dehydroacetic acid, CVII, decarboxylation is followed by stabilization to the γ-pyrone ring (CVIII) (*5*).



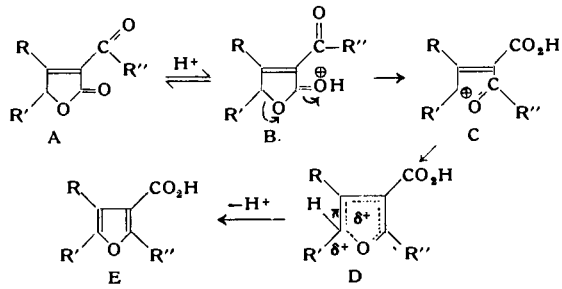
Special Mechanisms

The rearrangement of α-chloroacetyl-α-methyl-γ-butyrolactone (CIX) follows a special reaction course. In this instance too, the lactone ring is first opened by hydrolysis. For the further course of the reaction, Huffman and Tarbell (*49*)



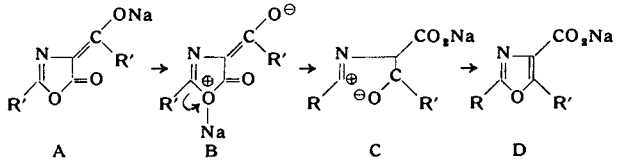
propose a mechanism involving an allylic rearrangement, as was postulated by Stevens and Lenk (*76*) for a similar case of hydrolysis of an α-haloketone. This would explain the formation of 2,3-dihydroxy-2,3-dimethyltetrahydrofuran (CX).

Lacey (*19*) suggests the following mechanism for the rearrangement of α,β-unsaturated γ-lactones (A):



Addition of a proton to the lactone group (B) yields an onium ion C via a kind of Saytzeff elimination; loss of the C_5-proton from C results in the formation of the complex D, followed by stabilization as the furancarboxylic acid E. This mechanism appears rather questionable to us as representative of rearrangements in an anhydrous medium, e.g. with BF_3 etherate. For the rearrangements in conc. HCl/acetic acid effected by Lacey, the hydrolysis of the acyllactone proposed in the preceding section appears more probable.

The rearrangement of the hydroxyalkylideneoxazolones A, which takes place by heating the Na salts at 200–300° according to the method of Cornforth, may be envisaged as proceeding via an oxonium structure, B. The thermal dissociation of the enol salt is followed by the formation of the oxonium salt B; alkyl-oxy fission opens the latter to a zwitterion, C, which stabilizes itself as the oxazolecarboxylic acid, D.



Limitations of the Rearrangement with Respect to the Ring Size and the Functional Groups

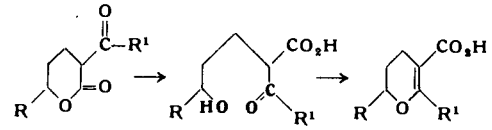
Ring Size

The application of the rearrangement to the preparation of macrocyclic ethers is hindered by the difficulties attendant on the synthesis of macrocyclic acyllactones. Even β-propiolactone undergoes no ester condensation, with the result that the rearrangement is thus far restricted to the synthesis of five- and six-membered ring heterocycles.

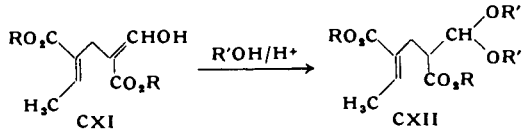
Functional Groups

The following functional groups are essential for the ring closure to the heterocycle in the rearrangement of five- and six-membered α-acyllactones (thiolactones and -lactams).

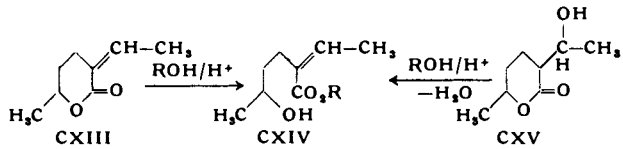
1. An alcoholic or enolic OH group in the γ- or δ-position.
2. A carbonyl group activated by an α-carboxyl group. In rearrangements effected in alcohol/H^+, this carbonyl group can also be present as the acetal or ketal (see preceding section).



If one of these groups is either absent or replaced by another active group, ring closure does not occur. If, for example, the OH group is replaced by an activated double bond (CXI) the rearrangement only yields the open-chain acetal CXII (*77, 78*).



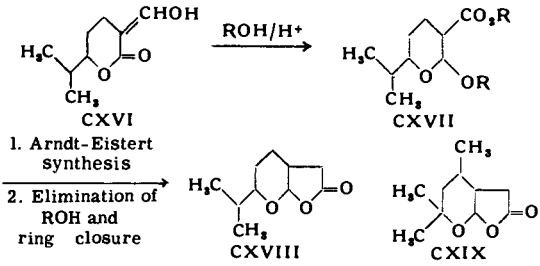
If the carbonyl group is replaced by an activated double bond (CXIII), the lactone is merely transesterified and the open-chain ethylidene compound CXIV is obtained.



Replacement of the carbonyl by an OH group (CXV) similarly yields merely the open-chain hydroxyester CXIV (*77*).

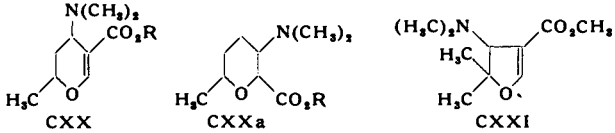
Application of the α-Acyllactone Rearrangement to Special Syntheses

During the investigations into the constitution of gentiopicrin, the hemiacetallactones CXVIII (*31*) and CXI (*79*) were discussed in relation to its skeleton. The synthesis of the tetrahydropyran ring of these bicyclic lactones from the corresponding substituted α-hydroxymethylenelactones (e.g., LXVI) was accomplished with the aid of the α-acyllactone rearrangement.

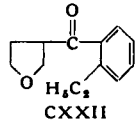


The bicyclic lactone was obtained from the 1-alkoxy-6-isopropyltetrahydropyran-3-carboxylic acid (CXVII) by the Arndt-Eistert synthesis and ring closure via dihydropyranacetic acid.

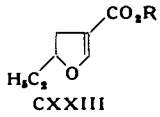
Aminopyrans (CXX and CXXa) and aminofurans (CXXI) (*23, 80*) can be synthesized via the dihydropyran esters, readily obtainable by the rearrangement.



o-Ethylphenyl-3-tetrahydrofuryl ketone (CXXII) is obtained from α-erythroidine by a repeated Hofmann degradation. Boekelheide and Morrison (*81*) have recently described a synthesis of the degradation product, in which α-hydroxymethylenebutyrolactone was rearranged to tetrahydrofuran-3-carboxylic ester, which was then allowed to react with *o*-ethylphenyllithium to give the ketone CXXII.

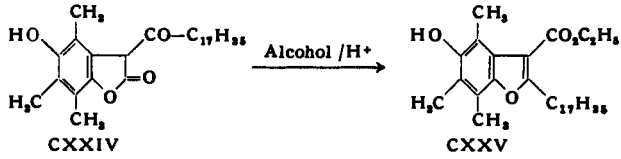


With a view to synthesizing muscarine, Eugster (*82*) also obtained 5-ethyldihydrofuran-3-carboxylic ester (CXXIII) by the application of the acyllactone rearrangement.



In connection with work on a synthesis of vitamin E, 2-heptadecyl-4,6,7-trimethyl-5-hydroxycoumarone-3-carboxylic ester (CXXV) was ob-

tained by the rearrangement of a 3-stearoylisocoumaranone (CXXIV) by English authors (*83*).



CXXIV CXXV

Conclusion

The examples given illustrate the great reactivity of the α-acyllactones and the general applicability of the rearrangement reaction. It renders five- and six-membered heterocyclic 3-carboxylic acids or their decarboxylation products readily accessible. It is interesting to note in this context the occurrence of the dihydropyran-3-carboxylic acid grouping in natural products, such as in the py-tetrahydroserpentine derivative class of compounds, to which ajmalicine and other rauwolfia alkaloids belong.

It is not impossible that the biosynthesis of these compounds proceeds via α-acyllactones.

Experimental

Preparation of the α-Acyl Compounds

α-Hydroxymethylene-δ-caprolactone (*7*). A solution of δ-caprolactone (145 gm, 1.27 mole) and ethyl formate (103 gm, 1.40 mole) in absolute ether (700 ml) is added dropwise over a period of 2 to 3 hr to a stirred suspension of powdered sodium (30.8 gm, 1.33 gm atom) in absolute ether (300 ml) containing absolute ethanol (3 ml); a cream-colored sodium salt is formed. After being allowed to stand overnight the mixture is decomposed with ice-water and the ethereal solution separated; the aqueous phase is freed from ether under vacuum, treated with animal charcoal, filtered, and acidified in the cold with dilute hydrochloric acid (pH 3.8–3.2) with stirring. Crystalline α-hydroxymethylene-δ-caprolactone separates. It is filtered, washed with ice-water, and dried *in vacuo*. Yield 148 gm, 82%. Recrystallization from acetone-water and hot water affords colorless needles, m.p. 108°. $FeCl_3$ reaction in water: violet.

α-Ethoxalyl-δ-thiovalerolactone (*8*). Diisopropylamine (35.4 gm, 0.35 mole) in absolute ether (100 ml) is added dropwise to a Grignard solution consisting of magnesium turnings (8.2 gm, 0.35 gm atom) and ethyl bromide (38.2 gm, 0.35 mole) in absolute ether (120 ml) at such a rate that the ether boils gently. The reaction liquid becomes cloudy, then pale

gray and viscous. This is cooled to below —10° with an ice-salt mixture and δ-thiovalerolactone (34.8 gm, 0.3 mole) and diethyl oxalate (73 gm, 0.5 mole) in absolute ether (150 ml) added dropwise with stirring. The viscous reaction mixture becomes orange-yellow. Stirring is continued for 12 hr, conc. HCl (55 ml) and ice-water (150 ml) added with cooling, and the mixture repeatedly extracted with ether. The combined ether extracts are dried over Na_2SO_4, the ether evaporated and the crude product repeatedly fractionated *in vacuo*, yielding a pale yellow oil (48 gm, 74%), b.p. 111–113°/0.1 mm. $FeCl_3$ reaction in methanol-water: blue. UV spectrum: $\lambda_{max\ 1}$ 312 mμ, log ε 3.79; $\lambda_{max\ 2}$ 208 mμ, log ε 3.56.

α-Acetyl-β-methyl-δ-caprolactone (30). β-Methyl-δ-caprolactone (52 gm, 0.4 mole) and absolute ethyl acetate (44 gm, 0.5 mole) are added dropwise to a stirred suspension of finely powdered sodium hydride (14.4 gm, 0.6 mole) in absolute ethyl acetate (176 gm, 2 moles) at room temperature. The reaction is initiated by gentle warming, and is then maintained at 5–10° by external cooling. The NaH goes into solution. After 24 hr the solution is treated with ice-water (250 ml) and extracted with ether (150 ml). The cooled aqueous layer is acidified to pH 3 with dilute hydrochloric acid and extracted four times with ether (120 ml portions). The combined ether extracts are briefly washed once with water and dried over Na_2SO_4. Evaporation of the ether leaves an oil which is fractionally distilled *in vacuo*, yielding a small quantity of acetoacetic ester (red enol reaction with $FeCl_3$ in 50% methanol) b.p. 35–38°/0.05 mm, and colorless α-acetyl-β-methyl-δ-caprolactone (19 gm, 28%), b.p. 68–70°/0.05 mm. $FeCl_3$ reaction in 50% methanol: violet. UV spectrum: $\lambda_{max\ 1}$ 262 mμ, log ε 3.9; $\lambda_{max\ 2}$ 204 mμ, log ε 3.2.

Rearrangements

In methanol at 20° (7). α-Hydroxymethylene-δ-caprolactone (118 gm) is dissolved in absolute methanol (1200 ml) containing HCl (3.4%) and allowed to stand for 48 hr at room temperature. The solution is then stirred into an excess of potassium carbonate solution and the 2-methoxy-3-carbomethoxy-6-methyltetrahydropyran extracted with ether. Distillation under vacuum yields a colorless oil (125 gm, 80%), b.p. 43–44°/0.05 mm. UV spectrum: λ_{max} 240 mμ, α15.8 (*84*); the product accordingly contains 17.9% of 3-carbomethoxy-6-methyl-5,6-dihydro-4H-pyran (α 88.5).

In benzyl alcohol at 20° (69). α-Hydroxymethylene-δ-caprolactone (10 gm) is allowed to stand in absolute benzyl alcohol (100 ml) containing HCl (4.3%) for 96 hr at room temperature and the solution stirred into a solution of K_2CO_3 (400 ml, 10%). The work-up is identical to that for the reaction in methanol. The crude 2-benzoxy-6-methyltetrahydro-

pyran-3-carboxylic acid benzyl ester absorbs at λ_{max} 240 mμ, α6.8 (and λ_{max} 210 mμ) and contains accordingly 11.5% of 6-methyl-5,6-dihydro-4H-pyran-3-carboxylic acid benzyl ester (λ_{max} 240 mμ, α59). Repeated fractionation affords the pure saturated compound (20 gm, 84%), b.p. 150–151°/0.05 mm.

In octanol at 20° (*69*). α-Hydroxymethylene-γ-caprolactone (15 gm) is dissolved in absolute *n*-octanol/4%HCl (150 ml) and allowed to stand for 10 days at room temperature, when the solution is stirred into a solution of K_2CO_3 (400 ml, 10%). The work-up is identical to that described for the reaction in methanol, and 2-octyloxy-6-methyltetrahydropyran-3-carboxylic acid octyl ester (34 gm, 89%) is obtained. The crude oil (λ_{max} 240 mμ, α9.4) contains 16% of 6-methyl-5,6-dihydro-4H-pyran-3-carboxylic acid octyl ester (α59). Repeated fractionation *in vacuo* affords the pure tetrahydropyran ester, b.p. 145–146°/0.05 mm.

In methanol/H⁺ under reflux (*4*). A solution of α-methoxalyl-γ-butyrolactone (151.8 gm) in absolute 1 *N* HCl/methanol (1200 ml) is heated for 14 hr under reflux; the solution is allowed to stand for 3 days at room temperature and then stirred into an excess of potassium carbonate in water (2000 ml), so that the solution remains permanently alkaline. The solution is extracted 8 times with ether (150 ml portions) and the combined extracts washed twice with water (300 ml portions). The ethereal solution is dried over $MgSO_4$, the solvent evaporated and the residual oil fractionated *in vacuo*, yielding 2-methoxytetrahydrofuran-2,3-dicarboxylic acid dimethyl ester (96.6 gm, 54%), b.p. 72–73°/0.03 mm, as a colorless oil which slowly crystallizes partially on standing.

In conc. HCl at 20° (*5, 8*). α-Hydroxymethylene-δ-caprolactone (*9*) (100 gm) is suspended in concentrated hydrochloric acid (300 ml) and stirred for 3 hr. The dihydropyrancarboxylic acid formed is filtered off and the mother liquors are diluted with an equal volume of water and stored for 24 hr at 0°, when a further crop of the acid crystallizes. The crystals are washed with ice-water and dried, yielding colorless crystals of 6-methyl-5,6-dihydro-4H-pyran-3-carboxylic acid (91 gm, 91%), m.p. 114–116°, λ_{max} 236 mμ, logϵ 4.06. More pyrancarboxylic acid can be isolated by extracting the mother liquors with ether.

If α-acetyl-δ-thiovalerolactone (10 gm) is dissolved in conc. HCl (40 ml), 2-methyl-5,6-dihydro-4H-thiopyran-3-carboxylic acid begins to crystallize within a few minutes. The mixture is allowed to stand for 1 hr at 0°, is diluted with H_2O (40 ml) and the colorless carboxylic acid filtered on a glass frit. Yield 8.9 gm (89%), m.p. 130°, λ_{max} 280 mμ, logϵ 4.06.

α-Acetyl-γ-butyrolactone (20 gm) is dissolved in concentrated hydrochloric acid (60 ml). Decarboxylation sets in within a few minutes and

the reaction mixture becomes brown. After being allowed to stand for 10 hr at 25°, the solution is brought to pH 3–4 with sodium carbonate and extracted 5 times with ether (50 ml portions). The extracts are dried over Na_2SO_4, the ether evaporated, and the residue fractionated under vacuum, yielding 5-chloro-2-pentanone (11.9 gm, 63%) as a colorless liquid with a fruity odor, b.p. 57–60°/12 mm.

In 2 N HCl at 20° or with warming (5). α-Acetyl-δ-caprolactone (4 gm) is suspended in 2 *N* HCl (16 ml) and the ice-cooled mixture stirred for 5 hr, during which time the carboxylic acid formed is partially decarboxylated. The 2,6-dimethyl-5,6-dihydro-4H-pyran-3-carboxylic acid which has precipitated is filtered and washed with ice-water. Yield 1 gm (25%); λ_{max} 244 mμ, log ε 4.08 (λ_{max} in 0.1 *N* NaOH, 236 mμ).

α-Acetyl-γ-butyrolactone (10 gm) is dissolved in 2 *N* HCl (40 ml) and heated under reflux for 5 hr. The solution is brought to pH 5–6 with K_2CO_3 and extracted with ether. The ether is dried over Na_2SO_4 and evaporated and the residue fractionally distilled *in vacuo*, yielding 5-hydroxy-2-pentanone (72 gm, 90%) as a colorless oil, b.p. 98–101°/12 mm.

In methanol, followed by $SOCl_2$ (26). 2-Phenyl-4-hydroxyethylidene-oxazolin-5-one (10 gm) is dissolved in methanol (100 ml) with gentle warming, and the excess methanol evaporated under vacuum. On cooling, the syrupy residue crystallizes as colorless cubes; these are powdered, recrystallized from petroleum ether (b.p. 60–90°), yielding colorless prismatic plates of α-benzoylaminoacetoacetic acid methyl ester (11.2 gm, 96.5%), m.p. 86–88°. These are dissolved in thionyl chloride (10 ml) and the solution warmed for several minutes until the evolution of gas subsides. Excess thionyl chloride is evaporated *in vacuo* and the residual crude 2-phenyl-5-methyloxazole-4-carboxylic acid methyl ester heated with 2 *N* sodium hydroxide (50 ml) until solution is complete; water (100 ml) is added and the mixture brought to the boil and filtered. On cooling, the filtrate is treated with 18% hydrochloric acid and the yellow precipitate filtered off. It is recrystallized from water (100 ml) containing a little ethanol and activated charcoal and dried *in vacuo* over $CaCl_2$, yielding colorless needles of 2-phenyl-5-methyloxazole-4-carboxylic acid (5.7 gm, 59%).

Preparation of the Dihydro Compounds

2-Methoxy-3-carbomethoxy-6-methyltetrahydropyran (20 gm) is treated with concentrated sulfuric acid (3 drops) and heated at 125–130° while dry nitrogen is bubbled through. The elimination of methanol is completed after approximately 1.5 hr. A little $NaHCO_3$ is added and the mixture fractionated under vacuum, yielding 3-carbomethoxy-6-methyl-

5,6-dihydro-4H-pyran (14.5 gm, 88%) as a colorless oil, b.p. 91°/11 mm (*7*).

2-Ethoxy-5,5-dimethyl-2,3-dicarbethoxytetrahydrofuran (5 gm) is treated with polyphosphoric acid (2 drops) and heated for 2 hr at 100° while dry nitrogen is bubbled through. The distillate is redistilled twice, yielding 5,5-dimethyl-2,3-dicarbethoxy-4,5-dihydrofuran (4.0 gm, 91%) as a colorless oil, b.p. 74°/0.1 mm, λ_{max} 258 mμ; logϵ 3.94 (*30*).

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Syntheses with Acid Amides, Particularly Formamide

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Introduction

In 1938 we succeeded in cleaving yeast nucleic acid to the nucleoside stage by the action of enzyme preparations of vegetable origin. This enabled us to develop a simple and productive method of preparing ribonucleosides, especially guanosine and adenosine (*1*). Nucleosides, in particular adenosine, were for many years manufactured on a commercial scale by this method (*2*). A short time later, we were able to effect a chemical cleavage of yeast nucleic acid by means of aqueous pyridine (*3*). The readily accessible nucleosides then served as starting materials for further syntheses.

The well-known pharmacological properties of the methylxanthines (caffeine, theophylline, theobromine) on the one hand, and of the nucleosides or nucleotides (adenosine, muscle adenylic acid, adenosine triphosphate) on the other, induced us to attempt the synthesis of methylated nucleosides and nucleotides in view of their possible pharmacological action. Apart from diazomethane, we used mainly dimethyl sulfate as the methylating agent. We then established that the methylation of nucleosides with dimethyl sulfate yields different methyl derivatives depending on the pH of the solution, and that complete methylation is preferentially effected in a weakly alkaline medium (*4*). Methylation of xanthine according to this method yielded over 90% of caffeine (*5*), while a more strongly alkaline medium caused the cleavage of the caffeine formed. This facile synthesis of caffeine caused us to seek a simple method of preparing xanthine. In 1942/43 we succeeded in obtaining very good yields of xanthine from uric acid and formamide (*5*). This, our first contact with formamide, already gave us an inkling of the exceptional capabilities of this small organic molecule. The difficult working conditions during the last years of the war, the loss of all the equipment essential to our nucleic acid work and then the inadequate working conditions under which our research was resumed after an interruption of several

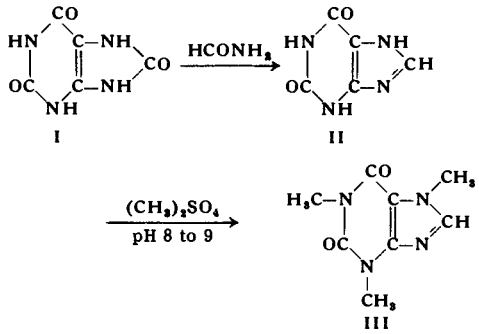
* My collaborators, Doz. Dr. R. Gompper, Dr. H. G. v. Schuh, and Dr. G. Theilig have played a decisive part in the development of this field. I am also indebted to many others of my co-workers, whose names appear in the references. *Bredereck*

years, all these caused the work on nucleic acid to recede in favor of the formamide reactions—restricted to the purine and pyrimidine field at first—which could be carried out with simple materials.

Syntheses in the Purine and Pyrimidine Series

Xanthine from Uric Acid—Synthesis of Caffeine

If uric acid (I) is heated in formamide, xanthine (II) is formed in very good yield (*5*). Snake excrement may be utilized instead of pure uric acid. Since xanthine can readily be converted into caffeine (III) (*5*) (see above), this method represents the simplest caffeine synthesis available.



I II III

If uric acid is replaced by 1-methyl- (*6*), 3-methyl-, or 1,3-dimethyluric acid (*5,6*), 1-methyl-, 3-methyl-, or 1,3-dimethylxanthine (= theophylline) are obtained. 8-Thiouric acid can similarly be converted into xanthine with formamide, though in lower yield (*6*). Uric acids containing an N-methyl group at position 7 or 9 (7-methyl-, 9-methyl-, 1,3,7-, and 1,3,9-trimethyluric acid) yield no xanthines (*6*). The reaction is by no means restricted to formamide; on the contrary, formanilide can also be used, though the yields obtained are then lower. The reaction of uric acid with acetamide gives 8-methylxanthine and that with propionamide 8-ethylxanthine (*5*).

Reaction Mechanism

The first obvious assumption, namely that the CO or COH group in the 8-position is reduced to CH by the formyl group of formamide, is incorrect. As mentioned earlier, acetamide and propionamide give 8-alkyl-substituted xanthines. Since rupture of the alkyl–$CONH_2$ bond in these acid amides is out of the question, the C_8 atom of the xanthine formed must originate from the $CONH_2$ group of the acid amide. In identical

manner, the C_8 of the xanthine formed from uric acid is the C of the formamide $CONH_2$ group. The acid amides consequently cause the fission of the —NH—CO—NH— grouping in the imidazolone ring of the uric acid.

An indication of the nature of the cleavage is given by the following experiments:

1. The action of formamide on mono- and disubstituted ureas and thioureas results in a fission to give N-substituted formamides (*7*).

$$R\text{–}NH\text{–}CO\text{–}NH_2 \xrightarrow{HCONH_2} R\text{–}NH\text{–}CHO$$

$$R\text{–}NH\text{–}CO\text{–}NH\text{–}R \xrightarrow{HCONH_2} 2\,R\text{–}NH\text{–}CHO$$

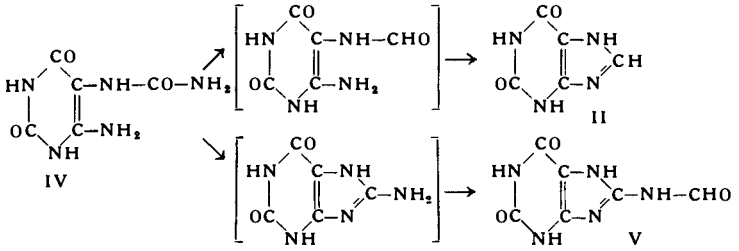
Biuret and cyanuric acid can also be detected in the reaction mixture. In our own experiments, we used mono- and diphenylurea, mono- and di-*p*-ethoxyphenylthiourea and 5-ureidouracil. This last compound yields 5-formylaminouracil.

The action of acetamide on substituted ureas correspondingly results in the formation of N-substituted acetamides (acetylamines). The ability of acyl amides to cleave a

—NH—CO—NH

bond is demonstrated by these experiments.

2. 4-Amino-5-ureidouracil (IV) reacts with formamide to give xanthine and 8-formaminoxanthine (V) (*6*).



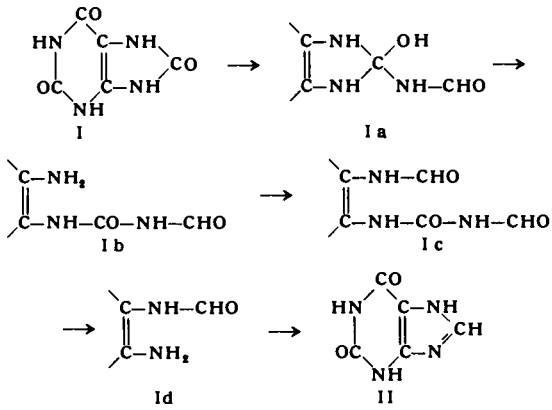
Since 8-aminoxanthine does not give xanthine with formamide—the imidazole ring is already present—4-amino-5-ureidouracil cannot be an intermediate in the practically quantitative formation of xanthine from uric acid (*6*).

The course of the formation of xanthine from uric acid consequently is as follows: The attack by formamide occurs at the CO group (C_8), in a corresponding manner to the initial step in the action of formamide on ketones (Leuckart reaction). This is followed by the cleavage of the carbinol Ia (*7a*) between N_7 and C_8 and formylation of the amino compound Ib thus formed. The ureide structure at C_4 (Ic) immediately breaks down to give an amino group (Id) which then reacts with the

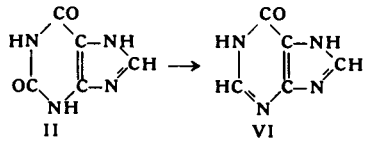
formylamino group accompanied by the elimination of water to form xanthine.

In conformity with this reaction scheme, interruption of the reaction between uric acid and acetamide at the proper time allows the isolation of 4-amino-5-acetylaminouracil. Furthermore, 1-methyl-4-amino-5-formylaminouracil (corresponding to Id) can be detected chromatographically in the reaction between 1-methyluric acid and formamide (*6*).

The question arises, whether the conversion of a —NH—CO—NH— grouping forming part of an imidazolone ring into a —NH—CH=N— grouping by means of formamide is restricted to uric acid, or whether other ring systems will also undergo a reaction of this type.



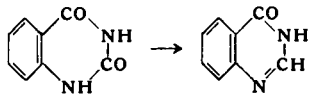
The incomplete experiments to date have shown the following: Benzimidazolone cannot be converted into benzimidazole with formamide. Xanthine, which also contains a —NH—CO—NH— grouping in its pyrimidine ring, yields hypoxanthine (VI) when the reaction is carried out in an autoclave (200°) (*8*).



Uric acid itself can be converted into hypoxanthine directly under similar conditions (*9*). The formation of decomposition and well-defined reaction products from formamide itself (see below) however, renders the separation of the hypoxanthine both laborious and wasteful.

2,4-Dioxoquinazoline (VII), which results in a good yield of 4-quinazolone (VIII) by reaction with formamide in an autoclave, possesses

the same arrangement in the pyrimidine ring as do xanthine and uric acid.

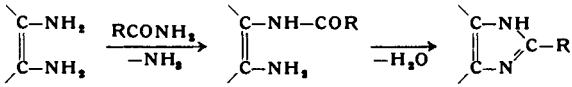


VII VIII

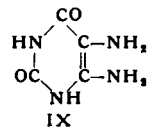
The experimental data to date are inadequate for the determination of which structural prerequisites are essential for ensuring the success of the formamide reaction. It may be of decisive importance that the readiness of the cyclic —NH—CO—NH— grouping to add via linkage with electrophilic groups (e.g., CO) be sufficiently great. It may furthermore be essential that the ring systems possess quasi-aromatic character both before and after the "reduction." We are at present determining experimentally the validity of these considerations.

4,5-Diaminopyrimidines and Acid Amides

The isolation or detection of 4-amino-5-acylaminouracils as intermediates during the conversion of uric acids into xanthines leads one to expect that the reaction of *o*-diamines with formamide and acid amides generally results in an imidazole ring closure.



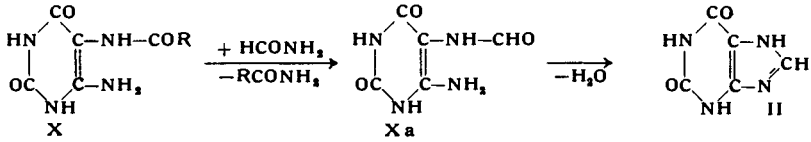
Whereas the reaction between *o*-phenylenediamines and acid amides to give benzimidazoles has long been known (*10*), we were the first (1942/43) to apply this reaction in the pyrimidine series (*5*). A brief period of boiling with formamide converts 4,5-diaminouracil (IX) into xanthine (*5*). Since that time, numerous diaminopyrimidines have been made to react with formamide, both by us and by other workers.



IX

After a longer reaction time, 4,5-diaminouracil and acetamide or propionamide give 8-methyl- or 8-ethylxanthine, respectively (*5*). If the reaction is interrupted, 4-amino-5-acetylamino- or 4-amino-5-propionylaminouracil (X, R = CH_3 or C_2H_5), respectively, can be isolated as intermediates.

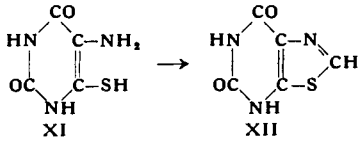
If a 4-amino-5-acylaminouracil is allowed to react with formamide, xanthine is obtained and the acyl group is eliminated as acyl amide (*11*).



If a 4-amino-5-acylaminouracil is allowed to react with a higher amide instead of formamide, the 8-alkylxanthine corresponding to the amide is formed. In general, the amide added in excess will determine the nature of the 8-substituted xanthine formed during the initial acylation, irrespective of the nature of the acyl group on the 5-amino group (*11*). As a result of this reaction of acylaminouracils we have devised new syntheses of the purine alkaloids, especially theobromine and theophylline, based on uric acid (see below).

Thiouramil and Formamide

Thiouramil (XI) reacts with formamide to give a good yield of 4,6-dioxo-4,5,6,7-tetrahydrothiazolo-(5,4-d)-pyrimidine (XII) (*12*).

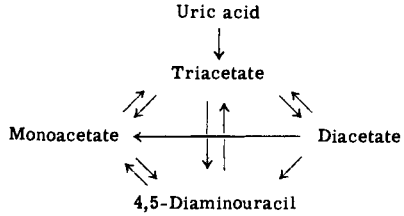


The 1,3-dimethyl compound obtained by methylation (dimethyl sulfate, pH 8) is an S analog of theophylline (*12*).

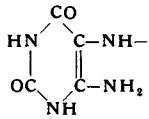
Syntheses of Caffeine, Theophylline, and Theobromine

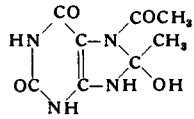
If uric acid is heated with acetic anhydride in the presence of pyridine, a good yield of the compound designated below as "triacetate" is obtained (*13*). Mild alkaline saponification or boiling with water causes the loss of one acetyl group to give a "diacetate"; warm alkali causes the loss of another acetyl group from the latter to form a "monoacetate." Finally, saponification with alkali will also effect the removal of the last acetyl group, resulting in the formation of 4,5-diaminouracil.

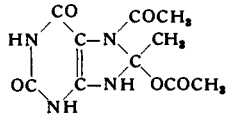
Conversely, the lower acetyl compounds can be reacetylated to the higher stages. The following simplified scheme summarizes the results of these experiments (*13*):



The monoacetate has the constitution of 4-amino-5-acetylaminouracil (XIII), the diacetate that of 8-hydroxy-2,6-dioxo-8-methyl-7-acetyl-1,2,3,6,8,9-hexahydropurine (XIV) and finally the triacetate that of 8-acetoxy-2,6-dioxo-8-methyl-7-acetyl-1,2,3,6,8,9-hexahydropurine (XV).


XIII


XIV


XV

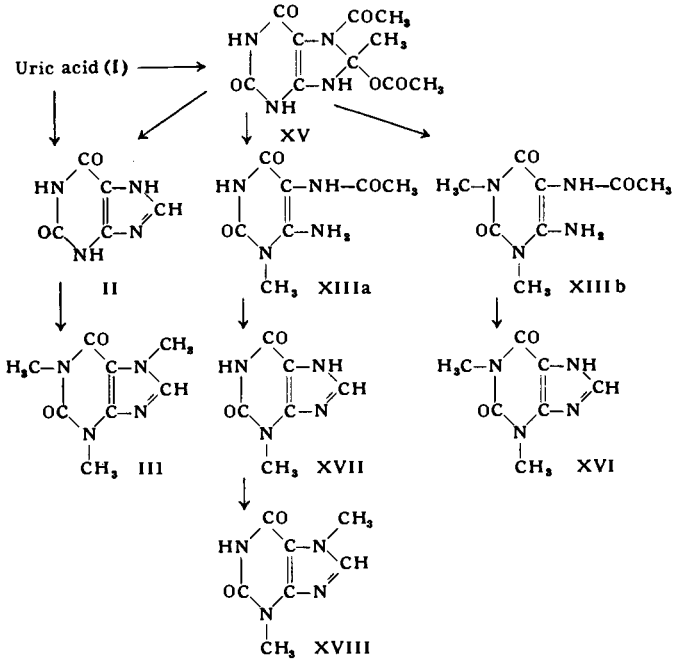
The monoacetate and, under the right conditions of temperature (see below), also the di- and triacetate yield xanthine after a short period of warming with formamide (*11*). All the acetyl groups are eliminated as acetamide during this process. If formamide is replaced by acetamide, the three acetates yield 8-methylxanthine.

The monoacetate reacts with formamide to give largely pure xanthine, suitable for further reactions. The di- and triacetate, on the other hand, yield both xanthine as the major product and, resulting from the elimination of acetic acid, 8-methylxanthine (ca. 10%), which renders the further processing of the xanthine more difficult. Under suitable temperature conditions (1 hr at a bath temperature of 100°, followed by boiling for 30 min under reflux) and the use of formamide containing NH_3, the formation of 8-methylxanthine can, however, be obviated.

The reaction with formamide discussed above can thus be effected with acetates methylated in positions 1 and 3. Suitable methylation will convert the monoacetate into both the 3-methyl- and 1,3-dimethylmonoacetate (*11*). It is worth noting that these compounds can also be prepared in very good yield (80–90%) directly from the triacetate in a single operation.

The 1,3-dimethylmonoacetate (XIIIb) and the 3-methylmonoacetate (XIIIa) can be converted directly into theophylline (XVI) and 3-methylxanthine (XVII), respectively, by boiling with formamide (*11*). The latter yields theobromine (XVIII) with dimethyl sulfate (pH 7 to

7.5) (*11*). The preparation of theophylline can further be simplified by the fact that when the triacetate is used as the starting material, neither the monoacetate nor the dimethylmonoacetate is isolated, but the theophylline prepared in one step (*11*).



The above scheme represents the syntheses which we have developed, based on uric acid, of caffeine, theobromine, and theophylline.

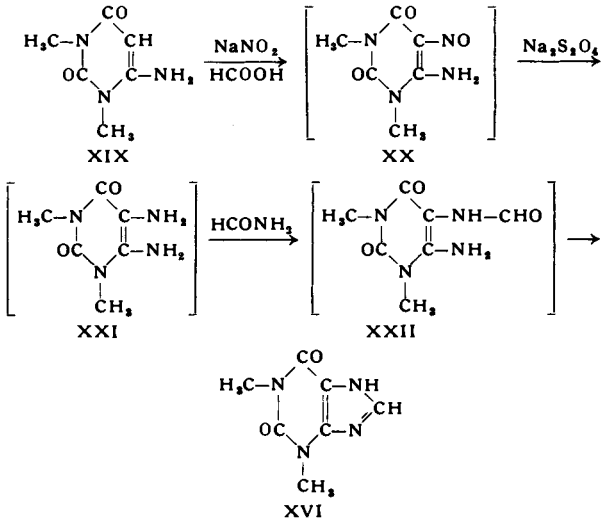
The commercial execution of these syntheses is hindered by the fact that it is at present not possible to prepare uric acid economically from guano. We have therefore attempted to apply our experience in the formamide field to the total synthesis of the purine alkaloids.

Simplification of the Traube Xanthine Synthesis

The Traube synthesis essentially constitutes the present-day preparation of xanthines, especially caffeine, theobromine, and theophylline. This method consists in the nitrosation of the 4-aminopyrimidine derivative obtained by condensation, reduction of the 4-amino-5-nitroso compound with, e.g. reducing sulfur compounds, to give the 4,5-diamino product, and formylation of the latter followed by ring closure. We were able to simplify this method considerably as follows: The 4-amino compound (e.g., XIX, XXIII) in formamide was nitrosated with nitrite–

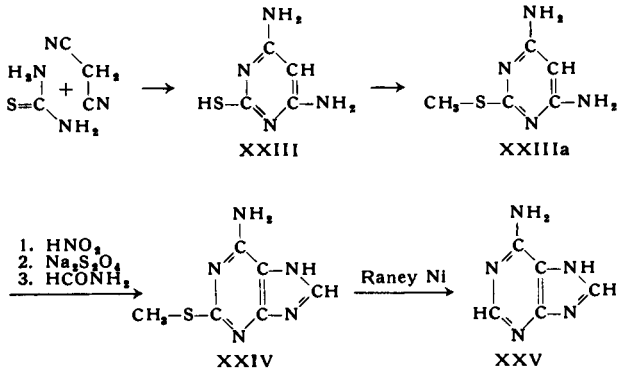
formic acid and the intermediate products not isolated, the 5-nitroso compound (e.g. XX) reduced by means of a small quantity (approximately ⅕ of the theoretical amount) of dithionite, the diamine (e.g., XXI) formylated (e.g., XXII) and cyclized to the xanthine (e.g., XVI, XXIV) (*14*). The yield of xanthine (calculated with respect to 4-aminouracil) amounts to 70–75%, that of theophylline (calculated with respect to 1,3-dimethyl-4-aminouracil) 80–85%. The synthetic routes followed in the preparation of theophylline (*14*) and adenine (*15*) are reproduced schematically.

Synthesis of theophylline (XVI):



Besides xanthine, theophylline, and adenine, guanine and 2-thioxanthine have also been prepared by this route in our Institute.

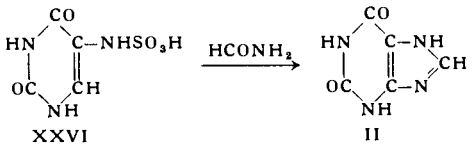
Synthesis of adenine (XXV):



The synthesis described above can be interrupted at various intermediate stages between the 4-amino compound and the final product. The reduction effected with dithionite (at 80°) is immediately followed by formylation with the formamide. If the reaction mixture is cooled after the reduction, a good yield of the 4-amino-5-formylamino compound (e.g., XXII) is often obtained. The formyl group is readily eliminated with alcoholic hydrochloric acid, yielding the 4,5-diaminopyrimidine. Both 1,3-dimethyl-4,5-diaminouracil (XXI) (*14*) and 2,4,5-triamino-6-hydroxypyrimidine (*16*), used in syntheses in the pteridine series, have been obtained by this route.

Xanthine Syntheses from 5-Sulfaminouracils

Even though the total syntheses mentioned above and their wide applicability may constitute the simplest and most economical method, another synthesis of xanthine by means of acid amides should be mentioned, particularly because of its especially peculiar nature. Fischer and his co-workers (*17*) obtained xanthine (80%) or 8-methylxanthine (80%) by allowing formamide or acetamide, respectively, to react with 5-sulfaminouracil (XXVI) (*17a*), prepared by reducing 5-nitrouracil with dithionite in alkaline solution [for theory cf. ref. (*17*)].



XXVI II

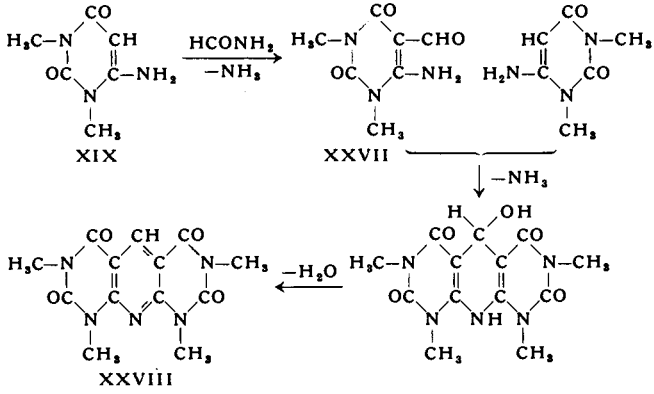
The reaction between 3-methyl-5-sulfaminouracil and formamide or acetamide correspondingly yields 3-methylxanthine (85%) or 3,8-dimethylxanthine (70%) (*14*). 1,3-Dimethyl-5-sulfaminouracil, on the other hand, only gives 1,3-dimethyl-5-formylaminouracil with formamide, and 1,3-dimethyl-5-acetaminouracil with acetamide; i.e., the sulfonic acid is merely replaced by an acyl group (*14*). The study of this reaction led us to another specific reaction undergone by formamide.

A C-formylation: 4-Aminouracil → 4-Amino-5-formyluracil

In addition to the reaction of the 5-sulfamino compound, we attempted to prepare a 4-sulfaminouracil and to allow the latter to react with formamide. By treating 4-aminouracil with chlorosulfonic acid, we obtained a compound which we initially regarded as being uracil-4-sulfaminouracil. We believed we had converted this compound with formamide into 4-formylaminouracil (*14*) and that methylation of the latter had given us 1,3-dimethyl-4-formylaminouracil, which can also be pre-

pared from 1,3-dimethyl-4-aminouracil and formamide or formic acid.

More recent investigations have, however, shown the alleged 1,3-dimethyl-4-formylaminouracil to be 2,4,6,8-tetramethyl-1,3,7,9-tetraoxo-öctahydrobipyrimido-[4,5-b,4′,5′-e]-pyridine (XXVIII) (*18*). Its formation from 1,3-dimethyl-4-aminouracil (XIX) can be explained as follows:



The first step therefore consists of a C-formylation at position 5. 1,3-Dimethyl-4-amino-5-formyluracil (XXVII) can in fact be isolated from the filtrate of XXVIII. This 5-formyluracil reacts further with unchanged 1,3-dimethyl-4-aminouracil to give XXVIII.

If the reaction between 1,3-dimethyl-4-aminouracil and formamide is carried out around 140°, 2,4-dimethyl-1,3-dioxotetrahydropyrimido-[4,5-d]-pyrimidine is obtained.

According to this, the alleged 4-formylaminouracil and 4-sulfaminouracil could in reality be the unmethylated bipyrimidopyridine derivative (tetraoxoöctahydrobipyrimidopyridine) and 4-aminouracil-5-sulfonic acid, respectively. It is worth noting that the formylation occurs not at the amino, but at the CH group. This reaction nevertheless becomes comprehensible when it is realized that the amino group is linked to a vinylene-homologous acid amide grouping. It is nonetheless surprising that the C_5 atom undergoes formylation rather than condensation to an aminomethylene compound (see below). On the basis of the reactions of dimethylbarbituric acid, to be discussed next, such a reaction lies well within the realm of possibility.

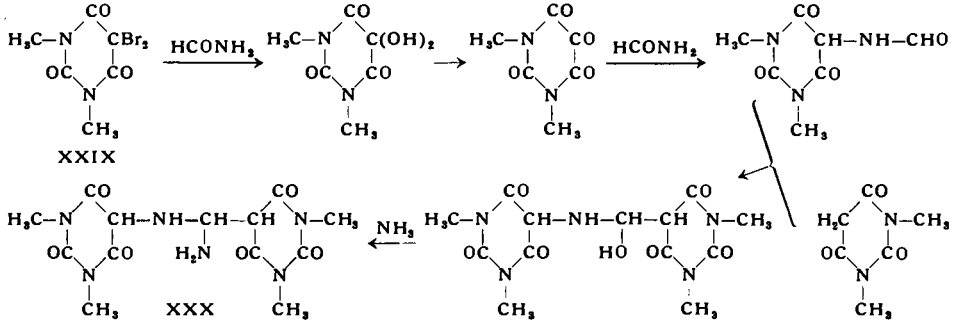
Dimethylbarbituric Acid and Acid Amides

Even though reactions analogous to the experiments described in this section were already known, our results are nevertheless briefly stated again, firstly, since our investigations were originally undertaken from

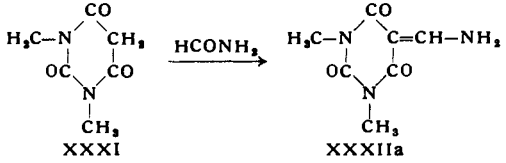
a different viewpoint and secondly, in order to point out the fresh reaction possibilities displayed by the acid amides.

As reported below in greater detail, ketones can be brominated in a single-stage reaction in formamide; the α-bromoketone formed can be converted by means of an excess of formamide into an imidazole by raising the temperature. We extended this reaction to dimethylbarbituric acid in the expectation that here too an imidazole ring would be formed (*19*). The reaction (170°) however, resulted in the formation of 5-aminomethylene-1,3-dimethylbarbituric acid and a compound which for the time being we consider to be N,C-bis[1,3-dimethylbarbituryl-5]-diaminomethane (XXX) (*19*).

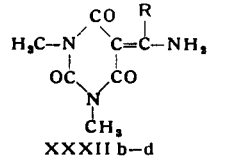
Proceeding from the fact that dibromodimethylbarbituric acid (XXIX) is partially formed first, the formation of XXX can be explained by the following reaction scheme:



The aminomethylene compound XXXIIa simultaneously produced can also be obtained directly from dimethylbarbituric acid (XXXI) and formamide (*19*).



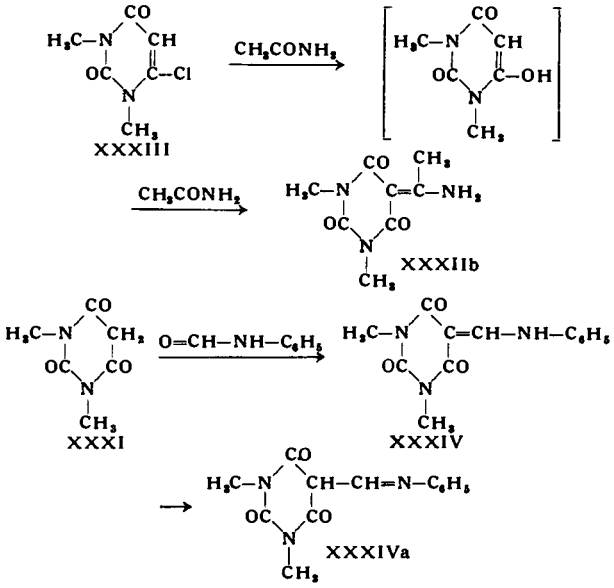
Barbituric acid had already been converted in this manner by Papini and Cimmarusti (*20*) and S. Hünig (*21*).



b: R = CH_3
c: R = C_2H_5
d: R = n-C_3H_7

The reaction between dimethylbarbituric acid and higher acid amides yields the corresponding aminomethylene compounds (*19*) XXXIIb–d.

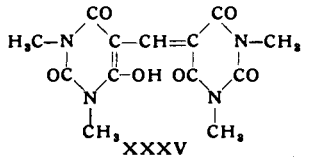
1,3-Dimethyl-4-chlorouracil (XXXIII) reacts with acid amides to give the same aminomethylene compounds (*19*):



This conversion readily fits into the scheme of the reactions between halogen compounds and acid amides (see below). If formanilide, being an N-substituted amide, is allowed to react with 1,3-dimethylbarbituric acid, 5-anilinomethylene-1,3-dimethylbarbituric acid (XXXIV) is obtained, though the examination of its IR spectrum shows this compound to exist in the form of a Schiff base (XXXIVa) (*19*). Barbituric acid reacts in an identical manner (*20*).

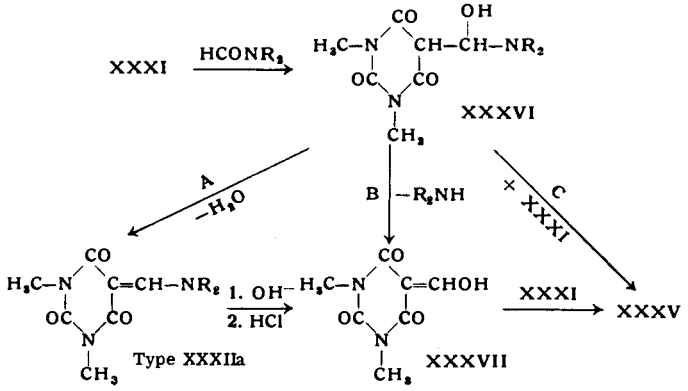
Reaction with dimethylformamide on the other hand results in the formation of the dimethylammonium salt of 1,3-dimethyl-5-(1′,3′-dimethylbarbituryl-5′)-methylenebarbituric acid (XXXV) (*19*). In this instance too, Hünig (*21*) had previously obtained the corresponding compound in the reaction with barbituric acid.

If the initial step in the course of the reaction between acid amides and compounds containing an acidic CH group is assumed to be the formation of the adduct XXXVI, it is noteworthy that route A (elimination of water) is followed in the reaction with formamide, formanilide, and higher acid amides, whereas route B or C is followed in the reaction with dimethylformamide. The formation of XXXV can be explained



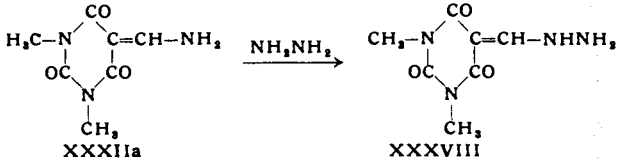
XXXV

either by the direct route (C), or via the hydroxymethylene compound XXXVII (see below).



The 5-aminomethylene-1,3-dimethylbarbituric acid (XXXIIa) is in its turn capable of undergoing numerous reactions. Sodium hydroxide, for example, causes the loss of NH_3 to give the sodium salt of 5-hydroxymethylene-1,3-dimethylbarbituric acid (XXXVII); acidification of the latter yields compound XXXV via the tautomeric 5-formyl compound (*19*). XXXV had previously been obtained by the condensation of dimethylbarbituric acid and formic acid (*22*).

The amino group in the aminomethylene compound can also be replaced by the hydrazine group (*19*).



XXXIIa XXXVIII

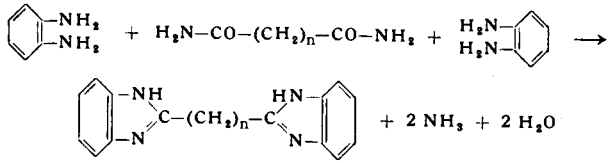
The hydrazine compound XXXVIII is itself capable of undergoing numerous reactions (*19*).

Acid Amides and o-Phenylenediamine

In addition to the reactions between 4,5-diaminouracil and acid amides, we have also undertaken corresponding reactions with other 1,2-diamines. Reactions between aromatic *o*-diamines or their hydrochlorides

and acid amides were already known (*10*). We have supplemented these experiments by reactions with dicarboxylic acid amides (*23*, *24*).

If *o*-phenylenediamine is heated with oxamide, malonamide, or succinamide, 2,2′-dibenzimidazolyl (XXXIXa), 2-dibenzimidazolylmethane (XXXIXb), or 2-(1,2-dibenzimidazolyl)ethane (XXXIXc) is obtained (*24*).

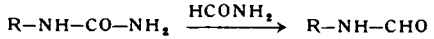


XXXIX

a: n = 0; b: n = 1; c: n = 2

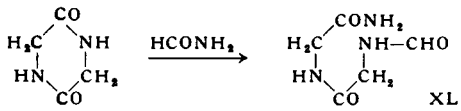
Formamide and Compounds Containing a —NH—CO— Grouping

The reaction of mono- and disubstituted ureas with formamide, yielding formylamines via the fission of the CO—NH— bond, has been mentioned earlier in connection with the discussion on the mechanism of the urea → xanthine reaction. This consists in effect of a transacylation, during the course of which the carbaminyl moiety is replaced by a formyl group.



Thus phenyl- and diphenylurea, *p*-tolylurea, and α-naphthylurea yield formanilide, *p*-formtoluidide, and α-formnaphthalide, respectively (*25*). The urea simultaneously produced during the course of the reaction is partially converted into biuret and cyanuric acid.

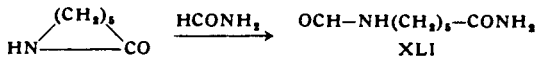
Piperazinedione reacts with formamide at 130–145° (the presence of a small quantity of water is advantageous) to give a good yield of formylglycylglycinamide (XL). The piperazinedione ring is consequently unilaterally opened (*26*, *28*).



XL

Micheel (*27*) observed an N-formylation only, during the reaction of amino acids and peptides with formamide or formamide–formic acid at 60°.

ϵ-Caprolactam undergoes ring opening to give equally good yields of ϵ-formylaminocaproamide (XLI) (*28*).



XLI

Stable lactams, e.g. dihydrocarbostyril, and butyrolactone, do not undergo fission under these conditions (*28*). Reaction of the polyamide from adipic acid and hexamethylenediamine (Ultramide A) gives a mixture of adipic acid diamide and N,N′-diformylhexamethylenediamine, from which both of these compounds can be isolated (*28*).

Syntheses of Imidazoles

From Acyloins

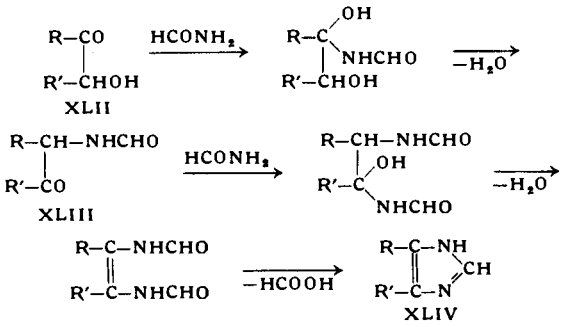
Novelli (*29*) had allowed benzoin to react with NH_3-containing formamide (prepared by the distillation of ammonium formate) and obtained diphenylimidazole with pyrazine as by-product; the formation of the latter is accounted for by the ammonia contained in the formamide. We allowed a large number of aliphatic, aromatic, and heterocyclic acyloins to react with formamide at 150–180° and invariably obtained good yields of 4,5-disubstituted imidazoles (*30*) (Table 1).

TABLE 1
Imidazoles from Acyloins and Formamide

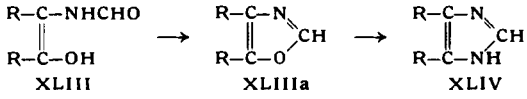
Acyloin (XLII)	Imidazole (XLIV)	Yield (%)
Acetoin	4,5-Dimethyl-	55
Propionoin	4,5-Diethyl-	67
n-Butyroin	4,5-Di-*n*-propyl-	81
Isobutyroin	4,5-Diisopropyl-	85
n-Valeroin	4,5-Di-*n*-butyl-	72
Isovaleroin	4,5-Diisobutyl-	61
n-Caproin	4,5-Di-*n*-amyl-	51
n-Enanthoin	4,5-Di-*n*-hexyl-	45
1,6-Diphenylpropionoin	4,5-Bis(β-phenylethyl)-	66
Cyclodecan-1-ol-2-one (Sebacoin)	4,5-Octamethylene-	87
Cyclohexadecan-1-ol-2-one (Thapsoin)	4,5-Tetradecamethylene-	91
Benzoin	4,5-Diphenyl-	91
Furoin	4,5-Di-α-furyl-	89
p-Dimethylaminobenzoin	4(5)-(*p*-Dimethylaminophenyl)-5(4)-phenyl-	62
α-Hydroxybutyrophenone	4(5)-Phenyl-5(4)-ethyl-	70

As illustrated by sebacoin and thapsoin, the —CH(OH)—CO— grouping can also form part of a large ring, to which the imidazole ring then becomes joined.

In accordance with Novelli (*29*), we assume the following reaction path for the formation of the imidazoles (*30*):



The correctness of this scheme is supported by two empirical observations: Firstly, it is possible to isolate the intermediate XLIII (α-formaminoketone) and to convert it into imidazole with formamide (*31*) (see below). Secondly, by the fact that the theoretically possible route from the formaminoketone via an oxazole XLIIIa can be excluded since α-formaminoketones give oxazoles to but a minor extent if heated in the absence of a condensing agent. The most convincing argument, however, lies in the fact that oxazoles are not converted into imidazoles at 150° (*32*) (see below).

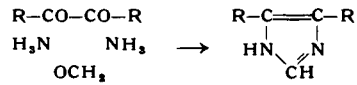


From α-Diketones

Since substituted benzoins are frequently prepared via the α-diketones (i.e. benzils), we checked whether α-diketones could not be utilized directly in the synthesis of imidazole. The importance of the direct conversion of α-diketones into imidazoles follows from the fact that aromatic α-hydroxyketones are often more difficult to prepare directly than are the α-diketones obtained with oxalyl chloride via a Friedel-Crafts reaction.

The action of formamide and formaldehyde on a benzil at 180–200° results in a good yield of the corresponding 4,5-disubstituted imidazole (*33*) (Table 2).

Formaldehyde does not, as originally thought, act as a reducing agent in this case; no α-hydroxyketone can be detected during the reaction. The formation of the imidazole must rather be explained by the generation of ammonia from formamide at 180–200°, and consequent reaction between the diketone, ammonia, and formaldehyde.



If formaldehyde is replaced by other aldehydes, imidazoles substituted in the 2-position are formed (Table 2).

TABLE 2
Imidazoles from α-Diketones, Aldehydes, and Formamide

Benzil	Aldehyde	Imidazole	Yield (%)	M. p.
Benzil	Paraformaldehyde	4, 5-Diphenyl-	67	231°
2, 2'-Dichloro-	Paraformaldehyde	4, 5-Bis-(2'-chlorophenyl)-	45	237°
4, 4'-Dibromo-	Paraformaldehyde	4, 5-Bis-(4'-bromophenyl)-	42	261°
4, 4'-Dimethoxy-	Paraformaldehyde	4, 5-Bis-(4'-methoxyphenyl)-	52	184°
Benzil	Benzaldehyde	2, 4, 5-Triphenyl-	61	274°
4, 4'-Dibromo-	Benzaldehyde	2-Phenyl-4, 5-bis-(4'-bromophenyl)-	36	297°
Benzil	3, 4-Dichloro-benzaldehyde	4, 5-Diphenyl-2-(3', 4'-dichloro-phenyl)-	52	243°
Benzil	2-Chlorobenzaldehyde	4, 5-Diphenyl-2-(2'-chlorophenyl)-	20	192°
Benzil	4-Diethylamino-benzaldehyde	4, 5-Diphenyl-2-(4'-diethylamino-phenyl)-	27	250°

This synthesis therefore resembles the well-known synthesis from α-diketones, ammonia, and aldehydes, devised by Radziszewski (*34*). The latter, however, does not proceed uniformly; the action of the ammonia causes the partial decomposition of the diketone, with the result that difficult-to-separate mixtures of di- and trisubstituted imidazoles are obtained. The yields are correspondingly unsatisfactory. The advantage of our method resides in the fact that the ammonia becomes available only gradually by the decomposition of the formamide. Furthermore, our reaction is complete within 3 hr, whereas the method of Radziszewski requires several days.

Benzil and substituted benzils could be converted into imidazoles with formamide in the presence of formic acid/sodium bisulfite (*34a*) (Table 3), in a manner analogous to the preparation of imidazoles from

TABLE 3
Imidazoles from α-Diketones and Formamide in the Presence of $NaHSO_3$/HCOOH

Benzil	Imidazole	Yield (%)	M. p.
Benzil	4, 5-Diphenyl-	78	231°
2, 2'-Dichloro-	4, 5-Bis(2'-chlorophenyl)-	40	237°
4, 4'-Dibromo-	4, 5-Bis(4'-bromophenyl)-	36	261°
4, 4'-Diphenoxy-	4, 5-Bis(4'-phenoxyphenyl)-	43	214°
4, 4'-Bis-phenylmercapto-	4, 5-Bis(4'-phenylmercaptophenyl)-	33	174°
2, 2'-Dimethoxy-	4, 5-Bis(2'-methoxyphenyl)-	57	193°

isonitroso compounds and formamide in the presence of reducing agents (see below).

The reaction proceeds via the benzoin stage; if it is interrupted soon after the addition of the reducing agent, a 95% yield of benzoin is isolated when the starting compound is benzil: The imidazole is then produced via the mechanism followed by the reaction between an α-hydroxyketone and formamide (see above). Sodium bisulfite and sodium dithionite proved to be the most suitable reducing agents. In conjunction with formamide–formic acid, a 5–20% equimolar quantity of the sulfur compound is adequate. This "catalytic" action of the bisulfite is due to the reduction by formamide–formic acid to the sulfide; this then effects the reduction of the benzil to benzoin, being itself oxidized to elementary sulfur. The latter is then once more reduced by formamide–formic acid to sulfide.

$$HSO_3^- + HCOOH/HCONH_2 \longrightarrow$$

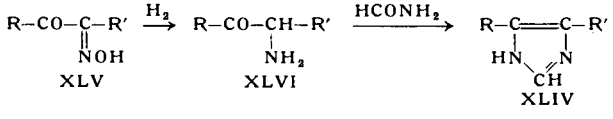
$$S^{2-} \underset{HCONH_2/HCOOH}{\overset{\text{Benzil} \rightarrow \text{Benzoin}}{\rightleftharpoons}} S$$

Good yields of imidazole are accordingly also obtained with elementary sulfur or the sulfides of sodium or potassium instead of bisulfite. The formamide–formic acid mixture is also capable of reducing the diketone alone, but the yields do not then exceed 20–30%.

From α-Aminoketones

Following the detection of the α-formaminoketone as intermediate in the synthesis of imidazole from α-hydroxyketone and formamide, we were able to convert several α-hydroxyketones (priopionoin, butyroin, benzoin) into the corresponding α-formaminoketones in yields of approximately 50% with formamide under certain conditions (*31*).

The conversion of α-aminoketones into imidazoles by means of formamide, briefly sketched earlier, proceeds extremely readily. Desylamine, for example, gives 4,5-diphenylimidazole in 90% yield (*30*). It is advantageous that the α-aminoketones (XLVI), accessible only with difficulty, can be replaced by their precursors, namely the α-isonitrosoketones (XLV). The isonitrosoketones are reduced in formamide at 70–100°, and the imidazole ring then closed at a more elevated temperature. Hydrogen and platinum oxide or sodium bisulfite (in catalytic amounts) can be used as reducing agent.



From α-Haloketones

The use of α-haloketones offers a further possibility in the synthesis of imidazoles. Unlike the reaction involving α-hydroxyketones or α-diketones, this method also permits the preparation of 4(5)-monosubstituted imidazoles (*30*). It furthermore enables the imidazole ring to become linked to cycloaliphatic α-haloketones (*35*). Table 4 shows the imidazoles which we have prepared by this method.

TABLE 4
Imidazoles from α-Haloketones and Formamide

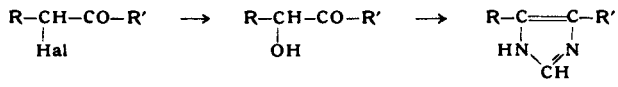
α-Haloketone	Imidazole	M. p.	Yield (%)
ω-Bromoacetophenone	4(5)-Phenyl-	128°	90
α-Bromo-isovalerophenone	4(5)-Phenyl-5(4)-isopropyl-	200°	69
α-Bromo-*n*-propyl ketone	4(5)-Ethyl-5(4)-*n*-propyl-	162° (Hydrochloride)	49
3-Bromobutanone	4, 5-Dimethylimidazole + 4, 5-Dimethyloxazole	265° (Hydrochloride) –	47 22
m-Nitro-ω-bromoacetophenone	4(5)-(*m*-Nitrophenyl)-	224°	72
p-Methoxy-ω-bromoacetophenone	4(5)-(*p*-Methoxyphenyl)-	137°	62
α-Chlorocyclohexanone	4, 5, 6, 7-Tetrahydrobenz- (= 4, 5-Cyclotetramethylene-)	149°	63
α-Chlorocycloheptanone	4, 5-Cyclopentamethylene-	202°	85
α-Chlorocycloöctanone	4, 5-Cyclohexamethylene-	166°	70

A substantial simplification of this process consists in brominating the ketones in formamide, and directly converting the α-bromoketones so formed into the imidazoles by heating with an excess of formamide.

TABLE 5
Imidazoles from Ketones, Bromine, and Formamide

Ketone	Imidazole	Yield (%)
Acetophenone	4(5)-Phenyl-	61
Propiophenone	4(5)-Phenyl-5(4)-methyl-	80
Butyrophenone	4(5)-Phenyl-5(4)-ethyl-	81.5
Methyl benzyl ketone	4(5)-Phenyl-5(4)-methyl-	43
Deoxybenzoin	4, 5-Diphenyl-	67

The initial step in the formation of imidazole from α-haloketones is the replacement of the halogen by an OH group (see below); the α-hydroxyketone is then converted into the imidazole according to the mechanism depicted earlier.



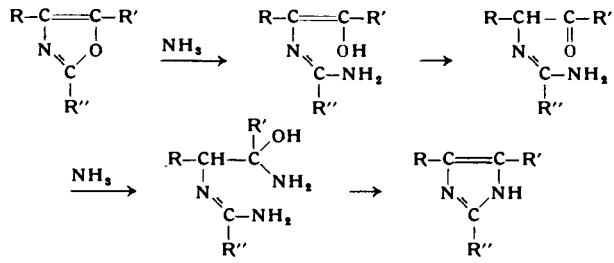
The imidazole syntheses described succeed only with formamide, and not with higher acid amides.

From Oxazoles

Blümlein (*36*) and Lewy (*37*) obtained a small yield of 4-phenyloxazole from ω-bromoacetophenone and a two molar quantity of formamide at 130°. After we had obtained a 90% yield of 4(5)-phenylimidazole from ω-bromoacetophenone and formamide at 150–180°, the assumption naturally suggested itself that oxazoles constitute an intermediate in the imidazole synthesis. This assumption has, however, proved to be incorrect.

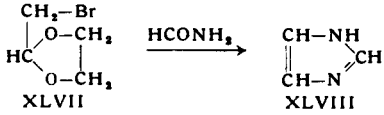
We discovered that oxazoles can be converted into imidazoles by heating at 180–190° in formamide or by reaction with formamide/ammonia in an autoclave (*32,38*). Since oxazoles can be prepared by a variety of processes (see next section), this method constitutes yet a further possible synthesis of imidazoles. The yields lie between 70 and 90%, and the method has thus far only failed in the case of benzoxazole and 2,4,5-triethyloxazole. The latter decomposes as a result of the vigorous reaction conditions. Inasmuch as the oxazoles themselves are stable therefore, the conversion of oxazoles into imidazoles is theoretically possible in all cases.

The replacement of the oxazole oxygen by NH presupposes a ring opening as the first step. This can be regarded as either an ammonolytic (by the action of the ammonia liberated by the formamide on boiling or the ammonia added as reactant) or a hydrolytic reaction (formamide invariably contains small quantities of water; water is furthermore liberated during the course of the reaction). A number of oxazoles had been converted into imidazoles earlier, by means of alcoholic ammonia or alcoholic aniline in a sealed tube at 300° (*39*). As far as comparable data regarding yields are available, those obtained by the formamide method are found to be substantially higher. The ammonolytic fission is certainly not the only effect influencing this reaction. This is indicated by the fact that while 2,4,5-triphenyloxazole remains unchanged in contact with ammonia in an autoclave at 210°, it affords an 85% yield of triphenylimidazole in the presence of formamide. Formamide appears on the one hand to allow salt formation with the oxazole [quaternary oxazolium salts are converted into imidazoles far more readily than are the free oxazoles (*39a*)] by the formation of formic acid, and on the other, to supply the nucleophilic agent simultaneously by decomposition to ammonia. To this must be added the solvent and condensing properties of formamide. We postulate the following reaction course on the basis of an ammonolytic fission (without protonation):



Synthesis of Imidazole

The imidazole synthesis, described above, from α-haloketones and formamide, allows the preparation of the parent substance of the series. In order to protect the aldehyde group in the bromoacetaldehyde we converted the latter into the acetal with ethylene glycol, and allowed the acetal (XLVII) to react with formamide at 180°, while ammonia was passed through the mixture. Imidazole (XLVIII) is formed in around 60% yield (*40*).



XLVII XLVIII

This method constitutes the simplest and most productive imidazole synthesis. The preparation from tartaric acid, via dinitrotartaric acid and imidazole-4,5-dicarboxylic acid, for example, gives a yield of 29–30% (calculated with respect to tartaric acid) (*41*).

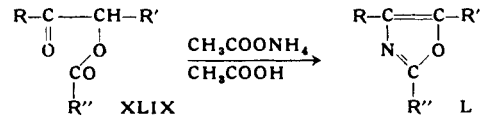
Further possibilities of synthesizing imidazoles are discussed later.

Syntheses of Oxazoles

From Acyloin Esters and the Ammonium Salts of Carboxylic Acids

The conversion, discussed earlier, of oxazoles into imidazoles, for which we required a large number of oxazoles, induced us to develop the existing oxazole syntheses and to supplement them with new ones. Some of these syntheses also utilize formamide, and others are indirectly connected with it. These methods are therefore briefly discussed.

Davidson and co-workers (*42*) had obtained 2-methyl-4,5-diphenyloxazole from benzoin acetate and ammonium acetate in glacial acetic acid; the corresponding reaction with benzoin benzoate gave them 2,4,5-triphenyloxazole. This method enabled us to prepare a series of hitherto largely unknown oxazoles (L) (*32*) using the esters of aliphatic or mixed



aliphatic-aromatic acyloins and aliphatic carboxylic acids (XLIX) in glacial acetic acid–ammonium acetate (cf. Table 6).

TABLE 6
Oxazoles from Acylated Acyloins

Acylated acyloin	Oxazole	Yield (%)
Propionoin acetate	2-Methyl-4,5-diethyl-	82
Propionoin propionate	2,4,5-Triethyl-	80
Butyroin acetate	2-Methyl-4,5-di-*n*-propyl-	85
Isobutyroin acetate	2-Methyl-4,5-diisopropyl-	67
Benzoin butyrate	2-*n*-Propyl-4,5-diphenyl-	44
Benzoin isovalerate	2-Isobutyl-4,5-diphenyl-	60
Benzoin enanthate	2-*n*-Hexyl-4,5-diphenyl	29
α-Acetoxybutyrophenone	2-Methyl-5-ethyl-4-phenyl-	50
p-Methyl-α-acetoxyisovalerophenone	2-Methyl-5-isopropyl-4-*p*-tolyl-	50
Acetol acetate	2,4-Dimethyl-	22
ω-Acetoxy-acetophenone	2-Methyl-4-phenyl-	11

One method of preparing the acyloin esters consists in allowing the α-bromoketones and the sodium salts of the carboxylic acids to react—either in alcohol, or in the acid to be esterified. The esters are not isolated, and the oxazoles are prepared directly by adding the ammonium salt to, or passing ammonia through, the mixture which is then boiled (*32*). Table 7 gives a list of the oxazoles prepared by this method.

TABLE 7
Oxazoles from α-Bromoketones and Acids

Bromoketone + acid	Oxazole	Yield (%)
α-Bromobutyrophenone + propionic acid	2,5-Diethyl-4-phenyl-	55
α-Bromoisocaprophenone + acetic acid	2-Methyl-5-isobutyl-4-phenyl-	72
α-Bromopropiophenone + propionic acid	5-Methyl-2-ethyl-4-phenyl-	62
α-Bromopropiophenone + butyric acid	5-Methyl-2-propyl-4-phenyl-	31
ω-Bromoacetophenone + butyric acid	2-Propyl-4-phenyl-	6
α-Bromopropiophenone + acetic acid	2,5-Dimethyl-4-phenyl-	66
α-Bromobutyrophenone + acetic acid	2-Methyl-5-ethyl-4-phenyl-	65
α-Bromovalerophenone + acetic acid	2-Methyl-5-*n*-propyl-4-phenyl-	50

From Enediolic Diesters and the Ammonium Salts of Carboxylic Acids

A further variation of the oxazole synthesis consists in the utilization of the diesters of the enediols. In the aliphatic series, these compounds are formed directly from acid chlorides and sodium in ether con-

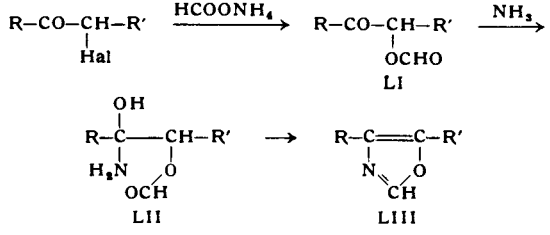
taining a trace of water (*32*). If the enediolic diester thus obtained is allowed to react with ammonia in the corresponding acid or glacial acetic acid, the previously unknown, symmetrical trisubstituted oxazoles are obtained (*32*) (Table 8). The formation of oxazole may result via the initial removal of one ester group, followed by the conversion of the acyloin ester produced into the oxazole by means of ammonia.

TABLE 8

Trisubstituted Oxazoles from Enediolic Diesters

Endiol diester	Oxazole	Yield (%)
Hex-3-ene-3,4-diol dipropionate	2,4,5-Triethyl-	63
Oct-4-ene-4,5-diol dibutyrate	2,4,5-Tripropyl-	61
2,7-Dimethyloct-4-ene-4,5-diol diisovalerate	2,4,5-Triisobutyl-	72

The above-mentioned methods are not suited to the preparation of 2-unsubstituted oxazoles. While the condensation of the acyloin formates and ammonia proceeds readily enough, the difficulty lies in the preparation of the acyloin formates themselves. The only exception is found in the case of benzoin formate, which is readily obtained from benzoin and a mixture of formic acid and acetic anhydride, and which affords a 72% yield of 4,5-diphenyloxazole with ammonium formate–formic acid (*32*). The method starting from the α-haloketones also fails in the case of the 2-unsubstituted oxazoles, when the reaction is effected with sodium formate followed by ammonium formate (sometimes in formic acid). If, on the other hand, the α-haloketone is allowed to react directly with ammonium formate in formic acid, 2-unsubstituted oxazoles (LIII) are readily obtained. This method allows the immediate conversion of the initially resulting α-formoxyketone (LI) into the oxazole (*43*). The oxazoles which we have prepared by this method are shown in Table 9.



This route rendered possible the first preparation of isomeric 4,5-disubstituted oxazoles, and hence of the corresponding imidazoles by means of formamide (see above). Comparison of the UV spectra of

TABLE 9

2-Unsubstituted Oxazoles from α-Haloketones [a]

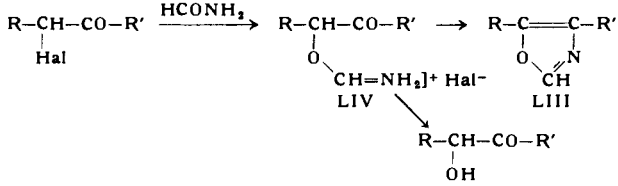
Oxazole	Yield (%)
4,5-Dipropyl-	59
4-Phenyl-	49
5-Methyl-4-phenyl-	60
4-Methyl-5-phenyl-	47
5-Ethyl-4-phenyl-	50
4-Methyl-5-benzyl-	30
5-*n*-Propyl-4-phenyl-	51
5-Butyl-4-phenyl-	55
5-Hexyl-4-phenyl-	68
5-Heptyl-4-phenyl-	61
5-Octyl-4-phenyl-	72
4(*p*-Bromophenyl)-	47
4,5-Diphenyl-	70

[a] See refs. (*43*, *44a*).

oxazoles and imidazoles allowed more accurate pronouncements concerning the structure of the imidazoles (*44*).

From α-Haloketones and Acid Amides

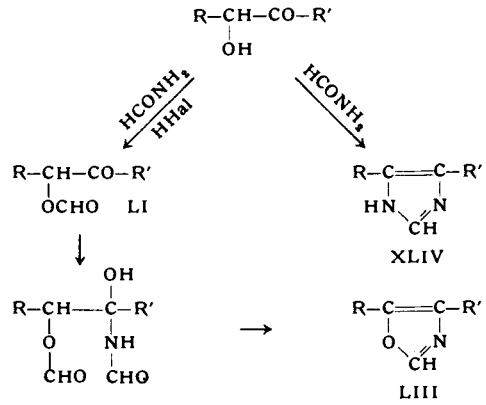
Finally, a method of preparing 2-unsubstituted oxazoles is described, which constitutes an interesting development of the oxazole synthesis of Blümlein (*36*) and Lewy (*37*). Whereas their method affords satisfactory yields of oxazoles from α-haloketones and higher amides, the use of formamide results in poor yields of 2-unsubstituted oxazoles. This we have ascertained to be due to the fact that predominantly imidazoles are produced (see above). Knowledge of the mechanism of the halogen compound–formamide reactions enabled us to follow the course of the oxazole formation from α-haloketone and formamide, and at the same time to modify the reaction to a more productive synthesis.



α-Haloketones react with formamide to give, initially, iminoesters (LIV), which then either ring-close to the oxazoles LIII, or decompose to give α-hydroxyketones.

The α-hydroxyketones react with excess formamide in the presence

of the liberated hydrogen halides to give α-formoxyketones (LI) which then yield the oxazoles LIII with formamide (*43*). On the other hand, hydroxyketones and formamide yield imidazoles (XLIV). These combine with the hydrogen halide, required for the formylation of the hydroxyketone, in the form of imidazole hydrochlorides, so that predominantly imidazole is formed. If, however, ring closure to the oxazole (starting from the initially formed iminoester LIV) or formation of the



formate (starting from the α-hydroxyketone produced subsequently) are favored by the addition of a copious quantity of sulfuric acid, oxazoles (LIII) are readily obtained (Table 10).

TABLE 10
Oxazoles from α-Haloketones with Formamide and Conc. Sulfuric Acid

α-Haloketone	Oxazole	Yield (%)
α-Bromopropiophenone	5-Methyl-4-phenyl-	21
α-Bromobutyrophenone	5-Ethyl-4-phenyl-	47
α-Bromoisovalerophenone	5-Isopropyl-4-phenyl	64
α-Bromocaprophenone	5-Butyl-4-phenyl-	71
α-Bromocaprylophenone	5-Hexyl-4-phenyl-	65

Synthesis of Imidazoles and Oxazoles Using Formamidine

We have also undertaken reactions with formamidine, analogous to the syntheses with formamide described above (*45*). The formamidine was liberated from its hydrochloride by the addition of sodium butoxide in butanolic solution.

Aromatic *o*-diamines gave benzimidazoles (Table 11) and *o*-aminophenols yielded benzoxazoles (Table 12).

TABLE 11
Aromatic o-Diamines and Formamidine

o-Diamine	Imidazole	Yield (%)
o-Phenylenediamine	Benzimidazole	93
N-Methyl-*o*-phenylenediamine	*N*-Methylbenzimidazole	80
1,2-Diaminonaphthalene	1,2-Naphthimidazole	83

Similar experiments were carried out with N,N′-diphenylformamidine/formic acid (*46*). It should be noted that 9-amino-10-hydroxyphenanthrene and benzamidine gave the imidazole (2-phenylphenanthroimidazole), and not the oxazole, which is obtained with formamidine (*47*).

TABLE 12
Aromatic o-Aminophenols and Formamidine

o-Aminophenol	Oxazole	Yield (%)
o-Aminophenol	Benzoxazole	59
1-Amino-2-naphthol	1,2-Naphthoxazole	85
2-Amino-1-naphthol	2,1-Naphthoxazole	64
9-Amino-10-phenanthrol	9,10-Phenanthroxazole	50

Experiments with α-hydroxyketones give the rather surprising result that whereas the aliphatic acyloins afford predominantly imidazoles, the benzoins yield mainly oxazoles (Table 13).

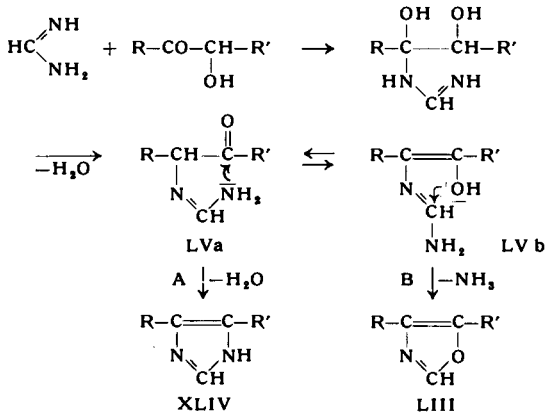
Even the alteration of concentration or reaction conditions has no

TABLE 13
Reaction Products Obtained from α-Hydroxyketones and Formamidine

α-Hydroxyketone	Imidazole	Yield (%)	Oxazole	Yield (%)
Propionoin	4,5-Diethyl-	68	–	–
Butyroin	4,5-Dipropyl-	56	–	–
Valeroin	4,5-Di-*n*-butyl-	64	–	–
Isovaleroin	4,5-Diisobutyl-	39	–	–
Caproin	4,5-Di-*n*-amyl-	48	–	–
Cyclohexanolone	Tetrahydrobenz-	35	–	–
α-Hydroxybutyrophenone	4-Phenyl-5-ethyl-	21	4-Phenyl-5-ethyl-	37
Benzoin	–	–	4,5-Diphenyl-	80
Furoin	–	–	4,5-Difuryl-	75
Anisoin	–	–	4,5-Di-*p*-methoxyphenyl	79
p,p′-Diphenylbenzoin	–	–	4,5-Di-*p*-biphenyl-	90
p-Dimethylaminobenzoin	–		4-(*p*-Dimethylamino-phenyl)-5-phenyl-	74
p-Bromobenzoin	–	–	4-(*p*-Bromophenyl)-5-phenyl-	75
p-Chlorobenzoin	–	–	4-(*p*-Chlorophenyl)-5-phenyl-	67
9,10-Dihydroxyphenanthrene	–	–	9,10-Phenanthro-	67

effect on this situation. It is worth mentioning that 9,10-dihydroxyphenanthrene affords phenanthroxazole in good yield. This reaction may be attributed to the tautomerism between the enediol and the hydroxyketone. 1,2-Dihydroxynaphthalene does not undergo this reaction; the aromatic character of the ring system is already so pronounced in this compound, that tautomerism with the hydroxyketone is no longer possible. α-Hydroxybutyrophenone occupies a position intermediate between the alpihatic acyloins and the benzoins. It gives rise to both the imidazole and oxazole derivatives.

Unlike formamidine, acetamidine and benzamidine react with both aliphatic acyloins and benzoins to give imidazoles exclusively. The formation of imidazoles and oxazoles is shown in the following reaction scheme:



Aromatic groups favor structure LVb, derived from the enediolic form of the hydroxyketone, and hence the formation of oxazole, while aliphatic groups favor structure LVa, derived from the hydroxyketone, and consequently promote imidazole formation.

The fact that higher amidines yield imidazoles exclusively, must obviously be explained by the steric hindrance associated with the attack on the enolic oxygen linked to the amidine carbon atom.

The preparation of imidazoles and oxazoles from trisformylaminomethane (see later) is closely related to the syntheses using formamidine.

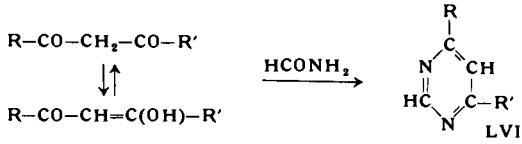
Syntheses of Pyrimidines

4,6-Disubstituted Pyrimidines

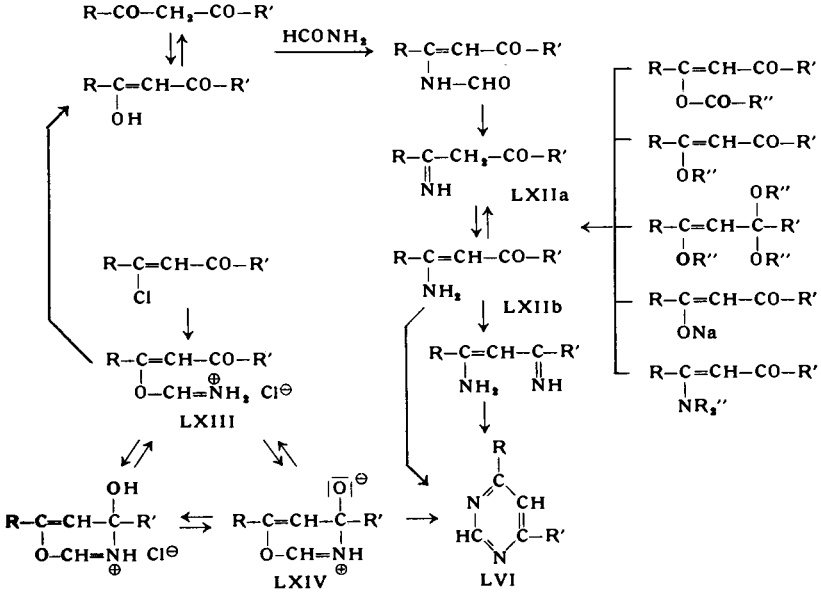
If, instead of α-hydroxy-, α-amino-, and α-haloketones, compounds of structure

R–CO–CH=C(X)–R′ X = OH, NH_2, Halogen

are allowed to react with formamide, pyrimidines would be expected to result. 4,6-Disubstituted pyrimidines (LVI) are in fact formed from β-diketones or β-iminoketones and formamide at 180–200° (*48*).



The enaminoketones can also be replaced by N-mono- and N,N-disubstituted, unsaturated aminoketones. During the course of the reaction with formamide, the NHR or NR_2 group is replaced by NH_2 in a single transamination. The reaction between the β-chlorovinylketones R—C(Cl)=CH—CO—R′ and formamide to give pyridines constitutes yet another simple process of widespread application (*48*).



We assume the α,β-unsaturated β-aminoketone LXIIb (=β-iminoketone LXIIa) to be the central intermediate. Under certain reaction conditions, we were able to isolate this compound. It can be formed from a β-diketone or its enol and either ammonia or formamide. That it can be converted into a pyrimidine was shown above. The chloroketone can

yield the pyrimidine either via the iminoester LXIII and the hydroxyoxazine LXIV, or via the iminoester and the diketone. The hydroxyoxazine is converted into the pyrimidine with formamide or ammonia, in corresponding manner to the oxazole → imidazole conversion (see above).

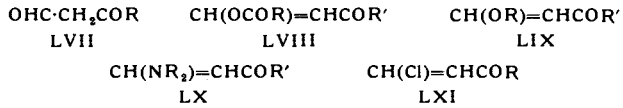
α,β-Unsaturated β-chloroketones are readily obtainable from acetylenes and acid chlorides in the presence of aluminum chloride. Conversion to pyrimidines surprisingly proceeds at temperatures as low as 150°, though better yields are obtained at higher temperatures. This fact is of theoretical importance, inasmuch as it eliminates the postulated formation of β-diketone intermediates, since these do not react with formamide below 180–200° (for explanation, see below).

The compounds thus far referred to as β-substituted α,β-unsaturated ketones can be regarded as vinylogs of carboxylic acids. This class of compounds can be extended to include β-alkoxy- and β-acyloxyvinylketones. The former, R—C(OR)=CH—CO—R′, can be regarded as vinylogs of esters, and the latter, R—C(OCOR″)=CH—CO—R′, as vinylogs of acid anhydrides. Members of both these classes of compounds react with formamide to give pyrimidines.

Finally, a further variation consists in using acetylenic ketones, which can be regarded as the "internal anhydrides" of β-diketones. They too, react readily with formamide to give pyrimidines (*49*).

4-Substituted Pyrimidines

4-Monosubstituted pyrimidines can be prepared from β-ketoaldehydes (LVII) and their enol derivatives LVIII–LXI (*48*).



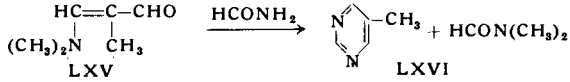
Because of its free aldehydic group, benzoylacetaldehyde affords but poor yields of 4-phenylpyrimidine. If, however, the aldehydic group is protected and the sodium salts of the β-ketoaldehydes or the acetals are used, good yields of pyrimidines are obtained (*48*).

5- and 4,5-Substituted Pyrimidines

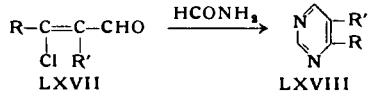
The pyrimidine ring-closure reactions mentioned hitherto permit the preparation of 4-, 4,6-, 2,4-, and 2,4,6-substituted pyrimidines. Utilization of the corresponding starting substances also enabled us to synthesize 5- and 4,5-substituted pyrimidines by this method (*50*).

Arnold and Sorm (*51*) had obtained α-methyl-β-dimethylaminoacrolein (LXV) from propionaldehyde acetal by means of a dimethylforma-

mide–phosgene complex. If LXV is allowed to react with formamide under the conditions of the pyrimidine synthesis, 5-methylpyrimidine (LXVI) is obtained.



Since the separation of the methylpyrimidine from dimethylformamide cannot be effected by distillation—it must be separated in the form of a $HgCl_2$ complex—we converted the propionaldehyde acetal into α-methyl-β-diethylaminoacrolein with the diethylformamide–phosgene complex. 5-Methylpyrimidine and diethylformamide can be separated by distillation, and an 85% yield of 5-methylpyrimidine is obtained. If α-alkyl-substituted β-chlorovinylaldehydes (LXVII) (*52*) are used, good yields of 4,5-substituted pyrimidines (LXVIII) are obtained (*50*). This conversion corresponds to the reaction between β-chlorovinylketones and formamide, described above.



Further syntheses, including those of 2,5-disubstituted pyrimidines, are still in progress.

2,4- and 2,4,6-Substituted Pyrimidines

Although the conversion of diketones cannot be carried out with higher amides, these will effect the conversion of the more reactive β-chlorovinylketones. Table 14 shows the 2-substituted pyrimidines obtained from β-chlorovinylketones and acetamide, propionamide, and butyramide (*53*).

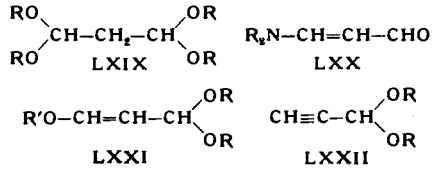
TABLE 14
2-Substituted Pyrimidines

β-Chlorovinyl ketone	Acid amide	Pyrimidine	Yield (%)
1-Chlorohex-1-en-3-one	Acetamide	2-Methyl-4-propyl-	40
1-Chlorohex-1-en-3-one	Propionamide	2-Ethyl-4-propyl-	23
1-Chlorohex-1-en-3-one	Butyramide	2,4-Dipropyl-	21
1-Phenyl-3-chloroprop-2-en-1-one	Acetamide	2-Methyl-4-phenyl-	41
4-Chlorooct-3-en-2-one	Acetamide	2,4-Dimethyl-6-*n*-butyl-	42
5-Chloronon-4-en-3-one	Acetamide	2-Methyl-4-ethyl-6-*n*-butyl-	47

Synthesis of Pyrimidine

The synthesis of pyrimidine, accessible thus far with difficulty, merited special interest; we succeeded in obtaining it from malondialde-

hyde acetal (LXIX), β-dialkylaminoacrolein (LXX), β-alkoxyacrolein acetal (LXXI), and propargyl aldehyde acetal (LXXII) (*48,49,54*).

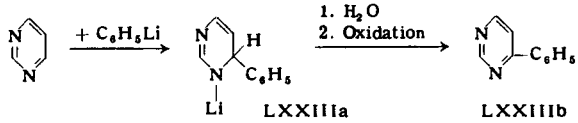


Compounds LXIX and LXX afforded yields of 60–65%. A mixture of the compound to be converted and formamide can be passed in a continuous process over a contact catalyst (aluminum oxide or aluminum silicate) heated to 200° (*54*). The method developed for the preparation of pyrimidine and 4-methylpyrimidine affords yields of approximately 70%.

Reactions of Pyrimidine (*54*)

Pyrimidine forms numerous salts with inorganic acids, and addition compounds with metallic salts. It can, for example, be quaternized with dimethyl sulfate and oxidation with acetic acid/perhydrol gives an N-oxide; the latter reacts with acetic anhydride to yield an acetyl compound, probably 4-acetoxypyrimidine.

Organometallic compounds, e.g. phenyllithium, substitute at C_4.



The 4-substituted pyrimidines which we have prepared by this route are shown in Table 15.

TABLE 15
4-Substituted Pyrimidines from Pyrimidine and Organolithium Compounds

4-Substituted pyrimidine	Yield (%)
Phenyl-	51
p-Tolyl-	51
p-Methoxyphenyl-	45
2-Thienyl-	46
2-Furyl-	53
2-Thiazolyl-	30
Mesityl-	25
2,6-Dimethoxyphenyl-	18
2-Benzothiazolyl-	27

Pyrimidine, in the form of its hydrochloride, can be brominated to give a 5-bromopyrimidine. The bromine is comparatively readily replaced by an alkoxy or ethylmercapto group, with ethoxide and ethylmercaptide, respectively.

Acid Amides and Halogen Compounds

Formamide and Halogen Compounds

Following upon the reactions between α-haloketones and formamide yielding imidazoles and oxazoles (see above), we allowed a large number of halogen compounds to react with formamide at 150° (*55*). The results are summarized in Table 16.

The halogen compounds yield either formylamino compounds (=N-substituted formamides, LXXIV) according to Eq. (a), or formates (LXXV) according to Eq. (b).

$$\text{(a)}\quad R\text{—Hal} + 2\ HCONH_2 \rightarrow \underset{\text{LXXIV}}{R\text{—NH—CHO}} + CO + NH_4Hal$$

$$\text{(b)}\quad R\text{—Hal} + 2\ HCONH_2 \rightarrow \underset{\text{LXXV}}{R\text{—OCHO}} + HCN + NH_4Hal$$

The amounts of carbon monoxide and ammonium chloride found agree with those demanded by Eq. (a).

The hydrogen cyanide formed according to Eq. (b) is polymerized at the elevated reaction temperature, and results in the darkening of the solution.

Small quantities of α-hydroxyesters are found as by-product in the preparation of the α-formoxyesters (Table 16). On the assumption that these hydroxyl compounds are intermediates in the formation of the formoxyesters, we investigated the behavior of hydroxyl compounds towards formamide at various temperatures. The formation of formic esters does not occur below 160°, and proceeds readily at 180° (*55*) (Table 17).

This proves that at our reaction temperature of 150°, the formoxyesters are not formed simply by the action of formamide on the hydroxyesters assumed to be initially produced. It is more probably a case of the joint reaction with formamide and the hydrogen halide liberated during the course of the reaction (see p. 276).

The preparation of the hydroxyl compounds from the halogen compounds, and hence the proof that they occur as intermediates, is accomplished by the addition of substances which inhibit the formation of formates, e.g. water, formic acid, ammonium formate, finely divided nickel, or urotropine (see below).

TABLE 16
Halogen Compounds and Formamide

Halogen compound	Reaction product	Yield (%)
Octyl bromide	Octyl formate	92
Benzyl chloride	Benzyl formate	74
	N-Benzylformamide	5
Benzyl bromide	Benzyl formate	27.5
	N-Benzylformamide	44.5
Benzyl iodide	Benzyl formate	15
	N-Benzylformamide	47.5
p-Methoxybenzyl chloride	N-(*p*-Methoxybenzyl)formamide	36
2,4,6-Trimethylbenzyl chloride	N-(2,4,6-Trimethylbenzyl)formamide	31
Benzhydryl chloride	N-Benzhydrylformamide	95
Triphenylmethyl chloride	N-Triphenylmethylformamide	94
Benzotrichloride	Benzoic acid	80
Diphenyldichloromethane	Benzophenone	50
α,α'-Hexabromo-*p*-xylene	Terephthalic acid	63
p-Nitrochlorobenzene		–
2,4-Dinitrochlorobenzene	2,4-Dinitroaniline	55
α-Bromobutyric acid	α-Hydroxybutyric acid	30
Phenylchloroacetic acid	Mandelic acid	13
Diphenylchloroacetic acid	N-Benzhydrylformamide	88
Ethyl chloroacetate	Ethyl *O*-formylglycolate	69
Ethyl α-bromopropionate	Ethyl *O*-formyllactate	72
Ethyl α-bromobutyrate	Ethyl α-formoxybutyrate	72
Ethyl α-bromocaproate	Ethyl α-formoxycaproate	82
Ethyl α-bromoenanthate	Ethyl α-formoxyenanthate	84
Ethyl diphenylchloroacetate	Ethyl diphenyl-N-formylglycine	85
Chloromethyl *n*-propyl ether	Bisformylaminomethane	50
Benzoyl chloride	Benzoic acid	82

The conversion of haloesters into hydroxyesters (*55*) with formamide in the presence of water is shown in Table 18. It is noteworthy that the ester grouping remains unattacked during the replacement of the halogen by the formoxy or hydroxyl group. This allows a simplified

TABLE 17
Hydroxy Compounds and Formamide

Hydroxy compound	Reaction product	Yield (%)
Octyl alcohol	Octyl formate	100
Cyclohexanol	Cyclohexyl formate	100
Benzyl alcohol	Benzyl formate	100
p-Methoxybenzyl alcohol	*p*-Methoxybenzyl formate	40
	N-(*p*-Methoxybenzyl)formamide	60
Benzhydrol	N-Benzhydrylformamide	95
Triphenylmethyl carbinol	N-Triphenylmethylformamide	100
α-Hydroxybutyric acid	α-Hydroxybutyramide	100

preparation of the hydroxyesters. The formoxyesters were previously unknown.

The experimental results show that the nature of the compounds produced depends on the structure of the halogen compound. The ability of the alkyl halide to form a relatively stable carbonium ion is an essen-

TABLE 18
α-Hydroxy Esters from α-Halo Esters

Halo ester	Hydroxy ester	Yield (%)
Ethyl chloroacetate	Ethyl glycolate	62
Ethyl α-bromopropionate	Ethyl lactate	61
Ethyl α-bromobutyrate	Ethyl α-hydroxybutyrate	91
Ethyl α-bromoisovalerate	Ethyl α-hydroxyisovalerate	55
Ethyl α-bromocaproate	Ethyl α-hydroxycaproate	73
Ethyl α-bromoenanthate	Ethyl α-hydroxyenanthate	76

tial prerequisite for the formation of a formylamine [reaction (a)]. This dissociation is favored by the formamide (dielectric constant 113.5). For the conversion of trityl chloride [LXXVI, Tr = $C(C_6H_5)_3$], we postulate the following reaction course (*55–57*):

$$\underset{\text{LXXVI}}{Tr{-}Cl} \rightleftarrows Tr^{\oplus} + Cl^{\ominus}$$

$$Tr^{\oplus} + NH_2CHO \rightleftarrows Tr{-}\overset{\oplus}{N}H_2CHO$$

$$Tr{-}\overset{\oplus}{N}H_2CHO + NH_2CHO \rightleftarrows \underset{\text{LXXIVa}}{Tr{-}NHCHO} + HCO\overset{\oplus}{N}H_3$$

$$HCO\overset{\oplus}{N}H_3 \rightarrow CO + NH_4^{\oplus}$$

This scheme is supported by the fact that higher amides yield the corresponding diacyl amides, since the $H_3\overset{\oplus}{N}COR$ cannot, in this case, dissociate (see below).

The formation of formate is capable of a twofold explanation (*57*). Firstly, dissociation of the halogen compound R–Hal can be postulated. Due to a lack of mesomeric stabilization, however, the unstable car-

$$R{-}Hal \rightleftarrows R^{\oplus} + Hal^{\ominus}$$

$$R^{\oplus} + HCONH_2 \rightleftarrows R{-}O{-}CH{=}\overset{\oplus}{N}H_2$$

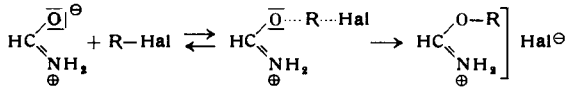
$$R{-}O{-}CH{=}\overset{\oplus}{N}H_2 + HCONH_2 \rightleftarrows \underset{\text{LXXVII}}{R{-}O{-}CH{=}NH} + HCO\overset{\oplus}{N}H_3$$

$$\underset{\text{LXXII}}{R{-}O{-}CH{=}NH} \rightarrow \underset{\text{LXXVIII}}{ROH} + HCN$$

$$\underset{\text{LXXVIII}}{ROH} + HCO\overset{\oplus}{N}H_3 + Hal^{\ominus} \rightarrow \underset{\text{LXXV}}{ROCHO} + NH_4Hal$$

bonium ion reacts immediately with the formamide oxygen, being the atom possessing the highest electron density.

Like reaction (a), this too is an S_N1 reaction. The end-product is nevertheless different from that in reaction (a), due to differences in the type of reaction undergone by unstable carbonium ions. The second explanation interprets the formation of formate as an S_N2 reaction; in carboxylic acid amides the oxygen is more nucleophilic than the nitrogen.



LXXII (Hydrochloride)

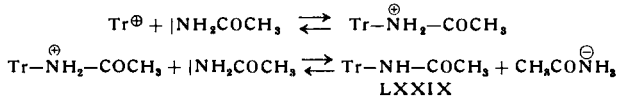
Both explanations include the formation of the iminoester LXXVII, which dissociates at the elevated reaction temperature. The formate constitutes a secondary product, formed by the formylation with formamide/hydrogen halide of the hydroxyl compound LXXVIII initially produced. Finely divided nickel or urotropine remove the hydrogen halide liberated and thus inhibit the formylation.

More thorough investigations have revealed that most halogen compounds in reaction (b) favor the S_N1 mechanism (*57*).

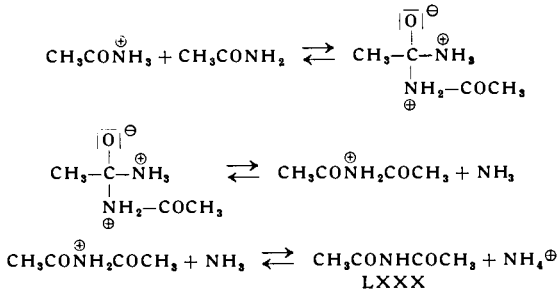
In the presence of water or water-releasing substances, the reaction course depends on the actual quantity of the water (*55*). Addition of 1 mole of H_2O per mole of haloester results in the formation of a formoxyester, and, at the high temperature obtaining, the hydrocyanic acid produced is immediately saponified by water to formamide or even formic acid. If 2 moles of water are added, hydroxyesters are formed almost exclusively; the water first causes the saponification of the hydrocyanic acid, and, second, prevents the further formylation of the hydroxyester.

Higher Acid Amides and Compounds of the Triphenylmethyl Chloride Type (*56*)

Corresponding to the preparation of N-tritylformamide, the higher acid amides (acetamide, propionamide, isobutyramide) also give N-trityl compounds (LXXIX) in very good yield. These preparations, however, necessitate a large excess of acid amide, elevated temperatures (210–220°) and prolonged reaction times (4–6 hr). These differences in reaction conditions are readily explained theoretically, as shown in the scheme below:



LXXIX



Whereas the reaction with formamide (see above) involves the irreversible decomposition of the protonated formamide $HCO\overset{\oplus}{N}H_3$ into CO and the ammonium salt, with the consequent displacement of the equilibrium in favor of the N-tritylformamide, formation of an ammonium salt in the case of the higher acid amides can only be effected with the assistance of a second amide molecule. Since the subsequent reactions are equilibria, and no longer irreversible reactions, such as those found with formamide, good yields of higher N-trityl amides are only obtained with an excess of acid amide, elevated temperatures, and prolonged reaction times. In accordance with this scheme we were successful in isolating good yields of the diacyl amides (e.g. LXXX).

N-Trityl amides are also obtained from trityl perchlorate, trityl carbinol, trityl methyl, and trityl ethyl ether. In these cases the trityl carbonium ion is also initially formed.

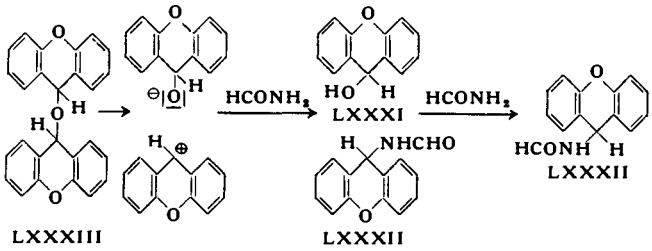
Being another compound capable of forming a relatively stable carbonium ion, xanthydrol was allowed to react with acid amides in the molten state. N-Xanthyl amides (e.g. LXXXII) are obtained in good yield after short reaction times (Table 19).

TABLE 19

N-Xanthyl Amides from Xanthydrol and Acid Amides

Acid amide	N-Xanthyl amide	Yield (%)
Formamide	-formamide	86
Acetamide	-acetamide	95
Isobutyramide	-isobutyramide	88
Benzamide	-benzamide	94
p-Nitrobenzamide	-*p*-nitrobenzamide	79

Dixanthyl ether (LXXXIII) also reacts very readily with formamide at 140° to give N-xanthylformamide. We postulate the following mechanism for this reaction:



Following upon the dissociation of the ether, formamide reacts with the xanthylium ion. The proton liberated combines with the alkoxide group to give xanthydrol (LXXXI), which dissociates anew and reacts with formamide to give N-xanthylformamide (LXXXII).

It is interesting to note that *p,p'*-bisdimethylaminobenzhydrol (Michler's hydrol) no longer reacts with acid amides. The melt merely becomes green, presumably due to the formation of the carbonium ion, which is strongly stabilized by resonance. Its electrophilic character is of such a low order that formamide no longer acts in a substituting capacity but as a reducing agent.

Formamide and Mannich-type Compounds

In reactions between keto Mannich bases (e.g. LXXXIV) and formamide, the amino group is replaced by formylamino (*58*). While the aliphatic Mannich compounds react best in the presence of metallic sodium, aromatic and heterocyclic compounds are advantageously allowed to react as their hydrochlorides (Table 20).

TABLE 20

Formamide and Mannich Compounds

Mannich compound	Reaction product	Yield (%)
1-Diethylamino-3-butanone	1-Formylamino-3-butanone (LXXXVI)	27
1-Dimethylamino-2-methyl-3-butanone	1-Formylamino-2-methyl-3-butanone	33
β-Dimethylaminopropiophenone	β-Formylaminopropiophenone	14
β-Dimethylaminopropiophenone hydrochloride	β-Formylaminopropiophenone	42
β-Dimethylamino-*p*-methyl-propiophenone hydrochloride	β-Formylamino-*p*-methyl propiophenone	40
β-Dimethylamino-*p*-methoxy-propiophenone hydrochloride	β-Formylamino-*p*-methoxy propiophenone	66
β-Dimethylamino-*p*-bromo-propiophenone hydrochloride	β-Formylamino-*p*-bromo propiophenone	23
2-Naphthyl-β-dimethylaminoethyl ketone hydrochloride	2-Naphthyl β-formylaminoethyl ketone	22

The course of the reaction can be explained by the initial formation of α,β-unsaturated ketones (e.g. LXXXV), followed by the addition of formamide to their double bond.

$$\underset{\text{LXXXIV}}{CH_3{-}CO{-}CH_2{-}CH_2N(C_2H_5)_2} \rightarrow \underset{\text{LXXXV}}{CH_3{-}CO{-}CH{=}CH_2} + HN(C_2H_5)_2$$

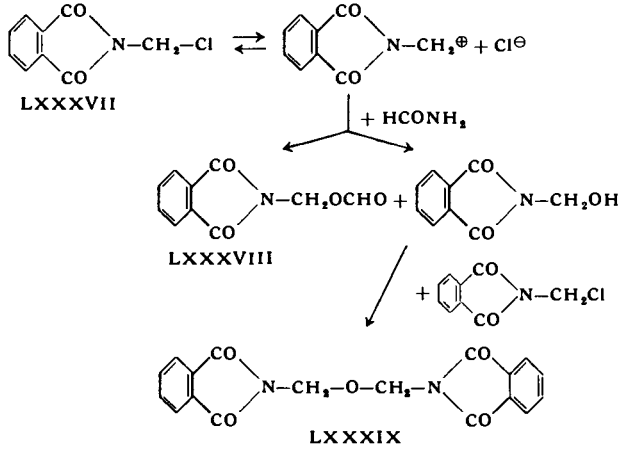
$$\underset{\text{LXXXV}}{CH_3{-}CO{-}CH{=}CH_2} + HCONH_2 \rightarrow \underset{\text{LXXXVI}}{CH_3{-}CO{-}CH_2{-}CH_2{-}NH{-}CHO}$$

In accordance with this hypothesis, formamide will add to α,β-unsaturated ketones to form monosubstituted formamides (Table 21).

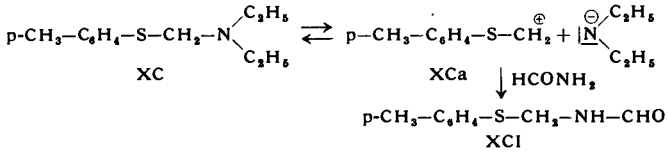
TABLE 21
Formamide and α,β-Unsaturated Ketones

Ketone	Reaction product	Yield (%)
Methyl vinyl ketone	1-Formylamino-3-butanone	38
Methyl propenyl ketone	1-Formylamino-1-methyl-3-butanone	50
Mesityl oxide	1-Formylamino-1,1-dimethyl-3-butanone	18
Phenyl vinyl ketone	β-Formylaminopropiophenone	32

N-Chloromethylphthalimide (LXXXVII) can formally also be regarded as a Mannich base. Reaction with formamide yields N-formoxymethylphthalimide (LXXXVIII) and diphthalimidodimethyl ether (LXXXIX).



According to this scheme, an unstable carbonium ion (the free electron pair at the N is claimed by both CO groups) is formed initially; it then attacks the formamide oxygen (an S_N2 mechanism gives the same result). If N-chloromethylphthalimide is replaced by diethylaminomethyl-*p*-tolyl sulfide (XC), formaminomethyl-*p*-tolyl sulfide (XCI) is produced exclusively. Since the carbonium ion (XCa) is stabilized by mesomerism, only N-substitution can occur during the reaction with formamide.



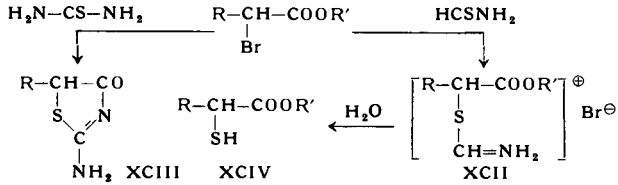
Thioformamide and Halogen Compounds

By allowing halogen compounds to react with thioformamide in ethereal solution (*59*), we obtained the previously little known thioformiminoester hydrohalides (Table 22).

TABLE 22
Halogen Compounds and Thioformamide

Halogen compound	Reaction product
Methyl iodide	Thioformiminomethyl ester hydriodide
Ethyl iodide	Thioformiminoethyl ester hydriodide
n-Butyl iodide	Thioformimino-*n*-butyl ester hydriodide
Benzyl bromide	Thioformiminobenzyl ester hydrobromide
Benzhydryl bromide	Thioformiminobenzhydryl ester hydrobromide
Trityl chloride	Thioformiminotrityl ester-thioformamide adduct

Unlike the reaction with formamide, that with thioformamide invariably occurs at the sulfur atom. The thioformiminoesters correspond to the isothiouronium salts obtained from the reaction with thiourea. Differences between thioformamide and thiourea become manifest in their behavior towards α-haloesters. Whereas thioformamide yields the salts of the thioformiminoesters (= α-iminoformylmercaptoesters, XCII) as anticipated, thiourea gives pseudothiohydantoins (XCIII). The α-iminoformylmercaptoesters are converted into α-mercaptoesters (XCIV) with water or alcohol.



The formation of the salts of the thioformiminoesters in ether requires 5–10 hr. If their isolation is dispensed with, and the reaction effected in boiling alcohol (95%), the previously unknown α-mercaptoesters are obtained after approximately 10 min (Table 23). These compounds are also formed by the reaction between haloesters, formamide, and phosphorus pentasulfide, with thioformamide occurring as intermediate.

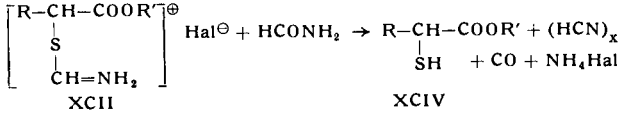
TABLE 23

α-Mercapto Esters from Halo Esters and Thioformamide in Boiling Ethanol

α-Mercapto acid ethyl ester	Yield (%)[a]
Thioglycolic	46 (58)
Thiolactic	82 (53)
α-Mercaptobutyric	78 (57)
α-Mercaptoisovaleric	78
α-Mercaptocaproic	63
α-Mercaptocaprylic	50

[a] The figures in parentheses refer to the reaction between α-halo esters, formamide, and P_2S_5.

The thioformiminoesters correspond to the formiminoesters postulated as intermediates in the analogous reaction with formamide. The fact that the former can be isolated may be due to the lower reaction temperature (below 60°) compared to that of the formamide reaction (150°). At 150° the thioformiminoesters (XCII) also decompose (in formamide solution) into the α-mercaptoesters (XCIV).



This reaction corresponds to the conversion of α-haloesters to α-hydroxyesters with formamide (see above). In this instance too, the darkening of the reaction solution is due to the formation of polymeric hydrocyanic acid.

Whereas both the reactions of thioformamide discussed above, and the previously known reactions of the higher thioamides (*60*) occur at the thioamide sulfur atom, the reaction between higher thioamides and trityl chloride in pyridine yields N-tritylthioamides (*56*) (Table 24).

TABLE 24

Thioamides and Trityl Chloride

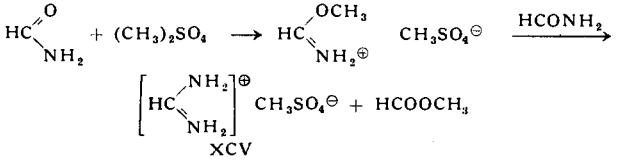
Thioamide	Reaction product	Yield (%)
Thioacetamide	N-Tritylthioacetamide	38
Thiobenzamide	N-Tritylthiobenzamide	32
4-Methylthiobenzamide	N-Trityl-4-methylthiobenzamide	36
4-Methoxythiobenzamide	N-Trityl-4-methoxythiobenzamide	37
Phenylthioacetamide	N-Tritylphenylthioacetamide	30

A reaction occurring at the nitrogen atom is also encountered in the reaction between xanthydrol and thioamides in xylene (80°) in the presence of anhydrous zinc chloride. The N-xanthyl thioamides formed are obtained in very good yield (*56*) and can be used in the detection of thioamides.

Synthesis of Trisformylaminomethane (*61*)

The thioformiminoesters discussed above and the formiminoesters postulated as intermediates in the reaction between halogen compounds and formamide are S- and O-alkylation products of thioformamide and formamide, respectively. It was therefore obvious that the preparation of the formiminoesters from formamide and alkylating agents be attempted at lower temperatures.

While the unambiguous synthesis of the formiminoester cannot be accomplished with a molar proportion of formamide: dimethyl sulfate = 1:1, the reaction using an excess of formamide (2 moles) yields the methyl sulfate salt of formamidine (XCV); this crystallizes out together with other reaction products (ammonium methyl sulfate, trisformaminomethane) from the mixture of formamide and dimethyl sulfate warmed for a few hours at 50–60°. Unlike our previous assumption (*61*), the preparation of the pure formamidine salt has thus far not proved possible.

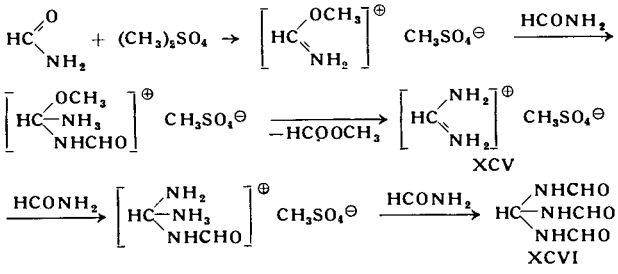


XCV

The proof of the correctness of this reaction course can be demonstrated by the reaction between the formiminoethyl ester hydrochloride and 1 mole of formamide; ethyl formate and formamidine hydrochloride are produced.

The ready formation of formamidine from formamide and dimethyl sulfate explains why the formiminoester cannot be obtained.

The reaction between formamide and dimethyl sulfate does not stop at the formamidine stage when the proportion of formamide is raised to a five- to tenfold excess. Methyl formate is eliminated on warming, and the hitherto unknown trisformylaminomethane (XCVI) crystallizes on cooling. In accordance with the reaction course depicted below, trisformylaminomethane can be obtained from both formiminoester hydrochloride and formamidine methyl sulfate.

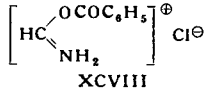


The structure of the new compound can be established by its formation from orthoformic ester (XCVII) and formamide.

$$\underset{\text{XCVII}}{HC(OC_2H_5)_3} + 3\ HCONH_2 \rightarrow \underset{\text{XCVI}}{HC(NHCHO)_3} + 3\ C_2H_5OH$$

Trisformylaminomethane can be prepared quite generally from formamide and alkylating agents. Thus, the compound is obtained with dialkyl sulfates (including diethyl and diisopropyl sulfate), alkyl sulfonates (benzenesulfonic esters, *p*-toluenesulfonic esters), and alkyl halides (ethyl iodide, isopropyl, and allyl bromide). Of the more powerful alkylating agents, triethyloxonium fluoborate can be used; with this reagent the reaction proceeds even at room temperature.

The fact that, apart from many halogen compounds, acid chlorides also attack the formamide oxygen atom (see above), explains why trisformylaminomethane is also obtained from reactions between formamide and acylating agents (acid chlorides). The acid chlorides we utilized include acetyl chloride, benzoyl chloride, chloroformic ester, phosphorus oxychloride, phosphorus trichloride, and sulfuryl chloride. The reaction then proceeds via the compound corresponding to the formiminoester. One such compound (XCVIII), for example, can be isolated in the form of a hygroscopic, crystalline product from an ethereal solution of formamide and benzoyl chloride.



XCVIII

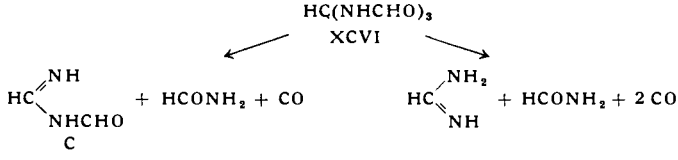
Reactions of Trisformylaminomethane

Trisformylaminomethane represents the formylated amide of the hypothetical orthoformic acid. A few of the reactions undergone by this reactive compound are cited briefly.

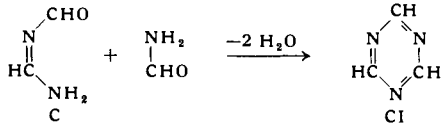
Reaction with acid anhydrides (acetic anhydride, propionic anhydride, butyric anhydride, benzoic anhydride) results in acylation (*62*).

$$\underset{\text{XCVI}}{HC(NH{-}CHO)_3} \xrightarrow{(RCO)_2O} \underset{\text{XCIX}}{HC(NH{-}CO{-}R)_3}$$

If trisformylaminomethane is heated above its melting point (165–167°, dec.), *s*-triazine (CI) is formed (*62*). This reaction proceeds particularly readily in formamide (*63*), and *s*-triazine has thus become conveniently accessible. We postulate the following reaction course: Initially, either formylformamidine (C) or formamidine is formed.



The fact that triazine can be formed from formamidine is known (*64*). With formylformamidine, the reaction must be formulated as follows:

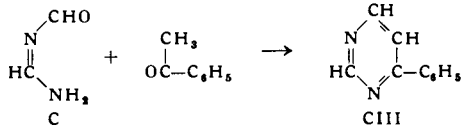


(For reasons of clarity, we formulate the following equations via formylformamidine as intermediate).

The reaction between trisformylaminomethane and benzaldehyde yields benzylidene bisformamide (CII) (*65*), also obtainable from formamide and benzaldehyde (*66*).

$$\underset{\text{XCVI}}{HC(NHCHO)_3} + C_6H_5CHO \rightarrow \underset{\text{CII}}{C_6H_5{-}CH(NHCHO)_2}$$

With acetophenone, 4-phenylpyrimidine (CIII) is obtained (*65*). If the reaction is carried out in formamide in the presence of an acid catalyst (*p*-toluenesulfonic acid), a yield of 72% is obtained. This synthesis can again be regarded as proceeding via the postulated formylformamidine intermediate.



This reaction constitutes a new route for the synthesis of 2-unsubstituted pyrimidines. 4-Phenylpyrimidine can be prepared directly from

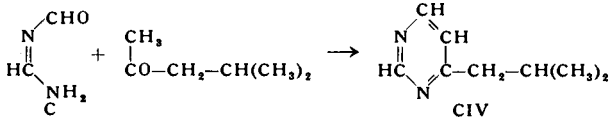
formamide, dimethyl sulfate (which, together, yield trisformylaminomethane), and acetophenone, without isolation of the trisformylaminomethane (*65*). This new synthesis also allows the preparation of 4,5- and 5-substituted pyrimidines. It can be effected with aliphatic, cycloaliphatic, aromatic, and heterocyclic ketones (Table 25).

TABLE 25

Pyrimidines from Trisformylaminomethane and Ketones

Ketone	Pyrimidine	Yield (%)
Acetone	4-Methyl-	39
Isobutyl methyl ketone	4-Isobutyl-	35
Pinacolone	4-*tert*-Buthyl-	17
Acetophenone	4-Phenyl-	72
2-Methyl-5-acetylpyridine	4-(2′-'ethyl-5′-pyridyl)-	43
Methyl ethyl ketone	4,5-Dimethyl-	47
Diethyl ketone	4-Ethyl-5-methyl-	37
Cyclopentanone	4,5-Trimethylene-	52
Cyclohexanone	4,5-Tetramethylene-	36
Propiophenone	4-Phenyl-5-methyl-	53
Butyrophenone	4-Phenyl-5-ethyl-	26

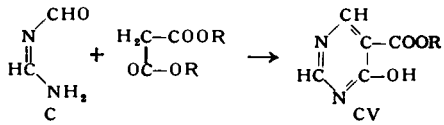
In the reaction between trisformylaminomethane and methyl ethyl ketone or methyl isobutyl ketone, the question arises whether reaction occurs at the CH_3 or the CH_2 group of the ketone. While the CH_2 group reacts in the case of methyl ethyl ketone—4,5-dimethylpyrimidine is formed exclusively—this is not so in the case of methyl isobutyl ketone, presumably on account of steric hindrance due to the isopropyl group, and the CH_3 group reacts to give 4-isobutylpyrimidine (CIV) (*65*).



CIV

Two other reactions may also proceed via N-formylformamidine.

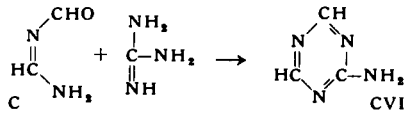
With malonic ester, 4-hydroxypyrimidine-5-carboxylic acid ester (CV) is formed (*66a*).



CV

With guanidine carbonate, a good yield of amino-*s*-triazine (CVI) is obtained (*63*); this compound had previously been prepared in low yield

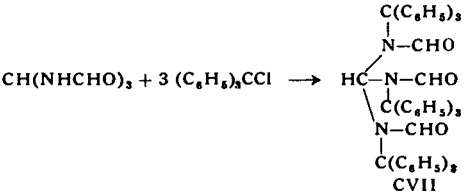
by Grundmann (*67*) from formylguanidine and formamide in the presence of a little alkali hydroxide.



CVI

The reaction between trisformylaminomethane and benzoins at 140° yields oxazoles exclusively, while comparative experiments with formamide/formic acid gave only imidazoles (*68*). Other keto compounds afford either mixtures of oxazoles and imidazoles or only oxazoles (Table 26).

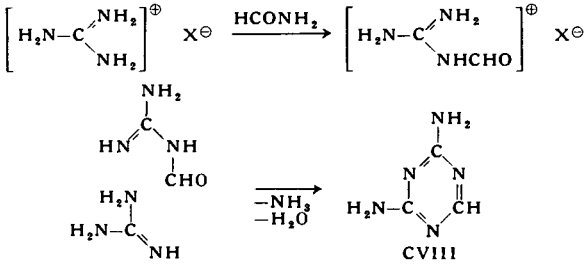
Trisformylaminomethane reacts with trityl chloride to give tris(N-formyl-N-tritylamino)methane (CVII), in a manner analogous to the reaction between higher amides and compounds of the trityl chloride type.



CVII

Synthesis of a Few *s*-Triazine Derivatives

The reaction between guanidine carbonate and formamide (20 moles) readily yields aminotriazine (CVI) (*68a*). If the quantity of formamide is reduced (3 moles), a good yield of the long-known diamino-*s*-triazine (CVIII) is obtained. We postulate the following reaction course for this conversion.



CVIII

The substantially higher concentration of guanidine and therefore also formylguanidine enables the reaction to occur between these two

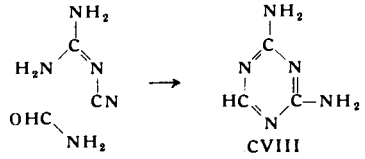
TABLE 26

Ketones and Trisformylaminomethane or Formamide/Formic Acid

Ketone	Reaction product with trisformylaminomethane		Reaction product with formamide/formic acid	
	Oxazole	Imidazole	Oxazole	Imidazole
Benzoin	4,5-Diphenyl- (87%)	-	-	4,5-Diphenyl- (76%)
p , *p'*-Dichlorobenzoin	4,5-Di-(*p*-chloro-phenyl)- (63%)	-	-	4,5-Di-(*p* chloro-phenyl)- (68%)
p -Methoxybenzoin	4(5)-Phenyl-5(4)-anisyl- (61%)	-	-	4(5)-Phenyl-5(4)-anisyl- (86%)
Butyroin	4,5-Dipropyl- (50%)	4,5-Dipropyl- (25%)	4,5-Dipropyl- (27%)	4,5-Dipropyl- (36%)
1-Bromobutanone	4-Ethyl- (25%)	-	4-Ethyl- (22%)	-
3-Bromobutanone	4,5-Dimethyl- (29%)	-	4,5-Dimethyl- (30%)	-
α-Bromopropiophenone	5-Methyl-4-phenyl- (58%)	5(4)-Methyl-4(5)-phenyl- (23%)	5-Methyl-4-phenyl- (22%)	5(4)-Methyl-4(5)-phenyl- (40%)
α-Bromocaprophenone	4-Phenyl-5-butyl- (55%)	-	4-Phenyl-5-butyl- (4%)	4(5)-Phenyl-5(4)-butyl- (60%)

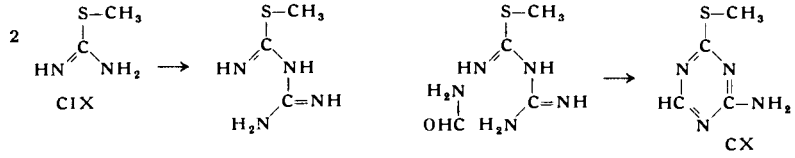
compounds to give diaminotriazine. The formamide merely serves to formylate part of the guanidine.

The reaction between dicyandiamide and formamide results in the particularly facile synthesis of diaminotriazine (72%) (*68a*). This method may well constitute the best preparation of this compound by virtue of its simplicity and the ready accessibility of its starting materials.



CVIII

The reaction between S-methylisothiourea (CIX) and formamide readily yields the hitherto unknown 2-methylmercapto-4-amino-*s*-triazine (CX) (*68a*). For this conversion we postulate the following reaction course:



CIX CX

The proof of the constitution was furnished by the reaction between the 2-methylmercapto-4-amino-*s*-triazine formed and dimethylamine to give the known (*69*) 2-dimethylamino-4-amino-*s*-triazine.

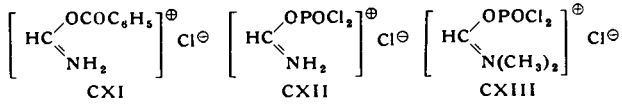
The methylmercapto group is readily replaced by the hydrazine group; a brief period of boiling with hydrazine hydrate solution affords an almost quantitative yield of 2-hydrazino-4-amino-*s*-triazine (*68a*), which is in turn the starting compound for further reactions.

Acid Amide-Acyl Chloride Adducts and Their Use in Synthesis

Amidine Syntheses

In order to account for the formation of trisformylaminomethane from formamide and acid chlorides, we have postulated an adduct of formamide and acid chloride as intermediate. We were able to isolate a hygroscopic, crystalline product from an ethereal solution of formamide and benzoyl chloride, to which we assign structure CXI (*61*). In analogous manner, the adduct of formamide and phosphorus oxychloride should be formulated as CXII. We were able to elucidate the structure of this type of compound in the case of the adduct of dimethylformamide and

phosphorus oxychloride, which we also succeeded in obtaining in crystalline form (*70*). On the evidence of the IR spectrum, we assign structure CXIII to this adduct (*70, 71*).

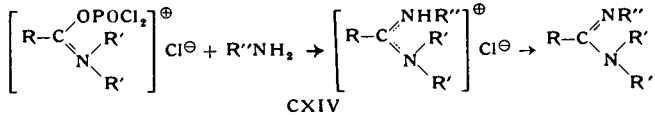


CXI CXII CXIII

The dimethylformamide–phosphorus oxychloride adduct plays a part in the aldehyde synthesis of Vilsmeier and Haack. A few more reactions undergone by this adduct are described below.

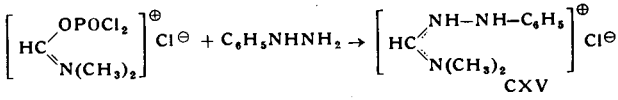
Reaction between the adduct and an amine yields the hydrochloride of the amidine; addition of alkali to the latter liberates the free amidine (*70*). The adduct itself need not be isolated; it is sufficient if a benzene solution of phosphorus oxychloride is added dropwise to a benzene solution of dimethylformamide, followed after a short time by the addition of a benzene solution of the amine.

We effected this amidine synthesis with a large number of amines (aniline, *p*-toluidine, α-naphthylamine, benzylamine, β-phenylethylamine, cyclohexylamine, and *n*-butylamine). N-Disubstituted acid amides generally, can be used in place of dimethylformamide. This provides a productive synthesis of N,N,N′-trisubstituted amidines (CXIV) in addition to the amidine syntheses already known.



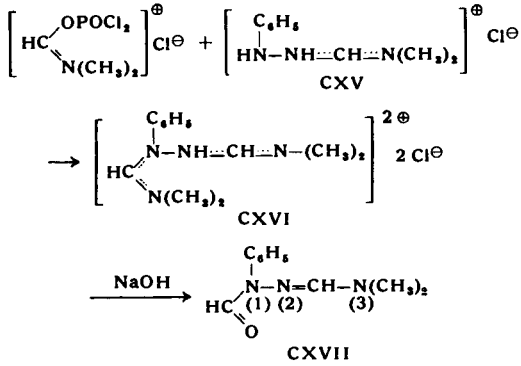
CXIV

If hydrazine is used instead of amines, the hitherto unknown formylformamidrazones are obtained. Phenylhydrazine, for example, yields N-3,N-3-dimethyl-N-1-phenyl-N-1-formylformamidrazone (XCVII). The reaction consists of the following two partial reactions.

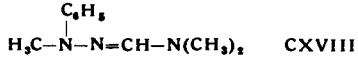


CXV

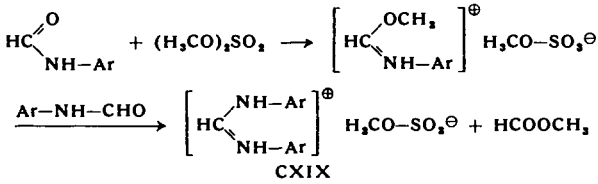
The first partial reaction corresponds to the formation of an amidine from amines (see above). In the second reaction the formamidrazone CXV reacts as a secondary amine with unchanged phosphorus oxychloride adduct to give the intermediate CXVI, which is both an amidrazonium salt (protonated at N-2) and an amidinium salt. The mesomerism of the formamidinium group linked to N-1 is disturbed by the positive



charge on N-2, and alkali effects immediate hydrolysis to the formyl compound CXVII. If N-methyl-N-phenylhydrazine is used, the reaction stops at the formamidrazone stage on account of the lack of an NH group, and N-1,N-3,N-3-trimethyl-N-1-phenylformamidrazone (CXVIII) is obtained.



Following upon the preparation of formamidine and trisformylaminomethane, we examined the behavior of substituted formamides towards alkylating agents. While mono- and dimethylformamide are unattacked by alkylating agents (with the exception of *tert* oxonium salts), the reaction between formanilide (=phenylformamide) and dimethyl sulfate in benzene gives a good yield of the methyl sulfate salt of N,N′-diphenylformamidine (CXIX) (*70*).

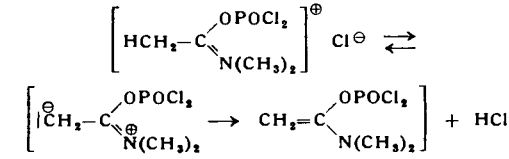


Formanilide and dimethyl sulfate can be replaced by other formylated aromatic amines and benzenesulfonic esters, respectively. The N,N′-diarylformamidines themselves have been known for a long time; they can be prepared by the condensation of the N-arylformamide and an arylamine in the presence of PCl_5, PCl_3, or $POCl_3$.

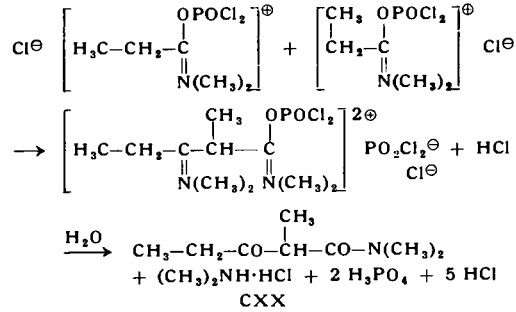
Autocondensation of N,N-Disubstituted Carboxylic Acid Amides (*72, 73*)

The adducts of N,N-dimethylcarboxylic acid amides and phosphorus oxychloride exhibit high reactivity towards nucleophilic compounds, as

shown by the amidine and formylamidrazone syntheses. In addition, the α-CH_2 group is particularly reactive, due to the inductive effect of the positive charge distributed over the nitrogen and oxygen, and the stabilization by mesomerism of the base resulting from the loss of a proton or the elimination of hydrogen chloride.



This fact can be utilized in a new synthesis of β-ketoacid amides: If a benzene solution of phosphorus oxychloride (1 mole) is added to a benzene solution of N,N-dimethylacetamide (1 mole), a good yield of the N,N-dimethyl amide of acetoacetic acid is obtained at moderate temperatures (70°). The N,N-dimethyl amides of α-propionylpropionic acid (from N,N-dimethylpropionamide), α-butyrylbutyric acid (from N,N-dimethylbutyramide), α-valerylvaleric acid (from N,N-dimethylvaleramide), α-caproylcaproic acid (from N,N-dimethylcaproamide), and α-caprylcapric acid (from N,N-dimethylcapramide) can be prepared in corresponding manner. The reaction course is illustrated by the synthesis of the N,N-dimethylamide of α-propionylpropionic acid (CXX).

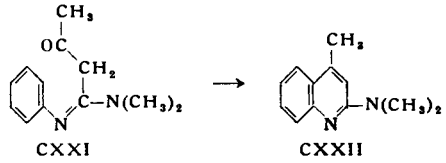


The proof of the structure of the hitherto unknown β-ketoacid dimethyl amides was furnished both by the synthesis via the corresponding ketenes (*74*) and by ketonic fission.

A New Synthesis of α-Aminoquinoline (*73, 75*)

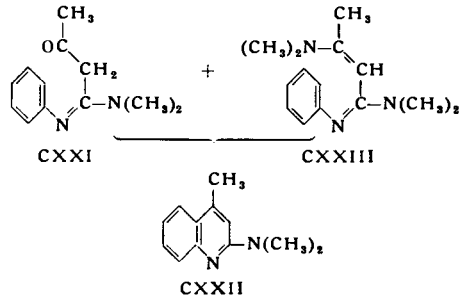
By extending the amidine synthesis to N,N-dimethyl-β-ketoacid amides and aromatic amines in the presence of phosphorus oxychloride, we succeeded in devising a new quinoline synthesis. If acetoacetic acid dimethyl amide is allowed to react with aniline and phosphorus oxychloride, the amidine (CXXI) is formed as expected; this is not isolated,

and treatment with sulfuric acid results in the elimination of water to give 2-methylamino-4-methylquinoline (CXXII) in 19% yield.



CXXI CXXII

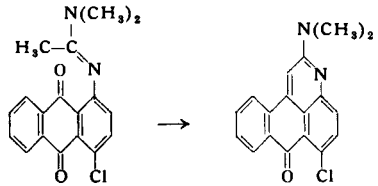
The low yield is due to the simultaneous production of β-anilinocrotonic acid dimethyl amide. Its formation can, however, be inhibited as follows: If the reactant is β-dimethylaminocrotonic acid dimethyl amide —readily obtainable from acetoacetic acid dimethyl amide and dimethylamine in 90% yield—a mixture consisting of approximately equal parts of N,N-dimethyl-N′-phenylacetylacetamidine (CXXI), and N,N-dimethyl-N′-phenyl-β-dimethylaminocrotonylamidine (CXXIII) is obtained. Treatment of this mixture with sulfuric acid affords 2-dimethylamino-4-methylquinoline (CXXII) in 60% yield.



CXXI CXXIII CXXII

This synthesis can be effected with a number of aromatic amines (*76*). We have thus far utilized *m*-toluidine, *p*-anisidine, *m*-anisidine, and α- and β-naphthylamine. The yields are approximately 50%. Substituents *ortho* to the amino group (e.g. in *o*-toluidine, *o*-chloroaniline) render the reaction more difficult and result in low yields. α-Aminopyridine does not react in the manner indicated.

In this connection, another combination of the amidine synthesis and ring-closure reaction must be mentioned: Dimethylacetamide reacts with 1-amino-4-chloroanthraquinone and phosphorus oxychloride to give the corresponding amidine, N,N-dimethyl-N′-(4-chloroanthraquinonyl-1)-acetamidine (CXXIV); heating in nitrobenzene in the presence of sodium acetate readily converts it into a 76% yield of 6-dimethylamino-4′-chloro[(10′-anthrono)-1′,11′,9′,2,3,4-pyridine] (CXXV) (*75*).

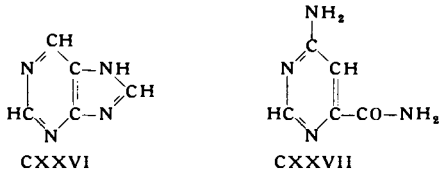


CXXIV CXXV

Gas-phase Reactions with Formamide

Preparation of Purine and a Derivative of Pyrimidine

It was mentioned earlier that the reaction between xanthine and formamide in an autoclave yields hypoxanthine, but that the work-up is difficult because of the formation of other compounds which also give picrates. This observation induced us to heat formamide on its own in an autoclave. Among the decomposition products, a small quantity of purine (CXXVI) (approximately 1% of the formamide allowed to decompose) and a compound identified as 6-aminopyrimidine-4-carboxylic acid amide (CXXVII) were isolated (*77*).



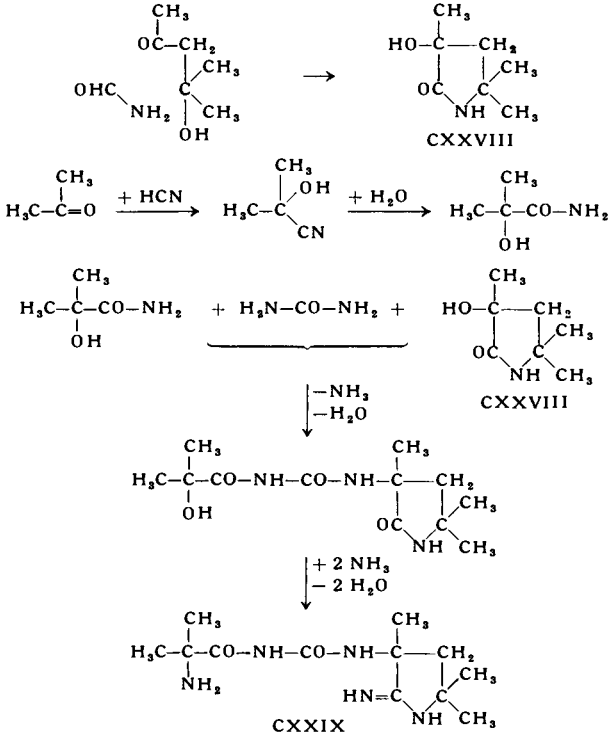
CXXVI CXXVII

The significance of this experiment lies less in the possibility of a preparation of purine, than in the very fact of its formation as such. It may be assumed that under the experimental conditions, gaseous decomposition products of formamide, e.g., CO, CO_2, NH_3, H_2O, HCN, H_2 are present as well as formamide itself, and that these take an active part in the formation of purine. It should furthermore be noted that the 6-aminopyrimidine-4-carboxylic acid amide molecule, for the formation of which the same observations hold true, already shows a similarity to the adenine molecule. It may perhaps be forgiven if, at the end of a report on experimental results, a totally unproven hypothesis is clothed in terms of a question: Is it not conceivable that during an early geological period of development, the pyrimidines and purines of such fundamental importance in the generation and propagation of life, may have been formed by a similar route?

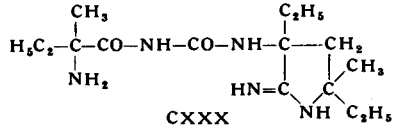
Reactions with Acetone (*78*) and Methyl Ethyl Ketone (*79*)

Formamide can be passed for a short time through a glass tube heated at 450°, without undergoing any noticeable decomposition. It is, however, completely decomposed over aluminum oxide at 350°, mainly into CO and NH_3 together with HCN and H_2O. These experiments induced us to allow carbonyl compounds to react with formamide in the gaseous phase over aluminum oxide.

If a mixture of formamide and acetone (3:1) is passed at 300° over an aluminum oxide contact catalyst, the major product (17% calculated with respect to acetone) consists of a crystalline compound, N-(α-amino-isobutyryl)-N'-(2-imino-3,5,5-trimethyl-3-pyrrolidinyl)urea (CXXIX); its structure is based on thorough chemical and spectroscopic investigations. The compound can be thought of as being formed from one molecule each of acetone, formamide (which yields hydrocyanic acid and water among its decomposition products), urea, 2 molecules of ammonia and the α-hydroxypyrrolidone derivative CXXVIII (3-hydroxy-3,5,5-trimethyl-2-pyrrolidone). The latter could be formed from 2 molecules of acetone and formamide via the initially formed diacetone alcohol.



If the reaction is effected with methyl ethyl ketone and formamide at 250–260°, a relatively good yield of N-(α-aminoisovaleryl)-N′-(2-imino-3,5-diethyl-5-methyl-3-pyrrolidinyl)urea (CXXX) is obtained (*79*).



CXXX

If, on the other hand, the reaction is carried out at 350–360°, the major product isolated is α-amino-α-methylbutyronitrile, formed from methyl ethyl ketone and the formamide decomposition products, hydrocyanic acid and ammonia. A small quantity of 5-methyl-5-ethylhydantoin is also found.

Unlike these reactions with ketones, aldehydes give pyrimidine bases (*80*) under the same conditions. In other words, the aldehyde merely reacts with the ammonia liberated from the formamide. Gas-phase reactions between aldehydes and ammonia have already been described by Tschitschibabin (*81*).

Experimental

Xanthine from uric acid (*5*). Uric acid (5 gm), formamide (50 ml), and water (0.5 ml) are heated under reflux for 1 hr. On cooling, the pale brown product (4.2 gm) is filtered. (Paper chromatography shows that the substance no longer contains any uric acid, only xanthine.) For purification, the crude product is dissolved in dilute NaOH, brought to a boil, a few drops of hydrogen peroxide added, and the solution added dropwise to boiling dilute acetic acid. Yield 3.7 gm.

In larger-scale preparations, the conditions must be slightly modified.

Theophylline from 4-amino-1,3-dimethyluracil (*14*). 4-Amino-1,3-dimethyluracil (10 gm) and sodium nitrite (4.5 gm) are heated at 60° in formamide (50 ml), and formic acid (10 ml) added dropwise to the stirred solution over a period of 10 min, when the 5-nitroso compound separates. Heating at 100° is continued for a further 10 min, during which time sodium dithionite (1.5-2 gm) is added in small portions. The temperature rises to 130–140° and the solution becomes yellow. The reaction mixture is heated for 30 min under reflux at 180–200°. On cooling it is filtered, and washed with a little water; the filtrate is diluted with water and extracted with chloroform. Yield 9–10 gm (78–87%), m.p. after recrystallization from alcohol, 270°.

Pyrimidine from 1-methoxy-1,3,3-triethoxypropane (*48*). 1-Methoxy-1,3,3-triethoxypropane (20 gm) is added dropwise over a period of 6 hr to a mixture of formamide (100 gm), ammonium formate (20 gm) and

water (2 ml) maintained at 180–190°. Heating is continued for a further 2 hr, and the alcohol formed distilled off. On cooling, the mixture is treated with dilute NaOH and extracted for 30 hr with chloroform. The chloroform is dried over Na_2SO_4 and distilled off. The residual pyrimidine is purified by repeated distillation, b.p. 122–125°/750 mm, yield 5.5 gm (65%).

4-Methylpyrimidine from β-oxobutyraldehyde dimethylacetal (48). β-Oxobutyraldehyde dimethylacetal (400 gm) is added dropwise over a period of 5 hr to a vigorously stirred mixture, maintained at 190°, of formamide (700 ml), ammonium formate (50 gm), and water (20 ml), contained in a 2 liter three-necked flask fitted with stirrer, dropping funnel, and large Liebig reflux condenser connected by a bridge to a Dimroth condenser leading downward. Heating is continued for 1–2 hr and the cooled reaction mixture poured into NaOH solution (1 liter, 1 *N*) and extracted for approximately 30 hr with chloroform. The chloroform is dried over Na_2SO_4 and distilled off. The dark-colored residue is distilled *in vacuo*. The crude product thus obtained is fractionally distilled, b.p. 141–142°/760 mm, yield 200–220 gm.

4-n-Propylpyrimidine from n-propyl β-chlorovinyl ketone (48). *n*-Propyl β-chlorovinyl ketone (20 gm), prepared from *n*-propylacetylene and acetyl chloride (*82*) is added dropwise over a period of 6 hr to formamide (120 gm) maintained at 180°. Heating is continued for another hour; on cooling, dilute NaOH is added and the mixture extracted with ether. The ether is evaporated, and the *n*-propylpyrimidine purified by vacuum distillation, b.p. 82–88°/12–15 mm; 175–178°/760 mm, yield 9 gm (60%). B.p. after fractional distillation through a column, 94–95°/50 mm, n_D^{20} 1.4883.

5-Methylpyrimidine from 2-methyl-3-diethylaminoacrolein (50). The solution of 2-methyl-3-diethylaminoacrolein (see below) (193 gm) in formamide (100 ml) is added dropwise over a period of 5 hr to formamide (500 ml) maintained at 180° in an oil bath. The mixture is heated for a further hour, cooled, saponified with a solution of potash (100 ml) and water (200 ml) and extracted for 24 hr with chloroform. The chloroform solution is dried over K_2CO_3 and distilled through a Vigreux column 80 cm long (back-flow ratio 1:30). B.p. 153.5–153.9°/733 mm, m.p. 32°, yield 109 gm (85%).

2-Methyl-3-diethylaminoacrolein is prepared as follows according to the method of Arnold and Sorm (*51, 83*): Phosgene (110 gm) is passed into a vigorously stirred, ice-cooled solution of N,N-diethylformamide (335 gm) in 1,2-dichloroethane (400 ml). The diethylformamide–phosgene adduct separates as a semiliquid precipitate. Ethylene dichloride (200 ml) is added, followed by the dropwise addition of propionaldehyde

diethylacetal (132 gm) over a period of 1 hr. The solution is slowly warmed to 75° (bath temperature) and maintained at this temperature for 15 min, during which time the precipitated adduct redissolves. The reaction mixture is cooled in ice, and crushed ice (500 gm) is added, followed by a concentrated potash solution (400 ml); the latter is initially added dropwise, and then rapidly when the evolution of CO_2 has ceased. The dichloroethane is distilled on a boiling water bath, and the residue diluted with water until the precipitated potassium chloride redissolves. The solution is extracted with chloroform (one 300 ml, and seven 100 ml portions), the combined chloroform extracts dried over K_2CO_3, the solvent evaporated, and the residue distilled *in vacuo*, b.p. 85–98°/10^{-3} mm, yield 103 gm (79%).

Trisformylaminomethane from formamide and dimethyl sulfate (61). Dimethyl sulfate (126 gm) and formamide (450 gm) are heated in a distillation apparatus for 1.5 hr at 70–80° at water-pump pressure. Trisformylaminomethane (87 gm, 60% calculated with respect to dimethyl sulfate) crystallizes out overnight from the clear solution. M.p. 165–166° (dec.). The product obtained in this manner is sufficiently pure for further reactions.

4-Phenylpyrimidine from acetophenone and trisformylaminomethane (65). Acetophenone (12 gm), trisformylaminomethane (29 gm), formamide (20 ml), and *p*-toluenesulfonic acid (1 gm) are slowly heated to 160° under reflux (the condenser is protected by a $CaCl_2$ tube). The addition of an anti-bumping stone is advisable. The reaction mixture is maintained at this temperature for 8 hr; on cooling, it is treated with an excess of NaOH solution (1 *N*) and extracted several times with small portions of chloroform. Drying of the chloroform extracts over Na_2SO_4 and fractional distillation afford the product, b.p. 140–144°/14 mm, yield 11.2 gm (72%).

s-Triazine from trisformylaminomethane and formamide (63). Trisformylaminomethane (58 gm) and formamide (90 gm) are heated at 160° in a distillation apparatus until solution is complete. The pressure (at 160°) is reduced to 70 mm, and the receiver cooled in carbon dioxide–methanol. Crude s-triazine (14 gm, 43%) distils over a period of 1 hour, and can be purified by distillation or vacuum sublimation. B.p. 112–115°/760 mm, m.p. 80–81°.

2-Amino-s-triazine from guanidine carbonate and trisformylaminomethane (63). Guanidine carbonate (18 gm, 0.1 mole) and trisformylaminomethane (77.5 gm, 0.5 mole) are suspended in dimethylformamide (100 ml) and the stirred suspension heated to boiling (bath temperature 160–170°). Heating under reflux is continued for 3 hr after solution is complete. A thin crystalline paste separates on cooling; it is rigorously

filtered and washed with ice-cold water to give 2-amino-*s*-triazine (15 gm, 78%), m.p. 226°. Concentration of the mother liquors on a water bath under vacuum (12 mm) yields a further, though less pure, crop of the product (2 gm, 10%).

4-Phenylimidazole from acetophenone, bromine, and formamide (30). Bromine (24 gm) is added dropwise over a period of 1 hr to a solution of acetophenone (16.6 gm) in formamide (29 gm) maintained at 65–70°. Formamide (151 gm) is slowly added, the temperature raised to 185° over a period of 1 hr, and this temperature maintained for a further 5 hr. The reaction mixture is poured into water, basified with dilute NaOH, and the precipitate filtered. For purification, the product is twice brought to the boil with dilute HCl containing activated charcoal, filtered, and the 4-phenylimidazole precipitated from the filtrate with dilute sodium hydroxide solution. It is recrystallized twice from butyl acetate and once from ethanol/water (3:1). M.p. 128°, yield 11.2 gm (54% calculated with respect to acetophenone).

4-Methyl-5-phenyloxazole from α-bromopropiophenone and formamide/sulfuric acid (43). A mixture of concentrated sulfuric acid (45 gm) and formamide (90 gm), prepared in the cold, is added dropwise over a period of 10–15 hr to a solution of α-bromopropiophenone (94 gm) in formamide (203 gm) maintained at 135°. On cooling, the dark-brown reaction mixture is poured into water (1 liter) and extracted four times with ether (250 ml portions). The combined ether extracts are dried over sodium sulfate and the ether distilled through a fractionating column (in order to prevent loss of 4-methyl-5-phenyloxazole). The residue is distilled through a Vigreux column 20 cm long, b.p. 128°/14 mm, yield 47 gm (67%).

N-Triphenylmethylformamide from triphenylmethyl chloride and formamide (56). Trityl chloride (10 gm) and formamide (16 gm) are slowly heated under reflux; the reaction sets in at around 110°, and is brought to completion by heating for approximately 10 min at 150°. The excess of formamide is removed by digestion with water, and the residue crystallized from acetone. M.p. 203°, yield 10 gm (94%).

N-Xanthylthiobenzamide from xanthydrol and thiobenzamide (56). Thiobenzamide (4.5 gm) is slowly added to vigorously stirred xanthydrol (6.6 gm) in absolute xylene (100 ml). After an initial 5–10 min period of stirring in the cold, anhydrous zinc chloride (moisture must be excluded) (3–4 gm) is added at 60–70° and heating continued at 80° for 2 hr. The mixture is filtered hot, cooled in an ice-salt mixture, and ligroin (20 ml) added. Yield 9.7 gm (92%). M.p. after recrystallization from xylene, 161–162°.

Acetoacetic acid dimethyl amide from N,N-dimethylacetamide (72,

73). A solution of N,N-dimethylacetamide (32.7 gm) in absolute benzene (50 ml) is added dropwise to a stirred solution of phosphorus oxychloride (57.5 gm) in absolute benzene (70 ml), care being taken that moisture be excluded. The mixture is boiled under reflux for 6–7 hr, the solvent evaporated and the residue warmed for 2 hr at 70–80° *in vacuo*. Following the addition of benzene (500 ml), ice-cold water (30 ml) is added to the stirred, cooled solution, followed by the dropwise addition of a solution of NaOH (30 gm) in water (50 ml). The mixture is allowed to stand at room temperature for 1 hr, after which time anhydrous powdered sodium carbonate (50 gm) is slowly added. The separated salt mixture is vigorously stirred, and the benzene layer decanted. The mixture is digested twice with benzene (200 ml portions), the combined benzene solutions dried over sodium carbonate and the solvent distilled off under vacuum. Distillation of the residue yields a first fraction (0.8 gm), b.p. $\leqslant$105°/12 mm, and acetoacetic acid dimethyl amide (18.1 gm, 75%), b.p. 105–118°/12 mm, n_D^{20} 1.4698. Repeated distillation through a Vigreux column 20 cm long affords a product, b.p. 109°/10 mm, n_D^{20} 1.4710.

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Organic Syntheses Using Chloramine

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The synthetic possibilities of chloramine were first thoroughly investigated by Raschig (*1*); his classical hydrazine synthesis was the result of these efforts. He also discovered that phenylhydrazine can be obtained from chloramine and aniline, and indophenol (N-*p*-hydroxyphenylquinoneimine) from chloramine and phenol, via the initially formed *p*-aminophenol. The yields were so poor, however, that he did not follow these reactions up. It took many years before chloramine was again employed for organic syntheses; it is especially in the last decade that it has yielded a large number of results.

Since the polarity of the N—Cl bond in chloramine is certain to be very weak (*2*), it can be polarized in different directions. This renders two types of reaction possible:

$$X{-}H\ (Me) + Cl{-}NH_2 \rightarrow X{-}Cl + NH_3\ (MeNH_2) \qquad (1)$$

chlorinating agent

and

$$X{-}H\ (Me) + Cl{-}NH_2 \rightarrow X{-}NH_2 + HCl\ (MeCl) \qquad (2)$$

aminating agent

e.g. (3),

$$OH^{\ominus} + Cl{-}NH_2 \rightarrow OCl^{\ominus} + NH_3$$

and (4)

$$OH^{\ominus} + Cl{-}NH_2 \rightarrow Cl^{\ominus} + HO{-}NH_2$$

Since fission into free radicals is also possible as a result of the weak polarity of the N—Cl bond, reaction (1) can be a cryptoionic reaction or a free radical reaction; nor is it thus far certain whether reaction (2) proceeds as a cryptoionic reaction via an S_N2 mechanism (*5*), or via an intermediate imine molecule or radical (*6*):

$$Cl{-}NH_2 \rightarrow HCl + NH \qquad (2a)$$

$$X{-}H + NH \rightarrow X{-}NH_2 \qquad (2b)$$

Whether a reaction proceeds according to (1) or (2) will depend on the reagent and the reaction conditions. Reactions of type (1), in which chloramine acts as a chlorinating agent, possess no significance, whereas reactions of type (2), in which chloramine acts as an aminating agent, command great interest. In certain cases, chloramine is also capable of adding to double bonds, e.g.:

$$(C_6H_5)_2C{=}C{=}O + Cl{-}NH_2 \rightarrow (C_6H_5)_2\underset{\displaystyle Cl}{\overset{|}{C}}{-}\underset{\displaystyle NH_2}{\overset{|}{C}}{=}O$$

Furthermore, chloramine can react with carbonyl compounds in a manner similar to hydroxylamine to give chlorimines:

$$\diagdown\!\!\diagup C{=}O + H_2N{-}Cl \rightarrow \diagdown\!\!\diagup C{=}N{-}Cl + H_2O.$$

Amines from Chloramine and Organometallic Compounds

Reaction with Organomagnesium Compounds

According to Coleman and Hauser (*7*), chloramine reacts at 0° with alkyl- and arylmagnesium halides in ethereal solution to give primary amines and ammonia. The yields of amine are highest when the chlorides are utilized, and fall steadily on changing to bromides and iodides. Benzylmagnesium chloride affords the best yields of amine, while phenylmagnesium chloride forms mostly ammonia and chlorobenzene (*8*). Both reactions (3) and (4) consequently take place:

$$R{-}MgX + NH_2{-}Cl \rightarrow R{-}Cl + MgX(NH_2)$$
$$\xrightarrow{H_2O} R{-}Cl + MgX(OH) + NH_3 \qquad (3)$$

and

$$R{-}MgX + Cl{-}NH_2 \rightarrow R{-}NH_2 + MgXCl \qquad (4)$$

In the latter case, the amine formed reacts with another molecule of the Grignard compound to give a hydrocarbon. The extent to which reaction

$$R{-}NH_2 + R{-}MgX \rightarrow R{-}NH{-}MgX + R{-}H$$
$$\xrightarrow{H_2O} R{-}NH_2 + Mg(OH)X + R{-}H$$

(4), important from the preparative point of view, occurs, depends on how strongly the Grignard reagent is able to polarize the N—Cl bond in the direction of the negative chlorine. It is thus understandable that the use of bromamine results in a lower yield of primary amine (*9*), since the N—Br bond is far less readily polarized in the sense discussed above.

Table 1 gives a survey of reactions of this type. The method possesses special significance for the preparation of primary amines in which the amino group is linked to a secondary or tertiary carbon atom (*10*), or are otherwise difficult to obtain (*11*). No anomalous behavior of the Grignard compounds is observed (*12*); benzylmagnesium chloride gives exclusively benzylamine (92%), and α-naphthylmethylmagnesium chloride and cinnamylmagnesium chloride yield α-naphthylmethylamine (47%) and cinnamylamine (14%), respectively.

TABLE 1
Reaction Between Chloramine and Organomagnesium Halides

RMgX R =	X = Cl		X = Br		X = I		Lit. ref.
	RNH_2 (%)	NH_3 (%)	RNH_2 (%)	NH_3 (%)	RNH_2 (%)	NH_3 (%)	
CH_3	–	–	26	68	8	88	(*7*)
C_2H_5	57	40	28	66	16	81	(*7*)
n-C_3H_7	58	37	27	64	14	70	(*7*)
iso-C_3H_7	66	30	37	55	9	79	(*10*)
n-C_4H_9	59	39	27	65	15	85	(*7*)
sec-C_4H_9	70	20	51	39	16	74	(*10*)
tert-C_4H_9	60	39	20	80	5	81	(*10*)
iso-C_5H_{11}	55	41	27	72	11	84	(*7*)
$(C_2H_5)CH$	71	19	32	62	14	79	(*10*)
tert-C_5H_{11}	66	31	14	79	2	80	(*10*)
C_6H_5	27	68	15	84	1	96	(*7*)
$C_6H_5 \cdot CH_2$	85	4	55	39	49	46	(*7*)
$C_6H_5 \cdot CH_2 \cdot CH_2$	74	18	42	53	15	74	(*7*)

As shown in the comparisons below, the yield of primary amine can be substantially increased by the use of magnesium dialkyls (*14*):

	n-C_4H_9MgCl		$(n\text{-}C_4H_9)_2Mg$	
	% Amine	% NH_3	% Amine	% NH_3
Ether, 0°C	57	43	82	14
Dioxane, 0°C	–	–	90	0
Ether–dioxane, 0°C	–	–	86	8
Ether–dioxane, -60°C	–	–	97	0
Ether, -60°C	63	37	–	–

The method can be considerably improved, since an ether–dioxane solution of magnesium dialkyl can readily be prepared by the addition of dioxane to an ethereal solution of alkylmagnesium halide (*15*).

Preparation of an ethereal solution of chloramine. According to the method of Marckwald and Wille (*13*), a molar solution of ammonia (500 ml), cooled to 0° by the addition of crushed ice, is added all at once to a similarly cooled molar solution of sodium hypochlorite (500 ml). An exothermic reaction ensues (care! inhalation of the pungent chloramine causes severe and persistent headaches!) which results in a slight warming of the mixture, and, depending on the extent of external cooling, the more or less vigorous evolution of gas; this is due to the decomposition of the chloramine to nitrogen. This mixture can be extracted with ether directly. Since the solubility of chloramine in ether hardly exceeds that in water, however, the mixture is best distilled at the water pump, using an efficient condenser and a receiver cooled in an ice–salt mixture.

The temperature of the vapor must not rise above 40°. After approximately 150 ml have come over, the still-cold distillate is extracted twice with ether (first 300 ml, then 200 ml), the combined ether extracts shaken with anhydrous calcium chloride, separated, and dried for another hour at 0° over fresh calcium chloride. This ethereal solution contains chloramine (10–12 gm).

The distillation, which requires 2–3 hr, can be avoided by the following process:

A commercial sodium hypochlorite solution (260 ml, 1.9 M) and ether (1 liter) in a 2 liter beaker are cooled to 0° in an ice–salt mixture and thoroughly mixed by intensive stirring. Aqueous ammonia (42 ml, $d = 0.910$) is added dropwise; a vigorous reaction ensues, and the solution foams. The ethereal layer is separated and dried for 1 hr over anhydrous calcium chloride. Yield of chloramine: 13–14 gm.

The first method, while being more troublesome, affords a purer product. The ethereal solutions of chloramine thus prepared must be used within 6 hr, on account of the instability of the compound. The chloramine content can conveniently and accurately be determined iodometrically (1 ml 0.1 N $Na_2S_2O_3 = 2.57$ mg $ClNH_2$).

Preparation of the amines (*7, 10*). The cold ethereal solution of chloramine is slowly added to a stirred excess of the Grignard solution, cooled to or below 0°. As soon as the chloramine solution comes into contact with the Grignard solution a precipitate results, which finally forms a more or less gelatinous mass. On completion of the reaction the vessel is fitted with a condenser equipped with an adapter which is connected to a receiver containing dilute hydrochloric acid. Decomposition is effected by the dropwise addition of water followed by mineral acid until solution is complete. The solution is made alkaline and steam-distilled until no more basic material comes over. The aqueous–ethereal distillate is thoroughly shaken, the ether separated, and the aqueous hydrochloric acid solution evaporated to dryness on a water bath. The residue is carefully dried in a vacuum desiccator, the amine hydrochloride dissolved in n-butanol, and any undissolved ammonium chloride filtered off. Evaporation of the butanol on a water bath yields the amine hydrochloride.

Reactions with Organolithium and Organozinc Compounds

Coleman and associates (*16*) also allowed chloramine to react with zinc dialkyls and lithium alkyls and aryls under various conditions; in general, however, the yields of amine do not exceed those obtained with organomagnesium halides.

Unsymmetrically Substituted Hydrazines from Amines and Chloramine

Preparation in Aqueous Solution

Audrieth has successfully extended the Raschig hydrazine synthesis to primary (*17, 18*) and secondary (*19*) amines, and has thus prepared mono- and unsymmetrically disubstituted hydrazines. The reaction proceeds more rapidly than that between ammonia and chloramine; it results in good yields even at a lower temperature and at much lower molar proportions of amine:chloramine than those required for the preparation of the unsubstituted hydrazine. In the case of secondary amines, an excess of ammonia in the chloramine solution substantially increases the yield of dialkylhydrazine. The presence of gelatin (for the bonding of heavy metal ions) and of a strong base, such as is formed in the preparation of chloramine from ammonia and hypochlorite:

$$NH_3 + NaOCl \rightarrow NH_2Cl + NaOH$$

is also necessary in this instance. Tables 2 and 3 show the substituted hydrazines prepared by this method.

TABLE 2
Monosubstituted Hydrazines

R—NH—NH_2 R =	% Yield calcd. w.r.t. NH_2Cl	Hydrazine isolated as	Lit. ref.
CH_3	64	Sulfate	(*17*)
C_2H_5	67	Sulfate	(*17*)
n-C_3H_7	62	Sulfate	(*17*)
iso-C_3H_7	55	Sulfate	(*17*)
n-C_4H_9	68	Sulfate	(*17*)
iso-C_4H_9	59	Sulfate	(*17*)
tert-C_4H_9	71	Hydrochloride	(*17*)
n-C_6H_{13}	57	Oxalate	(*18*)
Cyclohexyl	60	Sulfate	(*18*)
Allyl	52	Hydrochloride	(*18*)
β-Hydroxyethyl	58	Oxalate	(*18*)
β-Aminoethyl	75	Oxalate	(*18*)

Preparation of alkylhydrazines (*17, 18*). Gelatin solution (50 ml, 0.5%) is added to a solution of sodium hypochlorite (100 ml, 1.15 *M*) and the mixture cooled to 0°; a cold solution of ammonium hydroxide (100 ml, 1.15 *M*) is added dropwise and the mixture carefully shaken,

TABLE 3

Asymmetric Disubstituted Hydrazines

R_2N-NH_2	% Yield calcd. w.r.t. NH_2Cl	Hydrazine isolated as	Lit. ref.
R = CH_3	53	Oxalate	(*19*)
C_2H_5	41	Oxalate	(*19*)
n-C_3H_7	40	Oxalate	(*19*)
n-C_4H_9	42	Oxalate	(*19*)
N-Aminomorpholine	-	Hydrochloride	(*18*)
N-Aminopiperidine	51[a]	-	(*19*)
N-Amino-α-pyridone	28	Hydrazine	(*20*)

[a] Determined iodometrically.

care being taken to avoid the excessive evolution of gas. Chloramine solutions prepared in this manner are 0.16 *M*.

An aqueous solution of the primary amine or the amine itself is added in excess to this well-stirred 0.16 *M* chloramine solution (250 ml) cooled to 0° (molar proportion of NH_2Cl:amine = 1:8). The reaction solution is allowed to warm up to room temperature over a period of 2 hr, and then heated on a steam bath for 10–30 min in order to complete the reaction.

The isolation of the hydrazines can be accomplished by two methods:

(A) The reaction mixture is distilled in an atmosphere of nitrogen; this gives first an aqueous solution of the excess of amine, followed by an aqueous solution of the alkylhydrazine. The latter is treated with an excess of hydrochloric or sulfuric acid and concentrated to a small volume. The salts separate on cooling or on the addition of ether and can be recrystallized from methanol/ether.

(B) The reaction mixture is neutralized with acetic acid, and benzaldehyde or salicylaldehyde is added; the hydrazone formed is extracted with ether, the ethereal solution treated with aqueous oxalic acid and the ether and aldehyde distilled off. Extensive concentration of the aqueous solution results in the crystallization of the oxalate. The oxalates can be recrystallized from alcohols, to which ether is added if necessary.

Preparation of unsymmetrical dialkylhydrazines (*19*). An aqueous solution of the secondary amine or the amine itself is added to a well-stirred, ice-cold solution of chloramine, prepared by the addition of a cold 1 *M* sodium hypochlorite solution (250 ml, 0.25 mole) to a 1 *M* solution of ammonium hydroxide (750 ml, 0.75 mole), cooled to 0° (molar proportions NaOCl:amine = 1:4). The reaction mixture is allowed to warm up to room temperature over a period of 4 hr and, in the case of water-insoluble amines, vigorously shaken for 30 min. The water-soluble dialkylhydrazines are obtained by the fractional distillation of the reaction mixture, those less soluble by extraction with petroleum ether.

Preparation in an Anhydrous Medium

According to H. H. Sisler, chloramine can also be made to react with anhydrous amines by allowing a gaseous mixture of ammonia and chloramine—prepared from ammonia and chlorine—to pass into the liquid primary, secondary, or tertiary amine. This results in the formation of alkyl- (*20*) and unsymmetrical dialkylhydrazines (*21*), as well as 1,1,1-trisubstituted hydrazinium chlorides (*22*). Gelatin and permanent bases (such as NaOH) are not required in this case. Diethylamine occupies a special position (*21*) in that it rather surprisingly only yields monoethylhydrazine. Table 4 gives a list of the hydrazine derivatives prepared by this method.

TABLE 4

Hydrazine Derivatives Prepared with Gaseous Chloramine

Hydrazine derivative	% Yield calcd. w. r. t. NH_2Cl
Methylhydrazine	49
Ethylhydrazine	68
Isopropylhydrazine	50
1,1-Dimethylhydrazine	71
1,1-Diisopropylhydrazine	–
N-Aminopiperidine	–
1,1,1-Trimethylhydrazinium chloride	95
1,1,1-Triethylhydrazinium chloride	99
1,1,1-Tri-*n*-propylhydrazinium chloride	85
1,1,1-Tri-*n*-butylhydrazinium chloride	–
1,1,1-Tri-*n*-heptylhydrazinium chloride	–
1,1-Dimethyl-1-phenylhydrazinium chloride	99
1,1-Diethyl-1-phenylhydrazinium chloride	65
1,1-Dimethyl-1-*p*-tolylhydrazinium chloride	99
1,1-Dimethyl-1-(2-hydroxyethyl)hydrazinium chloride	99
1,1-Diethyl-1-(3-hydroxypropyl)hydrazinium chloride	99
1,1-Diethyl-1-cyclohexylhydrazinium chloride	95
N-Amino-N-methylmorpholinium chloride	80

If the nitrogen is tertiary and forms part of a ring system (e.g., pyridine), no reaction is generally observed with chloramine (*21*). Passage of chloramine into pyridine at room temperature for longer periods does, however, afford a small yield of 2-aminopyridine (*24*), and this C-amination appears to be a general reaction undergone by heterocyclic compounds possessing aromatic character. Quinoline gives the best yields by this method, affording more than 40% of 2-aminoquinoline (*24*).

Preparation of gaseous chloramine (*23*). The apparatus used is illustrated in Fig. 1. The glass reactor tube A is approximately 65 cm in

length and 50 mm in diameter and is fitted at each end with rubber stoppers. At one end the rubber stopper is fitted with five 8 mm glass tubes, B, one through the center and the other four symmetrically distributed around it. The center tube is flared slightly, and the outer tubes

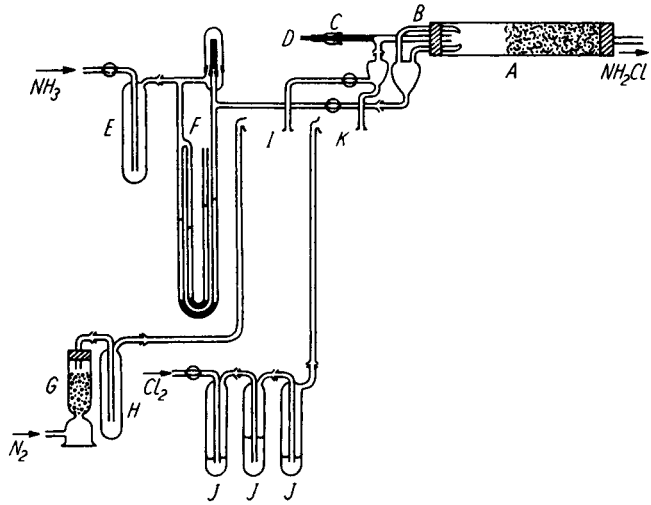


Fig. 1. Apparatus for the preparation of gaseous chloramine

end in jets bent to point into the effluent gas stream from the center tube. The outer tubes are for the introduction of ammonia gas, whereas chlorine and nitrogen are introduced through the center tube. The latter is fitted with a rubber collar C, through which a glass rod D is inserted. This is used to remove plugs of ammonium chloride which build up in the end of the chlorine inlet. The reactor tube is packed with glass wool, loosely in the fore part and more tightly near the outlet end. This serves to remove completely the ammonium chloride from the effluent gas stream. The apparatus is arranged for introduction of cylinder ammonia through expansion chamber E and a differential-manometer–type flow meter F; of cylinder nitrogen through an Anhydrone-Ascarite tower G, an expansion chamber H, and a similar flow meter inserted at I; and of cylinder chlorine through sulfuric acid bubblers J and a flow meter at K. Connections within the system are made with ball-and-socket-type ground-glass joints. Chlorine, nitrogen, and ammonia are introduced in the mole ratio 1:3:30, with a chlorine flow rate of 0.01 to 0.05 mole/hr. The quantity of ammonium chloride produced in A as a by-product from the reaction of chlorine with ammonia can be used to calculate the yield in terms of the expression

$$\% \text{ yield} = [2(a - b)/a] \times 100$$

where a is the total weight of chlorine introduced and b is the weight of chlorine recovered as ammonium chloride.

Allowing for the equation

$$2\ NH_3 + Cl_2 = NH_2Cl + NH_4Cl$$

the yield varies from 75 to 95% over generation periods of 60 to 90 min.

Preparation of alkyl- and unsymmetrical dialkylhydrazines (*21*). Chloramine (0.04 mole) (in the form of a gaseous chloramine–ammonia mixture) is passed over a period of 1 hr into the liquid amine (100 ml). The temperature depends on the boiling point of the amine and varies between —45 and +25°. The reaction mixture is then allowed to stand for approximately 2 hr, and the amine hydrochloride and ammonium chloride which separate are filtered off. The substituted hydrazine can be obtained either directly by fractional distillation, or, if it still contains amine, via the oxalate.

Preparation of the 1,1,1-trisubstituted hydrazinium chlorides (*22*). A stream of chloramine–ammonia is passed into the liquid tertiary amine until a sufficiently large quantity of the hydrazinium chloride has separated. The reaction temperature varies between —30 and +40°, depending on the boiling point of the amine. The salt is filtered off, and further crops may be obtained by evaporation of the amine. The product is separated from the ammonium chloride present by solution in absolute ethyl alcohol. The hydrazinium chlorides can be recrystallized from aqueous alcohols, aqueous acetone, or alcohol/acetone; if they are hygroscopic, they are first converted into the iodides or other salts.

Action of Chloramine on Phosphines

Tertiary phosphines react with gaseous chloramine to give an almost quantitative yield of aminophosphonium chlorides $[R_3P—NH_2]^+Cl^-$ (*25*). Triphenyl-,tri-*n*-butyl-,cyclotetramethylenephenyl-, and cyclopentamethylenephenylphosphine have been converted in this manner, either directly or in ethereal solution.

O-Alkyl- and O-Arylhydroxylamines from Chloramine and Alkoxides or Phenoxides

O-Alkylhydroxylamines

McCoy (*4*) has shown that the action of sodium hydroxide solution on chloramine results in the formation of hydroxylamine, which can be isolated in small quantities as cyclohexanone oxime by the addition of cyclohexanone.

$$NH_2Cl + OH^{\ominus} \rightarrow NH_2{-}OH + Cl^{\ominus}$$

In the absence of the ketone, the hydroxylamine immediately reacts with unchanged chloramine in the presence of sodium hydroxide to give nitrogen and ammonia. According to Truitt (*26*), alkoxides sometimes react with chloramine below 0° to give modest yields (1–5%) of O-alkylhydroxylamines; in other instances no hydroxylamine derivative could be

$$NH_2Cl + OR^{\ominus} \rightarrow NH_2OR + Cl^{\ominus}$$

isolated and it must then be assumed that the O-alkylhydroxylamines initially formed undergo complete or extensive decomposition. According to Theilacker and Ebke (*27*), these compounds can, however, be prepared in useful yield by the reaction between ethereal chloramine and a solution of the alkoxide in the corresponding anhydrous alcohol if the reaction is carried out at room temperature or higher (in the case of higher alcohols) in the presence of an excess (10–30%) of the alkoxide. The sodium alkoxides are the most favorable; potassium alkoxides afford lower yields. The O-alkylhydroxylamines prepared by this method are shown in Table 5.

TABLE 5
O-Alkylhydroxylamines

Alkyl	Reaction temp.	% Yield calcd. w.r.t. NH_2Cl
Methyl	20°	32
Ethyl	20°	29
n-Propyl	20°	38
Isopropyl	20°	38
n-Butyl	20°	46
Isobutyl	20°	37
sec-Butyl	80°	34
tert-Butyl	80°	44
n-Octyl	80°	26
sec-Octyl	80°	26
Benzyl	80°	51
Cyclohexyl	80°	25

Preparation at room temperature. The solution of alkoxide from sodium (6 gm) and the corresponding dry alcohol (250–300 ml) is added to a solution of chloramine (10 gm) in ether (approximately 500 ml) dried over calcium chloride, and the mixture allowed to stand for 24 hr.

Preparation at 80°. Sodium (6 gm) is dissolved in the corresponding dry alcohol (250–300 ml), and the solution diluted with dry dioxane (200 ml) if necessary. The solution is placed in a 1-liter three-necked

flask fitted with stirrer, dropping funnel, and fractionating column 75 cm long, and heated to 80°. A solution of chloramine (10 gm) in ether (approximately 600 ml) is added dropwise over a period of 90 min with vigorous stirring, so that the ethereal solution does not come into contact with the hot walls of the flask. The chloramine reacts immediately, while the ether distills off through the column. Heating is continued for 15 min after the addition of the chloramine and the mixture then allowed to cool.

If the alkoxide is insufficiently soluble, half of the sodium is used first, followed by half the chloramine solution, then the remainder of the sodium, and finally the remainder of the chloramine solution.

Work-up. The mixture is filtered, the filtrate completely distilled and dry hydrogen chloride passed into the distillate; this results in the initial precipitation of a small quantity of ammonium chloride, which is immediately filtered off. When the solution is saturated, the O-alkylhydroxylamine hydrochloride either separates in crystalline form and can be filtered, or remains in solution. The solvent is then distilled from the mother liquors or solution, down to a volume of about 50 ml and this is further concentrated on a water bath until one drop on a watch-glass solidifies on scratching. The sirupy liquid is now allowed to cool over phosphorus pentoxide in a desiccator, and the hydrochloride purified by sublimation or crystallization.

The free bases are obtained by the dry distillation of a mixture of powdered sodium hydroxide and the hydrochloride, either at normal pressure or under vacuum. They are colorless liquids, which do not reduce Fehling's solution even on heating.

O-Arylhydroxylamines

If analogous reactions are attempted between sodium phenoxide and chloramine, dark tars are obtained. In contrast, the previously unknown O-arylhydroxylamines can be prepared from 2,6-disubstituted phenols, by allowing the sodium phenoxides in the fused phenols to react with an ethereal solution of chloramine at 100° (*28*). Whereas the *p*-position need not be substituted, a free position *ortho* to the phenolic hydroxyl group gives rise to *o*-aminophenols. More strongly acidic phenols such as 2,4,6-trichlorophenol do not react as the sodium compounds. The few O-arylhydroxylamines prepared in this manner are shown in Table 6. They are colorless, crystalline, stable compounds, which do not reduce Fehling's solution but are affected by mineral acids.

Preparation of the O-arylhydroxylamines. The phenol (400 gm), placed in an apparatus identical with that described in the preparation of the alkylhydroxylamines at 80°, is fused by means of an oil bath at

120–150°; sodium (15–20 gm) is added in small portions, initially only as much as still permits the thorough stirring of the contents of the flask. If a solution of chloramine (35–45 gm) in dry ether (approximately 2.5 liter) is now added dropwise (over a period of 2 hr), the melt becomes so thin after 30 min that the remainder of the sodium followed by the remainder of the chloramine can be added. The molar proportions of

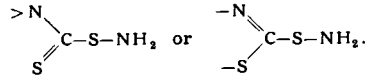
TABLE 6
O-Arylhydroxylamines

Aryl	Reaction temp. (Bath temp.)	% Yield calcd. w. r. t. NH_2Cl	M. p.
2, 4, 6-Trimethylphenyl (Mesityl)	120 - 150°	69	131 - 132°
2, 6-Dimethylphenyl	120°	62	122 - 123°
2, 6-Diethylphenyl	150°	43	93°
2, 6-Diisopropylphenyl	120 - 150°	-	~64°

Na:NH_2Cl should lie between 1.1 and 1.3. When all the chloramine has been used up, stirring is continued for another 15 min and the excess of phenol distilled off. As soon as the boiling point rises, the residue is allowed to cool, dissolved in an ether–water mixture, made very weakly alkaline with hydrochloric acid, and the ethereal solution separated and dried over sodium sulfate. Crystallization usually sets in on evaporation of the ether, and invariably when the residue is distilled *in vacuo* (b.p. 30–40°/12 mm higher than the corresponding phenols). Purification is accomplished by crystallization from ligroin, alcohol, or water.

Reaction Between Mercapto Compounds and Chloramine

Although mercapto compounds are not suited to the reaction with chloramine on account of their instability to oxidizing agents, well-defined products can be isolated in some cases. Thus reaction at 0 to 45° between the salts of dithiocarbamic acids (*29*) and of mercaptobenzothiazole (*30*) with chloramine in aqueous solution gives derivatives of thiohydroxylamine, possessing the following structure.



Aldehyde Chlorimines

Like hydroxylamine, chloramine is capable of reacting with aldehydes to give chlorimines. Raschig (*31*) and Forster (*32*) obtained oily benzaldehyde chlorimine in this manner, and on this basis Hauser (*33*) de-

veloped a simple process for the preparation of the chlorimines of both aromatic and aliphatic aldehydes. Shaking an approximately normal aqueous-ammoniacal chloramine solution (threefold excess) with a solution of the aldehyde in ether at 0° affords the fairly pure corresponding chlorimines in yields of 70–90% within a few minutes.

4-Chlorobenzaldehyde and α-chlorocinnamaldehyde require the presence of a little alkali; this must otherwise be avoided, since it causes the elimination of hydrogen chloride, resulting in the formation of nitriles (*34*). Nitrobenzaldehyde and nitrocinnamaldehyde only react with chloramine in acetic ester and dioxane, respectively. The condensation using ether or acetic ester as solvent fails in the case of 2,4-dinitro- and 2,4,6-trinitrobenzaldehyde, 4-methoxynaphthaldehyde, and α-bromocinnamaldehyde. Impure products in poor yield are generally obtained if the reaction is effected in alcoholic solution in the presence of sodium bicarbonate; this process represents the only route, however, by which *p*-dimethylaminobenzaldehyde chlorimine can be prepared.

Formaldehyde is an exceptional case, and yields trimeric formaldehyde chlorimine with chloramine in aqueous solution (*35*). The monomeric chlorimine is formed within a few minutes at 0°, while the trimerization requires 1 hr (*36*).

No ketone chlorimines have been prepared in this manner; they can be obtained from the imines with hypochlorous acid (*37*).

There are, in addition, a number of individual reactions of no practical significance, such as the addition of chloramine to diphenylketene to give diphenylchloroacetamide (*38*), the formation of diazocamphor and diazodeoxybenzoin from isonitrosocamphor or benzil monoxime, respectively, and chloramine (*32*), and the formation of phenyl- or *p*-nitrophenyl azide from benzene- or *p*-nitrobenzenediazohydroxide and chloramine (*32*).

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Preparation of Esters, Amides, and Anhydrides of Phosphoric Acid

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Introduction

The chemistry of the organic compounds of phosphorus has developed exceptionally rapidly in the last decade, and both the theoretical and practical importance of the methods of phosphorylation have grown considerably. This is due to a number of reasons: Many important natural products and coenzymes are esters or anhydrides of phosphoric acid. The synthesis of these unstable compounds requires extremely specific and careful methods of phosphorylation. Nucleic acid is a polyester of phosphoric acid; derivatives of phosphoric acid play a major role in biologial syntheses and processes for the transformation of energy. Moreover many esters and anhydrides of phosphoric acid are potent insecticides. Due to the abundance of material, this review must restrict itself to a selection of work carried out since approximately 1950; the monographs of Kosolapoff (*1*) and Schrader (*2*) may be used as a guide to the earlier literature. The monograph of van Wazer (*3*) discusses the physical principles underlying this class of compounds.

Use of Acid Chlorides. Classical Methods

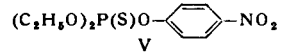
The use of phosphoric acid chlorides (I) in the preparation of esters of phosphoric acid has been known for more than a century (*1*).

$$\underset{\text{I}}{(RO)_2P(O)Cl} + R'OH \rightarrow (RO)_2P(O)OR' + HCl$$

The chlorine atoms in phosphorus oxychloride can be replaced stepwise by alkoxy or aryloxy groups, and, depending on the amount of alcohol used, the monoester dichloride (II), diester monochloride (III), and triester (IV) can be obtained.

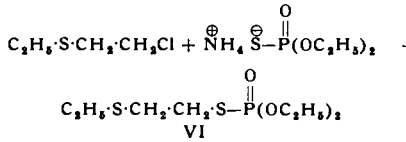
$$\underset{\text{II}}{ROP(O)Cl_2} \qquad \underset{\text{III}}{(RO)_2P(O)Cl} \qquad \underset{\text{IV}}{(RO)_3PO}$$

The commercial preparation of thiophosphoric acid O,O-diethyl-O-*p*-nitrophenyl ester (E 605) (V) is effected by allowing diethylthiophosphoric acid chloride to react with the sodium derivative of *p*-nitrophenol (*4*).



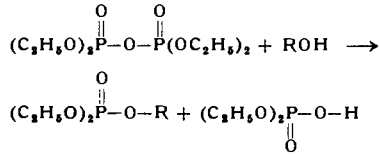
V

Compound V can also be prepared by allowing $PSCl_3$ to react first with 2 moles of sodium ethoxide, followed by 1 mole of the sodium derivative of *p*-nitrophenol (*5*). Many technically important phosphoric acid esters are prepared in this manner (*2*). Phosphoric acid esters can, however, also be obtained by reaction between the salts of phosphoric acid and alkyl halides. The silver salts of phosphoric acids react best with alkyl halides (*6*) (Clermont method); the alkyl bromides or iodides are used as far as possible. This process is used, among others, in the preparation of the thiol-Systox insecticide, VI (*7*), which is obtained by the reaction between the ammonium salt of diethylthiolphosphoric acid and β-chloroethyl ethyl sulfide (*8*).

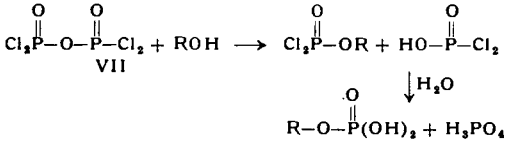


VI

The acid chlorides can also be replaced by the tetraesters of pyrophosphoric acid, though these are usually less readily accessible. Thus tetraethyl pyrophosphate and alcohol in the presence of a base yield the corresponding ester of diethylphosphoric acid and diethyl phosphate.



An interesting modification can now be effected using pyrophosphoryl chloride (VII) (*9, 10*) which undergoes fission at the P—O—P bond (and not, surprisingly, at the P—Cl bond) with alcohols, thus allowing the synthesis of monoesters of phosphoric acid.



VII

The direct oxidation of tertiary phosphites to triesters of phosphoric acid has long presented difficulties. A number of oxidation processes have recently been reported; according to these, esters of phosphorous acid

can be oxidized to esters of phosphoric acid by means of atmospheric oxygen, various oxidizing agents (*11*), or indirectly via halogenation (*11a*). Sulfur is readily taken up on heating with tertiary phosphites to give thiophosphates (*1*). Esters of phosphorous and phosphoric acid can undergo transesterification in the presence of acid or basic catalysts (*1, 12*); the lower boiling alcohol generally distils off, and the ester of the higher boiling alcohol is formed.

Amides of phosphoric acid (amidophosphoric acids, phosphoramidates) are obtained by the same methods, i.e., by the reaction between the corresponding phosphoric acid chlorides and aliphatic or aromatic amines; this reaction usually proceeds very readily. In this instance too, the individual Cl atoms in $POCl_3$ can be replaced one after the other by the amino or substituted amino group.

Phosphoric acid anhydrides (pyrophosphates) can be prepared by the classical method of allowing a salt to react with an acid chloride.

$$(RO)_2\overset{\overset{O}{\|}}{P}-O^{\ominus} + Cl-\overset{\overset{O}{\|}}{P}-(OR)_2 \longrightarrow \text{Pyrophosphate} + Cl^{\ominus}$$

Since some compounds in this class are interesting technically from the point of view of insecticides, simple industrial processes for their preparation have been developed; these include the preparation of tetraethyl pyrophosphate from triethyl phosphate and P_4O_{10} (*13*). Triethyl phosphate can also be "transesterified" by $POCl_3$, whereby an anhydride insecticide of formula $(C_2H_5O)_6P_4O$ is obtained (*14*) (Schrader process).

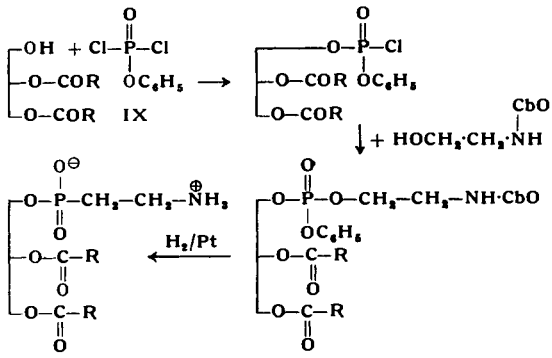
Esters Containing Protected Groups

In order to synthesize complicated natural products containing phosphorus, the necessity has existed for the past 20 years of using esters and chlorides of phosphoric acid in which some of the ester groups could be removed without affecting the sensitive parts of the molecule. The first step was the introduction of phosphoric acid diphenyl ester chloride (VIII) (*15, 16*),

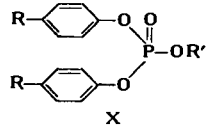
$$(C_6H_5O)_2\overset{\overset{O}{\|}}{P}-Cl$$

VIII

since the phenyl ester groups in phosphoric acid can be removed by hydrogenation with platinum/hydrogen (Adams catalyst) (*15, 17*). Glucose-6-phosphate, for example, was thus prepared from 1,2,3,4-tetraacetylglucose and VIII in pyridine, followed by hydrogenation (*17, 18*). The bifunctional monophenylphosphoric acid dichloride, IX, has been used in the preparation of phosphatides (*19, 20*).

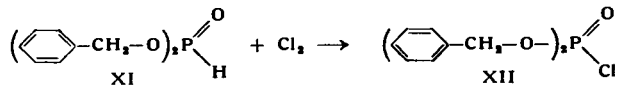


Tetraphenyl pyrophosphate (*21*) or tetra-*p*-nitrophenyl pyrophate (*22*) may sometimes profitably replace compound VIII. The reductive elimination of the two phenyl groups in esters of type X (R=H or NO_2)



X

proceeds at such similar rates that the intermediate compound containing one phenyl ester group cannot be isolated. Intermediates of this kind, with partially removed protecting groups, are very desirable for certain synthetic purposes, and can be isolated in the benzyl series. Mild alkaline hydrolysis of X (R=NO_2) does allow the isolation of mono-*p*-nitrophenylalkylphosphoric acids (*22*). The derivatives of dibenzylphosphoric acid are both more varied and more important (*23*). Its acid chloride (phosphoric acid dibenzyl ester chloride, dibenzyl phosphochloridate) XII, is obtained by the chlorination of dibenzyl phosphite (XI) with gaseous chlorine or N-chlorosuccinimide (*11a*) [cf. experimental section

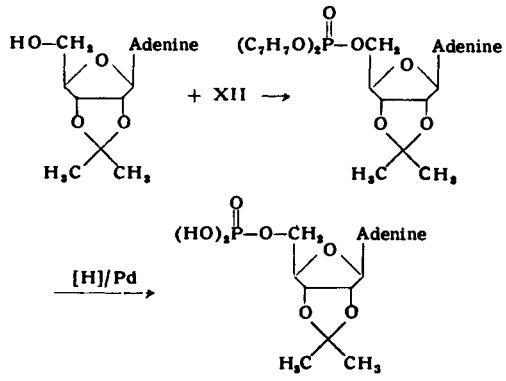


XI XII

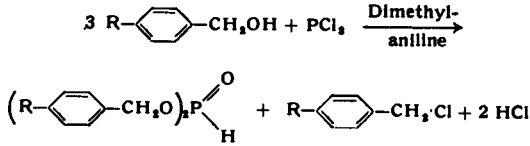
(*24*)]. Compound XII rendered the synthesis of adenosine monophosphoric acid (*25*) and other nucleotides (*26–28*) possible.

In the chemistry of the nucleotides, one is dependent on benzyl esters, as the nucleo bases would not survive the platinum-catalyzed hydrogenation required in the case of phenyl ester protecting groups.

Dibenzylphosphoric acid chloride is an unstable oil, which is utilized as soon as it has been prepared. In a manner analogous to dibenzyl phos-



phite (XI), the *p*-substituted dibenzyl phosphites (*p*-Cl,*p*-Br,*p*-nitro) (*29*, *30*) can be prepared from the benzyl alcohols and PCl_3.



Some of the *p*-substituted dibenzyl phosphites crystallize very well, and can be converted into the stable substituted acid chlorides with sulfuryl chloride. The identical acid chlorides can also be prepared from the phosphoric acid dibenzyl esters with phosphorus pentachloride (*31*, *32*).

Selective Removal of Protecting Groups

During phosphorylation, one group in a phosphoric acid triester must often be selectively saponified or removed.

Tertiary bases are capable of removing one benzyl group from tribenzyl phosphate and *p*-substituted tribenzyl phosphates by quaternization (*33*, *34*); N-methylmorpholine, for example, can be used to effect this elimination. Triesters are degraded to dibenzyl hydrogen phosphate,

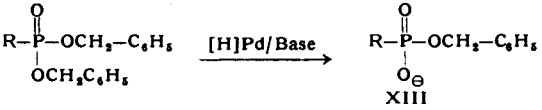
$$(BzO)_2P(O)–O–CH_2–R + :NR_3 \longrightarrow (RCH_2\overset{+}{N}R_3)(BzO)_2P(O)O^-)$$

etc., in yields of 80–90% by this route. Tetrabenzyl pyrophosphate affords tribenzyl pyrophosphate. The quaternization process is restricted to neutral esters, and consequently stops at the mono-anion stage.

The selective monodebenzylation by means of anions (anionic debenzylation) is more important still from the preparative point of view. The triester is allowed to react with inorganic salts such as ammonium

thiocyanate, lithium chloride, or sodium iodide in organic solvents (e.g., methyl ethyl ketone) (*32, 35, 36*). Also the alkyl groups can be eliminated in mixed esters such as diphenyl *n*-propyl phosphate, even though these are less susceptible to nucleophilic attack of the anion (*37*). The debenzylation by means of sodium iodide is an extremely convenient reaction; a brief period of boiling under reflux results in the precipitation of the sodium salt of the acid from the organic solvent (*32*). The yields are frequently quantitative. The diester stage remains intact even if an excess of sodium iodide is used.

Hydrogenolytic cleavage of phosphoric acid benzyl esters generally results in the complete removal of the benzyl groups and does not allow the isolation of partially debenzylated products. If, however, the reduction is effected in the presence of bases, the hydrogenolysis of the second or third benzyl groups is strongly retarded or inhibited entirely, so that the corresponding intermediates (XIII) can be isolated (*38–40*).



XIII

This method has proved particularly valuable in the preparation of phosphoric acid monobenzyl ester amides, which are otherwise difficult to obtain. Five or 10% palladium–charcoal is used as the catalyst, and cyclohexylamine, triethylamine, or NaOH as the base. In certain cases, the monodebenzylated product can be obtained after exactly 1 mole of H_2 has been taken up, even in the absence of added base; this is encountered with phosphoric acid monobenzyl ester isothioureide [XIII, R = HN = C(SC_2H_5)NH] which, itself a weak base, is evidently capable of arresting the hydrogenation by zwitterion formation (*41*).

Phosphonic Esters. Michaelis-Arbusov Reaction (*42*)

The reaction between *tert* alkyl phosphites and alkyl halides to give phosphonic esters has long been known (*43, 44*). R and R′ must both be aliphatic; the reaction cannot be effected with either triaryl phosphites



or aryl halides. During the course of the reaction, the basic electron pair of the *tert* phosphite combines with the alkyl halide to form a quater-

nary phosphonium salt, namely the alkyltrialkoxyphosphonium halide, XIV, which becomes stabilized as phosphonic ester by the elimination of alkyl halide (*45, 46*).

$$(RO)_3P + R'X \rightarrow \underset{\text{XIV}}{\left[R'-\overset{\oplus}{P}(OR)_3\right]^+ X^\ominus} \xrightarrow{-RX} R'-\overset{O}{\overset{\|}{P}}(OR)_2$$

Two reviews have recently appeared which deal with the scope of this reaction (*42*). If, in the Michaelis-Arbusov reaction, the alkyl group is the same in both the phosphite and the halide, only isomerization of the *tert* phosphite to the phosphonic ester occurs, catalyzed by the alkyl chloride (Arbusov rearrangement in the narrower sense), e.g.

$$(C_2H_5O)_3P \xrightarrow{C_2H_5Cl} (C_2H_5O)_2\overset{O}{\overset{\|}{P}}-C_2H_5$$

If the two groups are different, it is theoretically possible to obtain two different phosphonic acids. As a rule, however, triethyl phosphite is used as the starting material and the ethyl chloride formed is distilled off and removed from the reaction mixture. In other cases, an excess of the halide may be used. The yields are usually around 90%. Amidophosphites also readily undergo this reaction. Secondary phosphites in the form of their sodium salts react with alkyl halides.

$$(RO)_2\overset{O}{\overset{\|}{P}}Na + R'Cl \rightarrow (RO)_2\overset{O}{\overset{\|}{P}}-R' + NaCl$$

The reactivity of the halides in the Michaelis-Arbusov reaction increases in the order Cl,Br,I. Apart from a few exceptions such as the arylmethyl halides, secondary halides do not react readily, and the tertiary compounds not at all. Acid chlorides yield α-ketophosphonic acids (XV) (*47*):

$$R\cdot\underset{\|}{\overset{O}{C}}\cdot Cl + P(OR)_3 \rightarrow \underset{\text{XV}}{R-\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{P}}(OR)_2} + RCl$$

The reaction with α-haloketones or -esters is anomalous (see under enol phosphates). Secondary phosphites couple with diazonium salts to give azophosphonic esters XVI (*48*), which can be reduced to phosphoric acid hydrazides:

$$\text{C}_6\text{H}_5\text{-N=N}]^+ X^\ominus + H\overset{O}{\overset{\|}{P}}(OR)_2 \rightarrow \underset{\text{XVI}}{\text{C}_6\text{H}_5\text{-N=N-}\overset{O}{\overset{\|}{P}}(OR)_2} + HX$$

Secondary phosphites add to ethylenic double bonds, if these are activated by carbonyl, cyano, or ester groups (*49–51*).

Crotonic acid thus affords the corresponding β-phosphonic ester, XVII, in 82% yield (*49*):

$$(RO)_2\overset{O}{\overset{\|}{P}}H + CH_3{\cdot}CH{=}CH{\cdot}COOR \xrightarrow{Na} (RO)_2\overset{O}{\overset{\|}{P}}-\overset{CH_3}{\overset{|}{C}}-CH_2{\cdot}COOR \quad \text{XVII}$$

Sodium diethyl phosphite will also add to the double bond of enol esters (*52*):

$$(RO)_2PONa + CH_2=\overset{OAc}{\overset{|}{C}}-R \longrightarrow (RO)_2\overset{O}{\overset{\|}{P}}-CH_2-\overset{OH}{\overset{|}{C}}H-R$$

In other cases the olefinic double bond is regenerated, and unsaturated phosphonic esters are obtained (*53*). α-Aminophosphonic esters (XVIII) are very readily formed from aldehydes or ketones, ammonia or amines and *sec* phosphites (*54–56*):

$$R{\cdot}\overset{R'}{\overset{|}{C}}{=}O + NH_3 + H{\cdot}\overset{O}{\overset{\|}{P}}(OR)_2 \longrightarrow R-\overset{R'}{\overset{|}{C}}(NH_2)-\overset{O}{\overset{\|}{P}}(OR)_2 \quad \text{XVIII}$$

Additional special methods for the preparation of phosphonic esters must be relegated to reviews (*42*).

Enol Phosphates. Perkow Reaction

The Michaelis-Arbusov reaction with α-halocarbonyl compounds proceeds in an anomalous manner, especially in the case of polyhaloketones or -aldehydes. Thus chloral and triethyl phosphite yield phosphoric acid diethyl ester β,β-dichlorovinyl ester (XIX) (*57–60*):

$$(C_2H_5O)_3P + OCH-CCl_3 \longrightarrow (C_2H_5O)_2\overset{O}{\overset{\|}{P}}-O-\overset{H}{\overset{|}{C}}{=}CCl_2 + C_2H_5Cl \quad \text{XIX}$$

The reaction proceeds surprisingly readily; in the example given it is strongly exothermic and external cooling must be applied. The structure of the enol phosphates is proved by chemical and physical means. The reactivity of the aldehydes varies: Chloral and triethyl phosphite yield the dichlorovinyl phosphate in a spontaneous and uniform reaction. That with dichloroacetaldehyde is still exothermic, but less violent; with monochloroacetaldehyde, on the other hand, the reaction mixture must be heated at 110°C. The reactivity therefore decreases with the number of halogen atoms on the α-carbon. The reaction is by no means restricted

TABLE 1

Enol Phosphates of Diethylphosphoric Acid

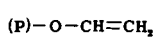
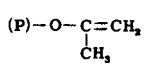
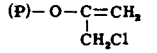
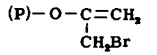
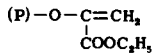
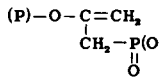
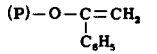
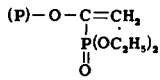
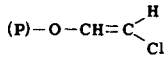
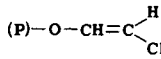
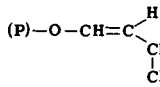
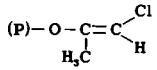
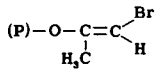
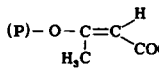
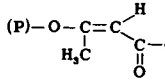
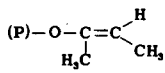
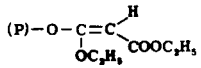
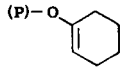
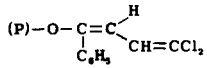
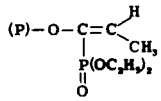
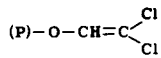
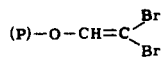
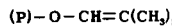
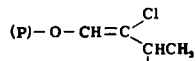
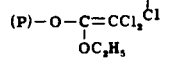
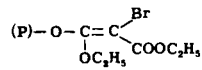
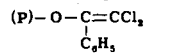
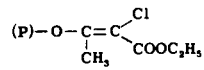
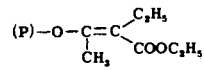
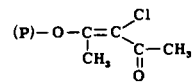
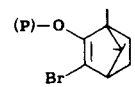
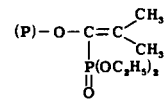
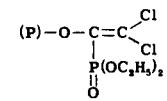
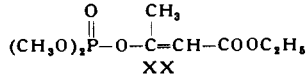
Formula[a]	Literature ref.	From $(C_2H_5O)_3P$ +	Yield (%)
	*62* *63*	Monochloroacetaldehyde	67 –
	*62* *64, 65* *66* *67*	Chloroacetone	56 95 65 80
	*62* *68*	α,α'-Dichloroacetone	82 ?
	*68*	α,α'-Dibromoacetone	?
	*69*	Bromopyruvic ester	74
	*68* *67*	1-Chloromethylvinyl diethyl phosphate	33 84
	*64* *63*	ω-Chloroacetophenone	90 81
	*70*	Chloroacetyl chloride	85
	*60* *62*	Dichloroacetaldehyde	60 54
	*60* *62*	2,3-Dichloropropanal	41 100?
	*62*	2,3-Dichloro-3-phenylpropanal	100?
	*71*	α,α-Dichloroacetone	76
	*71*	α,α-Dibromoacetone	–
	*71* *66*	Chloroacetoacetic ester	85 76
	*71* *74*	Chloroacetylacetone	66 71
	*76*	3-Chloro-2-butanone	–

TABLE 1 (*continued*)

Formula[a]	Literature ref.	From $(C_2H_5O)_3P$ +	Yield (%)
	*69*	Bromomalonic ester	82
	*77* *63*	Chlorocyclohexanone	88.5
	*62*	Phenyl trichloro-propenyl ketone	100
	*70*	α-Bromopropionyl bromide	78.6
	*59* *73* *62*	Chloral	85–90 98 98
	*59*	Bromal	70
	*72*	2-Chloroisobutanol	73
	*60*	2,2,3-Trichlorobutanal	45 90
	*73* *62* *63*	Trichloroacetic ester	40 53 51
	*62*	Dibromomalonic ester	–
	*73*	ω-Trichloroacetophenone	91
	*62* *71, 72* *74*	Dichloroacetoacetic ester	68 90 76
	*74*	α-Chloro-α-ethylacetoacetic ester	75
	*71, 72*	Dichloroacetylacetone	63
	*62*	Dibromocamphor	81
	*70*	α-Methyl-α-bromopropionyl bromide	90
	*70* *75*	Trichloroacetyl chloride	78.6

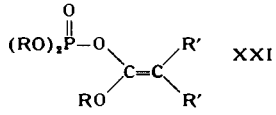
[a] (P) = $(C_2H_5O)_2P(O)$-



XX

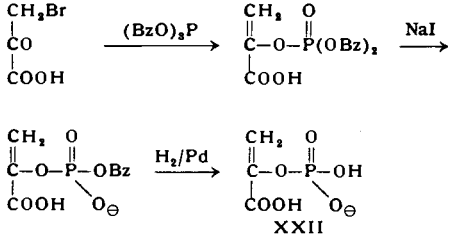
to the chloral series. Trimethyl phosphite and α-chloroacetoacetic ester yield the insecticide "Phosdrin" (XX) (*61*).

A number of α-haloesters also react with trialkyl phosphites in an interesting manner, yielding the extremely reactive keteneacylals (XXI) (see below).



XXI

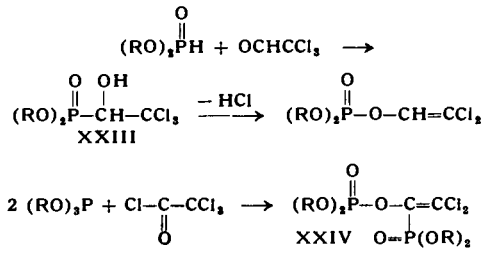
An application of the Perkow reaction is found in the preparation of phosphoenolpyruvic acid (XXII) (*78*):



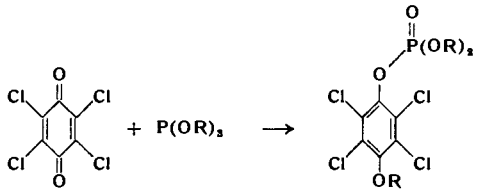
XXII

Secondary phosphites add to the carbonyl group of the α-haloketones to give addition compounds (XXIII), which are converted into enol phosphates by elimination of HCl (*79*). Some of these conversions result in the formation of the phosphonic esters as well as the enol phosphates, especially if bromoketones are used as the starting material (*66, 67*). Chloroacetone reacts with triethyl phosphite at 120° or 170°C, yielding the vinyl ester as the major product. In the reaction with bromoacetone, the proportion of vinyl ester is highest when the temperature is maintained as low as possible. With iodoacetone, even low temperatures result mainly in the formation of phosphonic ester (90%) (*80*). Elevated reaction temperatures favor the formation of the phosphonic ester in every instance. α-Halo-β-diketones give enol phosphates predominantly (*71, 72, 81*). If α-haloacid chlorides are used, Perkow and Arbusov reactions occur simultaneously, to form compounds of structure XXIV (*70, 75*).

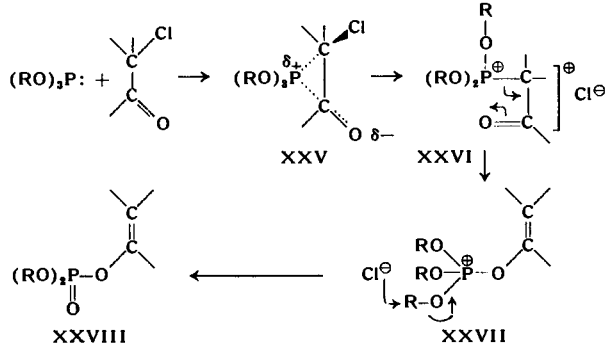
Thiophosphites too, react with chloral, but the sensitive alkyl group linked to the sulfur atom is then eliminated (*82*). The conversion of



α-haloquinones and triethyl phosphite into hydroquinonephosphoric acid esters is related to the Perkow reaction (*83, 84*).



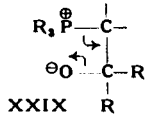
A number of opinions have been expressed with regard to the mechanism of the reaction (*70, 60, 66, 74, 64, 62, 73, 85*). In analogy to the Arbusov reaction, the first step is the attack by the lone electron pair of the phosphite phosphorus, on the carbon atom linked to the halogen, and the simultaneous formation of a phosphonium intermediate



XXVI (*85*). The transition state can be formulated as XXV, i.e., the question remains open as to whether the initial attack of the base occurs at the C—Cl bond or at the carbonyl group. Migration of the phosphorus to the carbonyl oxygen must precede the elimination of RCl from XXVI, since it has been found experimentally that no subsequent isomerization of phosphonic esters to enol phosphates occurs. The introduction of the

carbonyl oxygen's electron pair into the *d* orbitals of the phosphorus, followed by a disruption of the bond system via a cyclic four-point mechanism, therefore results in the formation of the enol phosphate or its phosphonium chloride, XXVII, which is immediately converted into XXVIII.

A reaction course corresponding to XXVI → XXVII is encountered in the Wittig reaction (*86*) where the "zwitterion" intermediate XXIX is formed.



XXIX

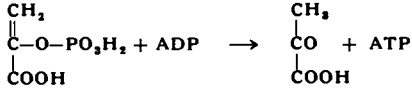
The proposed mechanism (*87*) explains a number of peculiarities of the reaction, but these cannot be entered into here.

Enol phosphates readily add chlorine or bromine; hydrogenation of the double bond can be effected with various catalysts, but reductive cleavage of the enol ester bond may also result (*67, 62*). A benzyl group is readily eliminated from the benzyl ester of phosphoenolpyruvic acid by hydrogenation, the double bond remaining unattacked (*78*). In general, the hydrogenation of the double bond of an enol phosphate proceeds at a slightly lower rate than that of an isolated double bond. Enol phosphates can undergo polymerization (*88*).

Like vinyl esters, the enol phosphate bond is readily saponified by acid, to yield the aldehyde.

Figure 1 gives a comparison of the rates of the saponification (85°C, 0.1 *N* HCl, 40% ethanol) (*89*).

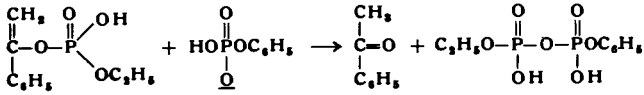
The naturally occurring phosphoenolpyruvic acid can transfer its phosphate group enzymatically to adenosine diphosphate with the for-

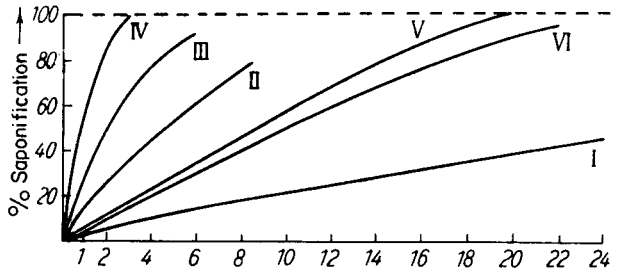


ADP = Adenosine diphosphate ATP = Adenosine triphosphate

mation of an additional anhydride linkage; this is equivalent to acidolysis of the enol bond.

Analogous transfer reactions are also possible in the case of simple enol phosphates (*89*), e.g.





I: $P-O-CH=CH_2$

II: $P-O-C(COOCH_3)=CH_2$

III: $P-O-C(C_6H_5)=CH_2$

IV: $P-O-C(CH_3)=CH_2$

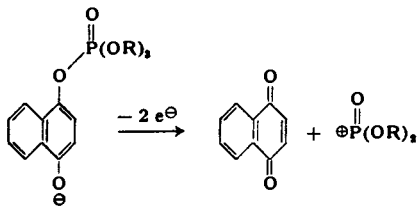
V: $P-O-CH=CCl_2$

VI: $P-O-C(CH_3)=CH-COOC_2H_5$

$[P=(C_2H_5O)_2P]$

Fig. 1. Rates of acid, saponification of enol phosphates

The keteneacylals (see below) are considerably more reactive in this sense. Enol phosphates can transfer their phosphate group during the oxidation, i.e. they can act as phosphorylating agents (*90, 91*). They con-



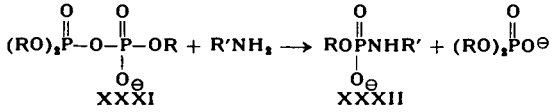
stitute models of a possible mode of action of coenzyme Q in oxidative phosphorylation.

Amides and Guanidides of Phosphoric Acid

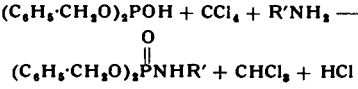
The amides of phosphoric acid diesters can be prepared—as described in the second section of this chapter—by allowing an acid chloride to react with the amine. Tetraalkyl or -aryl phosphates are aminolytically cleaved to give 1 molecule of diester amide (XXX), and 1 molecule of

$$(RO)_2P(=O)-O-P(=O)(OR)_2 + R'NH_2 \longrightarrow \underset{\text{XXX}}{(RO)_2P(=O)NHR'} + {}^{\ominus}O-P(=O)(OR)_2$$

acid (*93a*). Triesters of pyrophosphoric acid XXXI give the amides of phosphoric acid monoester, XXXII, exclusively (*93*).

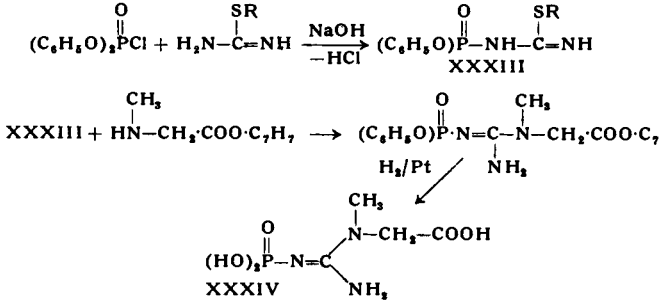


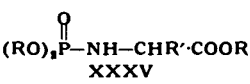
The phosphite–carbon tetrachloride method is a very elegant and simple preparation of XXX (*92, 94*). If a strong base such as cyclohexylamine is added to dibenzyl phosphite in carbon tetrachloride, much heat is generated and a 90% yield of the cyclohexyl amide of phosphoric acid dibenzyl ester can be isolated. Even alcohols can be phosphorylated in the presence of tertiary bases.



This noteworthy reaction probably proceeds via an acid chloride (*92, 95*). CCl_3Br has also been used. The reaction can even be carried out in a two-phase system with aqueous alkali, in which the substance undergoing phosphorylation is dissolved or suspended. The solution is then stirred with dibenzyl phosphite in CCl_4 (*92, 96*). The protecting groups can be removed by complete (*97*) or partial hydrogenolysis in the usual manner. Other methods for the preparation of phosphoric acid amides are described below.

Guanidides and amidides of phosphoric acid can, in principle, be prepared by the same method. In some cases, e.g. in the synthesis of the phosphagens (*98*), it is more expedient to follow a different route. An isothiourea is first phosphorylated to the N-phosphorylisothiourea XXXIII in the usual manner, and the latter is then allowed to react with amine to give the guanidine (*99*). Creatinephosphoric acid (XXXIV) can thus be synthesized according to the scheme below (*99, 100*).

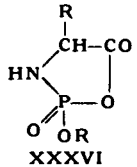




XXXV

α-N-Phosphorylamino acids or esters (XXXV) have variously been utilized as protected compounds in the chemistry of the peptides (*101–105*).

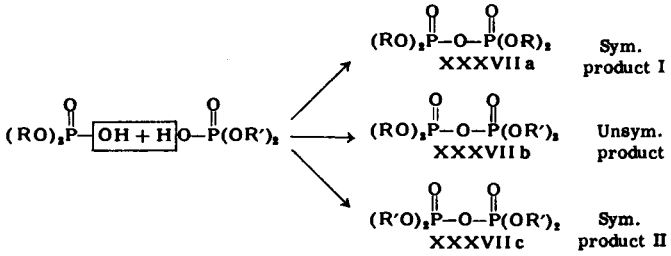
When R is a protecting group which can be removed by hydrogenation, e.g. benzyl, the free N-phosphorylamino acid can be obtained. In this instance, as in most others, the P—N bond is stable in an alkaline or neutral medium, but undergoes immediate fission in weakly acid conditions. It is an almost ideal protecting group for reactions in aqueous solution. A cyclic phosphoric acid–amino acid anhydride (XXXVI) was recently prepared (*106*), which combines the properties of both an anhydride and an N-protected amino acid. N-Dibenzylphosphorylamino acids (XXXV, R=C_7H_7) can also be obtained by the process described above (*107, 108*).



XXXVI

Problems of the Pyrophosphate and Phosphoric Acid Diester Synthesis

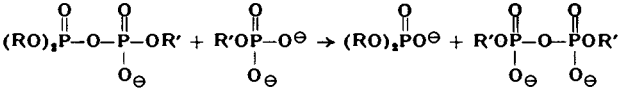
The union of two differently substituted phosphoric acids to give the pyrophosphate theoretically allows the formation of three pyrophosphoric acids (XXXVIIa, XXXVIIb, XXXVIIc).



The unsymmetrical pyrophosphates are a widespread, exceedingly important class of natural products and coenzymes; the synthetic problem consists in obtaining compound XXXVIIb as the major product (*109, 110, 111*) by the use of selective preparative methods. The tend-

ency of unsymmetrically substituted tetraesters of pyrophosphoric acid to isomerize to the symmetrical products (*112,93a*) represents yet a further difficulty. The equilibrium is established particularly in the presence of bases, and lies predominantly on the side of compounds XXXVIIa and XXXVIIc. In spite of these difficulties, such masterpieces in preparative chemistry as the synthesis of ADP, ATP (*113*), and UTP (*114*) were achieved by allowing the correspondingly substituted silver salts of phosphoric acid to react with dibenzylphosphoric acid chloride or analogous compounds according to the classical scheme (see above).

Unsymmetrical triesters (XXXVIII) of diphosphoric acid do not isomerize as readily, but they undergo hydrolysis with water. An exchange, however, does take place in the presence of phosphate anions (*93*), so that even in this case the symmetrical pyrophosphate can result from the ready hydrolyzability of XXXVIII and the formation of phosphate associated with it.

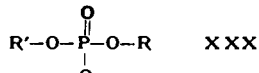


XXXVIII

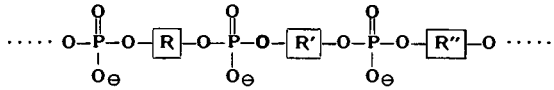
A series of coenzymes, e.g. flavine–adenine-dinucleotide (*115*) and uridine diphosphate–glucose (*116*), has been prepared via XXXVIII, by allowing the corresponding substituted salts of phosphoric acid monoesters to react with the corresponding phosphoric acid ester chlorides, followed by reductive debenzylation. The further development of the classical method, acid chloride + salt = acid anhydride, is limited, however, by the vulnerability of the esterified pyrophosphates to hydrolysis and exchange; there exists, moreover, a lack of methods yielding the desired unsymmetrical pyrophosphates (see below).

A further important task consists in discovering methods for the preparation of unsymmetrical diesters of orthophosphoric acid, XXXIX. The latter is particularly rewarding, for the nucleic acids are compounds of this type, i.e. polyesters of bifunctional phosphoric acid and bifunctional alcohols.

In spite of a certain initial success regarding the synthesis of di- and



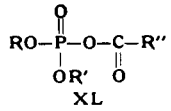
XXXIX



Fundamental structure of nucleic acid

polynucleotides (*117–119*), the solution of the problems associated with the polynucleotide synthesis still lies in the distant future.

Finally, the synthesis of phosphoric acid–carboxylic acid anhydrides (XL) must be mentioned in this connection. Anhydrides of this type are



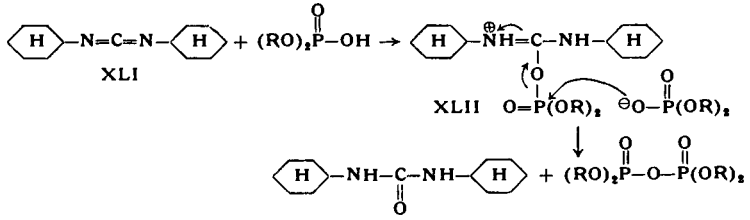
XL

carriers of acyl groups in enzyme systems, e.g. during the course of the biological peptide synthesis (*120*). The difficulties encountered in this synthesis are similar to those associated with the preparation of the unsymmetrical pyrophosphates (*121*); isomerization readily takes place. Acetyl phosphate (XL, R and R′ = H; R″ = CH_3) is prepared by allowing the silver salt of dibenzylphosphoric acid to react with acetyl chloride, followed by hydrogenation (*122*).

The following methods have been devised to allow the synthesis of specific pyrophosphates or diesters using sensitive materials.

Carbodiimide Method

Carbodiimides, especially the much-used dicyclohexylcarbodiimide (XLI), are suitable reagents for effecting the elimination of water from phosphoric acids, and therefore the formation of pyrophosphates. Di- and monoesters of phosphoric acid and inorganic phosphoric acid react to form anhydrides (*123*). Tetrabenzyl pyrophosphate, *sym*-diphenyl pyrophosphate, and similar compounds are frequently obtained in almost quantitative yield at room temperatures in pyridine. The reaction proceeds by the addition of 1 molecule of phosphoric acid to the CN double bond of the carbodiimide. The enol phosphate of the urea (XLII) thus formed reacts with a second molecule of phosphoric acid to give the pyrophosphate. The substituted urea is the only by-product.



XLI

XLII

This extremely elegant, mild, and simple synthetic method, which has also been applied with great success in peptide chemistry (*124*), has rendered possible the synthesis of numerous coenzymes. It is none-

theless true that the three possible pyrophosphates XXXVIIa, b, and c are formed simultaneously, in fact in a statistical distribution in the ratio of 1:2:1. Even from a 100% conversion, therefore, the maximum yield of unsymmetrical product which can be obtained is 50%. Since separation of mixtures of this kind is troublesome, wasteful, and beset with difficulties, and the starting materials are expensive, it is desirable to force the synthesis in one direction as far as possible. The reaction frequently does not proceed according to the
statistical ratio, since the addition of the carbodiimide and the subsequent reaction undergone by the intermediate XLII depend on the pH of the phosphoric acids and the nucleophilicity of its anions. This is the reason why, for example, the synthesis of diphosphopyridine nucleotide (cozymase) proceeds largely in the direction of the coenzyme (*125*). Another way of forcing the reaction in one direction consists in adding an excess of one of the two components, and carrying out the reaction in the presence of a large excess of LXI (*126*). The synthesis of the following coenzymes can be accomplished by the carbodiimide method.

Adenosine triphosphate (ATP) (*126*)
Uridine diphosphate and triphosphate (*126, 127*)
Diphosphopyridine nucleotide (*125*)
Cytidine diphosphate choline (*128*)
Cytidine diphosphate glycerol (*128a*)
Cytidine diphosphate ribitol (*128a*)

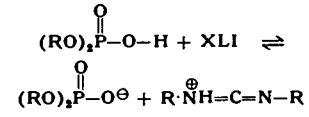
The yields, starting from the nucleoside monophosphate and using a fiftyfold excess of XLI and a tenfold quantity of H_3PO_4, are given in Table 2 (*127*).

TABLE 2
Coenzyme Syntheses

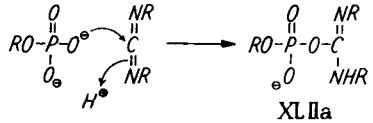
Starting nucleotide, monophosphate of	Reaction product (%)			
	Monophosphate	Diphosphate	Triphosphate	Higher
Adenosine	2	28	60	10
Cytidine	26	14	39	21
Guanosine	5	15	71	9
Uridine	5	21.5	64.5	9
Deoxycytidine	34	14	43	9
Deoxyguanosine	3.3	17.2	79.5	-

The mechanism of the carbodiimide reaction and the position of the equilibria, both in the XLI → XLII stages and in the subsequent formation of the pyrophosphate, have been thoroughly investigated (*129*). It

was found that essentially two factors determine the course of the reaction. The first is the protonation of XLI:

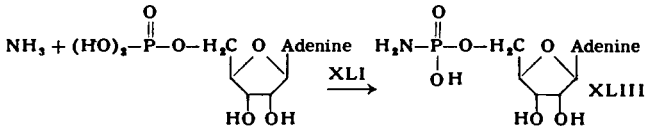


This equilibrium lies further to the right-hand side, the stronger the acid added. Stronger bases cause the deprotonation of the protonated carbodiimide; this is the reason why the diesters of phosphoric acids (pK 1–2) will only react as the free acids or the pyridinium salts, but not as the triethylammonium salts. In the case of the monoesters of phosphoric acid ($pK_1 = 2$ and $pK_2 = 7$) the nucleophilic attack of the phosphate dianion may be the rate-determining step, with the result that even tributylammonium salts react in this instance.

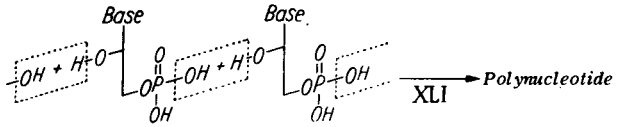


XLIIa

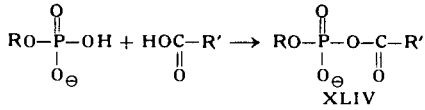
In analogous manner to the peptide synthesis, monoesters of phosphoric acid amides can also be prepared from XLI. Thus adenosine-5′-phosphoramidate (XLIII) was obtained in 87% yield from AMP, aqueous ammonia, and XLI (*130*).



The conversion of phosphoric acids, alcohols, and XLI into the phosphoric ester, i.e. the use of XLI as an esterifying agent, is also known. The direct esterification of the intermediate XLII or XLIIa, however, requires a large excess of alcohol; otherwise the reaction gives the pyrophosphate (*129*). The indirect esterification via an "activated pyrophosphate" is possible, however, and this offers interesting possibilities with regard to the polynucleotide synthesis (*118*).



Reaction between phosphoric acids and carboxylic acids yields the phosphoric acid–carboxylic acid anhydrides, XLIV, essentially via the same scheme as that followed in the pyrophosphate synthesis.

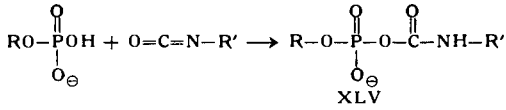


XLIV

Since compounds XLIV are intermediates in the enzymatic amino acid activation (as well as acylation in general, possibly), adenylic acid–amino acid anhydrides (XLIV, R=adenosine-5′) have been prepared from amino acids or carbobenzoxyamino acids and XLI (*131–135*).

Carbamyl Phosphates (*136*)

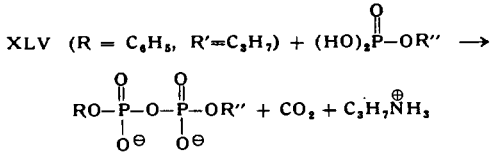
In their reactions with the allene system, isocyanates can, to a certain extent, be compared with the carbodiimides. Addition reactions of the isocyanates are generally initiated by the nucleophilic attack on the C atom of the group. The addition therefore proceeds more readily, the more nucleophilic (more strongly basic) the attacking reagent. The diesters of phosphoric acids accordingly do not react with isocyanates, while the monoesters add readily and usually quantitatively in the form of their anions to isocyanates to give carbamyl phosphates (XLV); unlike the comparable intermediate in the carbodiimide reaction XLIIa, the carbamyl phosphates are readily isolable, stable compounds. Potassium cyanate also combines with orthophosphoric acid to give the corresponding carbamyl phosphate (XLV, R and R′ = H) (*137*).



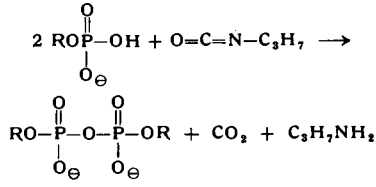
XLV

For preparative work, it is best to use the carbamyl phosphates with R′ = phenyl or *n*-butyl, which crystallize well as their triethylammonium salts and are stable in the absence of moisture. They decompose in aqueous acid solution, and alkali causes the reverse of the formation reaction. The formation equilibrium also lies on the left-hand side at higher temperatures. In the enzymatic reaction (*137*), the anhydride of type XLV acts as carrier for the carbamoyl group. In the corresponding substitution, compounds XLV react with phosphoric acid monoesters to give the pyrophosphate via a transfer of the phosphate group.

The reaction is carried out in pyridine and the yields of simple pyrophosphates are nearly quantitative.

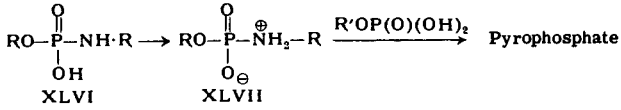


One of the advantages of the reaction lies in the fact that readily accessible starting materials are used as condensing agents; a disadvantage is the rapid setting up of the equilibrium of the formation of XLV, which lies partially on the side of the components at the temperature required for pyrophosphate formation (40°C). The indirect method used in the preparation of unsymmetrical pyrophosphates, on account of this equilibrium, has thus far invariably resulted in the formation of all three possible products. Even though derivatives of XLV can be isolated, the proportions are similar to those found in the carbodiimide method. The "single vessel method" for the direct preparation of pyrophosphates is exceptionally simple (*138*).

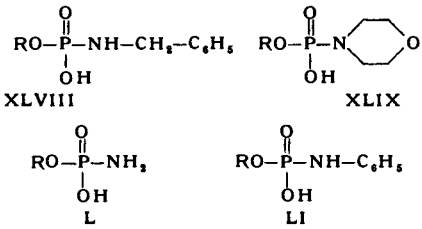


Reactions of Amidophosphoric Acids

Amidophosphoric acids possessing at least one free acid function (XLVI) are very stable in the form of their alkali salts but are readily hydrolyzed in weakly acid solution when they undergo fission of the P—N bond. In the presence of phosphate anions in anhydrous solvents, a "phosphatolysis," i.e. pyrophosphate formation, can also occur instead of the hydrolysis (*139, 140*). Alcohols are not phosphorylated however; this is a case of pure pyrophosphate synthesis.

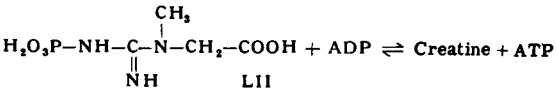


Since the phosphate transfer most probably results from the zwitterion structure XLVII, the reactivity of the amides decreases with the basicity of the amide nitrogen. According to the data available, therefore, the suitability for the pyrophosphate synthesis of the amides given below decreases in the order: XLVIII and XLIX > L > LI (*139–141*).



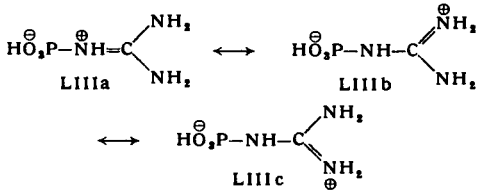
XLVIII XLIX L LI

In this connection, the phosphoric acid guanidides (phosphagens) must be mentioned; these are present in organisms as carriers of high energy content phosphoric acid, e.g. in phosphocreatine (LII), and are then utilized in the pyrophosphate synthesis.



LII

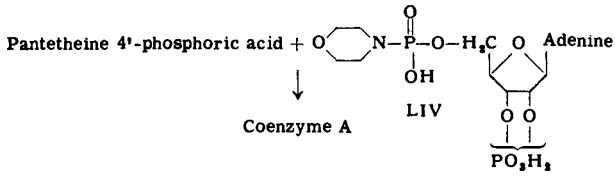
As guanidines are particularly strong bases, the phosphorylation with phosphoguanidines according to the above equation should proceed extremely readily. On the other hand, the positive charge in the zwitterion LIII can be distributed mesomerically over 3 atoms (LIIIa, b, c), with the consequent stabilization of the compound. These relationships, important for the understanding of the mechanism of enzymatic transphosphorylation, are being investigated further (*142*).



LIIIa LIIIb LIIIc

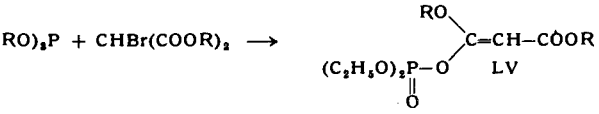
For the synthesis of nucleoside polyphosphates (*139, 140, 141a*) the starting compounds used are the readily accessible amides of phosphoric acid monobenzyl ester, which react with nucleotides in pyridine to give the diphosphate benzyl esters (replacement of the amides by amidophosphoric acid may be less favorable, since the possibility of inorganic polyphosphate formation then exists). The diphosphate itself is obtained by hydrogenolysis. The amide method allows the synthesis of flavine-adenine-dinucleotide (*141a*). The first synthesis of coenzyme A has recently been accomplished (*141b*); adenosine-2′ (3′)-5′-diphosphate (*143*) was first allowed to react with morpholine to give the corresponding morpholide, LIV, and then with pantetheine 4′-phosphoric acid in

pyridine for 15 hr at room temperature, when coenzyme A was obtained in 50% yield.

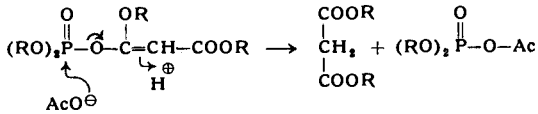


Keteneacylals of Phosphoric Acid

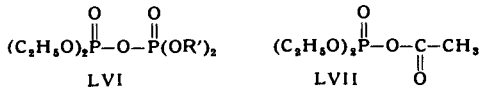
The Perkow reaction for the preparation of enol phosphates can be extended to certain α-halocarboxylic acid esters (*69*); thus, the phosphoric acid α-ethoxy-β-carbethoxyvinyl diethyl ester, LV, can be obtained from triethyl phosphite and bromomalonic ester.



Being a derivative of ketene, LV is highly reactive. It reacts with inorganic and organic acids to give anhydrides, according to the following equation:



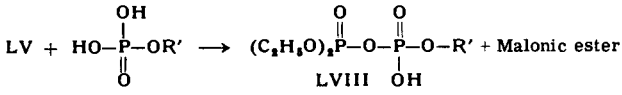
In this manner, tetraesters of pyrophosphoric acid containing unsymmetrical substituents can be prepared (*69*) (LVI); reaction with carboxylic acids results in the formation of good yields of phosphoric acid–carboxylic acid anhydrides, e.g., diethyl acetyl phosphate (LVII).



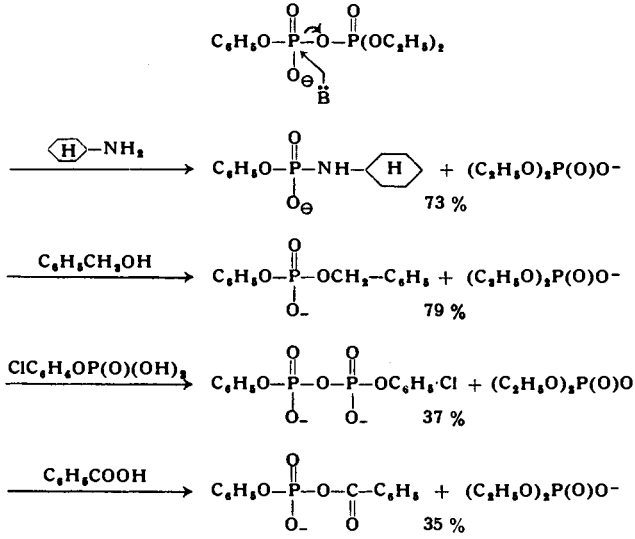
A peptide synthesis, using phosphoric acid–amino acid anhydrides in analogous manner to the enzymatic reaction (*131, 135*), can be developed from this reaction (*144, 145*).



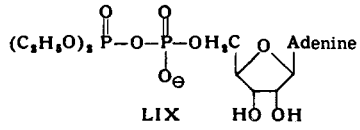
The reaction between LV and monoesters of phosphoric acid yields unsymmetrical triesters of pyrophosphoric acid (*93*) (LVIII), which thus become accessible (*93a*).



Compound LVIII reacts with acids, amines, alcohols, and phosphoric acid monoesters to give acyl phosphates, amides of phosphoric acid esters, unsymmetrical phosphoric acid esters, and unsymmetrical pyrophosphates, respectively; the reaction invariably proceeds via the transfer of the monoester group (right half of LVIII) (*93*), e.g.,



Adenosine monophosphate reacts with LV to give the diethyl ester of adenosine diphosphate (LIX). The sodium salt of LIX, which is formed in 90% yield, undergoes the same reactions as LVIII; thus methanol, cyclohexylamine, and monophenyl phosphate give AMP methyl ester (56%), AMP cyclohexyl amide (90%), and monophenyl ADP, respectively. Adenosine 3′-phosphate first yields 2′,3′-cyclophosphate which then reacts further with LV, and this reaction results in the formation of polynucleotide.

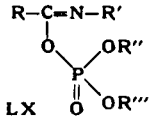


Conclusions concerning the enzymatic phosphate transfer of nucleoside polyphosphates may perhaps be drawn from the reactive behavior of LIX. In spite of their high thermodynamic energy content, ATP and analogous substances are notoriously stable kinetically; the esterification of the polyphosphate in LIX has a labilizing effect similar to that exerted by the enzyme (*146*).

If therefore, the enzyme had a similar influence to that produced by the esterification, e.g. suppression of the dissociation in only one-half of the pyrophosphate molecule, the enzymatic transfer of phosphate would be explicable. A number of experiments with an "inclusion compound model" point in this direction (*147*).

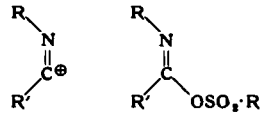
Imidoylphosphates, Trichloroacetonitrile Method

The reactive intermediate XLII in the carbodiimide method is an enol derivative of urea, an imidoylphosphate, LX, and a series of other enol phosphates of acid amides (=imidoyl phosphates) have been utilized in the pyrophosphate syntheses.

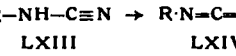


LX

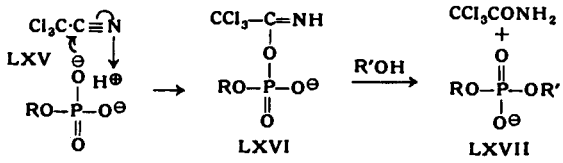
Imidochlorides of carboxylic acids react with the silver salts of phosphoric acids to give compounds LX which then react further to yield pyrophosphates (*148*). The intermediate cations LXI, formed in the Beckmann rearrangement of ketoxime sulfonates in anhydrous conditions, or the imidoylsulfonates, LXII, yield compounds of type LX by exchange with the strongly nucleophilic phosphate anion; these compounds of type LX are immediately converted into pyrophosphates (*149*), thus rendering possible the synthesis of coenzymes (*149*).



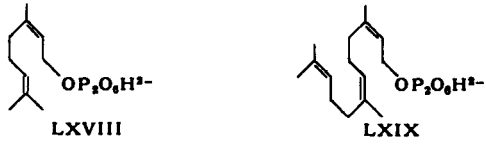
Cyanamide (LXIII) or its derivatives can react via a tautomeric carbodiimide form (LXIV) and may thus be used in pyrophosphate syntheses (*150*). The yields and proportions of symmetrical to unsymmetrical pyrophosphate are similar to those found in the carbodiimide method.



Trichloroacetonitrile (LXV) readily adds alcohols in a base-catalyzed reaction to give imido esters (*151*); the second dissociation stage of the phosphoric acid ester is, however, also sufficiently nucleophilic to add rapidly to LXV to form the reactive intermediate LXVI, which is converted into esters LXVII (R′ = alkyl) in the presence of alcohols, and into pyrophosphates [LXVII, R′ = P(O)(OR″)OH] with phosphoric acids (*152*).



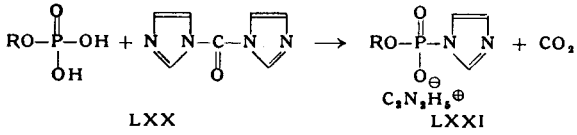
The reaction can also be carried out with unsubstituted orthophosphoric acid. The course of the reaction can be directed, by the addition of either 1 or 2 moles of base, so that it stops at either the monoester or diester stage, respectively. The esters geranyl pyrophosphate (LXVIII) and farnesyl pyrophosphate (LXIX) (*153*), important in the biosynthesis of carotenoids and steroids, were obtained in yields of 29 and 23%, respectively (*154*).



Comparison of the carbodiimide and trichloroacetonitrile methods reveals the following: With LXV, the esterification is strongly favored in the presence of stoichiometric quantities of alcohol; in the carbodiimide method, pyrophosphates are predominantly obtained under these conditions. In the pyrophosphate synthesis the two reagents behave in a similar manner, as far as has been ascertained. Thus as a rule symmetrical and unsymmetrical products are obtained together. The trichloroacetonitrile method is more selective, inasmuch as it can be controlled to give the mono- or diester as desired (cf. experimental section). Unlike the carbodiimide, LXV reacts with neither diesters of phosphoric acids nor carboxylic acids, water, etc., only with the second dissociation stage of phosphoric acid, which alone possesses the correct nucleophilic character.

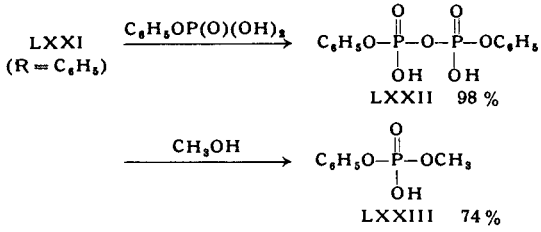
Imidazolides of Phosphoric Acid (*155*)

N-Acylimidazoles are mild and at the same time efficient acylating agents (*156*) which may conceivably take part in enzymatic acylations and saponifications. Phosphoric acid diphenyl ester imidazolide (*157*) is a phosphorylating agent, and phosphoric acid transfer is catalyzed via phosphoric acid imidazolides (*158*). Phosphoric acid monoester imidazolides (LXXI) can conveniently be obtained in good yield from the free phosphoric acids and carbonyldiimidazole (*159*) (LXX), by adding the components in, e.g., acetonitrile at room temperature, and waiting until the evolution of CO_2 has ceased.



LXX LXXI

Compounds LXXI react with phosphoric acids or alcohols to give the pyrophosphates LXXII or diesters LXXIII, respectively.



Experimental

Phosphoric acid diphenyl ester chloride (*diphenyl phosphochloridate*) (*15*). Phosphorus oxychloride (168 gm) and phenol (188 gm) are mixed in a 1 liter round-bottomed flask fitted with reflux condenser and thermometer, and slowly heated to 180°C in an oil bath. The hydrogen chloride generated is absorbed by NaOH. When the reaction is complete (after approximately 2 hr) the contents of the flack are subjected to vacuum distillation, and the fraction coming over at 140–155°C/1.3 mm redistilled. B.p. 147–148°C/1.3 mm; yield approximately 200 gm (75%).

The phosphoric acid monophenyl ester dichloride, b.p. 110°C/11 mm, is obtained by a corresponding alteration of the molar proportions.

Dibenzyl hydrogen phosphite and phosphoric acid dibenzyl ester chloride (*23,24*). A mixture of dimethylaniline (242 gm) and benzyl alcohol (216 gm) is added slowly over a period of 2 hr to a stirred, ice-

cooled solution of phosphorus trichloride (147.5 gm) in benzene (750 ml). Stirring is continued for another ½ hr and more benzyl alcohol (108 gm) added in similar manner. The reaction mixture is allowed to stand overnight at room temperature, water (500 ml) added, and the benzene layer washed with water, 5 *N* ammonia, and water (each washing being carried out twice, with 500 ml portions of the washing liquid). The benzene is dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residual yellowish oil is slowly heated to 150°C at 10^{-2} mm in a sufficiently large distillation apparatus, equipped with nitrogen capillaries in an oil bath. Above 150°C, especially if air is admitted, there is a danger of explosion. After all the benzyl chloride and excess of benzyl alcohol have come over, the oil bath is removed. The apparatus is allowed to remain evacuated until cool. The residue is a yellowish oil (190 gm) which solidifies after a few days in the refrigerator and has a m.p. of about 10°C. This crude dibenzyl phosphite is sufficiently pure for most reactions. For distillation, the crude product is first saturated with ammonia, separated from any precipitate by filtration, and distilled in small portions in the presence of 3% N-methylmorpholine. The same precautions as those mentioned above must be observed. The N-methylmorpholine distills first and is condensed in a trap. The oil bath is then rapidly heated to 180°C (care being taken to avoid local overheating), when the dibenzyl phosphite comes over at 165°C/10^{-1} mm.

For conversion into dibenzyl phosphoric acid chloride, dibenzyl phosphite (39.3 gm) is dissolved in carbon tetrachloride (200 ml) and a 1.4 *N* solution of chlorine in carbon tetrachloride slowly added at −15°C. The mixture is stirred and the temperature maintained throughout below −10°C. Dry nitrogen is then passed into the flask at room temperature until the evolution of hydrogen chloride has ceased (calcium chloride tube, 1–5 hr). The carbon tetrachloride is evaporated at room temperature and 0.2–2 mm pressure, and the residue, a yellow oil, consisting of the acid chloride, is utilized immediately.

Debenzylation of tetrabenzyl pyrophosphate (*36*). (*a*) *Removal of two groups.* A solution of tetrabenzyl pyrophosphate (0.199 gm) and sodium iodide (0.11 gm) in methyl ethyl ketone (3 ml) is boiled under reflux for 40 min. The dibenzyl pyrophosphate separates out, is filtered off, and recrystallized from aqueous acetone. Yield, 0.125 gm (84%).

(*b*) *Removal of one group.* Tetrabenzyl pyrophosphate (0.3 gm) and sodium iodide (0.083 gm) are dissolved in acetonitrile (15 ml) and the solution maintained at 51° for 1 hr. The product is allowed to crystallize at 0°C, filtered, and recrystallized from methyl ethyl ketone. Yield, 61%.

Cyclohexyl amide of phosphoric acid monobenzyl ester (*39, 40, 107*). Triethylamine (2.02 gm) is added to the cyclohexyl amide of phosphoric

acid dibenzyl ester (3.40 gm) in methanol (100 ml) followed by hydrogenation with palladium-charcoal(240 mg, 5% Pd). Hydrogen (236 ml) is taken up after 15 min, when the reaction stops. The catalyst is filtered off, the solvent evaporated *in vacuo,* and the oily residue taken up in water. It is filtered and acidified with dilute sulfuric acid. After being allowed to stand for 1 hr at 0°C, the crystals are filtered off, washed with water, dried, and recrystallized from benzene/cyclohexane/petroleum ether to give the product (2.16 gm, 85%), m.p. 99°C.

1-Naphthylmethanephosphonic acid (*160*). A mixture of 1-chloromethylnaphthalene (43 gm) and triethyl phosphite (41 gm) is heated at 150–160°C for 4 hr and distilled to yield diethyl 1-naphthylmethanephosphonate (87%), b.p. 205–206°C/5 mm. The ester is saponified by boiling under reflux with concentrated hydrochloric acid (200 ml) for 8 hr. The precipitated phosphonic acid is filtered off in the cold and recrystallized from hot water, m.p. 212°C; yield, 90%.

Dimethyl 1-carbomethoxy-1-propen-2-yl phosphate (*Phosdrin*) (*61*). Trimethyl phosphite (100 gm) is added dropwise over a period of 1 hr to methyl α-chloroacetoacetate (121.5 gm) in a flask fitted with a reflux condenser. The temperature rises to 85°C and methyl chloride is evolved. The mixture is distilled *in vacuo,* b.p. 107°C/1 mm; yield, 123 gm.

Dibenzyl ester of phosphoenolpyruvic acid (*78*). Bromopyruvic acid (33.6 gm) in ether is added dropwise to tribenzyl phosphite (86.5 gm, 83%), maintained below 10°. The reaction solution is stirred at room temperature for a further 30 min and poured into a separating funnel containing water (150 ml), $NaHCO_3$ (18 gm), and crushed ice. A little ether is added, the aqueous phase separated and again shaken with ether and the ethereal phases rejected. Ether (50 ml) is added to the aqueous solution at 0°C, followed by the slow addition of ice-cold conc. hydrochloric acid (25 ml) and water (50 ml). The oil which separates immediately goes into the ether. Extraction with ether (25 ml portions) is carried out twice, and the combined ethereal solutions are dried, evaporated under vacuum, and allowed to crystallize at —15°C for 10 hr. Yield, 42 gm (60%); m.p. 75–78°C.

Dibenzyl glycine ethyl ester phosphonate (*107*). Triethylamine (20.2 gm) is added to glycine ethyl ester hydrochloride (26.2 gm), suspended in chloroform (50 ml). After 10 min, dibenzyl phosphite (26.2 gm) in carbon tetrachloride (100 ml) is added to the shaken, ice-cooled solution. This is extracted after 1 hr with water, dilute sulfuric acid, and sodium bicarbonate, and taken up in ether. The residual oil obtained on evaporation crystallizes on cooling and is recrystallized from cyclohexane. Yield, 28.0 gm (77%); m.p. 37–40°C.

Phosphoric acid diphenyl ester S-methylisothioureide (*99*). Phosphoric

acid diphenyl ester chloride (13.4 gm) in benzene (100 ml) is stirred at room temperature with a solution of S-methylisothiourea sulfate (7 gm) in water (45 ml). NaOH (4 gm) in water (20 ml) is added within 10 min. After 1½ hr the organic phase is shaken with dilute sulfuric acid and sodium bicarbonate solution, dried, and evaporated. The ureide crystallizes on the addition of cyclohexane. Yield, 12.5 gm (78%); m.p. 78°C (from benzene/cyclohexane). The ureide (1.16 gm) in ethanol (30 ml) is boiled for 1 hr under reflux with mercuric oxide (0.54 gm) and aniline (0.5 gm). The mercaptide is filtered off and the solution concentrated and allowed to crystallize. Yield, 1.5 gm (81%); m.p. 139°C (from benzene/petroleum ether).

Tetrabenzyl pyrophosphate (*123*). Dicyclohexylcarbodiimide (0.227 gm) is added to dibenzylphosphoric acid (0.556 gm) in ether. After ½ hr the precipitated dicyclohexylurea is filtered off, the ether evaporated, and the residue recrystallized from chloroform/petroleum ether. M.p. 61–62°C; yield, 90%.

Adenosine triphosphate (*127*). Adenosine monophosphate (dihydrate) (0.766 gm) and phosphoric acid (2.32 gm, 85%) are dissolved in a mixture of pyridine (40 ml) and tri-*n*-butylamine (10 ml). Dicyclohexylcarbodiimide (20.6 gm) is added and the solution allowed to stand at 20°C for 46 hr. The dicyclohexylurea is then filtered off, washed with water, and the combined filtrates diluted to 100 ml. The aqueous solution is extracted three times with ether and the ether in turn washed with water. The combined aqueous solutions are evaporated *in vacuo* at 20°C, water (20 ml) again added and evaporated, and the residue then taken up in water (50 ml). Sixty per cent of the nucleotide present in this solution consists of ATP, which can be worked up with an ion-exchange column in the usual manner.

N-n-Butylcarbamyl O-phenyl phosphate (*136*). Triethylamine (5.05 gm) is added to a solution of monophenylphosphoric acid (8.70 gm) in acetonitrile (30 ml). *n*-Butyl isocyanate (4.95 gm) is then added, and the mixture becomes warm. Crystallization occurs on cooling, and after some time the product is filtered and washed with cold acetonitrile and ether. Yield, 33.4 gm (89.3%).

Preparation of P_1, P_2-diesters of pyrophosphoric acids (*138*). *n*-Butyl isocyanate (3 ml) is added to a monoester of phosphoric acid (0.01 mole) dissolved in pyridine (10 ml). The clear solution is maintained at either 50°C for 3–5 hr or room temperature for several days; the reaction can conveniently be followed by paper chromatography. Water (25 ml) and acetone (100 ml) are then added, followed by a slight excess over the calculated quantity of cyclohexylamine. The crude product is allowed to stand for a short time at 0°C, filtered, washed with acetone, and re-

crystallized from hot water containing pyridine. The yields of chromatographically pure compounds lie around 80%.

Propionylphosphoric acid diethyl ester (*69*). The enol phosphate of malonic ester is prepared first. A cooled solution of bromomalonic acid diethyl ester (9 gm) in twice its volume of ether is added dropwise to a stirred, ice-cooled solution of triethyl phosphite (6.2 gm) in twice its volume of ether. Care must be taken that any temperature rise be avoided. The ether is evaporated and the residue distilled under high vacuum, b.p. 124–126°C/0.05 mm, yield, 9 gm (82%). The enol phosphate (8 gm) thus obtained is treated with anhydrous propionic acid (2 gm), maintained at 37°C for 12 hr, and distilled under high vacuum, b.p. 68°C/0.05 mm; yield, 7 gm (63%).

*Carbamoylglycyl-*DL*-phenylalanine* (*145*). A mixture of carbamoylglycine (1.04 gm) in acetone (2 ml) and the enol phosphate (see above) (1.48 gm) is maintained at 70°C for 1 hr. On cooling benzene (2 ml) is added, and the mixture slowly added dropwise into a solution of phenylalanine (0.82 gm) and NaOH (0.2 gm) in water (2 ml). Phenolphthalein is added to the aqueous solution, followed by 2 *N* NaOH until the color disappears. The benzene layer is separated, and the aqueous phase carefully acidified with conc. HCl and the carbamoylpeptide recrystallized from water. Yield, 1.05 gm (61%); m.p. 160°C.

Monobenzylphosphoric acid (*152*). Benzyl alcohol (10 gm) and triethylamine (0.404 gm) are added to crystalline orthophosphoric acid (0.196 gm), followed by trichloroacetonitrile (1.44 gm), and the mixture is maintained for 4 hr at 75°C. The excess of acetonitrile is evaporated *in vacuo*, the residue taken up in water (20 ml), and the solution extracted twice with ether (15 ml portions) to remove the excess of benzyl alcohol. Cyclohexylamine (2 ml) is added and the solution evaporated to dryness under vacuum. The residue is dissolved in hot water (15 ml) and acetone added until a turbidity appears. The solution is allowed to crystallize and precipitation is finally completed by addition of acetone. Yield, 0.595 gm (76.5%). The salt can be converted into the free acid, m.p. 104–105°C by ion exchange.

If half the quantity of triethylamine (0.202 gm) is used, the other conditions being maintained constant, dibenzylphosphoric acid is the only product obtained. Yield, 0.360 gm (65%); m.p. 79°C.

Monophenylphosphoric acid imidazolide (*155*). Monophenylphosphoric acid (3.05 gm) is dissolved in a mixture of acetonitrile (3 ml) and benzene (10 ml), and carbonyldiimidazole (3.5 gm) added. The evolution of CO_2 is complete after 15 min at 20°C. The solution is then boiled for a short period, cooled, and finally cyclohexylamine (5 ml), water (0.2 ml), and ether (30 ml) added. The unreacted monophenylphosphoric

acid crystallizes out and is filtered off. The solution is concentrated under vacuum and the residual oil is taken up in acetone (50 ml) and treated with ether (50 ml). The cyclohexylammonium salt of monophenylphosphoric acid imidazolide (4.45 gm, 79%) crystallizes after 2 hr at 0°C, m.p. 115°C.

Diphenyl pyrophosphate (*155*). The cyclohexylammonium salt above (0.323 gm) is dissolved in dimethylformamide (3 ml), treated with monophenylphosphoric acid (0.175 gm) and pyridine (3 ml) and the mixture maintained at 100°C for 1 hr. Cyclohexylamine (1 ml) and acetone (10 ml) are then added, and the cyclohexylammonium salt of diphenyl pyrophosphate crystallizes out immediately. Yield, 0.521 gm (98.7%); m.p. 251°C.

Phosphoric acid monophenyl monomethyl ester (*155*). The above salt of monophenylphosphoric acid imidazolide (0.81 gm) is dissolved in methanol (5 ml), refluxed for 4 hr, concentrated, and taken up in acetone. The cyclohexylammonium salt of phosphoric acid phenyl methyl ester (0.117 gm, 74%) crystallizes out.

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Aromatic Compounds from Pyrylium Salts

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Introduction

The readily obtainable substituted pyrylium salts lend themselves to the preparation of numerous, often difficultly accessible, aromatic compounds of both the heterocyclic and isocyclic series. The first known example of these reactions is the formation of pyridine and pyridinium derivatives described by Baeyer. Another reaction of this kind is the formation of thiopyrylium salts reported by Wizinger. Especially numerous are the possibilities for the preparation of isocyclic aromatic compounds, whereby known phenols and alkylated amines together with new nitrocompounds, ketones, carboxylic acids, nitriles, phenol carboxylic acids, aminonitriles, or hydrocarbons of the benzene, naphthalene, and phenanthrene series can be prepared in generally good yield. The use of pyrylium salts as the starting materials for the preparation of azulenes is also possible.

In addition to a discussion of these reactions a survey of the methods available for the preparation of pyrylium salts will be given.

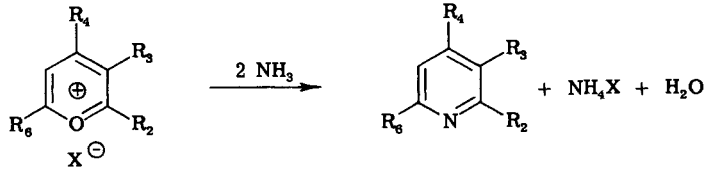
Conversion of Pyrylium Salts into Heterocyclic Compounds Possessing Aromatic Character

Derivatives of Pyridine

As found by Baeyer [*1*], the original worker in this field, pyrylium salts can readily be converted into pyridine derivatives by warming with an aqueous ammonium carbonate solution. Following the preparation by Baeyer and Piccard [*2*] of collidine (2a) and 2,6-dimethyl-4-phenylpyridine (2b) from 2,4,6-trimethylpyrylium perchlorate (1a) and 2,6-dimethyl-4-phenylpyrylium perchlorate (1b) respectively, this synthesis was extended to include other 2,4,6-tri-alkyl- and aryl-substituted pyrylium salts by Dilthey [*3*], Gastaldi [*4*], and others [*5*]. These reactions, however, served more to elucidate the constitution of the pyrylium salts, than in the preparation of specific pyridine derivatives. Nevertheless, a large number of difficultly accessible pyridine derivatives, e.g. 2,4,6-triphenylpyridine (2c) [*3a*], 2,3,4,6-tetraphenylpyridine (2d) [*3c*], pentaphenylpyridine [*3c*], or 1,4-bis-[3,5-diphenylpyridino(4)]benzene (2g)

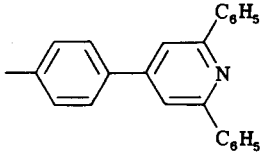
[*22*], can be obtained readily in this manner. The disubstituted 2,6-diphenylpyrylium perchlorate (1h) is also converted smoothly into 2,6-diphenylpyridine (2h) [*6*]; nucleophilic addition at C-2 (C-6) is preferred to that at C-4.

A summary of the preparative methods for pyridine derivatives is to be found in [*7*].



(1) (2)

(a) $R_2 = R_4 = R_6 = CH_3$; $R_3 = H$
(b) $R_2 = R_6 = CH_3$; $R_4 = C_6H_5$; $R_3 = H$
(c) $R_2 = R_4 = R_6 = C_6H_5$; $R_3 = H$
(d) $R_2 = R_4 = R_6 = R_3 = C_6H_5$
(e) $R_2 = R_6 = CH_3$; $R_4 = OCH_3$; $R_3 = H$
(f) $R_2 = R_6 = CH_3$; $R_4 = NHCH_3$; $R_3 = H$; $NCH_3 \cdot ClO_4$ instead of N in (2)

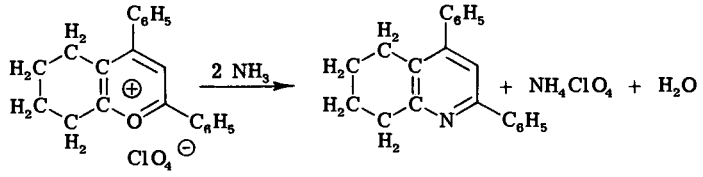
(g) $R_2 = R_6 = C_6H_5$; $R_3 = H$; $R_4 =$ 

(h) $R_2 = R_6 = C_6H_5$; $R_4 = R_3 = H$

The conversion of the pyrylium salts is almost always facile and quantitative; alcoholic ammonia is sometimes better suited than aqueous ammonium carbonate. As our own experiments [*8*] have shown, the reaction proceeds particularly favorably when the pyrylium salt is suspended in absolute *tert*-butanol, and dry ammonia passed through; warming effects solution of the salt, and the ammonium salt of the inorganic acid constituting the anion of the pyrylium salt (ammonium perchlorate or ammonium fluoborate) separates on cooling. The pyridine derivative which remains in solution often can be precipitated practically quantitatively by the addition of a little water.

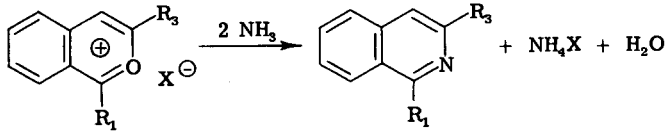
The conversion of pyrylium salts into pyridine derivatives fails when the heterocyclic oxygen atom of the pyrylium salt originates from a phenolic component. Hence neither chromylium nor xanthylium salts can be converted into quinoline or acridine derivatives. 2,4-Diphenyltetrahydrobenzopyrylium perchlorate (3), however, gives a quantitative yield of 2,4-diphenyltetrahydroquinoline (4), by treatment with ammonia in *tert*-butanol [*8*]. The conversion of 1,3-disubstituted iso-

chromylium salts (5b and c) into 1,3-disubstituted isoquinoline derivatives (6b and c) can be accomplished similarly [*8,9*].



(3) (4)

Unsubstituted isochromylium chloroferrate (5a), readily accessible from homophthalaldehyde, yields, like the aldehyde itself, isoquinoline with ammonia [*10*], respectively, N-substituted isoquinolinium compounds with primary aliphatic or aromatic amines [*11*].



(5) (6)

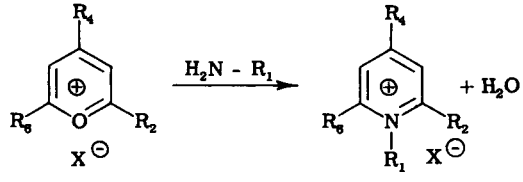
(a) $R_1 = R_3 = H$
(b) $R_1 = R_3 = CH_3$
(c) $R_1 = R_3 = C_6H_5$

Similarly, careful treatment of 2,6-dimethyl-4-methoxypyrylium perchlorate (1e) with aqueous ammonia yields 2,6-dimethyl-4-methoxypyridine (2e) [*1*]. According to Anker and Cook [*12*] the 4-methoxy, and to some extent also the 4-methylmercapto [*13*] group in the pyrylium salt, are sufficiently reactive to allow their replacement by other nucleophilic groups, such as alkoxy, alkylmercapto, alkylamino, or dialkylamino. The most diverse pyridine derivatives can accordingly be prepared by subsequent treatment with ammonia. If the methoxypyrylium salt (1e) is allowed to react with an excess of methylamine in methanol, both the heterocyclic oxygen atom and the methoxy group are replaced and 2,6-dimethyl-4-methylamino-N-methylpyridinium perchlorate (2f) is obtained on precipitation with perchloric acid.

Derivatives of Pyridinium Compounds

If 2,4,6-trisubstituted pyrylium salts (7) are allowed to react with primary aliphatic or aromatic amines instead of ammonia, the N-alkylated or N-arylated pyridinium salts (8a) are obtained. In this reaction too, the first examples were discovered by Baeyer and Piccard [*1,2*].

The method is exceptionally well suited to the synthesis of numerous pyridinium compounds, especially as it usually proceeds in excellent yield [*14*]. The only requirement is that the amine should not be too weakly basic. The simple aliphatic amines, such as methylamine, ethylamine, etc., can also be replaced by aromatic amines, such as aniline and its derivatives. Phenylhydrazine, α-methylphenylhydrazine [*15*], or semicarbazide [*16*] essentially react in similar fashion (to give 8b, c, d). Reaction with hydroxylamine yields pyridine oxides (8e), but only when the size of the α,α′-substituents is not excessive. Otherwise [e.g. with $CH(CH_3)_2$ and C_6H_5 in the α,α′-position] reduction occurs and the pyridine derivatives are obtained.

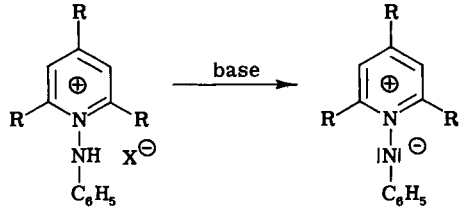


(7) (8)

R_2, R_4, R_6 = aliphatic and aromatic groups

(a) R_1 = alkyl or aryl, hydroxyaryl etc.
(b) $R_1 = NHC_6H_5$
(c) $R_1 = CH_3NC_6H_5$
(d) $R_1 = NHCONH_2$
(e) R_1 = OH

There exists thus far no other route for the preparation of the N—NH-arylpyridinium compounds (9) [*17*]. This class of compounds has been discovered as a result of the work of Schneider and co-workers [*15*], and is distinguished by a series of interesting reactions. With alkali they give strongly colored anhydro bases, which are to be regarded as $\overset{+}{N}—\overset{-}{N}$ betaines (10) [*18*], i.e. the heterocyclic pyridine nitrogen carries the positive, and the anilido nitrogen the negative charge.



(9) (10)

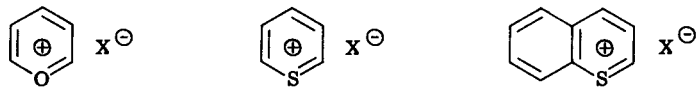
R = aryl or alkyl

Of especial interest are the N-hydroxyphenylpyridinium salts which are readily formed from pyrylium salts by reaction with aminophenols, and which can be converted into pyridinium-N-phenol betaines by the action of strong bases [*19*]. The compounds may also be considered phenologs of pyridine-N-oxide. By suitable substitution of the pyridine as well as the aminophenol it is possible to obtain stable betaines which have unusually large solvatochromic and thermochromic effects. They are especially useful for the measurement of the polarity of solvents [*20*]. The Z [*21*] or E_T values which are found in this way determine the polarity of the solvent much better than the dielectric constant.

The double conversion of a dipyrylocyanin dye (p. 371) into a dipyridiniumcyanine dyestuff is also possible. In a similar way the bis-pyrylium salt (p. 382) from terephthalaldehyde and acetophenone [*22*] with *p*-aminophenol and its derivatives give the bis-pyridinium-N-phenolbetaines [*23*].

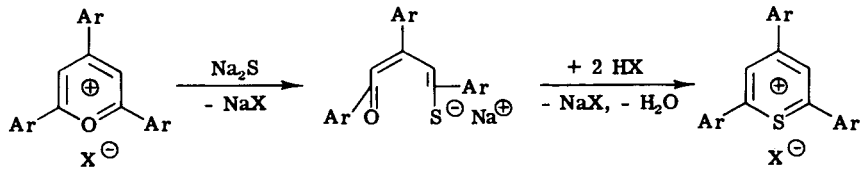
Derivatives of Thiopyrylium Compounds

While the unsubstituted pyrylium salt (11) is a rather unstable compound [*24*], the corresponding thiopyrylium salt (12) [*27*] is very stable and may be prepared readily by several different routes [*25*]. Its reactions, however, in contrast to those of benzothiopyrylium salts (13) [*26*] have hardly been investigated.



(11) (12) (13)

When treated with sodium sulfide in acetone, followed by precipitation with acid, 2,4,6-trisubstituted pyrylium salts (14) usually undergo replacement of the heterocyclic oxygen atom by sulfur to give the thiopyrylium salts (16) [*27*] within a few minutes. The presence of intermediates manifests itself by a blue coloration; Wizinger and Ulrich [*28*],

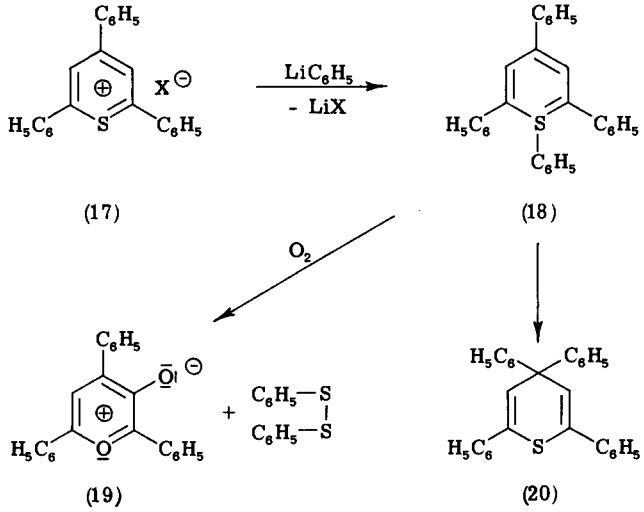


(14) (15) (16)

Ar = C_6H_5 or CH=CH—C_6H_5

the discoverers of this reaction, believe them to be the sodium salts of ketothioenols (15).

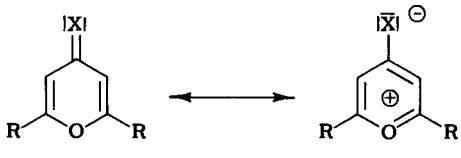
The reaction published by Suld and Price [*27*] between phenyl lithium and 2,4,6-triphenylthiopyrylium perchlorate (17) in ethereal solution at a low temperature and in the absence of light, gave a stable amorphous product with a purple color which was described as 1,2,4,6-tetraphenylthiobenzene (18). On passing oxygen through an ethereal solution of the compound an oxypyrylium salt (19) was formed as well as diphenyl disulfide. This salt (19) was also prepared by an independent synthesis from benzalacetophenone and ω-acetoxyacetophenone. The compound (18) was converted, in 25% yield, into the colorless 2,4,4,6-tetraphenylthiopyran (20) on being allowed to stand for a day.



Aliphatic Grignard compounds give deep-colored intermediates with (17) which are quickly converted into 2- or 4-thiopyran derivatives. An interesting rearrangement of compound (19) to 3,5,6-triphenyl-2-pyrone has recently been found [*28a*].

Derivatives of Pyridone and Thiopyridone from Pyrone Derivatives

4-Pyrones (21a) and, to an even greater extent, 2,6-alkyl-substituted 4-thiopyrones (21b) such as 2,6-dimethyl-4-thiopyrone, do not behave as true ketones or thioketones, but can be regarded as internal pyrylium salts (22a, b), i.e. they possess pseudoaromatic character [*29*]. They react in similar manner to pyrylium salts in a number of reactions.



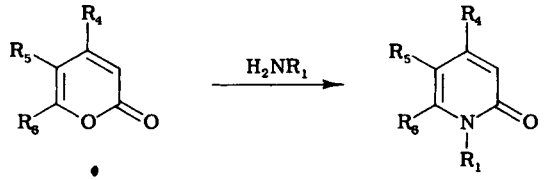
(21) (22)

(a) X = O
(b) X = S
R = aliphatic group

Ost [*30*] already had discovered that the heterocyclic oxygen in the substituted 4-pyrones (23) (such as meconic acid) can readily be replaced with ammonia or primary amines, to give pyridones or N-substituted pyridones (24), respectively. In a similar manner Von Pechmann [*31*] succeeded in converting a 2-pyrone [(25): $R_4=R_6=H$, $R_5=COOH$, coumalic acid] into the 2-pyridone or 2-hydroxypyridine derivative (26).



(23) (24)

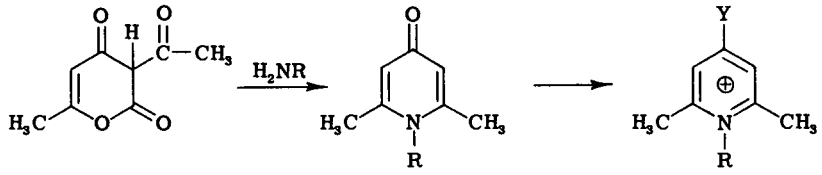


(25) (26)

$R_4 = R_6 = H$,
$R_5 = COOH$, coumalic acid

Numerous syntheses of pyridones and N-substituted pyridones from pyrones and ammonia or the most varied primary aliphatic amines, respectively, have since been described [*32*]. The reactions are readily accomplished by the mere treatment of the pyrone derivative with aqueous ammonia or aqueous alkylamine solutions. More complicated pyrones, such as naphthopyrones, often react in another way [*33*].

Dehydroacetic acid (27) readily reacts both on warming with ammonia and with methylamine in an autoclave to give lutidone (28a) and N-methyllutidone (28b) [*34*], respectively. An analogous N-phenyllutidone (28c) synthesis using aniline affords a yield of over 90% when the reactants are boiled for 2 hr under reflux in the presence of a little more than the equivalent amount of hydrochloric acid. 2,6-Dimethyl-4-pyrone [(23): $R_1 = R_2 = CH_3$] itself does not react with aniline under these conditions [*35*]. The unsubstituted 4-pyrone, on the other hand, initially reacts with aniline to give the dianilido derivative, and the action of acid on the latter results in the formation of N-phenylpyridone [*36*]. The reaction can also be carried out in a single operation by boiling with aniline/hydrochloric acid [*35*]. These reactions, unlike those with pyrylium salts, consequently require no protection by substituents in the 2,6- or 2,4-positions of the 4- or 2-pyrone, respectively. More conversions of this kind, of pyrones into pyridones, have recently been described by Hünig and Köbrich [*35*].

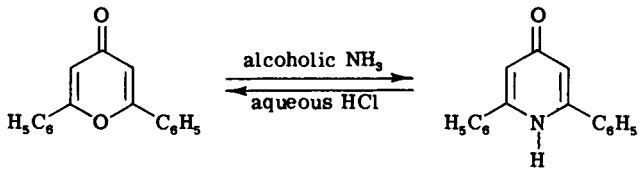


(27) (28) (29)

(a) R = H
(b) R = CH_3
(c) R = C_6H_5

Y = OR′ or halogen

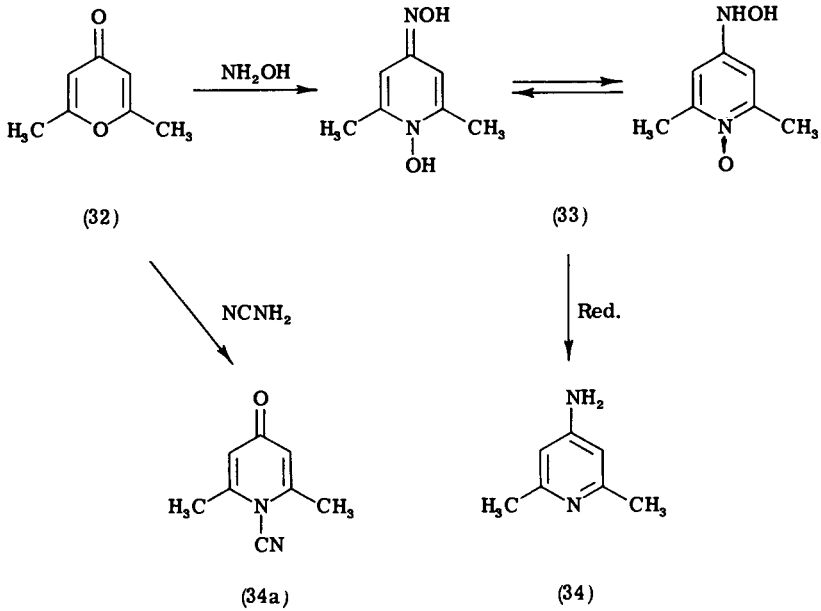
2,6-Diphenyl-4-pyrone (30) cannot be converted into the pyridone derivative either with aqueous ammonium acetate or with aniline acetate, even if the reaction is attempted at 0°C [*37*]. The conversion can, however, readily be accomplished with alcoholic ammonia. But since 2,6-diphenyl-4-pyridone is almost instantaneously reconverted into 2,6-diphenyl-4-pyrone in the presence of a trace of hydrochloric acid [*38*], it is possible that the previous observation was the result of inadequate precautions in the work-up.



(30) (31)

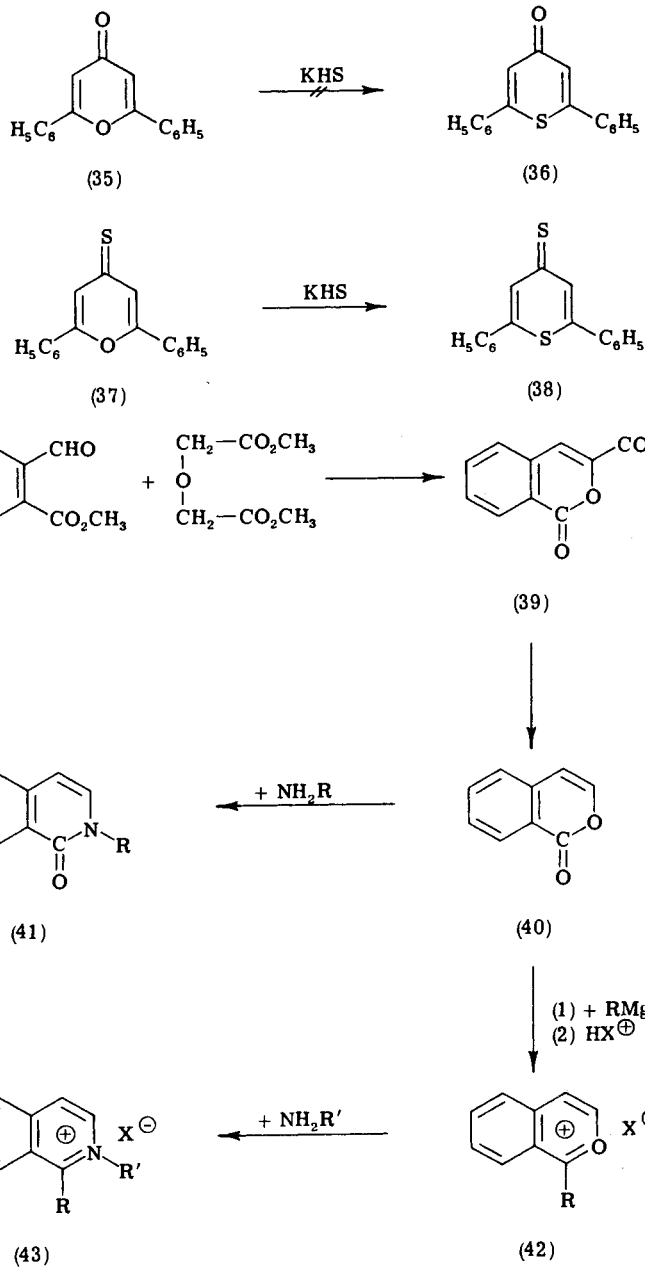
The N-alkyl- and N-arylpyridones constitute valuable intermediates for the preparation of numerous pyridinium compounds, since alkylation or halogenation yields reactive intermediates (29); these [cf. the methoxypyrylium salts (1e)] readily exchange the *p*-alkoxy group or halogen by other nucleophilic groups [*38*].

In the presence of alcoholic hydroxylamine, 2,6-diphenyl-4-pyrone gives N-hydroxy-2,6-diphenylpyridone [*37, 39*]. 2,6-Dimethyl-4-pyrone (32) forms 4-hydroxylamino-2,6-dimethylpyridine-N-oxide (33) which on catalytic hydrogenation gives 2,6-dimethyl-4-aminopyridine (34) [*40*]. Cyanamide reacts with 4-pyrones in aqueous ethanol (1:1) to give N-cyanopyridones in 70–80% yield (34a) [*41*]. For the reactions of 2-pyrone with sodium cyanide which lead to ring-opening see Vogel [*42*].



Pyrones can also be converted into thiapyrones by an essentially similar method [*43*]. The heterocyclic oxygen atom in 2,6-diphenyl-4-pyrone (35) is replaced by sulfur (albeit in traces only) to give (36) by the action of boiling alcoholic potassium hydrogen sulfide. 2,6-Diphenyl-4-thiopyrone (37), on the other hand, reacts more readily and affords 2,6-diphenyldithiopyrone (38) in approximately 50% yield [*45*].

The recent publication of a synthesis for the ready preparation of isocoumarin (40) by the decarboxylation of isocoumarin-3-carboxylic acid (39), obtained as a condensation product from dimethyl diglycolate and methylphthalaldehydate [*46*], allows a similar reaction with ammonia



(35) (36)

(37) (38)

(39)

(41) (40)

(43) (42)

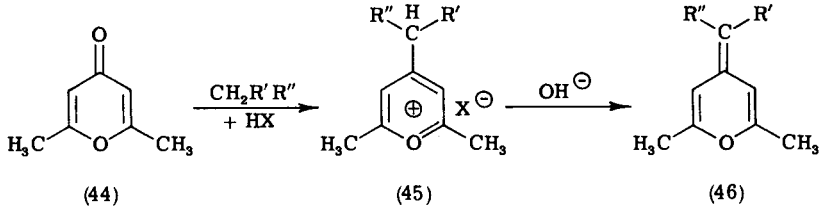
(a) R = H
(b) R = alkyl or aryl

and primary amines to give isoquinolones (41). With Grignard reagents and acids 1-substituted isochromylium salts (42) are formed, which with ammonia or amines can be converted into isoquinolines or isoquinolinium salts (43a and b). The reaction allows a wide range of substituted isoquinoline compounds to be formed, since both the isocoumarin and the compound which contains the nitrogen atom can carry new substituents.

Derivatives of Dihydropyridines and Thiopyrans

4H-4-Dehydropyrans

The carbonyl group of the 4-pyrones (44) can react with nucleophilic reagents, though its reactivity is relatively small. Thus, from 4-pyrones and compounds which contain an acidic CH group, such as malononitrile, in toluene or glacial acetic acid and acetic anhydride solution Woods [*47*] obtained pyrylium salts (45) which with alkali readily split out the proton in the α-position to the pyrylium ring to give 4H-4-dehydropyrans (46).

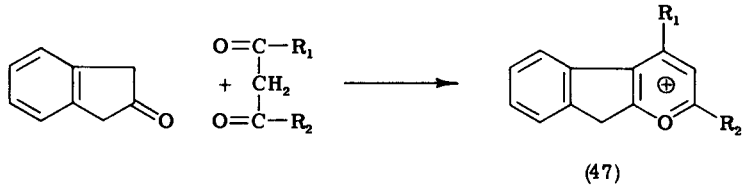


(44) (45) (46)

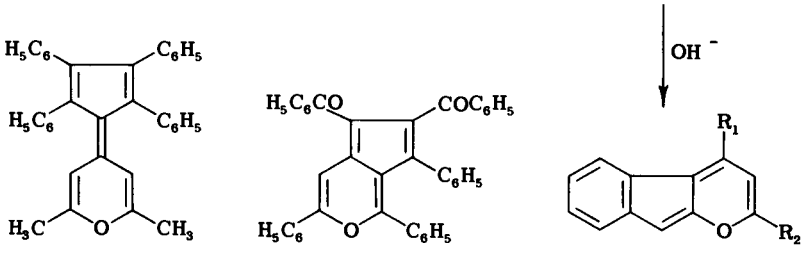
R' = R'' = CN

Similar reactions were carried out by Ohta and Kato [*48*], Eiden [*49*] and Wizinger [*50*]. Malonic ester, acetylacetone, cyclopentadiene, and nitromethane failed to give this reaction. The colored bases (48) recently obtained from a reaction between hydrindanone and 1,3-dicarbonyl compounds by Schroth and Fischer [*51*] also belong to this series of dehydropyrans; with acids they yield the indenopyrylium salts (47). The pyrancyclopentadiene compounds (48a, 48b) are very similar pyrane/pyrylium derivatives [*52*].

By the reaction of 2,6-diphenyl-4-thiopyrone (49) and diphenyl diazomethane Schönberg [*53*] obtained, by way of an intermediate product, 2,6-diphenyl-4-(α,α-diphenylmethylene)pyran (50). Reaction of the thiopyrone (49) with diazomethane and the subsequent removal of the sulfur with phenyl lithium leads to the very stable pyran derivative (51) [*53, 54*]; this compound is also obtained if the thiopyrone is heated to 230°. A further method for the preparation of the dipyranilidene is

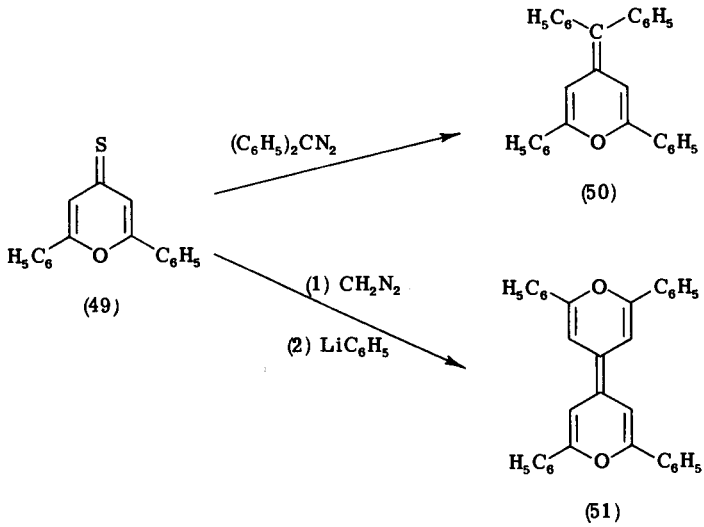


(47)



(48a) (48b) (48)

by the reaction of 4-thiopyrones with copper-bronze in refluxing toluene [*55*].

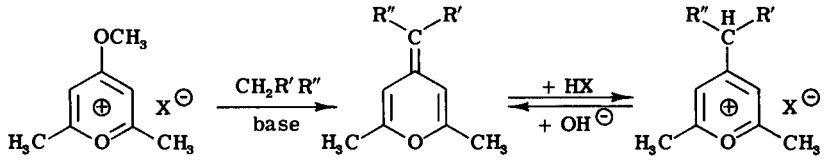


(49) (50) (51)

The reaction of 2,6-dimethyl-4-pyrone and diphenylketene gives 2,6-dimethyl-4-(α,α-diphenylmethylene)pyran [*56*].

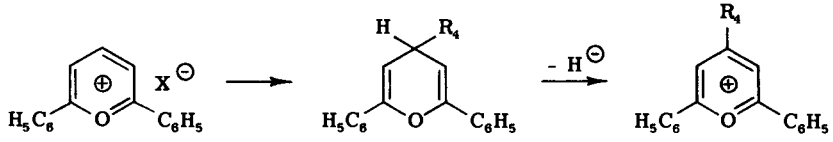
4-Methoxy-2,6-dimethylpyrylium perchlorate (52) can also be used as the starting material for the preparation of compounds of type (45) and (46). According to Ohta and Kato [*48*] the methoxyl group is so

reactive that it can enter into a reaction with the active CH group in such compounds as malononitrile, cyanoacetic ester, etc. In this method the reactants are warmed together in *tert*-butanol with sodium *tert*-butoxide, whereby the 4H-dehydro-4-pyrans (53) are formed, which with acids are converted into pyrylium salts (54).



4H-Pyrans Which Still Contain a Hydrogen Atom at C-4

4H-Pyrans which still contain a hydrogen atom at C-4 are prepared from 2,6-disubstituted pyrylium salts by the addition of nucleophilic reagents. The readily accessible 2,6-diphenylpyrylium perchlorate (see Experimental Section) always reacts at C-4. Only its reaction with ammonia is an exception to this [see structure (1h)]. In the presence of potassium *tert*-butoxide the anions formed from acetylacetone, cyanoacetic acid, benzoylacetone, and nitromethane, etc., react with (55) to form the 4H-pyrans (56a–d) [*57, 58*]. With Grignard reagents in ethereal solution, the pyrylium salt (55) may be substituted with a variety of aliphatic and aromatic groups to give the 4H-pyrans (56e–h) in yields of up to 80% [*59, 60*].



(a) $R_4 = CH(COCH_3)_2$
(b) $R_4 = CH(CN)(CO_2CH_3)$
(c) $R_4 = CH(COC_6H_5)_2$
(d) $R_4 = CH_2—NO_2$
(e) $R_4 = CH_3$
(f) $R_4 = CH(CH_3)_2$
(g) $R_4 = CH_2C_6H_5$
(h) $R_4 = C_6H_{11}$
(i) $R_4 = C(CH_3)_3$
(j) $R_4 = C_6H_5$
(k) $R_4 = CH_2—CH(CH_3)_2$ (only 57)

Such 4H-pyrans are also obtained from 2,4,6-trisubstituted pyrylium salts (together with a mixture of dienones) by the addition of a hydride ion from sodium borohydride to the C-4 position [*61*].

The nonsubstituted 4H-pyran (74) is itself a sensitive compound. It

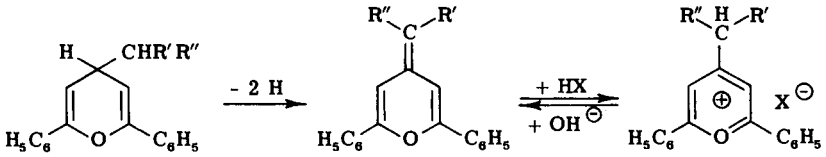
was prepared by the reaction of glutaraldehyde with hydrogen chloride to form 2,6-dichlorotetrahydropyran which splits out two moles of hydrogen chloride; 2-chloro-3,4-dihydro-2H-pyran was an intermediate product [*62*]. By rapid experimental and distillation procedures the pure pyran is obtained in 40% yield [*63*]. The pyrolysis of 2-acetoxy-3,4-dihydro-2H-pyran has been shown by Masamune and Castellucci [*64*] to give the compound, but since it was produced in only small quantities and not actually isolated, the method is not a preparative one.

Substituted 4H-pyrans of the type (56) give a series of interesting reactions.

(1) With strong acids the R_4 substituent on C-4 is replaced when it is capable of forming an enolizable and mesomeric stablized anion; this is the case of the compounds (56a–d). Simultaneously the 2,6-diphenylpyrylium salt is formed.

(2) When the substituent is tightly held, as in compounds (56e–j), the hydrogen atom at C-4 is split off and appears to be transferred to another molecule of the pyran, solvent, or cation, etc. Although the reaction is often successful with strong acids alone (e.g., with perchloric or fluoboric acids) it goes better in the presence of ferric chloride in glacial acetic acid. In this way numerous, otherwise difficultly accessible, 2,6-diphenylpyrylium salts substituted in the 4-position with alkyl or aryl substituents can be obtained; the yields can be as high as 70% [*59, 60*]. The unsubstituted pyrane (74), by triphenylcarboniumfluoborate, gives pyrylium fluoborate in a very convenient manner with a yield of 90% [*27*].

(3) Through the dehydrogenation of 4H-pyrans (58a–e), 4-dehydro-4H-pyrans (59a–e) can be obtained. The dehydrogenation can be carried out by shaking a benzene solution of the compound with alkaline ferricyanide, together with a 5–10% molar concentration of 2,4,6-triphenylphenol as a hydrogen carrier; the yields of product are on the order of 65–85% [*59*].



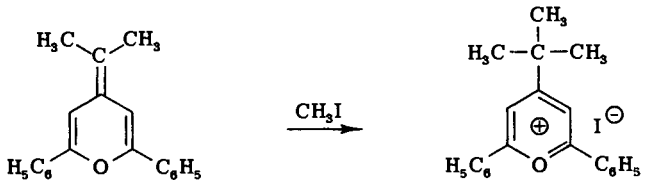
(58) (59) (60)

(a) R′ = $COCH_3$ R″ = $COCH_3$
(b) R′ = COC_6H_5 R″ = COC_6H_5
(c) R′ = NO_2 R″ = H
(d) R′ = C_6H_5 R″ = H
(e) R′ = CH_3 R″ = CH_3
(f) R′ = R″ = C_6H_{11}

The yield of product is poor when potassium permanganate in cold N,N-dimethylformamide is used, a reagent described by Kröhnke [*58*] for similar dehydrogenations in the flavene series. Spontaneous dehydrogenation of (58b) occurs on crystallization of this compound from glacial acetic acid.

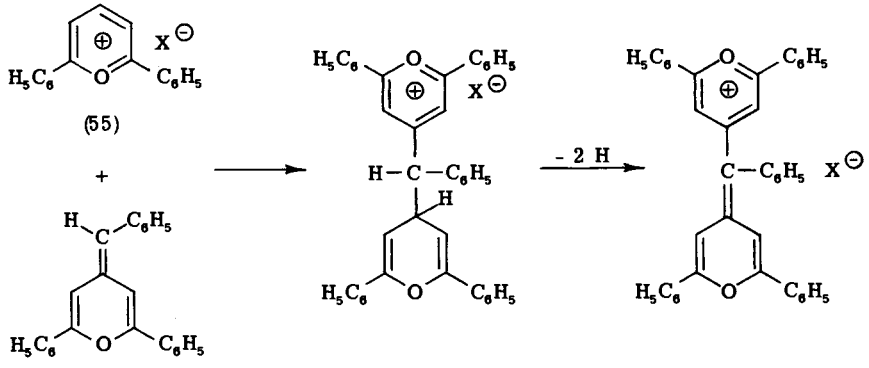
All 4-dehydro-4H-pyrans (59) form pyrylium salts (60) on treatment with acids; with bases the reverse reaction occurs and it is especially easy when R′ and R″ are electron-withdrawing substituents. Numerous 4-alkylated-4H-pyrans and alkyl-substituted pyrylium salts can be formed in this way.

Instead of protons, carbonium ions may be added, but in this case the reaction is not reversible: 2,6-Diphenyl-4-isopropylidene-4H-pyran (61) gives 2,6-diphenyl-4-*tert*-butylpyrylium iodide (62) on heating with methyl iodide [*62*]. This pyrylium salt (62) is also accessible from (55) and $(CH_3)_3CMgCl$ [*65*] (see reaction 56i → 57i).



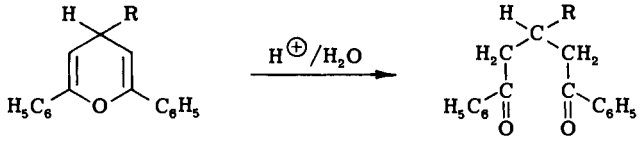
(61) (62)

The course of the reaction between 2,6-diphenyl-4-benzylidene-4H-pyran (63) and 2,6-diphenylpyrylium perchlorate (55) is very similar. In methylene chloride the pyran derivative (64) is smoothly formed and undergoes dehydrogenation to give the dipyrylocyanine dyestuff (65). The yield is better if chloranil is added as a dehydrogenation agent; the yields in these latter experiments are of the order of 75% [*66*]. Pyrylocyanines were first prepared by Wizinger and Riester [*67*].



(55) (63) (64) (65)

(4) By the hydrolysis of 4H-pyrans (e.g. 66a–o) with 25% hydrochloric acid, the heterocyclic ring is opened and 1,5-diketones (67a–d) are obtained [*60, 66*]. It is noteworthy that with the nitromethyl compound (66a) the CH_2NO_2 group is not split off under these conditions.



(66) (67)

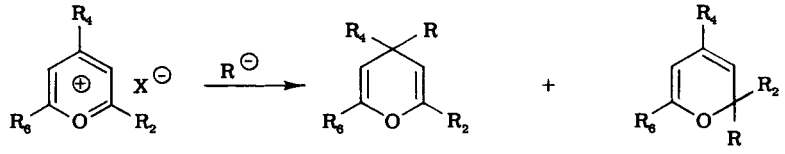
(a) R = CH_2NO_2
(b) R = CH_3
(c) R = $CH(CH_3)_2$
(d) R = CH_2—C_6H_5

2,6-Diphenylpyrone is hydrolyzed, though in alkaline solution, to give 1,3-diphenylpentan-1,3,5-trione [*68*].

1,5-Diketones react with alcoholic ammonia or with ammonium acetate in glacial acetic acid to give pyridine derivatives by dehydrogenation or by splitting out of an appropriate substituent [*69, 70*]. These reactions correspond to the usual synthesis employed for the preparation of pyridine derivatives, although generally the 1,5-dicarbonyl compounds are not isolated [*66*].

4,4-Disubstituted 4H-Pyrans

Through the addition of nucleophilic reagents to 2,4,6-trisubstituted pyrylium salts (68) [in addition to the 2,2-disubstituted 2H-pyrans (70) and their series of products] 4,4-disubstituted 4H-pyrans (69) are obtained.



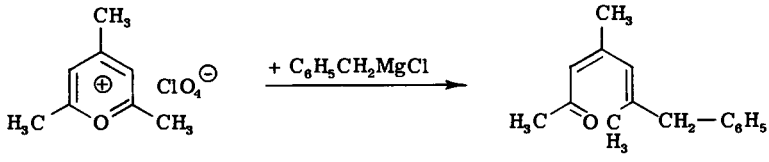
(68) (69) (70)

These reactions are dealt with more fully on pages 391 and 392.

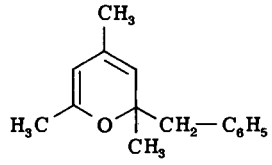
Although these pyrans generally react differently from the monosubstituted 4H-pyrans (66), they also are hydrolyzed to 1,5-diketones with aqueous alcoholic hydrochloric acid [*59, 66*]. In this way 2,6-diphenyl-4-phenyl-4-benzyl-4H-pyran (69, $R_2 = R_4 = R_6 = C_6H_5$, $R = CH_2$-C_6H_5)

is smoothly converted into 3-benzyl-1,3,5-triphenylpentan-1,5-dione.

By the acid hydrolysis of the addition product formed from benzyl magnesium chloride and 2,4,6-trimethylpyrylium perchlorate (71), we obtained the doubly unsaturated ketone (72) but no 1,5-diketone [*66*]. The addition product of benzyl magnesium chloride and 2,4-diphenyl-6-*tert*-butylpyrylium perchlorate behaved similarly; on reaction with an ethereal solution of hydrogen chloride it gave the pyrylium salt (2,4-diphenyl-6-*tert*-butylpyrylium chloride) together with 10% of an unsaturated ketone [*65*]. By the careful reaction of Grignard compounds such as phenyl magnesium bromide with 2,4,6-trimethyl and other aliphatically substituted pyrylium salts (71), Köbrich [*71*] isolated compounds of the type (73) which he considered were valence tautomers of the unsaturated ketones of type (72).



(71) (72)

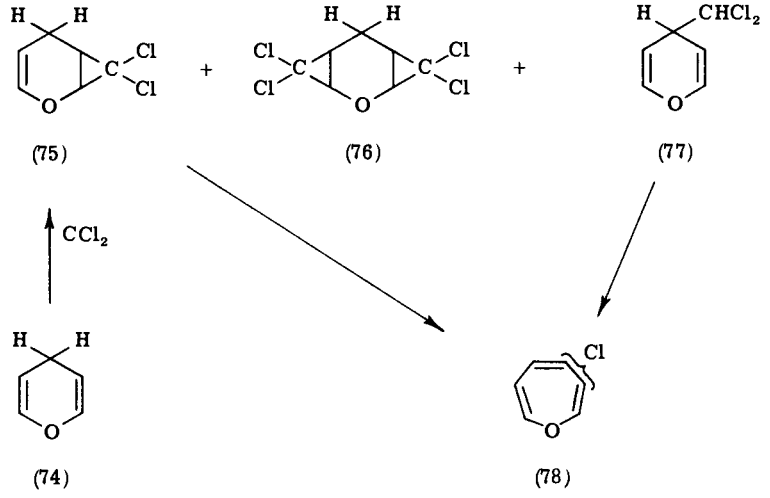


(73)

From the final products obtained in these experiments it is not possible to say with certainty whether the initial product is a 2H- or a 4H-pyran or an unsaturated ketone of the type (72), since it is not inconceivable that during the course of the reaction, hydrolysis followed by rearrangement occurs. The situation is similar to the reaction products of Grignard compounds with 2-pyrones according to Gompper [*72*].

The reactions of 4-mono- and disubstituted 4H-pyrans with dihalogenocarbenes by the addition of CCl_2 or CBr_2 to the double bond are now considered. The 4H-pyran (74) adds one molecule of the dihalogenocarbene to give (75) and with an excess of the dichlorocarbene two CCl_2 radicals add to give (76). In addition, compound (77) is formed through

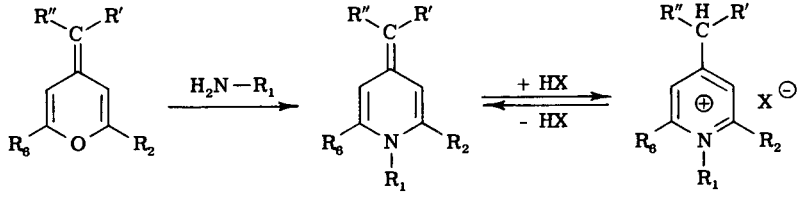
an insertion mechanism from compound (74). By careful thermal catalytic dehydrohalogenation of (77) instead of the rather unstable chloroxepin (78) 4-chloromethylenepyran was formed [73].



(75) (76) (77) (74) (78)

Pyridine Derivatives from 4H-Pyrans

4-Dehydro-4H-pyrans (79) react with primary amines to form N-alkyl-4-methylenedihydropyridine derivatives (80).



(79) (80) (81)

R′ or R″ = CN, COR, CO_2R, NO_2, etc.
$R_2 = R_6 = C_6H_5$ or CH_3
R_1 = alkyl, aryl, NH_2, and H

This reaction to prepare 4-alkylidene-1,4-dihydropyridine derivatives was discovered at almost the same time by Wolf [59], Kato and his co-workers [74], and Eiden [49]. It is of importance since, in contrast to 4-pyrones, 4-pyridones fail to condense with compounds which contain an acidic CH group. Reactions take place with aliphatic and aromatic primary amines and also with hydrazine or with formamide: in the last case the reaction gives the pyridine derivative (82) and not the N-substituted pyridinium salt.



(79) (82)

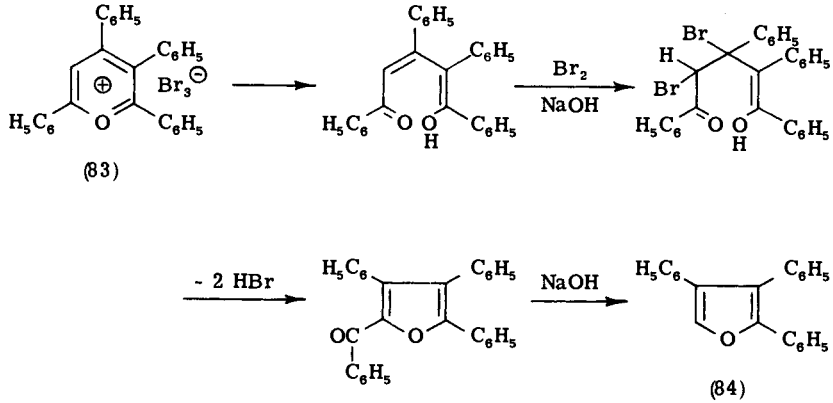
For all these reactions the 4-dehydro-4H-pyrans (79) have to be substituted with electron-withdrawing groups (R′ and R″); alkyl-substituted compounds on treatment with primary amines remain unchanged. The reactions of 4H-pyrans which still have one or two hydrogens present at C-4 do not seem to have been investigated. Although it has yet to be proved it seems possible that the heterocyclic ring is also formed by the reaction of the amines either with a 1,5-diketone (67) or with a doubly unsaturated ketone of type (72).

Thiopyrans

The 4H-thiopyran which is obtained by the action of H_2S and HCl on glutaraldehyde in methylene chloride seem considerably more stable than the 4H-pyran. 4H- and 2H-thiopyrans also are formed by the action of Grignard reagents on thiopyrylium salts [*75*]; in these reactions it is difficult to predict whether the addition will take place at C-2 or C-4.

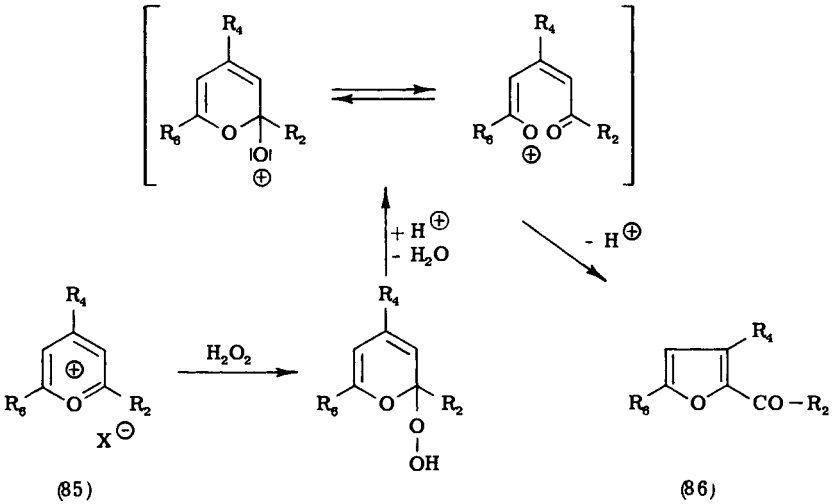
Derivatives of Furans

Dilthey [*76*] observed that 2,3,4,6-tetraphenylpyrylium perbromide (83) gave 2,3,4-triphenyl-5-benzoylfuran on hydrolysis and that this compound formed 2,3,4-triphenylfuran (84) in the presence of alkali. The course of the reaction can be illustrated as follows:



In a similar way, pentaphenylpyrylium salt with alkali gives, by way of the pseudobase or similar products, tetraphenylfuran [77].

According to Balaban and Nenitzescu [78] alkyl-substituted pyrylium salts form furan derivatives on reaction with hydrogen peroxide. The reaction is assumed by them to take place by the following path*:



(85) (86)

Examples of Furans (86)

$R_2 = R_6$	R_4
(a) CH_3	CH_3
(b) CH_3	C_2H_5
(c) C_2H_5	CH_3
(d) CH_3	$CH(CH_3)_2$
(e) $CH(CH_3)_2$	CH_3

The reaction takes place with pyrylium salts having different groups present (85a–e); with (85a) the yield is approximately 45%. In the light of these investigations the reactions of aryl-substituted pyrylium salts which Dilthey [79] has described may well stand further examination.

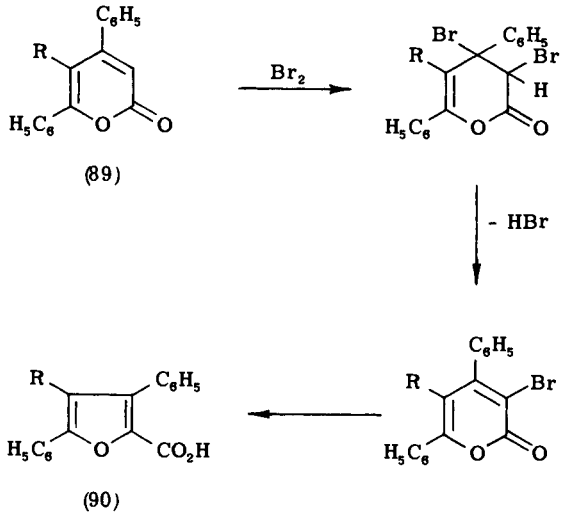
Pyrones can also be converted into furan derivatives. The investigations by F. Feist [80] of the conversion of bromocoumalic acid (87) into furan-2,4-dicarboxylic acid (88) by alkali have long been known.



(87) (88)

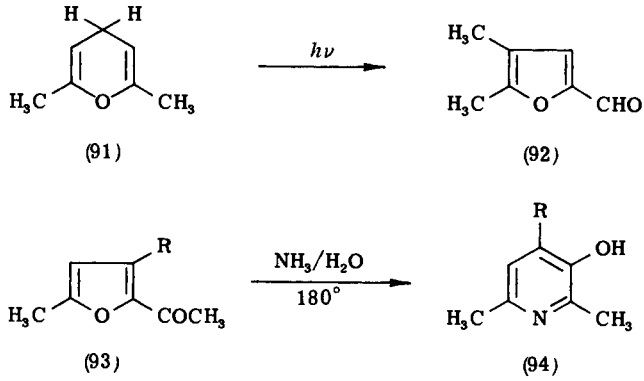
* A further possible mechanism is discussed on pages 404 and 405.

In a similar manner the rearrangement of a C-5-substituted 4,6-diphenyl-2-pyrone (89) with bromine and alcoholic alkali gives a 4-substituted 3,5-diphenylfuran carboxylic acid (90) [*81*].



The thermal rearrangement of 3,4,5,6-tetrachloro-2H-pyrone into 3,4,5-trichlorofuran-1-carboxylic acid chloride [*82*] has been described by Roedig and Märkl [*83*].

Also of interest in this connection is the photochemical conversion, in quite dilute solution (0.02% aqueous solution), of 2,6-dimethyl-4H-pyran (91) into both the four-membered ring dimer and 2,3-dimethyl-furan-5-aldehyde (92) in a 1% yield [*84*].



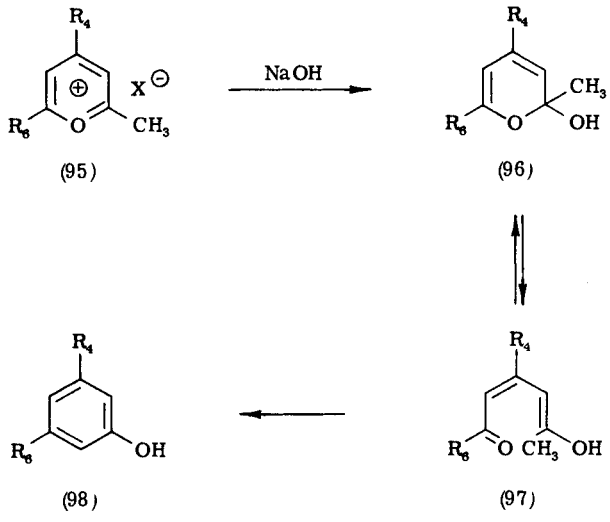
The reverse reaction in which furan-2-acyl derivatives are converted into pyridine derivatives is also known. An example of this is the con-

version of 2,4-dimethyl-5-acetylfuran (93, R=CH_3), with aqueous ammonia at 180°C in an autoclave, into 2,4,6-trimethyl-3-hydroxypyridine [*85*] (94, R=CH_3); the yield for the reaction is 75%.

Conversion of Pyrylium Salts into Benzene Derivatives

PHENOLS

2,4,6-Trisubstituted pyrylium salts containing a methyl group in the 2- or 4-positions yield 3,5-substituted phenols on boiling with 10% sodium hydroxide solution. The reaction was discovered by Baeyer and Piccard [*2*], who obtained *sym*-xylenol (98a) from 2,4,6-trimethylpyrylium perchlorate (95a). The pseudobase (96) may be formed first, and undergoes an irreversible phenol ring closure via the tautomeric ketone (97) to give (98). 2,6-Dimethyl-4-phenylpyrylium perchlorate (95b) yields 3-methyl-5-phenylphenol (98b); the 2,6-dimethyl-4-ethylpyrylium salt gives 3-methyl-5-ethylphenol, and so on. 2,6-Diethyl-4-methylpyrylium perchlorate yields 2,5-dimethyl-3-ethylphenol [*16*].

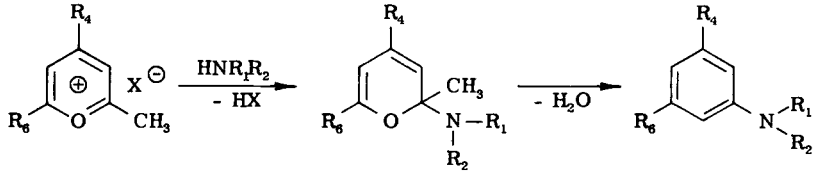


(a) $R_4 = R_6 = CH_3$
(b) $R_4 = C_6H_5$; $R_6 = CH_3$

This reaction is of interest in relation to the synthesis of *m*- and higher substituted phenols. Pyrylium salts with a phenyl group in the 6-position however, cannot be converted into phenyl-substituted phenols in this manner; they decompose in aqueous alkali and the benzoic acid fragment is eliminated [*16*].

Alkylated Amines

Diels and Alder [*86*] allowed an ethereal solution of secondary amines such as dimethylamine or piperidine to react in the cold with an ethereal suspension of 2,4,6-trimethylpyrylium perchlorate (95a) and other 2-methyl-substituted pyrylium salts (95c and d). A vigorous reaction ensues, and N-dimethyl-*sym*-*m*-xylidine (100a) and other *m*-substituted N-dimethyl- or N-pentamethyleneanilines (100c and d) are obtained via intermediates, (99), which are not isolated. The yields amount to approximately 65%. Scarcely any attention has thus far been paid to this



(95) (99) (100)

$R_1 = R_2 = CH_3$ or $(CH_2)_5$; $X^{\ominus} = ClO_4^{\ominus}$

(a) $R_4 = R_6 = CH_3$

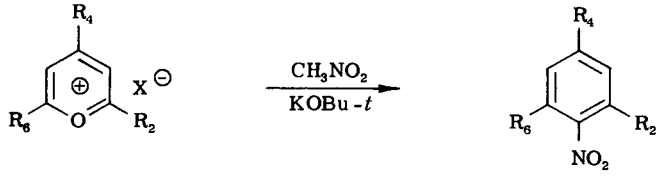
(b) $R_4 = C_6H_4CH_3(4)$; $R_6 = CH_3$

(c) $R_4 = C_6H_3(CH_3)_2(3,4)$; $R_6 = CH_3$

reaction, though it may be of considerable interest with respect to the synthesis of certain aromatic tertiary amines.

Nitro Compounds

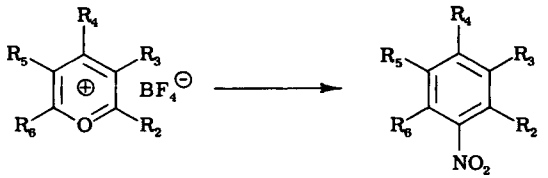
A reaction capable of widespread application was discovered in our laboratory in 1956 by Bräuniger and Neubauer [*87*]; it consists in the conversion of 2,4,6-trisubstituted pyrylium salts (101) into 2,4,6-trisubstituted nitrobenzene derivatives (102) by the action of nitromethane in the presence of alkoxide, and gives yields of 45–90%. The simplest procedure consists in suspending the pyrylium salt together with 1 mole of nitromethane in *tert*-butanol, adding 2 equivalents of potassium *tert*-butoxide, and warming for some time.



(101) (102)

R_2, R_4, R_6 = alkyl or aryl

TABLE 1
NITRO COMPOUNDS (104) FROM PYRYLIUM SALTS (103)

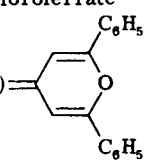


(103) (104)

R_2	R_3	R_4	R_5	R_6	Pyrylium fluoborate M.p. (°C)	Nitro compound M.p. (°C)	Yield (%)	Reference
CH_3	H	CH_3	H	CH_3	242 (dec.)[a]	41–42	72	[87]
CH_3	H	C_6H_5	H	C_6H_5	175[a]	96–97	48	[87]
$C(CH_3)_3$	H	C_6H_5	H	C_6H_5	253–256	96–97	44	[87]
C_6H_5	H	C_6H_5	H	C_6H_5	214–215	144–145	85	[87]
$CH(CH_3)_2$	H	C_6H_5	H	C_6H_5	247–257[c]	91.5–92	57	[60]
C_6H_5	H	CH_2—$CH(CH_3)_2$	H	C_6H_5	204–206[c]	126–127	38	[60]
C_6H_5	H	$C(CH_3)_3$	H	C_6H_5	231–234[c]	190–191	87	[65]
C_6H_5	H	C_6H_{11}	H	C_6H_5	219–223[a]	202–204	25	[60]
C_6H_5	H	R[b]	H	C_6H_5	298–302[c]	222–225	73	[66]
C_6H_5	H	$C_6H_4NO_2(4)$	H	C_6H_5	296–298[c]	166–167	55	[60]
C_6H_5	H	C_6H_5	H	$C_6H_4CH_3(4)$	215–218	126–127	58	[87]
$C_6H_4CH_3(4)$	H	C_6H_5	H	$C_6H_4CH_3(4)$	228–233	140–141.5	56	[87]
$C_6H_4Cl(4)$	H	C_6H_5	H	C_6H_5	219–221	164–164.5	72	[87]
$C_6H_4Br(4)$	H	C_6H_5	H	C_6H_5	220–225	157–157.5	64	[87]
$C_6H_4Br(3)$	H	C_6H_5	H	C_6H_5	211–226	136–137	80	[90]
$C_6H_4Br(2)$	H	C_6H_5	H	C_6H_5	190–195	110–112(82)	—	[90]

C_6H_5	H	$C_6H_4Br(4)$	H	C_6H_5	270–275	142	55	[91]
C_6H_5	H	$C_6H_4Br(3)$	H	C_6H_5	205–217	155–156	75	[90]
C_6H_5	H	$C_6H_4Br(2)$	H	C_6H_5	182–208	243–243.5	73	[90]
$C_6H_4Cl(4)$	H	C_6H_5	H	$C_6H_4Cl(4)$	257–275	179	62	[92]
$C_6H_4CH_3(4)$	H	$C_6H_4CH_3(4)$	H	$C_6H_4CH_3(4)$	~200	136–138	57	[93]
$C_6H_4Cl(4)$	H	$C_6H_4Cl(4)$	H	$C_6H_4Cl(4)$	190–210	205–207	71	[93]
C_6H_5	H	$C_6H_4OCH_3(4)$	H	C_6H_5	235–236	120–122	53	[97]
C_6H_5	H	$C_6H_4N(CH_3)_2(4)$	H	C_6H_5	Over 300°[a]	160–161	55	[89]
$C_6H_4OCH_3(4)$	H	C_6H_5	H	C_6H_5	207–209	119–120	88	[97]
$C_6H_4OCH_3(4)$	H	$C_6H_4OCH_3(4)$	H	C_6H_5	243–245	115–116	33	[87]
$C_6H_4OCH_3(4)$	H	C_6H_5	H	$C_6H_4OCH_3(4)$	262–263	150	67	[87]
$C_6H_4OCH_3(4)$	H	$C_6H_4OCH_3(4)$	H	$C_6H_4OCH_3(4)$	303–305	124–126	60	[87]
CH_3	H	C_6H_5	H	CH_3	217–220°[c]	49	89	[88]
C_6H_5	C_6H_5	C_6H_5	H	C_6H_5	230–233	221	72	[88]
C_6H_5	C_6H_5	C_6H_5	C_6H_5	C_6H_5	278–281	292	63	[88]
C_6H_5	H	C_6H_5	$CH_2—CH_2$	$—CH_2—CH_2$	207–208	165	45	[8]
CH_3	H	OCH_3	H	CH_3	195–196°[c]	50	62	[88]
CH_3	H	SCH_3	H	CH_3	174–175°[c]	62	42	[48]
$C_6H_5—C_6H_4$	H	C_6H_5	H	C_6H_5	225–238	189–190	76	[94]
$C_6H_5—C_6H_4$	H	C_6H_5	H	$C_6H_5—C_6H_4$	240–252	264–265	77	[94]
$C_6H_5—C_6H_4$	H	$C_6H_5—C_6H_4$	H	$C_6H_5—C_6H_4$	175–190	138–140	61	[94]
α-$C_{10}H_7$	H	C_6H_5	H	C_6H_5	215–234	164–165	43	[94]
C_6H_5	H	$C_6H_2(C_6H_5)_2NO_2$	H	C_6H_5	—	342–344	85	[94]

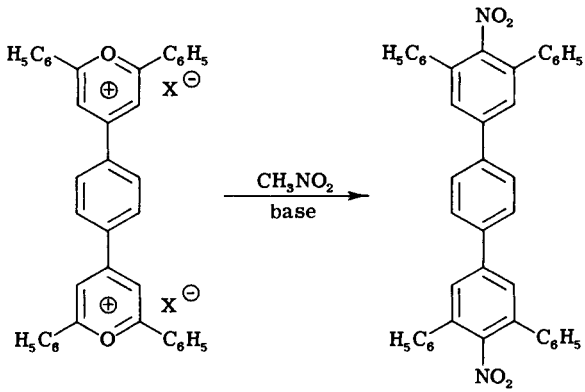
[a] Pyrylium chloroferrate

[b] R = 

[c] Pyrylium perchlorate

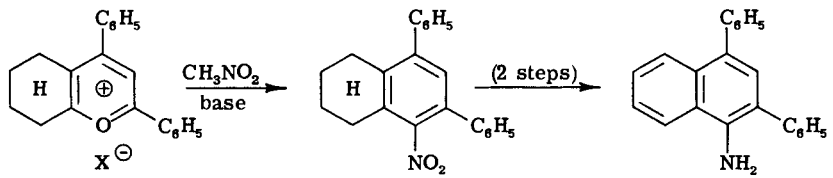
Both alkyl- and aryl-substituted pyrylium salts can successfully be subjected to this reaction; the latter can also be extended to pyrylium salts with other substituents, as illustrated by the facile preparation of 2,6-dimethyl-4-methoxynitrobenzene from 2,6-dimethyl-4-methoxypyrylium perchlorate and nitromethane [*88*]. 4-Thioalkyl-substituted pyrylium salts also undergo this reaction [*48*]. More highly substituted nitro compounds can, of course, also be obtained by this reaction. A selection of nitro compounds which we have prepared is given in Table 1.

The dipyrylium salt [*22*] reacts twice with nitromethane to give 4,4″-dinitro-3,5,3″,5″-tetraphenyl-1,1′,4′,1″-terphenyl [*95*].



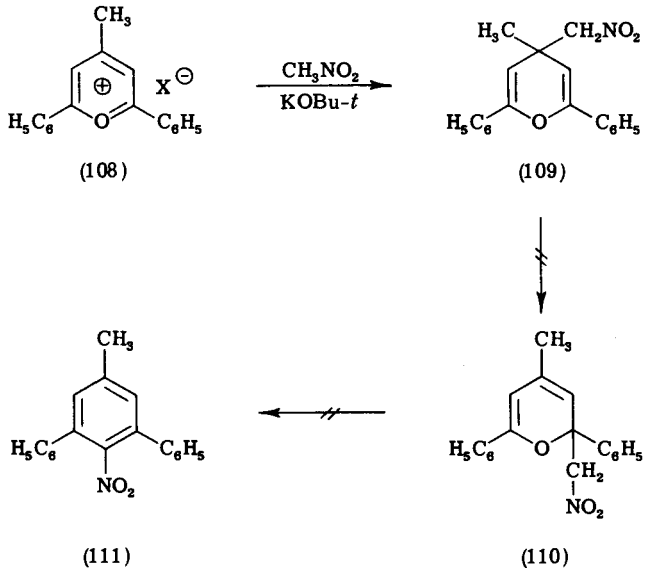
As in their failure to react with ammonia to give quinolines, chromylium salts also fail to react with nitromethane.

Isochromylium salts, e.g. 1,3-dimethyl- or 1,3-diphenylisochromylium fluoborate could not be converted into 2-nitronaphthalene derivatives in this manner, even though they readily give isoquinoline derivatives with ammonia and amines [*8*]. The conversion of 2,4-diphenyl-5,6,7,8-tetrahydrochromylium fluoborate (105) into 1-nitro-2,4-diphenyltetrahydronaphthalene (106), on the other hand, was successfully accomplished; (106) was then reduced to 2,4-diphenyltetrahydro-1-naphthylamine, dehydrogenated to give 2,4-diphenyl-1-naphthylamine (107), and converted into 2,4-diphenyl-1-naphthol [*8*].



(105) (106) (107)

The condensation of nitromethane and 2,6-diphenyl-4-methylpyrylium fluoborate (108) [*60*] fails to give the nitro compound (111) as was thought [*87*] at first and instead the 4-pyran (109) is obtained exclusively. It seems probable that the influence of the small methyl group favors the addition on C-4 so strongly that no addition at C-2 takes place. The subsequent reaction to give the 2-pyran (110) and the final formation of the aromatic nitrocompounds, therefore, is not possible.

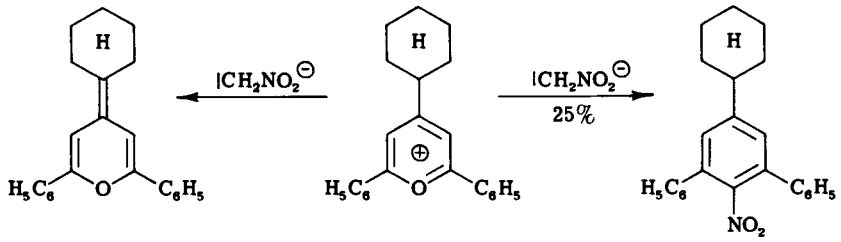


That the reaction does not occur for steric reasons has been proved by the reaction of 2,4-diphenyl-6-*tert*-butylpyrylium salt with nitromethane to give 2,4-diphenyl-6-*tert*-butylnitrobenzene [*60*]. Further evidence is supplied by the fact that 2,6-diphenyl-4-isobutylpyrylium fluoborate with nitromethane and *tert*-butoxide is smoothly converted into 2,6-diphenyl-4-isobutylnitrobenzene [*60*].

Pyrylium salts which have a hydrogen atom in the α-position on C-4 to the pyrylium ring which is capable of being split out as a proton, do not react with nitromethane to give aromatic compounds since the removal of the hydrogen atom to give 4-dehydro-4H-pyrans as a concurrent reaction proceeds much faster. The compounds (60a–c), (60d), and also (60e) failed to give nitrobenzene derivatives but formed instead their respective 4-dehydro-4H-pyrans (59).

2,6-Diphenyl-4-cyclohexylpyrylium fluoborate (112) reacts in two different directions. In addition to the formation of alkylidenpyran (113),

2,6-diphenyl-4-cyclohexylnitrobenzene (114) in a 25% yield is also formed. This evidently is favored because of the greater steric hindrance of the cyclohexyl portion opposite the isopropyl group in (60e).



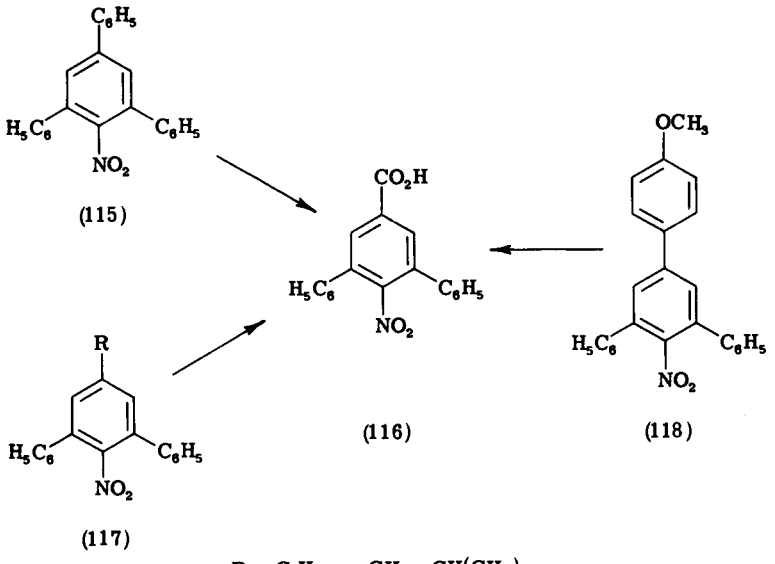
(113) (112) (114)

The condensation reaction compared with the addition reaction is favored by working at a higher temperature and by the addition of the pyrylium salt to a preformed mixture of nitromethane and potassium *tert*-butoxide (see the Experimental section).

Finally the nitromethane condensation with 2,6-disubstituted pyrylium salts such as (55) also failed to work. Here, the 4-addition compound (56d) was formed exclusively; this was dehydrogenated with triphenylphenol to give the alkylidene pyran (59c) [*59*] (see page 383), but could not be transformed to the aromatic nitro compound. With methylamine (59c) condenses without difficulty to give N-methyl-4-nitromethylene-1,4-dihydropyridine (80, R = H, R″ = NO_2, $R_2 = R_6 = C_6H_5$, $R_1 = CH_3$) [*59*].

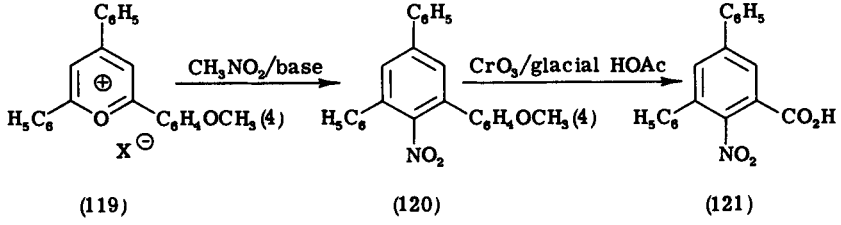
Since aromatic nitro compounds are key substances for numerous other aromatic compounds (amines, phenols, halides, nitriles, etc.), this reaction offers very many preparative possibilities [*96*]. Moreover, starting from the pyrylium salt, it proceeds unambiguously, so that it is eminently suitable for structure determinations. This is of particular importance in the case of aryl-substituted derivatives of benzene, since these give no useful data with regard to structure by degradative methods. The synthesis of all seven isomeric monobrominated 2,4,6-triphenylnitrobenzenes (or phenols) becomes simple with the aid of the pyrylium salt/nitromethane method; the course of the reaction between triphenylphenoxyl and bromine, for example, could thus rapidly be elucidated [*91*].

The synthesis of the nitro compounds from pyrylium compounds could also be used to elucidate the substitution of the nitrobenzoic acids [*97*]. 2,4,6-Triphenylnitrobenzene (115) is oxidized to 3,5-diphenyl-4-nitrobenzoic acid (116) which can also be prepared from 2,6-diphenyl-4-cyclohexyl- (or 4-isobutyl-) nitrobenzene (117) by oxidation.



A synthesis of phenyl-substituted nitrobenzoic acids of definite constitution is also possible by the following route. The pyrylium salts are prepared with anisyl (instead of phenyl) groups (e.g., 119) and converted into the corresponding nitrobenzene derivatives which are then oxidized with chromic oxide in glacial acetic acid. The anisyl groups are in this way, preferential to the phenyl groups, oxidized to carboxylic acid groups.

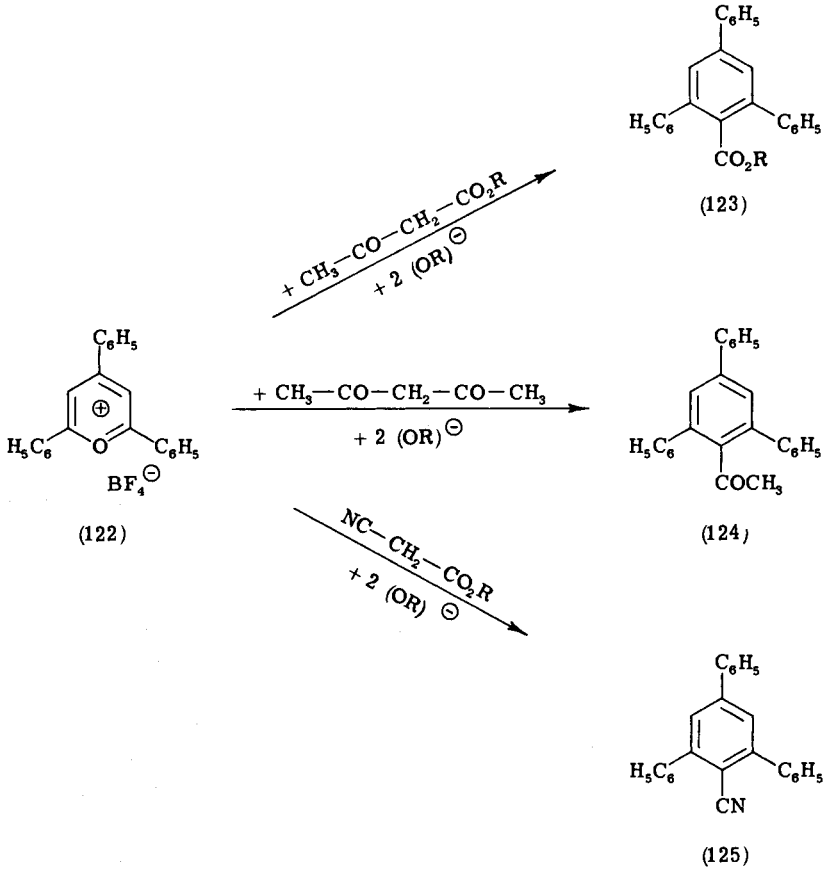
By this route 3,5-diphenyl-4-nitrobenzoic acid (116) has been prepared from 4-anisyl-2,6-diphenylnitrobenzene (118), and 3,5-diphenyl-2-nitrobenzoic acid (121) from 2-anisyl-4,6-diphenylnitrobenzene (120) [*97*].



KETONES, CARBOXYLIC ACIDS, NITRILES

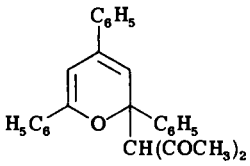
It was found in the case of 2,4,6-triphenylpyrylium fluoborate (122) that the pyrylium salt will also react with other compounds containing

an active methylene group, e.g. acetoacetic ester, acetylacetone, or cyanoacetic ester, in the presence of 2 moles of *tert*-butoxide [*98*]. Elimination of the acetyl group

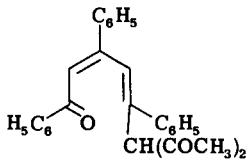


in the first two cases and the carboxyl group in the last results in the formation of 2,4,6-triphenylbenzoic ester (123), 2,4,6-triphenylacetophenone (124), and 2,4,6-triphenylbenzonitrile (125), respectively.

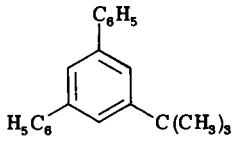
If the pyrylium salt (122) is allowed to react with acetyl acetone in the presence of only 1 mole of potassium *tert*-butoxide, then the primary addition product in the form of lemon-yellow crystals is isolated [*65*]. Its constitution is either that of a 2-pyran (126) or the isomeric ketone (127). With a hot potassium hydroxide solution it gives a 70% yield of red 2,4,6-triphenylacetophenone (124). The addition product of acetylacetone and 2,3,4,5,6-pentaphenylpyrylium perchlorate behaves similarly



(126)



(127)



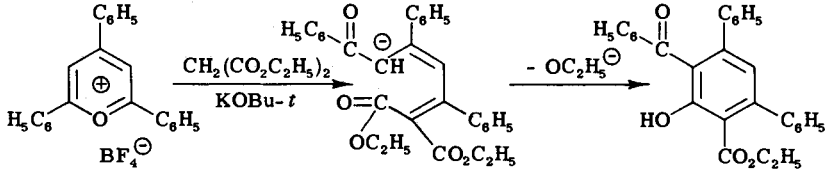
(128)

and on heating with aqueous alcoholic base gives pentaphenylacetophenone in 63% yield. It is noteworthy that the addition product of acetylacetone and 2-*tert*-butyl-4,6-diphenylpyrylium fluoborate, which is an analog of (126) or (127), splits out both acetyl substituents with base and gives an 82% yield of a hydrocarbon, $C_{22}H_{22}$, 2-*tert*-butyl-4,6-diphenylbenzene (128) [*65*].

The degree to which this reaction can be applied to other pyrylium salts, and the extent to which other compounds with active methylene groups are usable have thus far not been systematically investigated.* But since 2,4,6-triphenylpyrylium salts by no means represent the most reactive pyrylium salts, it is not improbable that a large number of alkyl- and aryl-substituted pyrylium salts will react with similar success. Isochromylium salts react just as poorly as with nitromethane.

Phenolic Acids

The reaction between 2,4,6-triphenylpyrylium fluoborate (122) and diethyl malonate in the presence of *tert*-butoxide proceeds quite differently from its reaction with the active methylene groups of the compounds mentioned above: Condensation to a phenolic ester, namely 2-hydroxy-3-carbethoxy-4,6-diphenylbenzophenone (130), takes place without elimination of a carboxyl group. Compound (129) may be an intermediate product [*99*]. The degree to which this reaction may be extended to other pyrylium salts has not yet been investigated.

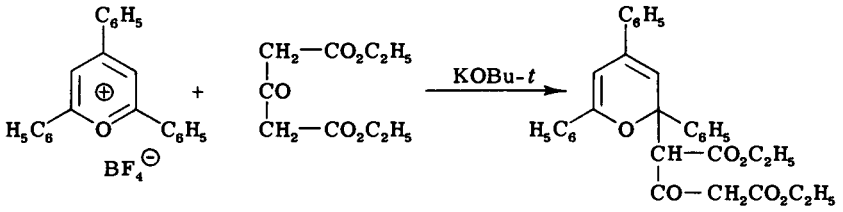


(122) (129) (130)

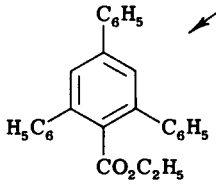
The reaction of 2,4,6-triphenylpyrylium fluoborate (131) and diethylacetonedicarboxylate in the presence of potassium *tert*-butoxide gives a

* Recently, we found that 2,4,6-triphenylpyrylium fluoborate and phenylnitromethane give an addition product which rearranges by heating to 1,2,3,5-tetraphenylnitrobenzene and in the presence of alkali to 2,3,4,6-tetraphenylphenol [*100*].

58% yield of the initial addition product [2H-pyran (132) or isomeric ketone] as yellow crystals [*100*]. With a further mole of the alcoholate the compound splits out the malonic ester and gives ethyl-2,4,6-triphenylbenzoate (123). A higher membered ring compound is not isolated.



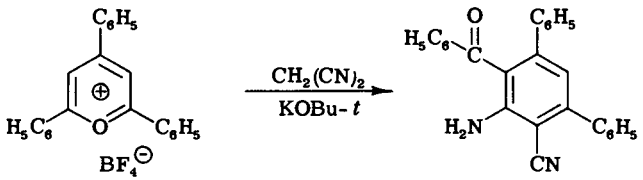
(131) (132)



(123)

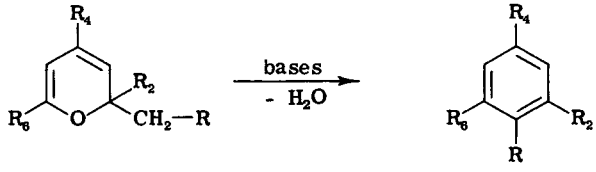
AMINONITRILES

The reaction between 2,4,6-triphenylpyrylium fluoborate (131) and malononitrile proceeds in similar manner to that with malonic ester. No elimination of the fragment containing the active methylene group occurs in this instance either. The aromatic ring is formed by incorporation of two C atoms of the active methylene-containing reagent, without participation of the C-6 or C-2 atom of the pyrylium salt. 2-Amino-3-cyano-4,6-diphenylbenzophenone (133) is formed in yields exceeding 75% [*99*]. Nor has it thus far been investigated whether alkyl-substituted pyrylium salts will undergo this reaction sequence.



(131) (133)

HYDROCARBONS

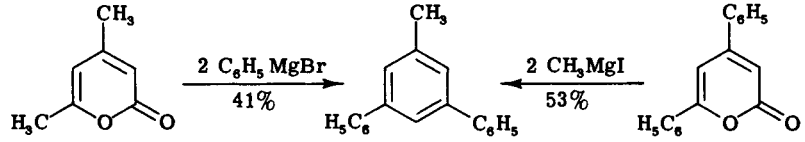


(134) (135)

Derivatives of Benzene

Derivatives of 2H-pyran (134) which have in the 2-position a methyl group or a reactive methylene group can, under the influence of basic reagents, form benzene derivatives (135); the reaction is analogous to the Baeyer phenol synthesis described above.

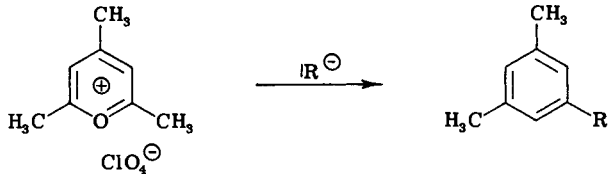
There are more possibilities for carrying out this reaction, depending upon the way the 2H-pyran derivatives (134) are formed; it is not necessary in every case to isolate the 2H-pyran. Gompper and Christmann [*72, 101*] used 2-pyrones as the starting materials. If the 2-pyrone is allowed to drop into an excess of Grignard reagent, the aromatic hydrocarbon is formed in one step. The assumption is that either the 2-pyrone or the Grignard reagent used in the reaction contains a methyl group necessary for the formation of the aromatic ring. Thus 3,5-diphenyltoluene (137) is obtained from either 2,4-dimethyl-6-pyrone (136a) with 2 moles of phenyl magnesium bromide, or in a similar fashion from 2,4-diphenyl-6-pyrone (136b) with 2 moles of methyl magnesium iodide.



(136a) (137) (136b)

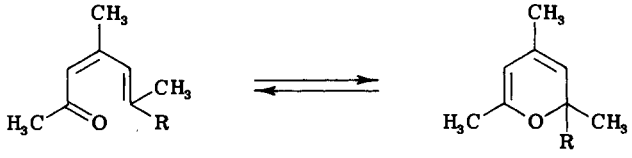
In a similar way trimethylpyrylium perchlorate (138) can react with Grignard reagents or compounds with an acidic CH in the presence of triethylamine to give derivatives of 3,5-dimethylbenzene (140a–c) [*72*]; the yields for the reaction vary between 27 and 81%.

Köbrich [*71*] successfully isolated an intermediate product for the reaction which he considered to be the doubly unsaturated ketone (139a); it cannot be ruled out that the compound was a 2H-pyran of the structure (139b).



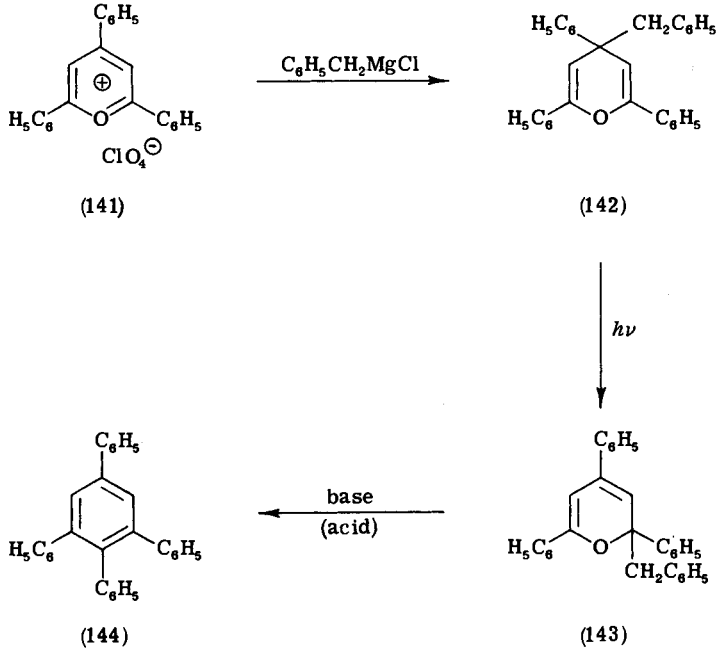
(138) (140)

(a) R = CH_3
(b) R = C_6H_5 or $C_6H_4CH_3$
(c) R = $CH(CH_3)_2$



(139a) (139b)

This reaction has a close similarity to the one used by Dimroth and Neubauer [*98*] for the preparation of hydrocarbons from 2,4,6-triphenylpyrylium perchlorate (141) and benzyl lithium or benzyl magnesium

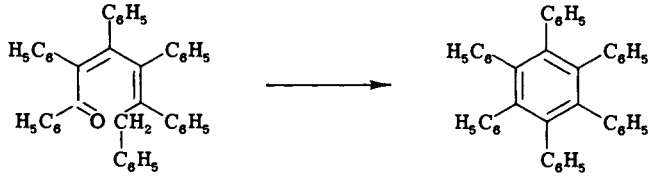


(141) (142) (144) (143)

chloride. Here a crystalline addition product of the 4,4-disubstituted 4H-pyran was formed (142) [*102*]. On heating this compound with calcium oxide, or better, with sodium diethylene glycolate at 240°C, 1,2,3,5-tetraphenylbenzene (144) was obtained in 50% yield; the 2H-pyran (143) must be formed in an intermediate step.

It is possible, by the irradiation of the 4H-pyran (142), to isolate the intermediate 2H-pyran (143) [*102*]. This compound is converted with extreme ease into the hydrocarbon (144) either with base or weak acid.

The reaction of 2,3,4,5,6-pentaphenylpyrylium fluoborate with benzyl magnesium chloride gives the 2H-pyran and not the 4H compound. This compound cleaves at once to give the unsaturated ketone (145), which upon heating with sodium diethylene glycolate, gives the hexaphenylbenzene (146) by ring closure.

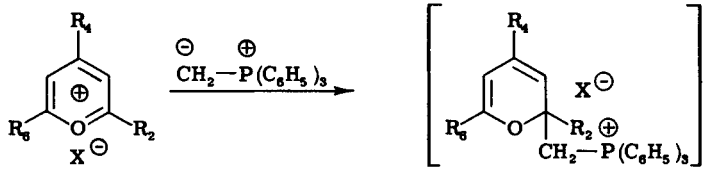


(145) (146)

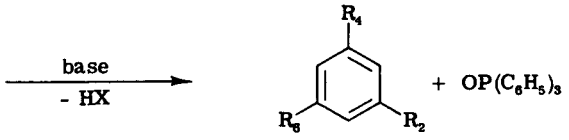
The synthesis is only successful if the 2H-pyran is formed, directly or as an intermediate product, by an allylic rearrangement from the 4H-pyran.

The 4,4-disubstituted 4H-pyrans of the type (142) are easily distinguished from the 2H-pyrans of the type (143) by their physical and chemical properties. The 4H-pyrans absorb at 248 mμ (see also reference [*72*]). With dilute acids they form diketones, but with strong acids naphthalene derivatives (see next section). The 2H-pyran (143), on the other hand, is a yellow crystalline compound which absorbs at 335 mμ, and with dilute acids in ethanol gives a quantitative yield of 1,2,3,5-tetraphenylbenzene [*102*]. The deep yellow color of the acidic solution formed is probably due to the valence tautomerism of 1,3,5,6-tetraphenylhexa-2,4-dien-1-one.

A further hydrocarbon synthesis of a different type has been described by Märkl [*103*] and other workers [*66, 104*]. In this synthesis, methylene triphenylphosphorane reacts with the pyrylium salt to give the benzene derivative (149) in generally good yield. In some cases the intermediate product (148) was isolated by Märkl. Since the reaction could not be applied to alkoxymethylene triphenylphosphorane, phenol



(147) (148)

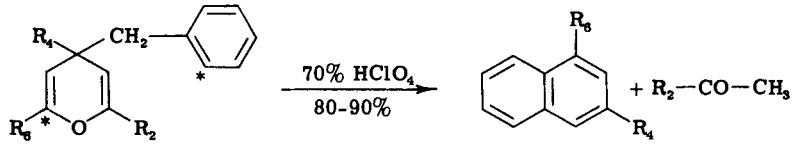


(149)

ethers could not be prepared and the reaction has not been followed further. The formation of azulenes, on the other hand, is interesting and is described in a later section (p. 397).

Derivatives of the Naphthalenes and Phenanthrenes

Tetrasubstituted 4H-pyrans of the type (150) with a benzyl or an α-methylnaphthyl group at C-4 undergo a surprisingly smooth reaction with 70% perchloric acid to give naphthalene or phenanthrene derivatives (151) [*105*] in 80–90% yields. At the same time 1 mole of methyl ketone is split out.



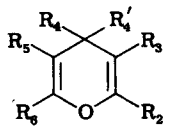
(150) (151)

The 4H-pyrans are easily accessible from 2,4,6-trisubstituted pyrylium perchlorates and benzyl- or α-methylnaphthyl magnesium chloride, and give yields of product in the region of 50–70% (see Table 2).

The naphthalene system can only be formed from the 4H-pyran. It can be concluded from this that the pyran (150c) gives 1-methyl-3-phenylnaphthalene (151c) and not the 1-phenyl-3-methylnaphthalene (154) expected from the 2H-pyran (153) [*102*].

TABLE 2

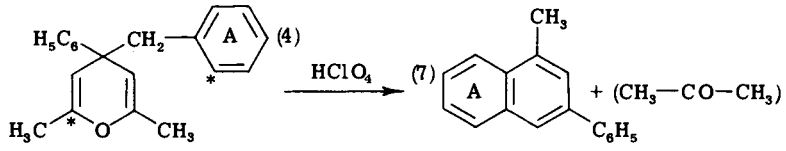
4,4-DISUBSTITUTED 4H-PYRANS (152) FROM 2,4,6-TRISUBSTITUTED PYRYLIUM SALTS[a]



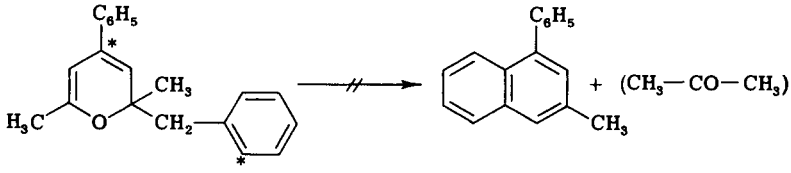
(152)

	R_2	R_3	R_4	R'_4	R_5	R_6	M.p. (b.p./mm) (°C)	Yield (%)
(a)	CH_3	H	CH_3	$CH_2C_6H_5$	H	CH_3	(130–131)/11	78
(b)	CH_3	CH_3	CH_3	$CH_2C_6H_5$	CH_3	CH_3	(95–97)/11	72
(c)	CH_3	H	C_6H_5	$CH_2C_6H_5$	H	CH_3	77–78	77
(d)	C_6H_5	H	C_6H_5	$CH_2C_6H_5$	H	$C(CH_3)_3$	86–87	52
(e)	CH_3	H	$C(CH_3)_3$	$CH_2C_6H_5$	H	CH_3	(120/3)	61
(f)	C_6H_5	H	C_6H_5	$CH_2C_6H_5$	H	C_6H_5	143–144	70
(g)	C_6H_5	H	C_6H_5	$CH_2C_6H_4OCH_3(4)$	H	C_6H_5	140–141	72
(h)	C_6H_4—$OCH_3(4)$	H	$C_6H_4OCH_3(4)$	$CH_2C_6H_5$	H	$C_6H_4OCH_3(4)$	123–124	51
(i)	C_4H_8		C_6H_5	$CH_2C_6H_5$	H	C_6H_5	149–150	54
(j)	C_6H_5	H	C_6H_5	α-$CH_2C_{10}H_7$	H	C_6H_5	146–147	57
(k)	C_6H_5	H	C_6H_5	α-CH_2— 	H	C_6H_5	169–170	68

[a] Taken from [*105*].



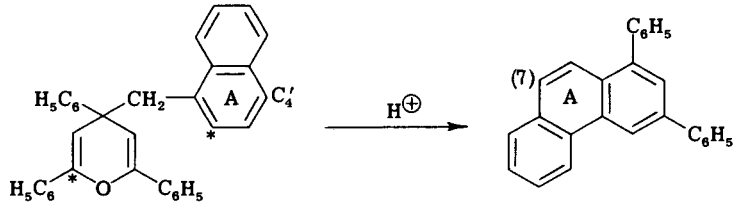
(150c) (151c)



(153) (154)

Moreover, the 2H-pyrans, which can be obtained from the 4H-pyrans by UV irradiation, fail to form naphthalenes but give hydrocarbons of the type (135) in the presence of acids and bases [*102*]. If the 4H-pyran (150) contains dissimilar substituents in the 2- and 6-positions, one of the substituents can be exclusively split out. This is the case with the pyran (150d), when only 1,3-diphenylnaphthalene and no 1-*tert*-butyl-3-phenylnaphthalene is obtained as a product. The *tert*-butyl residue is removed as methyl *tert*-butyl ketone, and not the phenyl group as acetophenone.

Substituents at C-4 in ring A of the Grignard reagent are present at C-7 in the naphthalene ring after ring closure. From α-naphthylmethyl magnesium chloride and triphenylpyrylium perchlorate the pyran (155) is formed, from which 1,3-diphenylphenanthrene (156) is obtained on ring closure.

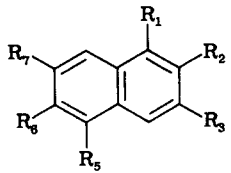


(155) (156)

A summary of the different methods of preparing naphthalene derivatives is given in Table 3.

The hydrolysis of the pyrans (152) with aqueous alcoholic hydrochloric acid gives the 1,5-diketones which, as well as the unsaturated

TABLE 3
NAPHTHALENE DERIVATIVES (157) FROM TETRASUBSTITUTED 4H-PYRANS



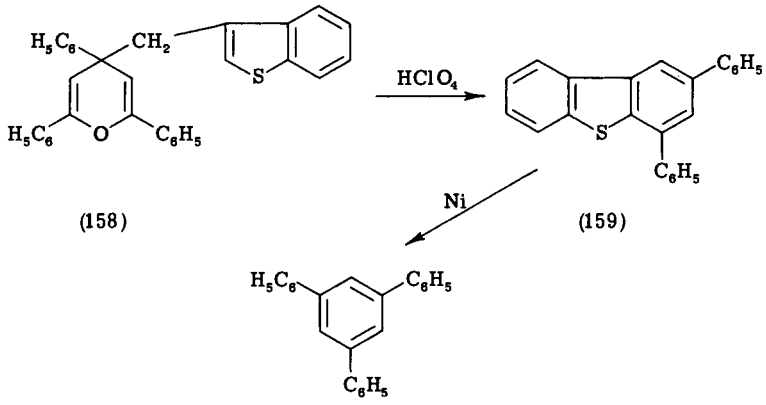
(157)

	R_1	R_2	R_3	R_5	R_6	R_7	M.p. (°C)	Yield (%)
(a)	CH_3	H	CH_3	H	H	H	Picrat, 115–116	70
(b)	CH_3	CH_3	CH_3	H	H	H	Picrat, 142–143	52
(c)	CH_3	H	C_6H_5	H	H	H	67–68	89
(d + f)	C_6H_5	H	C_6H_5	H	H	H	77–78	84 + 93
(e)	CH_3	H	$C(CH_3)_3$	H	H	H	Liquid, b.p. 135/5mm	71
(g)	C_6H_5	H	C_6H_5	H	H	OCH_3	117–118	91
(h)	C_6H_5—OCH_3(4)	H	C_6H_5—OCH_3(4)	H	H	H	98–99	45
(i)	C_4H_8		C_6H_5	H	H	H	Oily[a]	—
(j)	C_6H_5	H	C_6H_5	C_4H_4		H	154–155	94

[a] Gives the known 9-phenylphenanthrene by dehydrogenation with palladium.

ketone obtained from (152d), also give good yields of the corresponding naphthalene derivatives when treated with 70% perchloric acid.

The method, as (155) → (156) show, also allows the formation of phenanthrene derivatives of definite constitution. The method may hold an important position in the preparation of both naphthalene and phenanthrene derivatives of unambiguous structure. The reaction of 2,4,6-triphenyl-4(3-thionaphthylmethyl)-4H-pyran (158) with perchloric acid gives an 88% yield of 2,4-diphenyldibenzothiophene (159), which with Raney nickel gives 1,3,5-triphenylbenzene (160) [*102*].

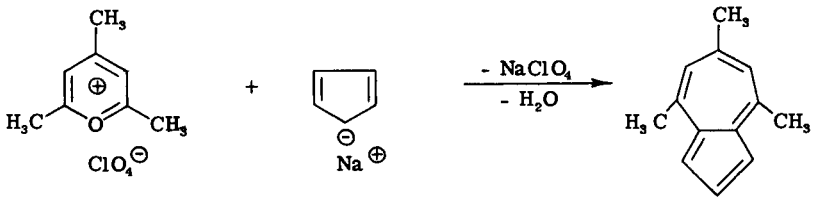


(158) (159)

(160)

Conversion of Pyrylium Salts into Azulene Derivatives

According to Hafner and Kaiser [*106*], 2,4,6-trimethylpyrylium perchlorate (161) will react with the sodium derivative of cyclopentadiene in tetrahydrofuran to give 4,6,8-trimethylazulene (162); the reaction proceeds at room temperature and affords yields of over 60%.



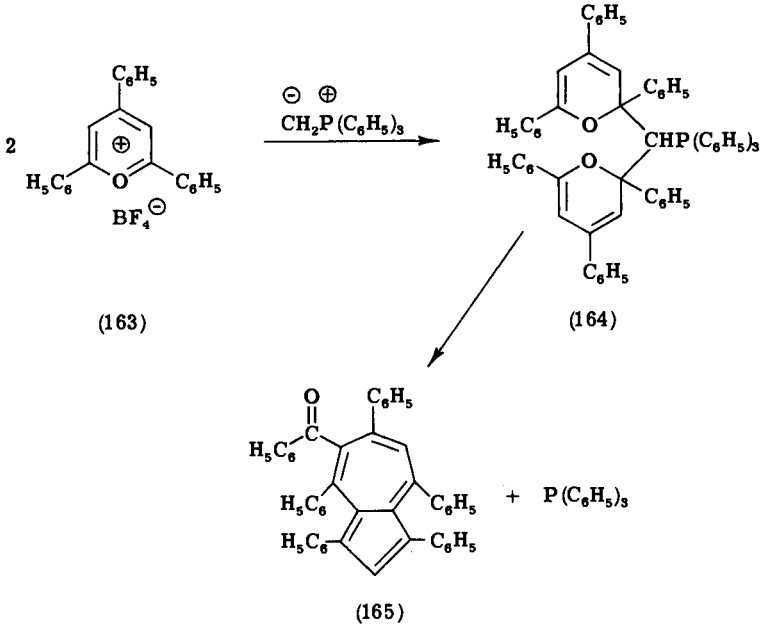
(161) (162)

This elegant azulene synthesis is closely related to earlier syntheses devised by Hafner and co-workers [*107*], in which the pyrylium salt is

replaced by pyridine derivatives; these are initially converted into derivatives of glutaconaldehyde by opening of the pyridine ring.

The azulene synthesis from trimethylpyrylium salt can be extended to other pyrylium salts. It is essential, however, that all three reactive positions (2,4,6) are occupied and that at least one 2-group is not too large. 2,4,6-Triphenylpyrylium perchlorate no longer yields an azulene derivative, though 2,6-dimethyl-4-phenylpyrylium perchlorate and 2,4-diphenyl-6-methylpyrylium perchlorate will do so (87 and 25%, respectively). 2,6-Dimethyl-4-methoxypyrylium salt also reacts readily with the sodium derivative of cyclopentadiene to give 4,8-dimethyl-6-methoxyazulene (55%). Further variations in the synthesis are possible by modification of the cyclopentadiene constituent.

The reaction of 2,4,6-triaryl-substituted pyrylium salts (163) and methylene triphenylphosphorane [*105*] constitutes a quite different type of azulene synthesis. An excess of an ethereal solution of methylene triphenylphosphorane solution is added to a solution of the pyrylium salt in acetonitrile, whereupon the deep blue aryl-substituted azulene (165) is obtained in approximately 30% yield.



(163) (164) (165)

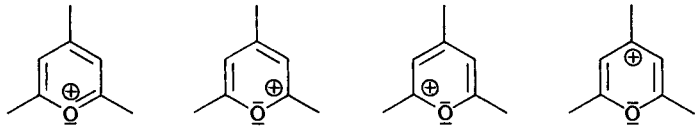
The reaction must proceed by way of an intermediate (164) in which two molecules of the pyrylium salt are in combination with one molecule

of the phosphorane. By a transannular reaction, triphenylphosphine is split out and the azulene results.

The Reaction Mechanism

The Primary Reaction

The pyrylium cation (166a) is a cation stabilized by aromatization, whose carbon atoms 2,6, and 4 (formulas 166b–d, respectively) readily add nucleophilic reagents. The question of whether the addition will be preferred at C-2 and C-6 to that at C-4 cannot be answered generally. The calculation of the electron density indeed shows that positions C-2 and C-6 (166b and c) [*108*] are the favored ones for nucleophilic addition, although experimental evidence—as in the series of thiopyrylium salts [*27*]—shows that no definite conclusions can be drawn. The reaction conditions must be closely investigated to determine how far the kinetic and thermodynamic considerations govern the formation of the initial addition product.



(a) (b) (c) (d)

(166)

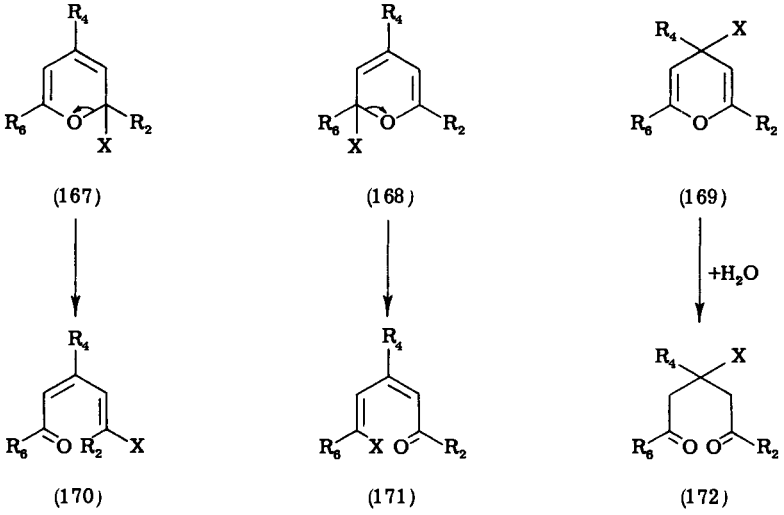
It is, however, known with certainty that bulky (lipophilic?) substituents decisively influence whether the C-4 or the C-2 positions will be favored [*60*].

The primary addition products are either the 2H- or the 4H-pyrans; in some cases either one or the other could be isolated [*102*]. Theoretically these compounds should be interconverted by an allylic rearrangement.

Exhaustive recent investigations have shown that the 2H-pyrans formed initially cannot generally be isolated since, through opening of the six-membered ring, they form doubly unsaturated ketones (170) and (171), respectively (if X = OH, the enol ketone and the 1,5-diketone) [*71*]. If the pyrylium salt is unsymmetrically substituted then two different structural isomers for (167) and (170), respectively, and (168) and (171) could be formed.

Moreover stereoisomers (geometrical isomers) are possible:

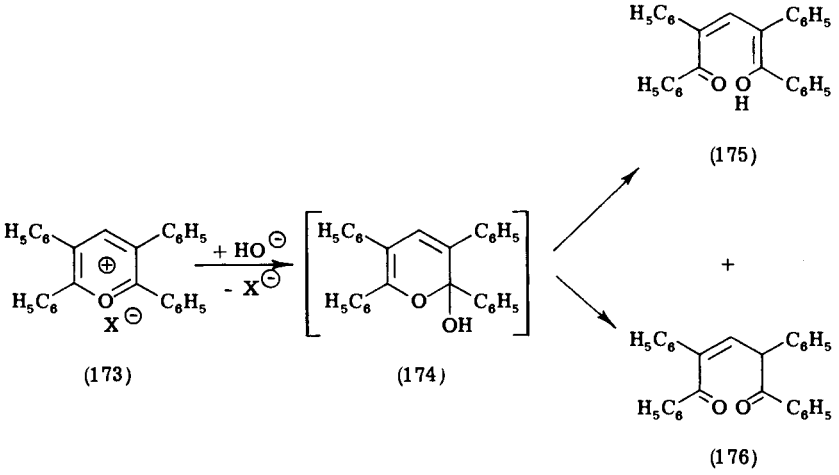
(a) The nucleophile can be added *cis* (R_2 and H on the same side of the double bond $>C_2{=}C_3<$ or *trans* (R_2 and H on different sides of the double bond).



(b) During, or after the addition, the second double bond can also undergo *cis–trans* rearrangement.

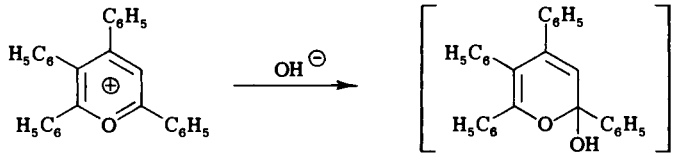
The addition products from hydroxyl ions [*109, 110*], cyanide ions [*111*], and phenylhydrazine [*112, 113*] were carefully investigated.

While the careful hydrolysis of 2,3,5,6-tetraphenylpyrylium salts (173) gave two isomers which were distinguished as the enol-ketone (175) and the *cis*-diketone (176) [*110a*], the isolation of enol-ketones or cyclic hemiacetals of the structure (174) was not successful in other cases.

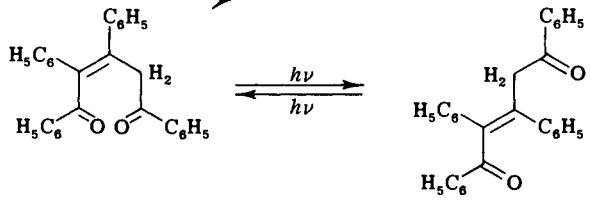


Two different diketones (179) and (180) were isolated from 2,3,4,6-tetraphenylpyrylium salt (177) [*110*]. Light brings about an intercon-

version of the two ketones, and an equilibrium mixture is formed. With hydroxyl or methylate ions only the *trans* diketone (180) is formed.

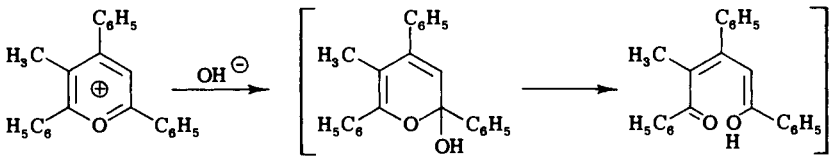


(177) (178)

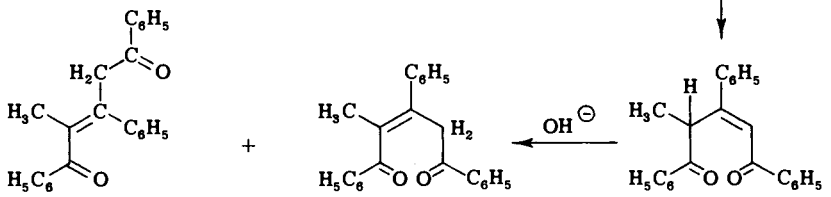


(179) (180)

Finally, from 3-methyl-2,4,6-triphenylpyrylium salt (181) by careful hydrolysis, the diketone (184) is formed; it undergoes rearrangement with further hydroxyl ions to give a mixture of the structural isomers, *cis*- and *trans*-diketones (185) and (186) [*110b*]. From this it can be concluded that the initial attack of the hydroxyl ions takes place on C-6,

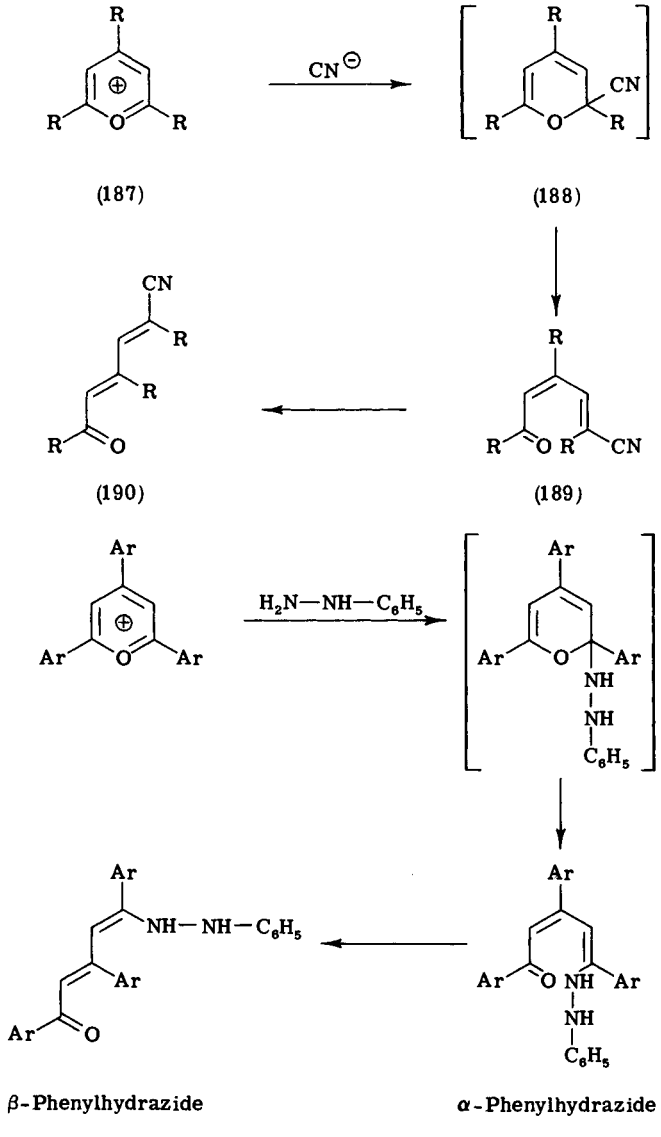


(181) (182) (183)



(186) (185) (184)

and that the reaction products (182) and (183) are rapidly produced. Similar results are obtained for the reaction of cyanide ions with alkyl-substituted pyrylium salts (187). Here, Balaban and Nenitzescu [*111*] established that initially cyano-*cis*-alkyldienone (189) was formed which with acid was converted into the *trans* isomer. The steric position of the two substituents on the double bond in (190) is not certain.



The reactions of aryl-substituted pyrylium salts with phenylhydrazine have long been known to give two isomers. Only the so-called α-phenylhydrazides are transformed to the pyridine compounds [*15*]. Once again it is a matter of geometrical isomers [*112, 113*]:

The primary product of the addition of a nucleophile to a pyrylium salt is, in the case of neutral nucleophiles (e.g. H_2O, NH_3, NH_2R, etc.), a cation, and in the case of nucleophilic anions (e.g. OH^-, SH^-, CH_2R^-, etc.), a neutral compound.

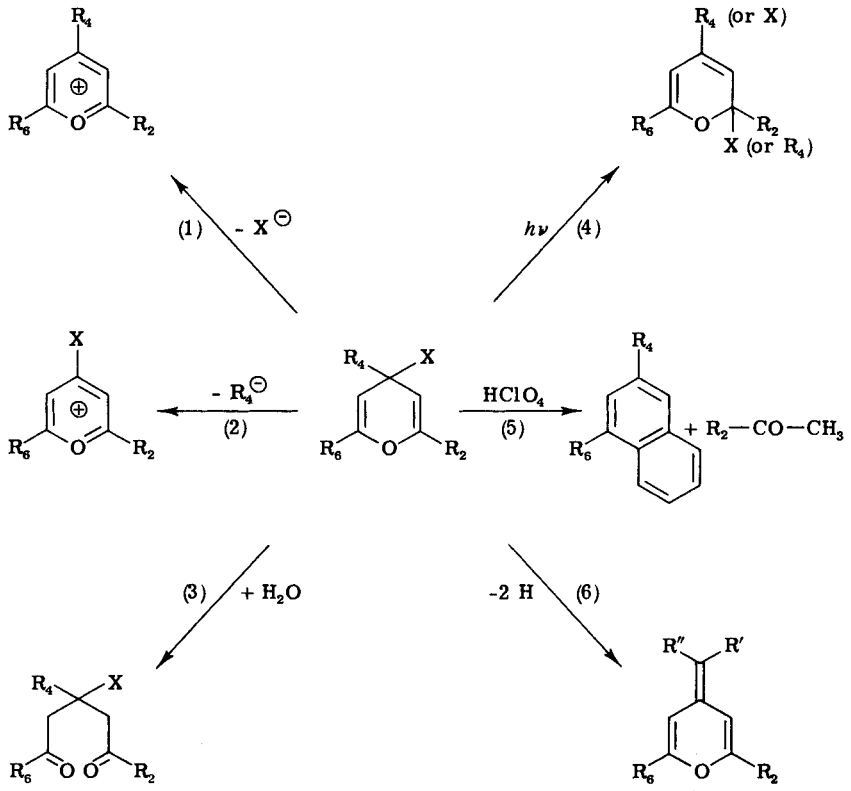
The Secondary Reactions

Addition Products at C-4

The most important secondary reactions are:

(1) The splitting out again of the added nucleophile X to give the original pyrylium salts.

(2) The splitting out of the group R_4 or of the hydrogen atom as an



anion (hydride ion) with the formation of a new pyrylium salt. An example of this type of reaction is the formation of pyrylium salts from 4-pyrones with organometallic compounds, which in acid solution split out the OH group.

(3) The hydrolytic splitting of the pyran ring to give 1,5-diketones.

(4) The allylic rearrangement of a 4H-pyran into a 2H-pyran by alkali, light, etc.

(5) In the case of X = CH_2-Aryl (CH_2-naphthyl, CH_2-thienyl, etc.) and R_4 = alkyl or aryl, R_2-CO-CH_3 can be split out and a derivative of naphthalene, phenanthrene, thianthrene, etc., is formed.

(6) In the case of X = $CH_2R'R''$ and R_4 = H, dehydrogenation can take place and a 4H-4-dehydropyran is formed.

For each of these possibilities we have given examples

Addition Products at C-2

The important secondary reactions are:

(1) The splitting out of the added nucleophile X or the R_2 substituent already present as an anion to give the original or a new pyrylium salt. The formation of pyrylium salts from 2-pyrones is an example of this type of reaction.

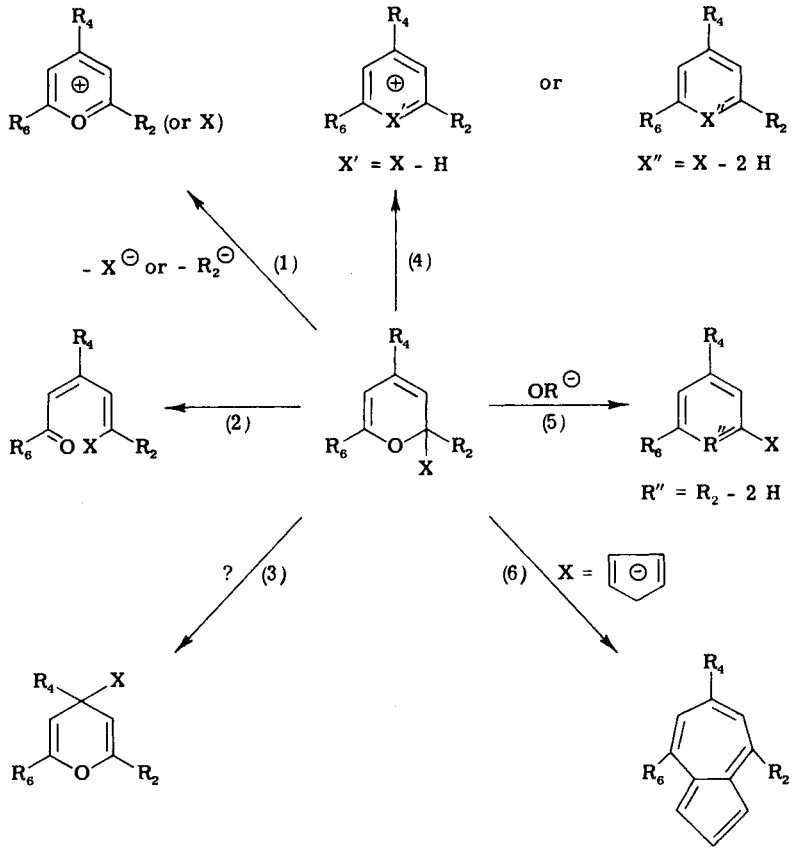
(2) The opening of the pyran ring with the formation of a doubly unsaturated ketone. The reaction can occur with or without steric rearrangement at either one, or both of the double bonds. With X = OH ("pseudobase") enol ketones or simple unsaturated 1,5-diketones of different structure and exhibiting geometrical isomerism are formed.

(3) Allylic rearrangement to give a 4H-pyran (unknown).

(4) In the case of a nucleophile added at C-2 which also contains a hydrogen atom or a substituent which is capable of being split off to give an electrophile, an aldol-type condensation can take place between the carbonyl group at C-6 to give heterocyclic or isocyclic six-membered aromatic ring systems (through splitting out of OH^- from C-6 or HOH, HOR, etc., from C-6 and X).

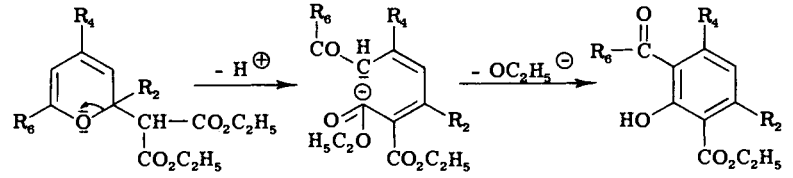
(5) An analogous reaction to (4) can also occur with the group R_2 already present at C-2 if this possesses a suitable constitution (CH_3, $CH_2 \cdot CH_3$, etc.). With X = OH, NR_2', 3,5-disubstituted phenols and NR_2' anilines are produced.

(6) If the reaction takes place with a cyclopentadienyl substituent, the aldol condensation which follows is between the carbonyl group at C-6 and the neighboring atom to C-2 and not C-2 itself. In this way the triply unsaturated seven-membered ring of the azulenes is produced (synthesis of Hafner).

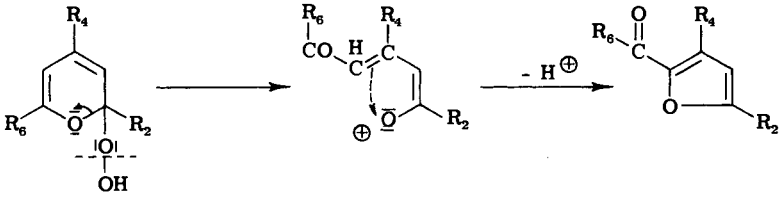


The secondary reactions of 2H-pyrans are still not exhausted. In addition to the reactions by which structural or steric changes can occur at the double bond and those in which the substituent on the C-5 atom is split into fragments, the C-5 atom adjoining the carbonyl group of C-6 can react nucleophilically with the electrophilic substituent at C-2. Three examples are given.

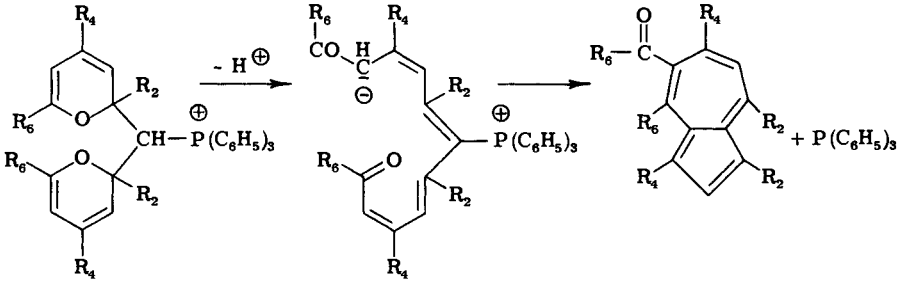
(7) The reactions of pyrylium salts with malonic ester and malondinitrile to give phenols and amines:



(8) The reaction of pyrylium salts with hydrogen peroxide to give furan derivatives:



(9) The reaction of 2 moles of pyrylium salt and methylene triphenylphosphorane to give an unsaturated ten-membered ring, which is stabilized by the formation of an azulene:



Methods of Preparation of Pyrylium Salts

The formation of pyrylium salts frequently proceeds astonishingly readily. The more important and versatile syntheses are mentioned below.

Conversion of Pyrones into Pyrylium Salts

Disubstituted 2- or 4-pyrones will react with nucleophilic agents in acid solution, to give pyrylium salts. This method is useful when suitably substituted pyrones are readily accessible. This is true particularly for 2,6-dimethyl-4-pyrone, which is formed in almost quantitative yield from dehydroacetic acid by boiling with hydrochloric acid [*114*], as well as for 2,6-diphenyl-4-pyrone [*115*], 4,6-dimethyl-2-pyrone [*116*], and 4,6-diphenyl-2-pyrone [*117*]. An interesting synthesis of 3,5-dibenzyl-4-pyrone should also be noted [*118*].

Many 2,4,6-trisubstituted pyrylium salts with almost any substituent can be prepared in this way by the use of Grignard reagents, dimethyl aniline [*119*], and other compounds. Altogether, pyrones are accessible by several methods and by acylation at C-3 [*120*], or condensation with aldehydes at the methyl group at C-2 [*121*], even further modifications can be made.

4-Pyrones condense with malononitrile or cyanoacetic ester [*47*],

and diphenylketone also produces a pyrylium salt [*56*]. Thiapyrones form thiopyrylium salts [*28*].

In a similar way, 3-phenylisocoumarin reacts with phenyl magnesium bromide to give the 1,3-diphenylisochromylium salt [*122*].

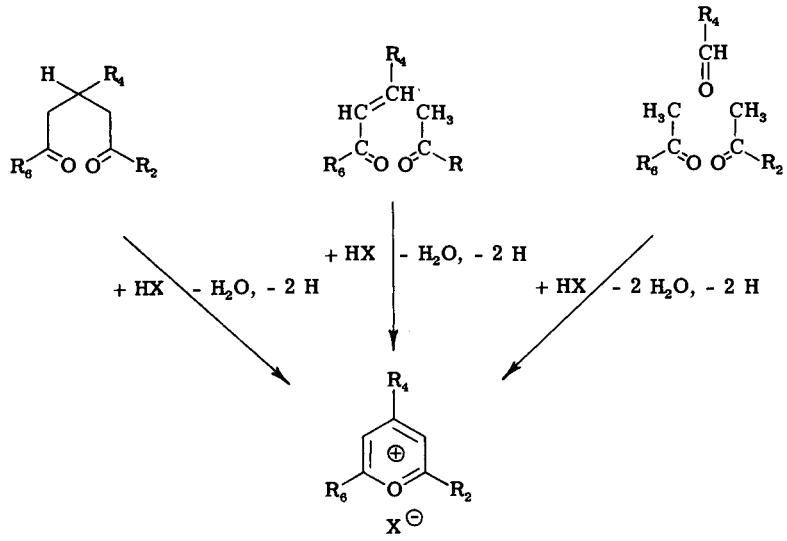
4-Alkoxypyrylium salts are obtained by the reaction of 4-pyrones with alkylating agents such as methyl iodide or dimethyl sulfate [*2*]. In a similar way 4-thiopyrones form 4-thioalkylpyrylium salts [*123*]. On the other hand, the 2-ethoxypyrylium salt is only obtained by the action of triethyloxonium fluoborate on the 2-pyrone. The compound is unstable and decomposes rapidly in damp air to give the original 4-pyrone [*124*]. The 2-thiopyrones are essentially much easier to alkylate and react readily with methyl iodide and dimethyl sulfate.

The Synthesis of Pyrylium Salts from 1,5-Dicarbonyl Compounds, from Ketones and α,β-Unsaturated Ketones, or from 2 Moles of Ketone and 1 Mole of Aldehyde

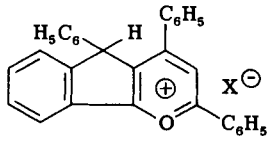
According to Dilthey and co-workers [*125*], 1,5-diketones are converted into 2,4,6-trisubstituted pyrylium salts in yields usually exceeding 50%, by the action of dehydrating complexing agents such as $FeCl_3$, $SbCl_5$, $POCl_3$, concentrated H_2SO_4 and triphenylcarbonium fluoborate which can act as acceptors for hydride ions [*126*]. Homophthalaldehyde and perchloric acid yield isochromylium perchlorate [*10, 11*], whereas glutaconaldehyde gives the unsubstituted pyrylium perchlorate in a very poor yield [*24*]. A much better way for getting pyrylium fluoborate is by dehydrating 4H-pyran (74) with triphenylcarbonium fluoborate [*127*]. The 1,5-diketones can be replaced by α,β-unsaturated aromatic ketones (chalcones) which will condense with methyl ketones (acetophenone and its derivatives) [*128*]. Numerous pyrylium salts are accessible by this route. Chalcone reacts with acetophenone, deoxybenzoin, and cyclohexanone to give 2,4,6-triphenylpyrylium salt, 2,3,4,6-tetraphenylpyrylium salt [*129*], and 2,4-diphenyl-5,6,7,8-tetrahydrochromylium salt [*130*], respectively.

Finally, 2 moles of aryl methyl ketone react with 1 mole of aryl aldehyde to give pyrylium salts [*3a*], e.g., acetophenone and benzaldehyde yield triphenylpyrylium salt. Even 3 moles of acetophenone, however, give 2,4,6-triphenylpyrylium salt; the mechanism was elucidated by Elderfield [*131*].

Dienones, e.g. cinnamylideneacetophenone, can also be condensed to give pyrylium salts (2,6-diphenylpyrylium salt), though the yields are rather lower (20%) [*132*]. We could improve this synthesis to give a 45% yield, as described in the Experimental section. Stetter obtained

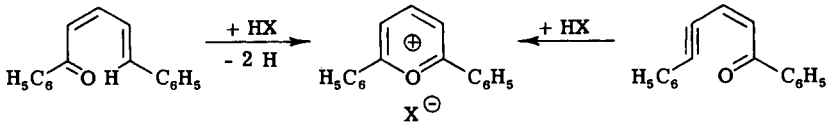


the same compound in 60% yield from the difficulty accessible 1,5-diphenylpent-1-yn-3-en-5-one [*133*].



(191)

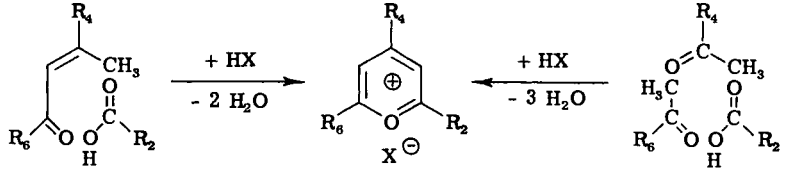
In the absence of another reactant of high reactivity chalcone alone forms the pyrylium salt (191) [*93*].



Pyrylium Salts from α,β-Unsaturated Methyl Ketones and Carboxylic Acid Derivatives

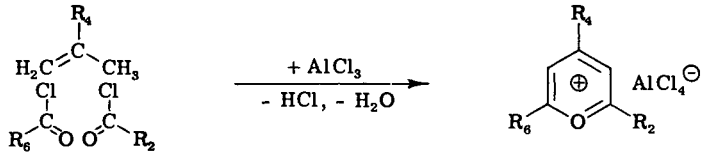
Another very frequently used synthesis was also devised by Dilthey and his collaborators [*134*]; this involves the condensation of α,β-unsaturated methyl ketones such as, *inter alia*, dypnone or mesityl oxide, and carboxylic acid anhydrides, chlorides, or other carboxylic acid derivatives in the presence of complex acids to give 2,4,6-substituted

pyrylium salts. Schneider [*135*] used "sulfoacetic acid" in the preparation of α-methyl-substituted pyrylium salts. The synthesis of 2,4,6-trimethylpyrylium perchlorate from glacial acetic acid/perchloric acid and mesityl oxide according to the method of Diels and Alder [*86*] proceeds particularly readily. Numerous carboxylic acids have been utilized in the synthesis of pyrylium salts containing various α-substituents [*136*]. Instead of the α,β-unsaturated methyl ketones, 2 moles of methyl ketone (acetophenone) can be made to react with the carboxylic acid derivative [*137*]. This reaction takes place without dehydrogenation.



Synthesis from Olefins and Acid Chlorides

According to Balaban and Nenitzescu [*16*], olefins react with 2 moles of acid chloride in the presence of complexing agents such as aluminum trichloride to give 2,4,6-substituted pyrylium salts; the yields usually amount to 20–40%. Many pyrylium salts, especially those containing branched aliphatic groups in positions 2 and 6 have been prepared via this recently discovered synthesis:



Extensive work has been carried out on this method, especially on the use of different Lewis acids for the preparation of different pyrylium salts; a detailed review of this work has already been published [*138*].

Conversion of Pyrylium Salts into Different Pyrylium Salts

2,4,6-Substituted pyrylium salts containing a 4-alkoxy or thioalkyl substituent readily exchange that alkoxy (or thioalkyl) group for other nucleophilic groups. Thus secondary amines yield the 4-dialkylamino derivatives [*13*], while malononitrile or cyanoacetic ester give methylene-4H-pyrans [*48*], which are converted into pyrylium salts by the action of acid.

2,6-Substituted pyrylium salts unsubstituted in the 4-position readily

add nucleophilic groups at that position; with compounds such as acetylacetone and nitromethane, which contain an acidic CH group, 4H-pyrans are formed which can be dehydrogenated to give 4-alkyl-4H-pyrans. These on treatment with acid form the 4-alkylpyrylium salts [*58, 59*]. With Grignard reagents 4H-pyrans are formed which on oxidation with ferric chloride in glacial acetic acid directly form new 4-substituted pyrylium salts [*59, 60*]. 2,6-Diphenyl-4-methylpyrylium salt [*66*] is formed in 25% yield from the reaction between 2,6-diphenylpyrylium salt and diazomethane.

The condensation of aldehydes or ketones with 2- or 4-methyl-substituted pyrylium salts gives rise to the formation of new pyrylium salts which contain unsaturated side chains [*139*]. Numerous condensations of this type have been carried out by Wizinger [*119*].

By the nitration of 2,4,6-triphenylpyrylium perchlorate, Le Fevre [*140*] succeeded in obtaining trinitrotriphenylpyrylium perchlorate in which the 2- and 6-phenyl groups were nitrated in the *meta*, and the 4-phenyl group in the *para* position.

Experimental

Pyrylium Salts

2,4,6-Trimethylpyrylium perchlorate [*141*]. Perchloric acid (15 gm, 70%) is added dropwise to acetic anhydride (30 gm) cooled in ice. Freshly distilled mesityl oxide (10 gm) is then added, followed by more acetic anhydride (20 gm) and the mixture heated on a boiling water bath for 15 min. On cooling the crystalline mass is filtered and washed with glacial acetic acid, alcohol, and finally ether, yielding an almost colorless product (14–16 gm, 64–72%), m.p. 245–247°C. These directions also allow the preparation of larger quantities (500 gm, yield 67%), but the perchlorate should not be stored dry; it should be utilized immediately in the form of a suspension in a little solvent. Recrystallization of larger quantities from glacial acetic acid also demands care.

The fluoborate, m.p. 206–208°C, is obtained from an aqueous solution of the perchlorate and hydrofluoboric acid in glacial acetic acid.

2,6-Diphenylpyrylium perchlorate [*66*]. A boiling solution of freshly sublimed ferric chloride (100 gm) in glacial acetic acid (300 ml) is added slowly to a boiling solution of cinnamylideneacetophenone (20 gm) in glacial acetic acid (450 ml). The mixture froths and darkens. The mixture is heated for 2–3 min and then quickly cooled, whereupon the diphenylpyrylium chloroferrate separates as deep blue crystals. The compound is dissolved in a solution of tartaric acid and immediately filtered

into 40–50% perchloric acid (200 ml). If necessary, the precipitate which remains on the filter is washed through with more aqueous tartaric acid. The perchlorate is precipitated from the filtrate (13.0 gm, 45%), m.p. 220–225°C.

2,6-Diphenyl-4-isopropylpyrylium chloroferrate [*97*]. (*a*) *2,6-Diphenyl-4-isopropyl-4H-pyran.* A Grignard compound prepared from isopropyl chloride (5.0 gm) and magnesium (1.5 gm) in ether (45 ml) is added rather quickly to a suspension of 2,6-diphenylpyrylium perchlorate (5.2 gm) (see above) in dry ether (60 ml) until the pyrylium salt is in solution. The resulting mixture is stirred for 20 min at room temperature and the yellow slightly turbid solution is then cooled in an ice bath and decomposed with cold aqueous ammonium chloride. The ether layer is washed once with 1 *N* sodium carbonate solution, and three times with water, and finally dried overnight with calcium chloride. The ether is removed under vacuum at 40°C to leave an orange oil which slowly crystallizes. By careful crystallization of the product from isopropanol in the absence of light, colorless crystals are obtained (3.5–3.7 gm, 80–85%), m.p. 58–59°C.

(*b*) *2,6-Diphenyl-4-isopropylpyrylium chloroferrate.* Sublimed ferric chloride (25 gm) is added portionwise to a refluxing solution of 2,6-diphenyl-4-isopropyl-4H-pyran in glacial acetic acid (120 ml). The heating is continued for 1 min under reflux and then the mixture is cooled. The pyrylium salt is obtained as dark-yellow crystals which are crystallized from glacial acetic acid (18.5 gm, 90%), m.p. 156–157°C.

2,4,6-Triphenylpyrylium chloroferrate [*142*]. Acetophenone (12 gm) is added to benzaldehyde (10.6 gm) and the mixture treated with a solution of sodium methoxide (6 ml, 10%). The mixture is allowed to stand in the refrigerator overnight, and the solid mass triturated with a little glacial acetic acid. Crystalline benzalacetophenone (19 gm, 89%) is obtained, m.p. 57.5–58°C after recrystallization from methanol.

Benzalacetophenone (62.4 gm) and acetophenone (36 gm) are dissolved in carbon disulfide (450 ml) contained in a three-necked flask fitted with stirrer, reflux condenser, and dropping funnel, and sublimed ferric chloride (146 gm) added to the well-stirred and cooled solution. Acetic anhydride (25 ml) is then slowly run in through the condenser and, as soon as the reaction has subsided, the mixture is warmed on a water bath. More acetic anhydride (65 ml) is added in small portions. The reaction mixture is boiled for 2 hr and stored for 1–2 days in the refrigerator. The dark-brown mass is thoroughly triturated several times with ether–glacial acetic acid (9:1), filtered, and washed with ether, yielding pyrylium salt (93 gm, 55%), m.p. 276–278°C.

Conversion into the fluoborate is effected as follows: The 2,4,6-tri-

phenylpyrylium chloroferrate (80 gm) is dissolved by stirring into boiling water (3.5 liters) to which a few ml of glacial acetic acid are added. On addition of hydrofluoboric acid (125 ml, 40%), a thick yellow precipitate separates. This can be purified by bringing to the boil portionwise, and adding glacial acetic acid (total quantity 550 ml) to the boiling solution. The solution is filtered hot and on cooling 2,4,6-triphenylpyrylium fluoborate (39 gm, 62%), crystallizes as yellow needles, m.p. 214–215°C.

For conversion into the iodide, the chloroferrate is dissolved in slightly acidified water at 70–80°C and sodium bisulfite and a saturated solution of potassium iodide are added. The red iodide, m.p. 221°C, is obtained in quantitative yield.

2-Methyl-4,6-diphenylpyrylium salts [*15*]. Acetic anhydride (100 ml) is slowly mixed with conc. sulfuric acid (30 ml), external cooling being applied throughout. When the reaction has subsided, the mixture is warmed for 2–3 hr on a water bath maintained at 75–80°C; the internal temperature must not be allowed to exceed 80°C. Free sulfuric acid can then only be detected in traces. Acetic anhydride (10–20 ml) and acetophenone (30 ml) are added to the mixture at room temperature, followed by heating for 24 hr at 45–50°C. The initially red-brown mixture becomes dark green after one-half hour. After addition of an equal volume of ethanol and cooling, the sulfoacetate of the pyrylium salt separates as a thick crystalline mass. This is filtered, washed with alcohol containing a little ether and dried; yields amount to approximately 50%. Addition of ether to the mother liquors affords a second crop. The preparation can be carried out without modification on ten times this scale, but the over-all yield is then lower. The sulfoacetate can be purified by recrystallization from ethanol, to give a product of m.p. 204°C. It is rather insoluble in pure water, and undergoes hydrolysis and decomposition, especially on warming. It is readily soluble without decomposition in acidified water.

Addition of a saturated solution of sodium chloride or potassium iodide to a warm, acidified solution of the sulfoacetate yields the chloride, m.p. 125–126°C, or the iodide, m.p. 222°C, respectively.

2-tert-Butyl-4,6-diphenylpyrylium chloroferrate [*18*]. Benzalpinacolone (4 gm) (m.p. 41°C, b.p. 154°C/25 mm), prepared in quantitative yield from pinacolone and benzaldehyde in aqueous-alcoholic sodium hydroxide by the method of Organic Syntheses [*142a*], is mixed with acetophenone (2 ml) and acetic anhydride (5 ml); sublimed ferric chloride (5 gm) is added in small portions, causing the mixture to become warm. It is allowed to stand overnight, filtered, and washed with glacial acetic acid and ether, yielding yellow needles (2.6 gm), m.p. 171–172°C; m.p. of iodide 249–250°C.

2,6-Diisobutyl-4-methylpyrylium chloroaluminate [*16*]. Aluminum chloride (14 gm) is slowly added from a large stock bottle to stirred isovaleryl chloride (27 gm) cooled to 0–10°C, care being taken to exclude moisture. The aluminum chloride largely goes into solution. If the mass becomes too viscous, this is remedied by the addition of a small quantity of *tert*-butyl chloride. After the *tert*-butyl chloride (total quantity 9.5 gm) has gradually been added, the cooling bath is removed and stirring is continued at room temperature until the mass liquefies and the evolution of HCl subsides, which requires 3–4 hr.

On the following day, the reaction mass is poured on to some crushed ice. Starting materials or by-products are removed by steam distillation or extraction with ether. The chloroaluminate is obtained from the concentrated aqueous solution by salting out; more pyrylium salt is obtained from the mother liquors by precipitation with $HClO_4$, HBF_4, H_2PtCl_6, or picric acid; yield 40%, m.p. of the perchlorate 106°C.

1,3-Diphenylisochromylium perchlorate [*8,122*]. (*a*) A mixture of *o*-carboxydeoxybenzoin (7.5 gm) and benzene (100 ml) is distilled until the distillate is clear and free from water. The mixture is then heated at 200°C in an open dish, cooled, carefully treated with water (150 ml), acidified with hydrochloric acid (10 ml) and the hot suspension filtered. The precipitate which separates is washed with warm 3 *N* hydrochloric acid and the washings combined with the filtrate. Yield of 3-phenylisocoumarin 7.2 gm (almost quantitative), m.p. 88–89°C.

(*b*) Phenylmagnesium bromide (0.09 mole) in ether (75 ml) is added to a stirred solution of 3-phenylisocoumarin (7.4 gm, 0.03 mole) in ether (75 ml) cooled to 0.5°C. Stirring is continued for 5 hr, followed by hydrolysis with ammonium chloride (42 gm) in water (250 ml). The ethereal layer is separated, washed, and dried over magnesium sulfate; addition of a solution of perchloric acid (6.35 ml) in acetic anhydride (25 ml) and absolute ether (20 ml) at 0°C causes the separation of an orange-red precipitate. A further crop is obtained from the filtrate. The salt is recrystallized from glacial acetic acid to which one drop of perchloric acid has been added, to give a 45% yield of pale orange crystals, m.p. 245–256°C. On combustion the salt decomposes explosively. Addition at 0°C of ferric chloride dissolved in a small quantity of hydrochloric acid to the stable carbinol (obtained from the perchlorate by the addition of alkali) in ether–acetic anhydride yields the chloroferrate.

2,6-Dimethyl-4-tert-butylpyrylium perchlorate [*141*]. Following the directions given by Baeyer and Piccard [*2*] for the preparation of 2,6-dimethyl-4-phenylpyrylium perchlorate, 10 ml of a solution of *tert*-butyl chloride (80 gm, 0.87 mole) in ether (120 ml) are poured on to magnesium (22 gm, 0.92 mole) activated by a little iodine. As soon as the

reaction has set in, ether (100 ml) and the remainder of the butyl chloride solution are added dropwise with gentle warming.

The Grignard solution thus prepared is stirred into 2,6-dimethyl-4-pyrone (50 gm, 0.4 mole) dissolved in dry anisole (1 liter), and the temperature rises to 25°C. The red solution is then stirred into 20% perchloric acid (1 liter) cooled to −10°C, and allowed to stand for 2 hr. The crystals are filtered and washed with alcohol and ether, yielding the perchlorate (52 gm, 49%), m.p. 220–221°C.

2,6-Dimethyl-4-ethoxypyrylium perchlorate [*143*]. 2,6-Dimethyl-4-pyrone (6.6 gm) dissolved in methylene dichloride (22 ml) is added to a solution of triethyloxonium fluoborate (10.1 gm) in methylene dichloride (3 ml), care being taken to exclude moisture. The solution is allowed to stand for 3 days and the methylene dichloride distilled off *in vacuo*; the residual crystalline mass is purified by solution in methylene dichloride and precipitation with ether. Yield, 90%; m.p. 90–91°C. Addition of a concentrated sodium perchlorate solution to an aqueous solution of the fluoborate precipitates the perchlorate, m.p. 126–128°C.

Heterocyclic Aromatic Compounds from Pyrylium Salts

2,4,6-Trimethylpyridine [*2*]. An aqueous solution of 2,4,6-trimethylpyrylium perchlorate is added to an excess of aqueous ammonia and the mixture gently warmed. Extraction with ether and evaporation of the solvent afford an almost quantitative yield of 2,4,6-trimethylpyridine in the form of an oil, from which the picrate, m.p. 155–156.5°C is readily precipitated by addition of aqueous picric acid.

2,4,6-Triphenylpyridine [*3a, 4, 8*]. 2,4,6-Triphenylpyrylium fluoborate (10 gm) is suspended in absolute *tert*-butanol (100 ml) and the suspension heated to boiling. A rapid stream of dry ammonia is passed in, and the pyrylium salt goes into solution. After 30 min the precipitated ammonium fluoborate is filtered off, and a little water added to the filtrate until a turbidity appears. The solution is allowed to stand for some time in the refrigerator, yielding colorless flakes (8 gm, 90%), m.p. 138°C.

N-Anilido-2-methyl-4,6-diphenylpyridinium iodide [*15, 18*]. 2-Methyl-4,6-diphenylpyrylium iodide (0.8 gm) is suspended in boiling benzene, and a solution of phenylhydrazine (0.3 gm) in benzene is added dropwise. After a few moments the red iodide vanishes and is replaced by a microcrystalline yellow salt (0.9 gm), m.p. 200°C after recrystallization from alcohol. It is almost insoluble in water and rapidly turns brown on exposure to light.

Addition of NaOH to a solution in alcohol-water precipitates dark-blue needles of the anhydro base (N^+–N^--betaine), m.p. 108°C.

1,2,6-Trimethyl-4-methoxypyridinium iodide [*13*]. Aqueous methyl-

amine (25%, 4.4 ml) in methanol (30 ml) is slowly added to an ice-cooled solution of 2,6-dimethyl-4-methoxypyrylium iodide (9.1 gm) in methanol (50 ml). The solution is refluxed for 30 min and the solvent evaporated; addition of a small quantity of acetone causes the immediate crystallization of the pyridinium salt (4 gm, 42%), m.p. 204–205°C after recrystallization from ethanol.

2,4,6-Triphenylthiopyrylium perchlorate [*28*]. Crystalline sodium sulfide (1 gm) in water (10 ml) is added to a solution of 2,4,6-triphenylpyrylium perchlorate (0.82 gm) in acetone (40 ml) and the mixture, shaken at frequent intervals, is allowed to stand for half an hour, when the color changes to an intense bluish red. The solution is acidified with perchloric acid (20%, 10 ml) and diluted with water (40 ml); after 2 hr the mixture is filtered to give yellow needles, m.p. 210–211°C.

2,6-Diphenyl-4-nitromethylene-4H-pyran [*59*]. 2,6-Diphenyl-4-nitromethyl-4H-pyran (0.5 gm) and triphenylphenol (10 mg) are dissolved in carbon tetrachloride (30 ml). The colorless solution is shaken for ½ hr with a solution of potassium ferricyanide (3.5 gm) in 2 *N* sodium hydroxide solution. Yellow needles of 2,6-diphenyl-4-nitromethylene-4H-pyran separate (0.43 gm), and are crystallized from ethanol to give a product with a m.p. of 170–171°C.

N-Methyl-2,6-diphenyl-4-nitromethylene-1,4-dihydropyridine [*66*]. Aqueous methylamine (40%, 60 ml) is added to a boiling solution of 2,6-diphenyl-4-nitromethylene-4H-pyran (0.7 gm) in ethanol (80 ml). The initially pale-red solution rapidly darkens to a deep red color, which later reverts to a pale red. The solution is allowed to cool slowly, and after approximately 2 hr water (200 ml) is added. Light brown crystals (0.6 gm, 82%), m.p. 243–245°C (dec.) separate, and can be recrystallized from ethanol-water. A further crop may be isolated from the mother liquors. Total yield, 90%.

4-(Dicyanomethylene)-2,6-dimethyl-1,4-dihydropyridine [*74*]. 4-Dicyanomethylene-2,6-dimethyl-4H-pyran (5 gm) is heated at 150°C for 1 hr in formamide (5 gm). On cooling, the crude product (1.7 gm) separates and is crystallized from formic acid to give a product of m.p. 330–331°C.

Benzene Derivatives from Pyrylium Salts

3,5-Dimethylphenol [*2, 16*]. A mixture of 2,4,6-trimethylpyrylium perchlorate (11 gm) and sodium hydroxide solution (10%, 16 ml, 4 moles) is boiled for 1 hr. Nonphenolic material is extracted with ether, and the residue acidified and again extracted with ether. Evaporation of the solvent affords 3,5-xylenol (15–35%), m.p. 65°C, which can be characterized as its tribromide, m.p. 164–167°C.

3,5-Dimethyl-N,N-dimethylaniline [*86*]. A solution of dimethylamine (10 gm) in ether (10 ml) is slowly added to 2,4,6-trimethylpyrylium perchlorate (22 gm) suspended in ether (50 ml). The suspended perchlorate coagulates during the course of the reaction, and white crystals of dimethylamine perchlorate can be observed in the liquid. These subsequently redissolve in the water formed. When the reaction is complete all solid particles have disappeared, and the reaction mixture consists of two liquid layers. The ethereal layer is separated, dried with alkali, and evaporated; the oily residue yields N-dimethyl-*sym*-*m*-xylidine, which distils almost completely at 222–224°C. The nearly colorless base (10 gm) is obtained on drying and distilling a second time.

2,4,6-Triphenylnitrobenzene [*87*]. A warm solution of the potassium derivative of nitromethane in *tert*-butanol [freshly prepared from *tert*-butanol (60 ml) and potassium (1.6 gm) followed by the addition of nitromethane (24.4 gm)] is added to a well-stirred suspension of 2,4,6-triphenylpyrylium fluoborate (11.5 gm) in absolute *tert*-butanol (60 ml). The reaction mixture becomes deep red and flakes of potassium fluoborate are precipitated. A further solution of potassium (1.6 gm) in *tert*-butanol (60 ml) is added, the mixture boiled under reflux for 45 min, filtered hot to free from potassium fluoborate, and treated with a little water. On cooling, the nitro compound separates, m.p. 144–145°C; yield, 87%.

2,6-Dimethyl-4-methoxynitrobenzene [*88*]. A solution of potassium (5 gm) in absolute *tert*-butanol (190 ml) is added dropwise to a stirred suspension of 2,6-dimethyl-4-methoxypyrylium perchlorate (15 gm) in nitromethane (160 ml). The mixture is boiled for 45 min, filtered free from precipitated potassium fluoborate, and evaporated under vacuum; the residual red oil gradually solidifies. Recrystallization from methanol/water (and purification with animal charcoal if necessary) yields pale yellow-green crystals (7 gm, 62%), m.p. 49.5–50.5°C.

2,6-Diphenyl-4-isobutylnitrobenzene [*97*]. Dry nitromethane (45 ml) and a solution of potassium *tert*-butoxide (40 ml, 1 *M*) are mixed with stirring in a dry atmosphere to give a thick white viscous suspension which is heated on a water bath at ca. 50°C. 2,6-Diphenyl-4-isobutylpyrylium perchlorate (7.5 gm) is added rapidly through a powder funnel with continued stirring, and the reaction mixture is then heated to reflux point. The mixture, which rapidly becomes intensely red, is heated for a further 20–30 min under reflux. The precipitated potassium perchlorate is filtered off while still hot and the filtrate is evaporated under vacuum with the temperature kept below 50°C. The addition of a little absolute ethanol to the oily residue gives the nitro compound in the form of fine small yellow needles (2.4 gm, 35%). Crystallization of these from alcohol gives a colorless product of m.p. 126–127°C.

2,4,6-Triphenylacetophenone [*98*]. Dry 2,4,6-triphenylpyrylium fluoborate (40 gm) is suspended in absolute *tert* butanol (150 ml) contained in a three-necked 1 liter flask, care being taken to exclude moisture. A mixture consisting of potassium (8 gm) in absolute *tert*-butanol (250 ml) and freshly distilled acetylacetone (10 gm) in *tert*-butanol (200 ml) is added to the stirred suspension from a wide-stemmed dropping funnel, and the contents of the flask acquire a transient red-violet color. The mixture is refluxed for 1 hr, filtered hot, and allowed to cool. A portion of the triphenylacetophenone (m.p. 125–126°C) separates out, and the remainder is obtained on concentration and extraction with ether. After recrystallization from alcohol, the total yield amounts to 24.4 gm (70%).

Ethyl 2,4,6-triphenylbenzoate [*98*]. The condensation is carried out exactly as above, the only difference being that ethyl acetoacetate is used instead of acetylacetone. Yield of ester, 32%; m.p. 93–94°C.

2,4-Diphenyl-5-benzoyl-6-aminobenzonitrile [*99*]. Malononitrile (6.6 gm) is added dropwise to a well-stirred solution of potassium (8 gm) in absolute *tert*-butanol (250 ml). The mixture is warmed for a brief period, and added to a suspension of dry 2,4,6-triphenylpyrylium fluoborate (39.6 gm) in absolute *tert*-butanol (150 ml). This is then heated under reflux for several hours until the deep violet color has disappeared; hot water (300 ml) is added to the hot mixture, and the latter is allowed to cool overnight. Pale yellow crystals (24 gm) separate, m.p. 175°C after recrystallization from methanol (1500 ml) and glacial acetic acid. A further crop (3.3 gm) is obtained from the mother liquors. Total yield is 73%.

3,5-Diphenyltoluene [*72*]. (*a*) An ethereal solution of 4,6-dimethyl-2-pyrone is added, in less than 1 min and with vigorous stirring, to the Grignard compound formed from bromobenzene (23.6 gm) and magnesium (3.7 gm) in ether (100 ml). The resulting mixture is heated under reflux for 8 hr. After cooling, the mixture is decomposed with ice acidified with 15% hydrochloric acid. The reaction mixture is repeatedly extracted with ether and the extracts are dried over anhydrous sodium acetate and magnesium carbonate. The ethereal residue distils at 128°C/0.001 mm and melts at 130°C. The yield of product is 5.0 gm (41%).

(*b*) The Grignard compound formed from methyl iodide (21.3 gm) and magnesium (3.7 gm) in ether (100 ml) is added dropwise over 1 hr to a refluxing solution of 4,6-diphenyl-2-pyrone (12.4 gm) in anisole (100 ml), the temperature being maintained at 100–120°C. The resulting mixture is warmed for a further 4 hr at 40°C and then allowed to stand for 12 hr. The reaction mixture is worked up as described in procedure (*a*) to give the product (6.5 gm, 53%).

1,2,3,5-Tetraphenylbenzene [*102*]. (*a*) *2,4,6-Triphenyl-4-benzyl-4H-pyran.* The Grignard compound formed from benzyl chloride (15.5 gm) and magnesium (3.0 gm) in ether (80 ml) is added dropwise to a stirred suspension of 2,4,6-triphenylpyrylium perchlorate (25 gm) in ether (600 ml). The pyrylium salt goes into solution (if it fails to do this a further quantity of the ethereal solution of the Grignard compound is added). A brownish precipitate forms, and the reaction mixture is stirred for a further 4–5 hr. The precipitate is filtered off and the ethereal solution is washed once with an approximately 1 *N* solution of hydrochloric acid and two to three times with water. The ether is removed by evaporation from the reaction mixture and the product crystallized from ethanol. Colorless crystals of the pyran (17.4 gm, 71%), m.p. 142–144°C are obtained.

(*b*) *1,2,3,5-Tetraphenylbenzene.* 2,4,6-Triphenyl-4-benzyl-4H-pyran (1.0 gm) is added to a solution of sodium (1.25 gm) in diethylene glycol (25 ml) and the mixture is heated for 1½ hr on an oil bath at 240°C. On cooling most of the 1,2,3,5-tetraphenylbenzene separates out. The cooled mixture is treated with two or three aliquots of water and then extracted with benzene. The combined benzene extracts are washed with 2 *N* hydrochloric acid and water, and finally dried. After the evaporation of the solvent, 1,2,3,5-tetraphenylbenzene remains (0.49 gm, 51%), m.p. 219–220°C; this is crystallized from isopropanol (ca. 500 ml).

1,3-Diphenylnaphthalene [*102*]. 2,4,6-Triphenyl-4-benzyl-4H-pyran (see above) and 70% perchloric acid (60 ml) are vigorously shaken and slowly heated to 90°C, whereupon a brown oil separates. After 5–10 min, the yellow-brown mixture is cooled and the oil is separated and dissolved in a little warm alcohol. On slowly cooling the solution, 1,3-diphenylnaphthalene crystallizes as colorless needles (3.25 gm, 87%), m.p. 77–78°C.

Azulene Derivatives from Pyrylium Salts

4,6,8-Trimethylazulene [*106*]. (*a*) *Sodium derivative of cyclopentadiene.* Sodium (69 gm, 3 gm atoms) is finely suspended in boiling absolute toluene (500 ml) by means of a vibromixer (Bopp and Reuther, Mannheim). When the suspension is cool the toluene is decanted off, and the sodium dust is washed with absolute tetrahydrofuran and suspended in absolute tetrahydrofuran (750 ml). Freshly distilled cyclopentadiene (198 gm, 3 moles) is slowly added dropwise to this vigorously stirred, ice-cooled sodium suspension kept under absolutely pure nitrogen, at such a rate that the temperature does not exceed 25–30°C. When the reaction is complete, a pale pink solution of the sodium derivative of cyclopen-

tadiene (approximately 3 *M*) is obtained; this solution is stable indefinitely in the absence of air and moisture, but rapidly turns dark brown when exposed to the atmosphere.

(*b*) *4,6,8-Trimethylazulene.* 2,4,6-Trimethylpyrylium perchlorate (60 gm, 0.27 mole) is added in small portions to a vigorously stirred solution of the sodium derivative of cyclopentadiene in tetrahydrofuran (300 ml, 1.9 moles). The addition is carried out under pure nitrogen and at such a rate that the temperature does not exceed 45–50°C. Stirring is continued for a further 15 min, and ⅔ of the tetrahydrofuran is distilled off. The residue is diluted with water and the azulene formed is repeatedly extracted with petroleum ether (b.p. 60–70°C). The combined petroleum ether extracts are washed with water and dried over $CaCl_2$. The solvent is evaporated, and the residue, a deep violet oil, is distilled under high vacuum. After a small first fraction, the azulene comes over between 90° and 100°C and solidifies in the receiver. Recrystallization from ethanol yields 4,6,8-trimethylazulene (28.5 gm, 62% as violet-black crystals, m.p. 81–82°C.

4,8-Dimethyl-6-ethoxyazulene [*106*]. 2,6-Dimethyl-4-ethoxypyrylium perchlorate (23.6 gm) is suspended in vigorously stirred absolute tetrahydrofuran (100 ml), the operation being carried out in an atmosphere of pure nitrogen. A solution of the sodium derivative of cyclopentadiene in tetrahydrofuran (53 ml, 1.9 moles) is added dropwise to this suspension cooled to −18°C, at such a rate that the temperature does not exceed −15°C. The mixture, initially strongly colored, becomes almost colorless towards the end of the addition. The mixture is treated with a solution of potassium *tert*-butoxide in *tert*-butanol (250 ml, 1 *M*) at −10°C, slowly allowed to warm up with stirring, and finally refluxed for 3 hr. The working up is identical to that described under 4,6,8-Trimethylozulane. Red crystals (45%), m.p. 88–89°C, are obtained, which are recrystallized from alcohol.

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The Formation of the Acetylenic Bond

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Introduction

The formation, reactions (*1,2*), and nature of the triple bond (*3,4*) in acetylenes have already been repeatedly reviewed. Only the newer methods leading to the formation of the triple bond are given here. This can involve either the conversion of a given compound into an acetylene, or the formation of an additional triple bond.

The method predominantly used for the formation of the acetylenic bond is the dehydrohalogenation of the corresponding halogenated compounds. Dichloro or dibromo compounds and chloro- or bromoölefins are the chief starting materials (I–VII).

$$\underset{\text{I}}{XCH_2{-}XCH{-}R},\ \underset{\text{II}}{X_2CH{-}CH_2R},\ \underset{\text{III}}{CH_2{-}CX_2{-}R},\ \underset{\text{IV}}{R_1{-}CHX{-}CHX{-}R_2}$$

$$\underset{\text{V}}{CH_2{=}CXR}\qquad \underset{\text{VI}}{CHX{=}CHR}\quad \text{and}\quad \underset{\text{VII}}{R_1CX{=}CHR_2}$$

The compounds may be obtained from carbonyl compounds and phosphorus pentachloride, or by the addition of halogens to olefins followed by partial dehydrohalogenation.

Alkali hydroxides, amides, and alkoxides are the favorite dehydrohalogenating agents; alkali carbonates, metal hydrides, and organometallic compounds are less frequently used. Other, nondehydrohalogenation methods for the production of the triple bond are also known.

The Dehydrohalogenation of Dihalides or Haloalkenes

The comprehensive review by T. L. Jacobs (*2*), which also deals with the preparation of acetylenes by the alkylation of metal acetylides, covers the subject to 1949. It is consequently the more recent work which is chiefly considered here.

Using Alkali Hydroxide

Treatment with alkali hydroxide is the oldest method used in the preparation of an acetylene from a halogenated compound. Methylacetylene, which was the first substituted acetylene, was prepared from 1,2-dibromopropane and ethanolic sodium hydroxide (*5*).

Bromides react in general more rapidly than chlorides with alkali

hydroxides, and when starting materials of formula I to IV are used, the reaction is frequently carried out in stages; this is due to the fact that the elimination of the second molecule of hydrogen halide is more difficult and requires more energetic conditions. Dihalides of general formula I to IV and haloalkenes of formula V to VII can be made to react in this manner. Dihalides in which the halogen atoms are not linked to adjacent carbon atoms also give rise to a triple bond, as long as the intervening carbon chain already contains a double or triple bond. The quantity of hydroxide is always greater than equimolar, and the concentration is generally above 4 normal. The solvents chiefly used are methanol, ethanol, and higher alcohols, as well as alcohol–water mixtures, glycol, glycol ether, glycerol, and even hydrocarbons. Examples are occasionally encountered where solvents are dispensed with; finely powdered or fused alkali hydroxide is then used with vigorous stirring. In the latter case the reaction temperature must be raised to 180–200°C. The normal reaction temperature is the boiling point of the solvent though higher temperatures, under increased or reduced pressures, are not infrequently employed. The reaction time varies from a few minutes to several hours.

Methylacetylene is thus obtained in good yield when 1,2-dichloropropane is treated with at least 2 moles of 14–23% aqueous sodium hydroxide solution at 150–175°C, the pressure being maintained above 17.5 atm. A duration time of 17 to 42 min in the reaction vessel gives good results. Ten per cent allene, a little *trans*-1-chloro-1-propene, 2-chloro-1-propene, and acetone are obtained as by-products (*6*). In an improved preparative method for 1-alkynes, 1,2-dihalides or 1- or 2-monohaloalkenes are added continuously to a stirred mixture of alkali hydroxide or alkoxide and inert solvents (e.g., higher alcohols) heated to above 110°C. The 1-alkyne formed distills off. Methylacetylene is thus obtained in 63% yield by the dropwise addition of 1,2-dichloropropane to a mixture of ethoxyethoxyethanol, commercial gas oil, and sodium hydroxide at 160–170°C (*7*).

Trifluoromethylacetylene has been prepared from dihalotrifluoropropanes or monohalotrifluoropropenes (*8, 9*). Comparisons with regard to the yields of acetylene and the lability of the different halogens split off as hydrogen halide are obtained from the experimental data. The following classes of compounds have been used in the synthesis of the corresponding acetylenes:

$$CF_3CH_2-CHX_2,\ CF_3-CHX-CH_2X,\ CF_3-CH=CHX$$

Table 1 shows the results of well-stirred reactions with powdered potassium hydroxide in the absence of solvent and under otherwise similar conditions.

It will be seen that better yields are obtained in a shorter reaction time from the bromo than from the chloro compounds. Fluorine is practically unaffected under these conditions.

TABLE 1

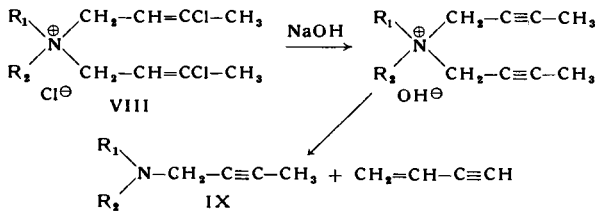
Preparation of Trifluoromethylacetylene

Starting material	Trifluoromethylacetylene (%)	Yield (%)-Trifluoropropene (%)	Reaction time (hr)
3,3-Dichlorotrifluoropropane	45	(Cl) 16	12
3-Chloro-3-bromotrifluoropropane	55	(Cl) 8	4
3-Chloro-3-iodotrifluoropropane	52	(Cl) 10	6
3-Bromo-3-iodotrifluoropropane	66	(Br) 11	6
2,3-Dichlorotrifluoropropane	12	(Cl) 50	12
1-Chlorotrifluoropropene	70	-	5
1-Bromotrifluoropropene	72	-	5
1-Iodotrifluoropropene	70	-	6

It is worth noting that cycloheptadecyne, the first cyclic acetylene, was prepared from 1-bromo-1-cycloheptadecene and potassium hydroxide in absolute alcohol in a pressure tube at 180°C (*10*). Furthermore, in the course of the synthesis of large rings, the ethylene ketal of 9-oxo-17-cycloheptadecyne was obtained in 98% yield from the dibromide and potassium hydroxide in amyl alcohol (*11*).

A laboratory method for the preparation of vinylacetylene starts from 1,3-dichloro-2-butene, which is allowed to react with potassium hydroxide in glycol and butyl glycol at 165–170°C (yield 50%) (*12*).

Quaternary ammonium salts containing the 3-chloro-2-butenyl residue can be dehydrochlorinated by aqueous sodium hydroxide at 55°C. Even at room temperature the dehydrochlorination proceeds at an appreciable rate. Dialkylaminobutynes are obtained, and thermal decomposition then affords pure, chloroprene-free vinylacetylene. This reaction is also applied to compounds containing two 3-chloro-2-butenyl residues (*13*) (VIII), to give dialkylaminobutyne (IX) free from dialkylamino-3-chloro-2-butene:



Diacetylene is obtained in varying yields from 1,4-dichloro-2-butyne and sodium hydroxide. Incompleteness of this reaction results in the formation of by-products, namely 2-chlorobut-1-en-3-yne, 1-chlorobut-1-en-3-yne, and 4-chlorobut-1-en-3-yne, together with acetylene and methylacetylene. One of the processes described consists in stirring a 40% solution of sodium hydroxide into a 25% solution of the starting material in ethanol at 65–75°C (*14, 15*). Diacetylene has been obtained by other workers in 60% yield from the same starting material, by vigorous stirring with aqueous potassium hydroxide at the reflux temperature (*16, 17*).

Triacetylene may be prepared from an ethereal solution of 1,6-dichlorohexadiyne and powdered sodium hydroxide, and collected in a receiver cooled in liquid air (*18*).

Cyclohexylacetylene has been obtained in 47% yield by treatment with alcoholic potassium hydroxide of 1,1-dichloro-2-cyclohexylethane, prepared by condensing cyclohexyl chloride with vinyl chloride (*19*).

1-Phenyl-2-propyne can be prepared in 84–88% yield by allowing sodium hydroxide to react with a warm alcoholic solution of the mixture of 2-chloro-1-phenylpropene and 2-chloro-3-phenylpropene, obtained from phenylacetone and PCl_5 (*20*).

Phenylacetylene is most conveniently prepared by the dehydrohalogenation of styrene dibromide; the reaction is carried out by boiling under reflux with methanolic potassium hydroxide. Yields of approximately 65% are obtained (*21*). Boiling 6-1′-chlorovinyl-1,2,3,4-tetrahydronaphthalene for 5 hr under reflux with ethanolic potassium hydroxide affords 6-ethynyl-1,2,3,4-tetrahydronaphthalene in good yield (*22*). Several dipyridylacetylenes have recently been prepared in almost quantitative yield by boiling 1,2-dipyridyl-1,2-dibromoethanes with potassium hydroxide in absolute methanol (*23*).

1-Hydroxy-2-butyne can be obtained in 80% yield by maintaining 1-hydroxy-3-chloro-2-butene and 20% alcoholic potassium hydroxide at the boiling point for 7 hr (*24, 25*).

5-Hydroxy-1-pentyne has been prepared by a five stage synthesis from tetrahydrofurfuryl alcohol via 1-hydroxy-4,5-dibromopentane (*26*) [cf. the more advantageous method (*27*)].

The preparation of ethoxyacetylene from 1,2-dibromoethyl ethyl ether (obtained from vinyl ether) provides an example of stepwise dehydrohalogenation with various alkaline reagents. The removal of the first molecule of hydrogen bromide is effected by diethylaniline, that of the second by potassium hydroxide under vacuum (*28, 29*). Methoxyacetylene and 1-ethoxypropyne can be obtained in like manner (*28, 29*).

It is worth noting in this connection that it has not thus far been found possible to prepare 1,2-dialkoxyacetylenes from the corresponding

1-halo-1,2-dialkoxyethylenes (*30, 31*). Neither will the halogen atom of such a compound undergo an exchange reaction. 1-Bromo-3-ethoxy- and 1-bromo-3-phenoxypropyne are obtained from 1,1-dibromo-3-ethoxy- and 1,1-dibromo-3-phenoxypropane, respectively, with potassium hydroxide in glycerol. In accordance with the known fact that bromides are more easily dehydrohalogenated than chlorides, 1,3-dibromo-1-chloropropene and potassium hydroxide in glycerol give 1-chloro-3-hydroxypropyne (*32*).

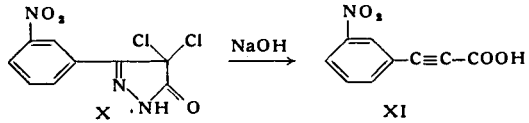
Stepwise dehydrohalogenation is used in the preparation of ethynyl ethyl sulfide, just as in the preparation of ethoxyacetylene (*33, 34*). Unlike the case of the 1-halo-1,2-dialkoxyethylenes, the corresponding sulfur compound, 1,2-bisethylmercaptochloroethylene, does form 1,2-bisalkylmercaptoacetylene in 60% yield by heating at the boiling point with alcoholic potassium hydroxide (*35*).

The preparation of 2-ethynylthiophene from 2-β-bromovinylthiophene by the use of fused potassium hydroxide at 200–240°C affords unsatisfactory yields (*36*), as does that of β-2-thienylpropiolic acid from β-2-thienylbromoacrylic ester.

Aldehyde groups unstable to alkali hydroxide are protected by acetal formation, with the result that even dihalogenated aldehydes can be dehydrohalogenated. Propargyl aldehyde diethyl acetal may be prepared from 2,3-dibromopropionaldehyde diethyl acetal (*37*).

The usefulness of the alkali hydroxides ends with the presence of groups unstable to alkali. Thus the preparation of acetylenecarboxylic or dicarboxylic acids is only accomplished in isolated cases free from simultaneous decarboxylation or other side reactions: acetylenedicarboxylic acid from dibromosuccinic acid (*38*), 16-heptadecynoic acid (*39*), and a few chlorophenyl-, nitrophenyl-, and methoxyphenylpropiolic acids (*40, 41*). The decarboxylation of α,β-acetylenecarboxylic acids, which frequently proceeds relatively easily, can be used for the preparation of aryl acetylenes when cinnamic acid or its derivatives are used as starting materials. Acetylenecarboxylic acid is, however, more easily obtained by a different route, e.g. the carboxylation of metal acetylides (*40*).

A preparation worth noting is that of *m*-nitrophenylpropiolic acid (XI) from 3-*m*-nitrophenyl-4,4-dichloro-2-pyrazolin-5-one (X) by dehydrohalogenation accompanied by hydrolysis and loss of nitrogen, using



X XI

aqueous sodium hydroxide at 5–10°C, and affording a yield of 75% (*42*). The corresponding alkylpropiolic acids, not easily prepared otherwise, can similarly be obtained in this manner.

A further disadvantage of using alkali hydroxide as dehydrohalogenating agent is the possibility of triple bond migration away from the end of the chain, especially at higher alkali concentrations or temperatures, resulting in the formation of disubstituted acetylenes instead of, or together with, the 1-alkyne. Examples have been described by Faworskij (*43*). The details quoted above for the preparation of methylacetylene show that under the conditions employed for triple bond formation by dehydrohalogenation, allenes can also be produced (*6*). It has been observed in the preparation of alkynyl ethers from *cis*- and *trans*-β-haloalkenyl ethers that whereas the *trans* compound yields the alkynyl ether exclusively the *cis* isomer is also partly converted into allenes (*29*).

The acetylene–allene isomerization resulting from the treatment of 1,4-nonadiyne with alkali has been thoroughly investigated. It was found that isomerization to 1,2-nonadien-4-yne takes place first, followed by that to 2,4-nonadiyne. The rearrangement to the dienyne proceeds at a substantially faster rate than that to 2,4-nonadiyne (*44*). A further complication occasionally arises in the dehydrohalogenation of α,β-dihalides. It is well known that β-quinolyl-, β-pyridyl-, and β-(benz-2-thiazolyl)-α,β-dibromopropionic acid, when treated with aqueous or alcoholic alkali hydroxides or other basic reagents, yield the acrylic acids and not the corresponding acetylenic compounds as major product (*3, 44a*). This reaction is by no means confined to heterocyclic compounds; instead of the acetylenes, olefins have also been obtained from α,β-dihalogenated stilbenes (*3*). A further possible side reaction is the addition of alcohol to the acetylenic linkage in the course of the dehydrohalogenation, especially at higher alkali concentrations and temperatures. Acetylenic compounds in which the triple bond is strongly activated, e.g. by phenyl, vinyl, ethynyl, or other functional groups, are particularly susceptible to this side reaction (*3*).

Using Alkali Amide

The use of sodamide in the formation of the acetylenic bond from dibromoethane and its homologs has been known since the twenties (*45, 46*). It is especially applicable to the conversion into acetylenes of dihalides in which the halogen atoms are linked to the same or neighboring carbon atoms, or of haloalkenes in which the halogen is attached to the double-bonded carbon atom. Dilution is effected by the addition of inert, high-boiling hydrocarbons, the working range of which extends to at least 100°C and preferably to 130–160°C (*47*). Liquid ammonia is an

excellent solvent, recently often used in the conversion of the above-mentioned dihalides, haloalkenes, or other starting materials into acetylenic compounds by means of alkali amides. Dehydrohalogenation can be effected under very mild conditions in this manner: in an open container at the boiling point of ammonia, or in a pressure vessel at room temperature. Reaction times are generally shorter with ammonia than with hydrocarbons. This method is particularly well-suited to reactions in which the acetylene is to be converted further via an alkali acetylide; in such a case, sufficient quantities of the alkali (lithium, sodium, or potassium) amide are simply added for simultaneous acetylide formation. Admittedly the use of liquid ammonia in the laboratory requires greater expenditure than that of solvents boiling above room temperature. Also, the quality of the amide must always be tested. Moisture causes a sodium hydroxide coating to be formed on sodamide and, especially in the case of commercial grades, the danger exists that a considerable proportion of the material is present as the hydroxide. The dehydrohalogenation may then partly proceed under the action of the latter, when, as pointed out above, the comparatively high temperature required by the hydrocarbon method may cause migration of the triple bond in the newly formed acetylene. It must be noted, furthermore, that sodamide may contain peroxide; the crushing of such a product can cause violent explosions. In preference to the use of commercial sodamide therefore, it is recommended that sodium be allowed to react with anhydrous liquid ammonia in the presence of catalytic amounts of ferric chloride or nitrate, or salts of cobalt (*48, 49*).

By the use of sodamide in light oil at 140°C it is possible to obtain a 62% yield of 3-methyl-1-butyne from 1,1-dichloro-3-methylbutane, 3-methyl-1-pentyne (68%) from 1,1-dichloro-3-methylpentane, 4-methyl-1-pentyne (80%) from 2-chloro-4-methyl-1-pentene, and 3,3-dimethyl-1-butyne (45%) from 1,1-dichloro-3,3-dimethylbutane at 95–100°C (*16*). The preparation of a series of 1-, 2-, and 3-alkynes is discussed later in connection with observations concerning triple bond migration due to the presence of alkali amide as dehydrohalogenating agent.

Sodium vinylacetylide required for further transformations is conveniently obtained from 1,4-dichloro-2-butene and 1,2-dichloro-2-butene or a mixture of the two at −35°C (*50*). 1,5-Hexadiyne can be made in 63% yield from 1,2,5,6-tetrabromohexane (obtained from 1,5-hexadiene) in liquid ammonia at −33°C (*16, 51*).

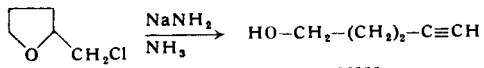
5-Hydroxy-1,3-pentadiyne may be prepared in 65% yield by the dehydrochlorination of 1,4-dichloro-2-butyne in liquid ammonia, followed by the action of paraformaldehyde on the diacetylene so obtained (*18, 52*).

The dehydrochlorination of 1,6-dichloro-2,4-hexadiyne to form 1,3,5-hexatriyne [also obtainable via another route (*53*)] is accomplished in 10 min by the use of sodamide in liquid ammonia at —70°C. Following decomposition with ammonium chloride and warming to —33°C, the highly explosive triyne can be extracted with butane. At —5°C the semi-solid residue left after evaporation of the solvent can be sublimed at 0.1 mm pressure into a receiver cooled by liquid air. Approximately 300 mg of triyne are obtainable in this manner from 7.4 gm of 1,6-dichloro-2,4-hexadiyne (*54*). Identical treatment of 1,6-dichloro-2,4-octadiyne affords 1,3,5-octatriyne, which is substantially more stable than the hexatriyne (*52*). 3-Isopropylphenylacetylene, an example of an arylacetylene, is obtainable in 78% yield from 3-isopropylphenylethylene dibromide (*55*).

Phenyldiacetylene can be obtained in distillable form via 1-phenyl-1,4-dichloro-2-butyne (*56*) or from phenylbutadiene tetrabromide (*57*). Diphenyltriacetylene may be prepared in similar manner from 1,6-dichloro-1,6-diphenyl-2,4-hexadiene (*18*).

1-Hydroxy-2-butyne can be obtained from 1-hydroxy-3-chloro-2-butene, itself prepared by the action of 10% sodium carbonate solution on 1,3-dichloro-2-butene; yields of the same order are obtained, whether the reagent is sodamide in ammonia (*58*) or ethanolic potassium hydroxide (*24, 25*).

The use of sodamide in liquid ammonia in the production of 5- and 6-hydroxyacetylenes represents an improvement and simplification of the method previously used. Whereas the older preparation of these compounds, from tetrahydrofurfuryl alcohol, respectively, 2-hydroxymethyltetrahydropyran, requires five steps (*26*), the single-stage conversion of 2-chloromethyltetrahydrofuran (XII) (accessible by the chlorination of the corresponding alcohol) into 5-hydroxy-1-pentyne (XIII) by sodamide affords yields of 85%.

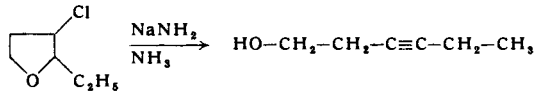


XII XIII

1-Hydroxy-4,5-dibromopentane, on the other hand, affords yields of only 56% of XIII. Similarly, up to 80% of the theoretical yield of 6-hydroxy-1-hexyne is obtained from 2-chloromethyltetrahydropyran, and 46% of propargyl alcohol from epichlorhydrin.

3-Chloro-2-ethyltetrahydrofuran (XIV) is converted into 1-hydroxy-3-hexyne (XV) in similar manner, albeit in lower yield; 2-ethyldihydrofuran is also formed.

Reaction times of 12 to 20 hr are quoted for dehydrohalogenation and ring-opening accompanied by triple bond formation (*27*).



XIV XV

The simultaneous elimination of hydrogen halide and alcohol from dialkoxychloroacetals (XVI) caused by the action of sodamide in liquid ammonia constitutes a convenient method for the preparation of alkoxyacetylenes, which are important intermediates in many further syntheses (*59*). Methoxyacetylene, ethoxyacetylene, and butoxyacetylene can be obtained by this route in 57, 61, and 44% yields, respectively.

$$\underset{\text{XVI}}{ClCH_2-CH(OR)_2} + 3\ NaNH_2 \rightarrow H-C\equiv C-OR$$

Lithium amide is recommended for the conversion of β-chlorovinyl ethers into alkoxyacetylenes with the concurrent formation of the alkoxyacetylene–lithium compound for immediate further reaction (*60*).

1-Diethylamino-2-propyne has been obtained in 82.5% yield from 1-diethylamino-2-bromo-2-propene, readily prepared from diethylamine and 2,3-dibromopropene. N-*n*-Butyl-di-2-propynylamine was obtained in 76.5% yield under the same conditions (*61*); liquid ammonia is used as the solvent. In contrast, 1-dimethylamino-2-propyne is obtained in only 25% yield from the corresponding starting material and a suspension of sodamide in mineral oil at 165°C (*62*).

2-Ethynylthiophene, a comparatively unstable acetylene derivative, can be prepared in 60% yield by allowing sodamide to react with 2-(β-bromovinylthiophene) in absolute ether containing a small amount of aniline. 3-Methyl-2-ethynyl-, 4-methyl-2-ethynyl-, 5-chloro-2-ethynyl-, and 2,5-dimethyl-3-ethynylthiophene can likewise be obtained in 65, 63, 24, and 45% yields (*63*). In the preparation of these heterocyclic acetylenes, the dehydrohalogenation using sodamide in liquid ammonia is superior to the alkali hydroxide method; the latter has afforded yields of only 20–25% of 2-ethynylthiophene (*36*).

While the presence of alkali hydroxides sometimes causes isomerization of the desired 1-alkynes to 1,2-disubstituted acetylenes, several examples are known where treatment with alkali amides results in the formation of 1-alkynes instead of the expected disubstituted acetylenes. These reports, however, are limited to reactions at elevated temperatures in high-boiling aliphatic or aromatic hydrocarbons (*3*). No triple bond migration has been observed in the case of ethylamylacetylene with sodamide in liquid ammonia at —34°C (*49*). On the other hand, it is known from other work that under similar conditions, 2-alkynes are formed from *sym*-3-alkenes via their dibromides. Thus chiefly 2- and

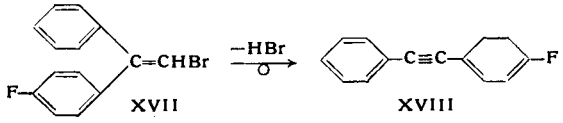
very little 3-hexyne are obtained from a predominantly *cis*-containing mixture of *cis*- and *trans*-3-hexene via the corresponding dibromides. The same is true when *trans*-3-hexene is the starting material. *trans*-3-Octene, on the other hand, gives predominantly 3-octyne with some 2-octyne. *sym*-4-Octene affords 4-octyne in 56% yield. If 3-hexyne is treated with sodamide in liquid ammonia, mainly 2-hexyne is obtained, as it is from the dibromides of the isomeric *cis*- and *trans*-3-hexenes. 2-Pentyne is formed from *cis*- and *trans*-2-pentene (70% *trans* and 30% *cis* isomer). No isomerization was observed in the preparation of 4-methyl-1-pentyne from 4-methyl-1-pentene via the dibromide, when a yield of 74% was obtained. 3-Methyl-1-butene and 3,3-dimethyl-1-butene give the expected 1-pentyne and 1-butyne compounds (*64*).

The fact that opposite directions of isomerization are encountered with alkali hydroxides and alkali amides at higher temperatures can be accounted for by the greater stability of the 2-alkynes. This is in accord with results from measurements of pure 1-pentyne: The equilibrium mixture at 175°C in the presence of potassium hydroxide (with or without ethanol) consists predominantly of 2-pentyne (*65*), with a little 1-pentyne and 1,2-pentadiene. The opposite isomerization with alkali amide at higher temperatures is due to alkali acetylide formation.

Finally it must be added that even in the earlier literature, mention is made, in connection with the decomposition of 1,2-dihalides with sodamide at higher temperatures, of a side reaction leading to olefin formation, similar to that encountered in isolated cases when alkali hydroxides are used (*3*).

In cases where special structural conditions obtain, a different type of dehydrochlorination reaction with alkali amides is also known. 1,1-Diaryl-2-haloethylene or 1,1-diaryl-2,2-dihaloethane are converted into 1,2-diarylalkyne in liquid ammonia (*66*). This transformation has for a long time been known to occur when 1,1-diphenyl-2-chloroethylene and 1-methyl-1-phenyl-2-bromoethylane are treated with sodium ethoxide at 200°C and potassium hydroxide at 180°C, respectively (*67–70*). Whereas it requires several hours and a high temperature with sodium ethoxide or potassium hydroxide, the reaction is completed in but a few minutes when sodamide in liquid ammonia is used. The investigations into the mechanism of the reaction have been reviewed by Franzen (*71*).

A more recent example is found in the conversion of 1-*p*-fluorophenyl-



XVII XVIII

1-phenyl-2-bromoethylene (XVII) into 1-phenyl-2-(*p*-fluorophenyl)-acetylene (XVIII) in 75% yield, by the action of potassium amide in liquid ammonia (*72*).

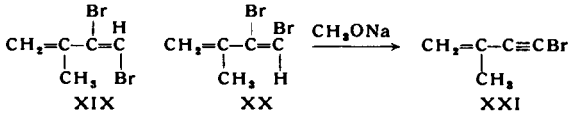
Using Other Alkaline Reagents

Alkali alkoxides and, less frequently, alkali carbonates and hydrides are additional alkaline dehydrohalogenating agents mentioned in the preparation of acetylenes. Basic anion exchange materials have also been used.

Sodium ethoxide was the first dehydrohalogenating agent, after sodium hydroxide, used in the preparation of a substituted acetylene, namely methylacetylene, obtained from bromopropene (*3, 73*).

Potassium butoxide has recently been used in the preparation of methylacetylene from 1,2-dibromopropane, when a yield of 70% was obtained (*74*). Diarylacetylenes have been synthesized with sodium ethoxide or *tert* butoxide. *p*-Chlorophenylphenylacetylene may be prepared in 60% yield from *p*-chlorophenylacetophenone and sodium *tert* butoxide via the trichloro derivative. Similarly, bis-*p*-chlorophenylacetylene has been obtained in good yield by the use of sodium in absolute ethanol (*75*). Potassium ethoxide has been used to prepare 1,6-diphenylhexatriyne from 1,6-diphenyl-1,6-dichloro-2,4-hexadiyne (*76*), 1,8-diphenyloctatetrayne from 1,8-diphenyl-3,6-dichloro-1,4,7-octatriyne, and 1,10-diphenyl-decapentayne from 1,10-diphenyl-3,8-dichloro-1,4,6,9-decatetrayne (*57*).

It is worthy of note that *cis*- and *trans*-3,4-dibromo-2-methyl-1,3-butadiene differ markedly in their behavior towards sodium methoxide. Whereas XIX remains unchanged, XX forms isopropenylbromoacetylene (XXI) even at 20°C.



In analogous manner 1-(1′-cyclohexenyl)-1,2-*cis*-dibromoethylene produces 1-cyclohexenyl-2-bromoacetylene (*77*). Phenylpropiolic acids containing substituents in the benzene ring can often be prepared in good yield when sodium ethoxide is used as the dehydrohalogenating agent (*41*).

It has been observed that in the dehydrobromination of bromocrotonaldehyde diethyl acetal (XXII) by aqueous potassium carbonate solution, some 1-butynal-4-acetal (XXIV) and probably a small amount

of 1,2-butadienal-4-acetal (XXV) are produced together with the major product, 2-butynal-1-acetal (XXIII) (*78*).

$$\underset{\text{XXII}}{CH_3CBr{=}CH{-}CH(OC_2H_5)_2} \rightarrow \underset{\text{XXIII}}{CH_3{-}C{\equiv}C{-}CH(OC_2H_5)_2} +$$

$$\underset{\text{XXIV}}{CH{\equiv}C{-}CH_2{-}CH(OC_2H_5)_2} + \underset{\text{XXV}}{CH_2{=}C{=}CH{-}CH(OC_2H_5)_2}$$

A benzene solution of sodium hydride in the presence of a little absolute alcohol has proved useful in the conversion of phenyl-substituted α,β-dibromopropionic esters into the phenylpropiolic esters. The sodium alkoxide formed is thought to be the actual dehydrohalogenating agent:

$$C_2H_5OH + NaH \rightarrow C_2H_5ONa + H_2$$

The alkoxide is neutralized by the eliminated hydrogen bromide and the alcohol is regenerated; the molar quantity of sodium hydride used can thus once again form sodium alkoxide. Very small amounts of alcohol therefore suffice; this results in the suppression or elimination of side reactions, e.g. ether formation, which occur at higher alkali, alkoxide, or hydroxide concentrations in reactions where alcohol is the solvent.

The preparation of phenylpropiolic ester from β-phenyl-α,β-dibromopropionic ester by the method indicated above proceeds with relatively little β-ethoxycinnamic ester formation; if, on the other hand, sodium ethoxide is used under normal conditions, β-ethoxycinnamic ester constitutes practically the whole of the product. *o*-Chlorophenylpropiolic ester is obtainable in 89.5% yield from the corresponding dibromide, and *p*-chlorophenylpropiolic ester can be prepared in similar manner (*41*).

It has been pointed out that the use of alkali alkoxides may give rise to alkoxy compounds as by-products. This undesirable effect is also generally enhanced at elevated temperatures and higher alkoxide concentrations.

In the first preparation of triacetylene from 1,6-dichloro-2,4-hexadiyne, the solution of the complex formed by silver salts, aqueous alkali, and concentrated ammonium hydroxide solution was used. Acidification of the precipitated triacetylene silver with dilute aqueous acid is followed by the removal of the silver as the sulfide, and 1,3,5-hexatriyne can then be isolated in a cold-trap (*53*). A yield of 10% is obtained; the use of sodamide afforded no better result (*54*).

Weakly basic anion exchange materials have also been used in the dehydrohalogenation of a number of 1,2-dibromides; 1-hexyne, 1-heptyne, and 1-octyne were obtained in approximately 40% yield by this method. The reaction is carried out in high-boiling hydrocarbons, e.g. tetralin; the solution is heated for several hours at 160°C with the anion

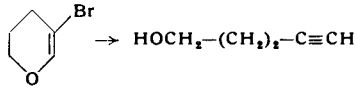
exchanger, the acetylene being distilled as it is formed. Phenylacetylenes could not be obtained (*79*).

Using Organometallic Compounds

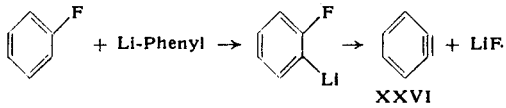
A number of organometallic compounds, e.g. butyllithium, butylsodium, and phenyllithium have in recent years been used for the dehydrohalogenation in the preparation of acetylenes. It was discovered quite a long time ago in connection with the action of phenyllithium on ω-chlorostyrene (or ω-bromostyrene) in ether that the hydrogen of the vinyl group becomes acidic under the influence of the halogen, and is replaced by lithium. Loss of lithium halide results in the formation of phenylacetylene in yields exceeding 70% (*80*). Thus, in the reaction between butyllithium and ω-bromostyrene in ether at —35°C in the presence of powdered solid carbon dioxide, acetylene formation, and carboxylation give rise to a 45% yield of phenylpropiolic acid after a few minutes.

$$C_6H_5CH{=}CHBr \xrightarrow{C_4H_9Li,\ CO_2} C_6H_5C{\equiv}C{-}COOH$$

α-Bromostyrene, on the other hand, gives α-phenylacrylic acid (*81*). 2,3-Dehydro-3-bromopyran and butylsodium in the presence of a small amount of butanol at 0°C afford 5-hydroxypentyne in 87% yield (*82*).



The formation of dehydrobenzene (XXVI) as intermediate in the reaction between fluorobenzene and phenyllithium in ether or tetrahydrofuran is worthy of notice (*83*). Although the "dienyne" cannot be isolated as such, it can be detected by its secondary products, e.g. the furan adduct (*84, 85, 85a*).



XXVI

Dehalogenation and Reductive Dehalogenation Using Metals

Metals, usually finely divided, are relatively little used as dehalogenating, or, in the presence of alcohols as reductive dehalogenating, agents in the preparation of acetylenes. 1,2-Dihaloalkenes, as well as polyhalogen compounds in the case of reductive dehalogenation, are the

usual starting materials. Repeated attempts to prepare cyclic acetylenes used sodium in the removal of chlorine or bromine from 1,2-dihalocycloölefins. 1,2-Dibromocyclopentene was treated in this manner, as were the corresponding halogen compounds of the six- and seven-membered rings; the results were unsatisfactory, however (*86*). Cycloöctyne was subsequently prepared by the action of sodium on 1-chloro-2-bromocycloöctene (*87, 97*). The synthesis of cyclodecyne was attempted in a similar manner; this merely produced a mixture, which was shown by oxidative degradation to consist mostly of 1,2-cyclodecadiene and only a little cyclodecyne (*88*). Zinc dust in alcohol gives a 25% yield of diacetylene from polychlorobutadiene (*89*), and triacetylene from perchlorohexadiene (*90*).

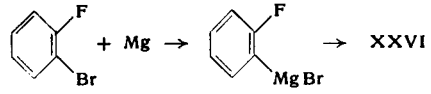
$$Cl_2C{=}CCl{-}CCl{=}CCl_2 \rightarrow HC{\equiv}C{-}C{\equiv}CH$$

$$Cl_2C{=}CCl{-}CCl{=}CCl{-}CCl{=}CCl_2 \rightarrow HC{\equiv}C{-}C{\equiv}C{-}C{\equiv}CH$$

Trifluoromethylacetylene is obtainable in 25% yield from 2,3-dichloro-1,1,1-trifluoropropene, by heating under reflux for 120 hr with zinc dust and absolute ethanol. The 2,3-dibromo compound, on the other hand, gives the same product in 96% yield after only 6 hr (*8*).

$$CF_3{-}CX{=}CHX \rightarrow CF_3C{\equiv}CH$$

A 90% yield of hexafluoro-2-butyne has been obtained by allowing 2,3-dibromo-1,1,1,4,4,4-hexafluoro-2-butene to react with zinc dust and absolute ethanol under reflux (*91*). The formation of dehydrobenzene (XXVI) from *o*-fluorobromobenzene and magnesium in tetrahydrofuran, via the nonisolable *o*-fluorophenylmagnesium bromide, is worth noting.



Dehydrobenzene required for immediate further use is best prepared by this route (*83, 84*).

Decomposition of Nitrogen-Containing Compounds

Bisquaternary Ammonium Compounds

The conversion of quaternary ammonium hydroxides into olefins, known as the Hofmann degradation, can be applied to the preparation of acetylenes from 1,2-diquaternary ammonium hydroxides (XXVII):

$$[(CH_3)_3N{-}CH_2{-}CH_2{-}N(CH_3)_3](OH)_2 \rightarrow HC{\equiv}CH$$

XXVII

This route was investigated as a laboratory method for the production of acetylene and its homologs (*92*). Acetylene is obtained in 80% and 2-hexen-4-yne in 85% yield. Methylacetylene can also be prepared in good yield by this method.

A yield of 60% is afforded by the laboratory preparation of diacetylene. The 1,4-diquaternary ammonium hydroxides of 2-chloro-2-butene or of the corresponding 2-butyne compound, obtained from their quaternary salts, may be used as starting materials; warming with aqueous alkali converts them into diacetylene (*93*).

$$[(CH_3)_3N{-}CH_2{-}CH{=}CCl{-}CH_2{-}N(CH_3)_3]Br_2 \text{ or}$$

$$[(CH_3)_3N{-}CH_2{-}C{\equiv}C{-}CH_2N(CH_3)_3]Br_2 \xrightarrow{NaOH} HC{\equiv}C{-}C{\equiv}CH$$

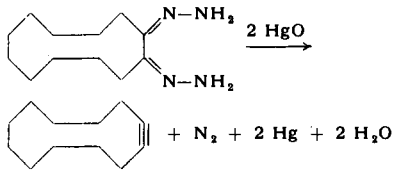
A noteworthy reaction occurs between trimethyl-2,2,3,3-tetrachlorobutylammonium iodide (XXVIII) and aqueous alkali hydroxide, whereby tetrolic acid is formed (*94*).

$$[CH_3{-}C(Cl_2){-}C(Cl_2){-}CH_2{-}N(CH_3)_3]\ I \rightarrow CH_3{-}C{\equiv}C{-}COOH$$

XXVIII

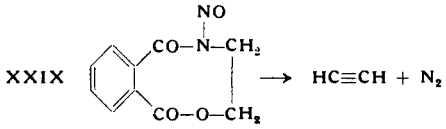
Bishydrazones

Tolan (diphenylacetylene) can be obtained in a pure state and almost quantitative yield by the oxidation of benzil dihydrazone, effected by boiling under reflux with excess yellow mercuric oxide in benzene solution (*75*). More recently a number of substituted tolans were synthesized by this method, with silver benzoate or trifluoroacetate as the oxidizing agent. N-Methylpyrrolidone, triethylamine, acetonitrile, etc., are suitable solvents. The reaction is complete after approximately 4 hr, and, e.g., *o*-chlorophenylphenylacetylene is obtained in good yield with silver benzoate. When silver trifluoroacetate is used as the oxidizing agent, *m*-chlorophenylphenylacetylene is obtainable in 80%, and diphenylacetylene and di-*p*-methoxyphenylacetylene in 85% yield (*95*). The method starting from diketones can sometimes be used with advantage in the preparation of cyclic acetylenes. Attempts to synthesize these compounds by other routes either met with no success, or yielded also cyclic allenes (sometimes exclusively) (*86,96*); the products are almost invariably obtained in poor yields and an impure state (*10,88,97;* but see ref. *11*). Cyclodecyne can be obtained from sebacil in 36% yield with yellow mercuric oxide in benzene in the presence of ethanolic potassium hydroxide and anhydrous sodium sulfate (*88*). Sebacic acid can be used as the starting material; this is converted first into sebacoin, and then into sebacil with chromium trioxide. Cyclododecyne results in similar manner from the dihydrazone of the corresponding 1,2-diketone (*96*).

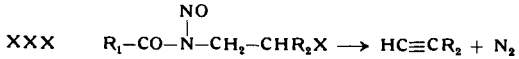


β-Substituted Nitrosoacylamines

It is well known that the action of dilute alkali on N-nitroso-O,N-phthalylaminoethanol (XXIX) produces acetylene with elimination of nitrogen (*97a*).



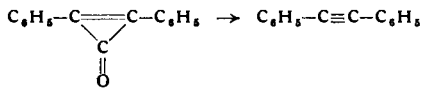
Phenyl-substituted acetylenes, e.g. tolan, may be obtained from 3-nitroso-2-oxazolidones under similar conditions (*97b*). More recently, 1-alkynes have become accessible in good yield via β-substituted nitrosoacylamines (XXX) (*97c*). Even under very mild conditions, namely with dilute alcoholic alkali hydroxide solutions, acetylenes possessing a terminal triple bond are obtained; this is particularly the case when nitrosoacylamines with β-hydroxyl or acetoxy groups (X) are used.



Miscellaneous Methods

Acetylenes may be synthesized by a number of other methods which cannot be assigned to any of the groups mentioned hitherto.

Loss of carbon monoxide at 130–140°C gives a 20% yield of tolan from diphenylcyclopropenone (*98*), obtainable from phenyldichloromethane and 1-phenyl-2,2-dimethoxyethylene (phenylketene acetal).



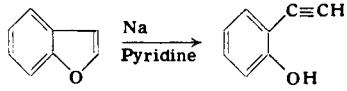
Ethylmercaptoacetylene can be prepared by allowing 1,2-bis(ethylmercapto)ethylene to react with 2 moles of butyllithium in ether. Lithium ethyl mercaptide and the lithium derivative of ethylmercaptoacetylene

are formed; water decomposition of these affords a 47% yield of ethylmercaptoacetylene and ethylmercaptan (*99*).

$$C_2H_5S-CH=CH-S-C_2H_5 \rightarrow C_2H_5S-C\equiv CH + C_2H_5SH$$

Phenylmercaptoacetylene is obtained in analogous manner in 60–80% yield from *cis*- and *trans*-1,2-bis(phenylmercapto)ethylene in ether after a reaction time of 2 hr, followed by water decomposition (*100*).

The transformation of coumarone—formally to be regarded as an isomerization—by the action of sodium metal in the presence of pyridine produces *o*-hydroxyphenylacetylene (*101*). The sulfur analog, thionaphthene, on the other hand, affords phenylacetylene in 30–40% yield on treatment with sodium at 150–180°C in the absence of oxygen (*102*). Thionaphthenes with substituents in the phenyl ring can also be used. Iodine in ethanol converts 1,2,3-butatriene into 1,4-diiodo-2-butyne, which can be isomerized to 2,3-diiodo-1,3-butadiene by potassium iodide in acetone (*103*).



By the Pyrolysis of Hydrocarbons and Other Compounds

The use of pyrolysis as a means of obtaining acetylenic compounds is restricted to the lower members of the series. Large-scale technical processes are known, and the essentials only are mentioned here.

The production of the triple bond is thermodynamically based on the fact that whereas the free energy of the formation of acetylene from its elements decreases with increasing temperature, most of the paraffins and olefins under consideration show a free energy curve rising with temperature (*104, 105*). At higher temperatures, in other words, the stability relationship is reversed. Thus, methane is thermodynamically less stable than acetylene above 1600°K; the temperature functions of the free energy of ethane and acetylene cross around 1300°K, and those of propane and acetylene around 1220°K. The large-scale processes for the manufacture of acetylene by high-temperature cracking are differentiated mainly in their method of producing the required temperature and in their choice of starting material.

If methane, ethane, propane, and other hydrocarbons are sparked by an electric arc (*104, 106*) (using direct current, between two electrodes at 8000–10,000 volts and 800 amps), the major products are acetylene, ethylene, propylene, and hydrogen. In a modified process, hydrogen is introduced into the arc, giving activated hydrogen atoms; these react with

the hydrocarbon to form acetylene in particularly high yield (up to 85%) (*107*). In the Sachsse process (*108,109*), part of the hydrocarbon is burned to carbon monoxide with oxygen (1100° to 1500°C), thus providing the energy for the conversion of the remainder. Similarly, the heat required in Hoechster pyrolysis is supplied by the combustion with oxygen of the residual gases accumulating in the reaction (*110*). One method of cracking liquid hydrocarbons at low pressures involves the use of small carbon rods as auxiliary electrodes, connected to an alternating current source. Arcs of shorter length and burning time are thus obtained. The cooling required in other pyrolytic alkyne syntheses is unnecessary in this case, and soot formation is slight (*111*). A process for the thermal decomposition of liquid hydrocarbons (e.g. Diesel oil) has also been patented, in which the heat required is produced by the surface combustion of part of the hydrocarbon with oxygen or oxygen-containing gases (*112*). Here too, auxiliary cooling to lower temperatures is unnecessary, as this already occurs at the surface of the liquid.

In another process, methane, propane, and liquid hydrocarbons, diluted with steam, are converted into acetylene in a cracking oven at 1300°C under vacuum (*113*). A similar cracking process (*114*) converts petroleum in the presence of catalysts into a mixture of olefins in the first step; these, diluted with an inert gas, are then decomposed at 1000° to 1200°C to acetylene in the second step.

A more recent technique involving partial combustion resembles that of Sachsse, though lower pressures and smaller quantities of oxygen are used (*115*). Relatively high yields of acetylene (45–50%) are obtained. The use of catalysts is found to be advantageous when methane is used as the starting material. The high temperature required can be obtained by the combustion of hydrogen and oxygen (*116*). A modified process utilizes petroleum as the fuel; this is burned with air or oxygen in the presence of steam in a reaction chamber. The hot gases are then led into a pipe, where they mingle with the gas to be decomposed, providing it with the heat required (*117*). There is further a patented process which makes use of molten iron at 1650–1930°C and finds favorable application in the conversion of methane; this is accomplished by passing the hydrocarbon into or over the molten metal (*118*).

In all these pyrolytic processes, it is to be expected that much hydrogen, ethylene, and higher acetylenes will be produced. Thus, in the electric arc method of the Chem. Werke Hüls A.G., methylacetylene, allene, vinylacetylene, diacetylene, triacetylene, and phenylacetylene are obtained, together with other thermodynamically favored products, e.g. benzene, styrene, naphthalene, and other aromatic compounds (*53,106*). These by-products are separated by oil washing or intense cooling.

Methylacetylene can be obtained together with allene from isobutylene and *tert* butyl alcohol at 800–1050°C (*119, 120*), with a maximum yield of approximately 30%. Steam, in quantities of 50 to 90 mole %, is used. Another patent describes the production of methylacetylene and allene from propylene and steam at 800–1100°C (*121*). Dichloropropane or chloropropene can be converted thermally into methylacetylene at 920–1050°C; it is best to dilute with inert gases, such as nitrogen, carbon dioxide, methane, or water vapor. A yield of up to 58% of methylacetylene, and 12.7% of allene, is obtained (*122*). Methylacetylene and much allene are produced in the decomposition of itaconic anhydride at 900°C and 3–4 mm pressure (*123*). Methylacetylene is also obtained by the thermal decomposition of citraconic anhydride at 750°C and 50 mm pressure (*123*).

Recent investigations into the position of the equilibrium between propyne and allene in the temperature range of 100° to 370°C have shown that in the presence of all the catalysts used, an isomerization equilibrium dependent on temperature alone is set up. The equilibrium constant K_p has a value of 0.172 at 400°K and 0.242 at 600°K (*124*).

2-Butyne is a by-product in the large-scale dehydrogenation of butane to 1,3-butadiene at 600°C (Houdry process). It may be isolated from the residues of the butadiene distillation (*125*).

Fluoroacetylene is obtained in almost quantitative yield in the pyrolysis of monofluoromaleic anhydride at 650°C and 5–7 mm pressure (*125a*).

In the temperature range of the pyrolyses mentioned above, the free elements carbon and hydrogen are thermodynamically still substantially more stable than acetylene and its homologs. The preparation of acetylenic hydrocarbons therefore necessitates short reaction times and rapid cooling (*126*) of the reaction mixture to under 200°C. Thus, the duration time in the electric arc preparation of acetylene must not exceed 0.001 second, nor that of propyne from isobutylene or *tert* butanol 0.01 to a maximum of 10 sec.

Experimental

Diacetylene (*15*). Sodium hydroxide (570 gm of a 40% aqueous solution) is added dropwise to a mixture of 1,4-dichloro-2-butyne (123 gm) and ethanol (100 to 500 gm) maintained at 75°C. The gaseous diacetylene formed is collected. It is then washed with dilute sodium hydroxide and dried with calcium chloride. Yield, 79.3%.

Phenylacetylene (*127*). Bromine (410 gm) is added dropwise over a period of 2 hr to a cooled and stirred mixture of chloroform (200 ml) and

styrene (312 gm). Stirring at 30°C is continued for a further half-hour. The chloroform is distilled off, and drying in air affords pure white styrene dibromide. Yield, 653 gm; m.p. 73°C.

Styrene dibromide (264 gm) is added in small portions over a period of 1.5 hr to a stirred mixture of potassium hydroxide (240 gm) and methanol (240 ml) under reflux. The reaction mixture is boiled for a further half-hour and cooled. Water (400 ml) is added, the oily layer formed is separated, dried over potassium carbonate, and distilled under vacuum. At 10 mm and below 100°C an oil (75 gm) is obtained which, on redistillation at atmospheric pressure, gives phenylacetylene (67 gm, 66%) b.p. 141–143°C.

5-Hydroxy-1-pentyne (*27*). Tetrahydrofurfuryl chloride (242 gm) is added dropwise over 25 min to a stirred suspension of sodamide (made from 161 gm of sodium) in liquid ammonia (3500 ml). After 16 hr stirring, anhydrous ammonium chloride (350 gm) is gradually added, the greater part of the ammonia allowed to evaporate, and the reaction product extracted with ether. The ether is evaporated and the product distilled under vacuum. 5-Hydroxy-1-pentyne (142 gm, 85%) is obtained. B.p. 64–65°C/16 mm, $n_D^{10} = 1.4451$. After purification via the silver salt: B.p. 77°C/37 mm, $n_D^{25} = 1.4464$.

o-Chlorophenylpropiolic acid (*41*). Bromine (305 gm) is added dropwise to a solution of *o*-chlorocinnamic ester (400 gm) in methylene dichloride (500 ml). After an initial period of induction the reaction becomes violent and cooling is necessary. The solvent and unreacted bromine are evaporated under reduced pressure, benzene is added and the mixture distilled for 5 min to remove any water present. Sodium hydride (22 gm) is added to the stirred, dry ester (163 gm) in benzene (200 ml), followed by ethanol (3 ml). The reaction mixture becomes warm, and requires initial cooling. After standing for 1 hr, the mixture is boiled under reflux for an hour, after which time there is practically no further evolution of hydrogen. The reaction mixture is stirred into water, and an acidic and neutral fraction are separated. The acidic fraction yields *o*-chlorophenylpropiolic acid (6.4 gm, 8%). Distillation of the neutral fraction affords crude *o*-chlorophenylpropiolic ester (82.2 gm, 89.5%), b.p. 110–117°C/1–2 mm, $n_D^{20} = 1.5590$–1.5580. The dry ester is saponified with a slight excess of a 20% aqueous solution of sodium hydroxide to which a little alcohol has been added. The alkaline solution is extracted with ether to remove neutral material and slowly acidified with hydrochloric acid. A small amount of *o*-chlorocinnamic acid is first precipitated and is removed. *o*-Chlorophenylpropiolic acid is then precipitated, and is purified via its potassium salt (obtained by the addition of a hot 3% alcoholic solution of potassium hydroxide and precipitation

by cooling the solution). The free acid may be recrystallized from benzene; m.p. 132.7–133.8°C. Total yield 54% (calculated with respect to *o*-chlorocinnamic ester).

Phenylacetylene (*80*). A mixture of ω-chlorostyrene (0.05 mole, 6.9 gm), b.p. 79–81°C, and phenyllithium (0.1 mole) in ether (total volume 100 ml) is allowed to warm up to the boiling point of the solvent; at this temperature the lithium chloride is precipitated. After cooling, the mixture is allowed to stand for 15 min, and the solution hydrolyzed (52% LiOH is recovered). Fractionation of the ether layer yields phenylacetylene (3.6 gm, 70%), b.p. 141–143°C, and chlorostyrene (0.6 gm).

Trifluoromethylacetylene (*8*). 1,2-Dibromo-3,3,3-trifluoropropene (12.7 gm) is treated for 6 hr with zinc dust (20 gm) and absolute alcohol (200 ml) in a flask fitted with a reflux condenser maintained at —40°C; after this period the reaction is complete. Trifluoromethylacetylene (4.5 gm, 96%) is obtained, b.p. —48 to —46°C (*9*).

Polyfluoro-2-butyne (*91*). 2,3-Dibromo-1,1,1,4,4,4-hexafluoro-2-butene (1.98 gm) is vigorously stirred for 4 hr under reflux with zinc dust (20 gm) and absolute alcohol (60 ml). 1,1,1,4,4,4-Hexafluoro-2-butyne (0.90 gm, 90%) is obtained, b.p. —24°C.

Cyclododecyne (*96*). 1,2-Cyclododecanedione bishydrazone (21.25 gm) is added portionwise to a mixture of mercuric oxide (41.1 gm), sodium sulfate (50 gm), potassium hydroxide (2.1 gm), and toluene (220 ml) in a three-necked flask fitted with a stirrer and separator; the addition is carried out with vigorous stirring, at a bath temperature of 140°C. After heating for 2 hr, the solid is filtered off and the filtrate is put on an alumina column (200 gm, activity I–II). Cyclododecyne, b.p. 106–109°C/11 mm, is eluted with pentane.

Phenylmercaptoacetylene (*100*). A solution of *cis*-1,2-bis(phenylmercapto)ethylene (*129*) (ca. 2 gm) in ether (5 ml) is added dropwise to a solution of *n*-butyllithium (prepared from lithium turnings, 1.65 gm) and *n*-butyl bromide (14.1 gm) according to the method of Gilman and Morton (*128*) in ether (55 ml). After the reaction mixture has been cooled to —10 to —15°C, the remainder of the *cis*-1,2-bis(phenylmercapto)ethylene (total quantity, 14.03 gm) is added dropwise with stirring; the reaction mixture thus obtained is stirred for a further 2 hr at —10°C, allowed to warm up to 0°C, and decomposed by the dropwise addition of water (40 ml). The mixture is allowed to warm up to room temperature, stirred for 2 hr and refluxed for 30 min. After cooling, the two layers are separated. The ether layer is dried over sodium sulfate, concentrated, and the orange-yellow residue (9.37 gm) distilled. Phenylmercaptoacetylene (4.63 gm, 60%) is obtained, b.p. 78–79°C/7 mm, $n_D^{25} = 1.5938$.

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Syntheses Using Diazoketones

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Introduction

Since the work of Arndt, Eistert and co-workers (*1*), followed by that of Bradley and Robinson (*2*), first rendered diazoketones readily accessible by the reaction between acid chlorides and diazomethane, these compounds have assumed increasing importance in the realm of preparative organic chemistry. The first review on the preparative significance of diazoketones was published by Eistert (*3*). Huisgen (*4*) subsequently summarized the reactions undergone by aliphatic diazo compounds and again indicated their usefulness. In view of the abundance of recent publications in this field, which continually describe novel reaction sequences starting from diazoketones, a review dealing with the preparative aspect seems not unjustified.

Mode of Reaction of Diazoketones

Diazoketones undergo a number of fundamental reactions, and these are now briefly outlined (cf. ref. *4*).

Elimination of Nitrogen from Diazoketones

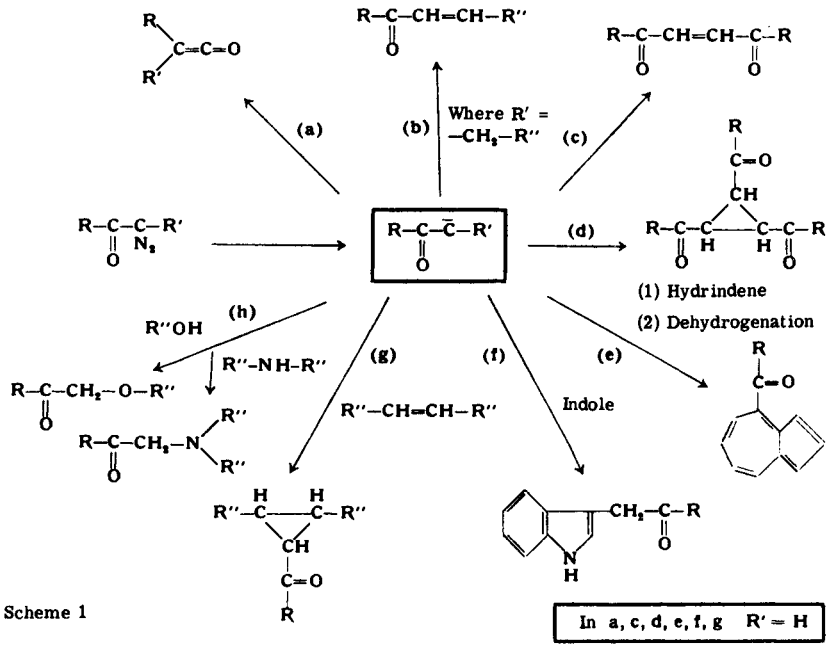
When a diazoketone loses nitrogen a sextet of electrons remains on the carbon atom which was linked to the diazo group. The α-keto carbene thus formed is capable of undergoing the most diverse reactions, depending on the conditions under which nitrogen elimination takes place (thermal, metal-catalyzed, or photolytic). Scheme 1 summarizes the preparative possibilities employed to date.

(*a*) If the α-keto carbene stabilizes itself by an intramolecular rearrangement a ketene is formed (Wolff rearrangement) (*5*) which can then react further in the presence of suitable reactants (e.g., with water to give carboxylic acids).

(*b*) Intramolecular hydrogen displacement produces unsaturated ketones from carbenes of the form R—CO—C—CH_2—R′ (*6*).

(*c*) and (*d*) Dimerization and trimerization give 1,2-diacyl ethylenes and triacyl cyclopropanes, respectively (*7*).

(*e*) At elevated temperatures, α-keto carbenes can enlarge the ring of hydrindene (*8*), or



Scheme 1

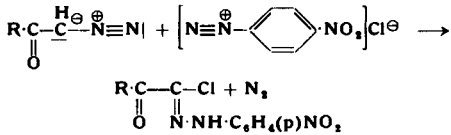
(*f*) substitute certain heterocyclic and isocyclic rings (*8–10*).

(*g*) α-Keto carbenes can react with compounds containing a double bond, to form derivatives of cyclopropane (*9*).

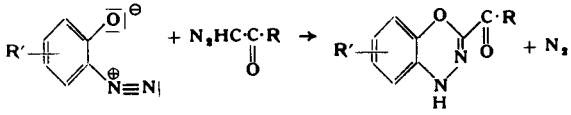
(*h*) Decomposition of diazoketones with copper powder in the presence of amines, alcohols, or mercaptans gives rise to α-amino ketones, α-ketol ethers, or α-ketol thioethers, respectively (*10*). Other reactions proceeding in similar manner are discussed later.

Reaction with Electrophilic Agents

In addition to the well-known reactions of diazoketones with hydrohalic acids, carboxylic acids, water, and halogens (cf. ref. *3*), a number of further reactions possessing preparative interest have recently been discovered. Thus Huisgen and Koch (*11*) found that diazoketones react with aryldiazonium salts to give the hydrazide chlorides of α-keto acids:



The same research team reported the action of diazoketones on quinone diazides, resulting in the formation of 2-acyl-4H-1,3,4-oxadiazines (*12*).

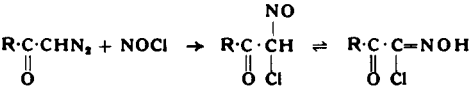


The reaction, investigated by Weygand and Bestmann (*13*), between diazoketones and sulfenyl chlorides yields α-chloro-α-alkyl(or aryl)mercapto ketones.

$$R{-}CO{-}CHN_2 + R'{-}S{-}Cl \rightarrow R{-}CO{-}CHCl{-}S{-}R' + N_2$$

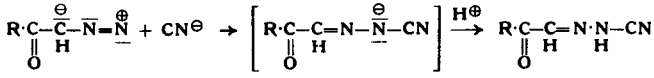
These new compounds are bifunctional and can be regarded as either α-haloketones or the hemimercaptal chlorides of α-keto aldehydes. The multiplicity of reactions resulting from this dual character has been comprehensively reviewed (*14*).

The reaction, described without further detail, between diazoketones and nitrosyl chloride (*15*) must also be mentioned:



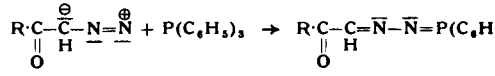
Reactions at the Terminal Nitrogen Atom of the Diazo Group

As early as 1902, Wolff (*16*) found that diazoketones react with potassium cyanide to give the potassium salts of the cyanohydrazones of α-keto aldehydes:



The use of these compounds in the synthesis of triazine derivatives is discussed later.

Similarly, diazoketones are capable of reacting with tertiary phosphines, especially triphenylphosphine (*17*):



The α-keto triphenylphosphazines, rendered readily accessible by this reaction, are the starting materials in new preparative methods, some of which are reported for the first time in this review.

Canonica (*18*) investigated the reaction between diazoketones and Grignard reagents. Since, however, the reaction does not yield homogeneous products, it has not, thus far, been of preparative interest. In contrast, it may be anticipated that the recently discovered ability of

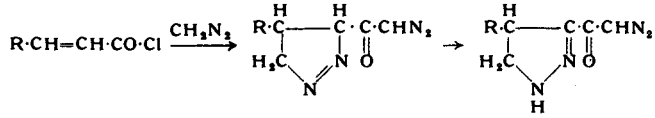
diazoketones to couple with reactive phenols such as phloroglucinol will offer wide application (*19*).

Preparation of Diazoketones

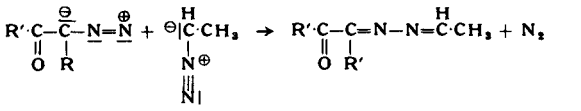
The general method of preparation of diazoketones from diazomethane and acid chlorides according to the stoichiometric equation

$$R{-}CO{-}Cl + 2\,CH_2N_2 \rightarrow R{-}CO{-}CHN_2 + CH_3Cl$$

has been thoroughly discussed by Eistert (*3*). The addition of triethylamine frequently renders the second molecule of diazomethane unnecessary. The base neutralizes the hydrochloric acid formed (*20*). When diazomethane is generated *in situ* (from nitrosomethylurethane), 1.1 to 1.5 moles of the urethane suffice (*21*). Besides ether, methylene dichloride is also used as the solvent for diazomethane and the acid chloride (*22, 23*). While the presence of unsaturated bonds in the molecule does not as a rule inhibit diazoketone formation (*24, 25*), the reaction [as shown unambiguously by Moore (*26*)] between α,β-unsaturated acid chlorides and diazomethane frequently gives 3-diazoacetyl-Δ^1-pyrazolines (*24, 27, 28, 29*), which are then readily converted into the more stable Δ^2-pyrazolines:



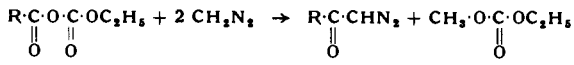
This method of preparation of diazoketones can be extended to include higher diazoalkanes (*30*), but an excess of the diazo compound must then be stringently avoided (*6*). As found by Yates and co-workers (*31*), diazoethane for example can react with diazoketones to form azines (*6, 30, 32*):



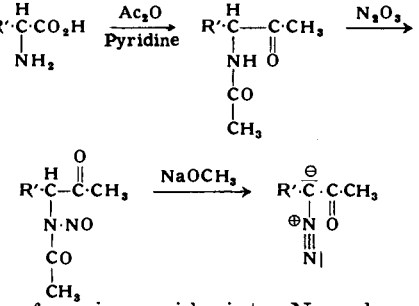
N-Acyl-α-amino acid chlorides frequently yield azlactones (*33*). Investigations by Carter and Hinman revealed that this was due to the fact that the so-called N-acylamino acid chlorides are in reality oxazolone hydrochlorides (*34*). If N-phenylmercaptoformyl-α-amino acids are used, diazoketones of the amino acid series are formed in the usual manner (*35*), and the same holds true for phthalylamino acids (*35a*).

Diazoketones are also formed by the action of diazomethane on acid anhydrides (*2*). In the preparation of trifluorodiazoacetone, this method

is preferable to the reaction with trifluoroacetyl chloride (*36*). In certain cases the reaction between the mixed carbethoxy anhydrides and diazomethane (*37*) may be advantageous:

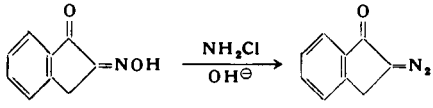


The increasing preparative interest commanded by diazoketones induced several research teams to seek further methods leading to their preparation. Thus Franzen (*6*) describes the following route for the preparation of compounds of structure $H_3C—CO—CN_2—CH_2R$, thereby obviating the above-mentioned difficulties encountered in the use of higher diazoalkanes:

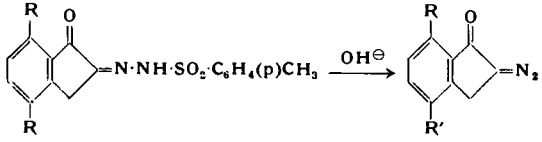


The conversion of amino acids into N-acyl-α-amino ketones has already been investigated by Dakin and West (*38*). Nitrosation with N_2O_3 in glacial acetic acid yields the N-nitroso compounds, which can be decomposed with sodium methoxide to give diazoketones. Azobenzil (carbonyl-C^{14}) was synthesized in similar manner (*39*).

Cyclic diazoketones have been prepared by a variety of methods in the past few years. Cyclic α-ketoximes can be allowed to react with chloramine to give α-diazoketones (*41–44*), a reaction based on work by Forster (*40*):



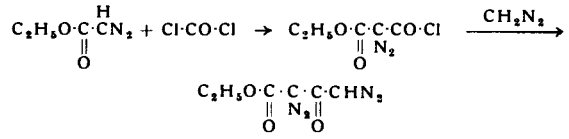
As reported by Litle and Cava, the same diazoketones are formed by the alkaline decomposition of the *p*-toluenesulfonylhydrazones (*45, 42*).



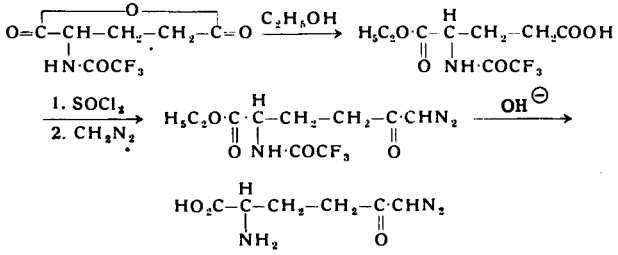
Azipyridil was obtained from the *p*-toluenesulfonylhydrazone of α-pyridoin in analogous manner (*46*).

In a few cases, the old method of oxidizing α-ketohydrazones with HgO has recently been invoked (*47*). A variant by Newman and Arkel consists in oxidizing the hydrazones with mercuric trifluoroacetate in the presence of triethylamine (*48*).

α-Diazo-β-keto esters have long been accessible via the ready reaction between acid chlorides and diazoacetic ester (*49*). The reaction between trifluoroacetic anhydride and diazoacetic ester has been found useful in the preparation of trifluoroacetyldiazoacetic ester (*50*). In this connection, the first synthesis of a 1,3-bisdiazoketone, namely bisdiazoacetoacetic ester, should be mentioned (*51*).



Somewhat surprisingly, a natural diazoketone was found in 6-diazo-5-oxo-L-norleucine (*52*). The synthesis of this compound developed by our research team follows the reaction scheme (*53, 54*):



Preparative Methods

1-p-Chlorobenzoyl-1-diazoethane (*30*). *p*-Chlorobenzoyl chloride (11 gm, 0.062 mole) is added dropwise over a period of 15 min to a stirred solution of diazoethane (0.131 mole) in ether (355 ml) maintained at —20°C. The solution is allowed to stand for a further 15 min, and any unchanged diazoethane distilled off at —20°C. The ether is then evaporated under vacuum at 0°C. Digestion with ice-cooled petroleum ether yields the crystalline product (7.87 gm). Cooling of the petroleum ether solution to —80°C affords a further crop (0.81 gm). Total yield, 8.68 gm (71%), yellow prisms from petroleum ether.

2-Diazo-1-indanone (*41*). A chloramine solution is prepared [from NaOCl (0.42 mole, 1.5–2 *N* aqueous solution) and NH_4OH (0.84 mole, approximately 63 ml conc. NH_4OH, $d = 0.904$)] under ice-cooling, and a copious quantity of crushed ice, followed by a solution of 2-oximino-1-

indanone (28 gm, 0.175 mole) in NaOH (105 ml, 2 *N*), added. The mixture is allowed to stand for 4–5 hr in ice and the crude diazoketone (19.2 gm, 70%) filtered off. Recrystallization from petroleum ether yields long yellow needles, m.p. 89°C.

Azi-α-pyridil (*46*). A solution of *p*-toluenesulfonylhydrazine (4.5 gm) in methanol (25 ml) is added to α-pyridil (5 gm) dissolved in methanol (50 ml) and the solution allowed to stand at room temperature for 3 hr. 2 *N* NaOH (13.5 ml) is added to the now intense yellow solution which becomes slightly warm. On evaporation *in vacuo* to a volume of 25 ml, a rich crop of yellow crystals separates. Fractional crystallization from acetone yields pure azipyridil, m.p. 151°C, and a small quantity of α-pyridoin, m.p. 156°C.

Trifluoroacetyldiazoacetic ester (*50*). A solution of trifluoroacetic anhydride (131 gm) in methylene dichloride (75 ml) is added dropwise over a period of 1 hr to a stirred solution of diazoacetic ester (73.5 gm) and dry, pure pyridine (51 gm) in methylene dichloride (100 ml). The precipitated pyridinium trifluoroacetate is filtered off, and the filtrate washed in turn with sodium carbonate solution and oxalic acid solution and dried over $MgSO_4$. Fractional distillation *in vacuo* yields the product (109 gm, 83%), b.p. 75–77°C/10 mm.

Syntheses Using Diazoketones

Homologous Compounds with Functional Groups From Carboxylic Acids

Homologous Carboxylic Acids

The greatest preparative significance of the diazoketones to date resides in their use in the preparation of homologous carboxylic acids according to the method of Arndt and Eistert (*55*):

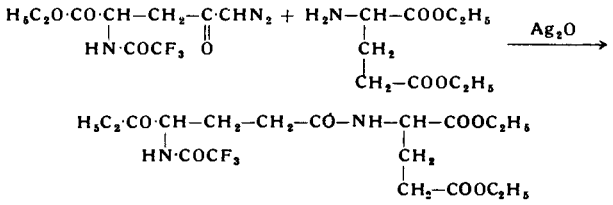
$$R\text{–}CO\text{–}OH \rightarrow R\text{–}CO\text{–}CHN_2 \xrightarrow[H_2O]{Ag^{\oplus} \text{ or } h\nu} R\text{–}CH_2\text{–}COOH$$

This method has been thoroughly discussed by Eistert (*3*). In addition, Franzen (*56*) has recently reviewed the decomposition of diazoketones (Wolff rearrangement), so that only a few recent results need be reported here.

Besides the use of finely divided silver, platinum, or copper as catalyst in the Wolff rearrangement a solution of silver benzoate in triethylamine (*57*) is also recommended, as is performing the reaction in acetonitrile/alcohol in the presence of CuI (*58*). In many instances, the rearrangement effected by irradiation (*59, 60*) is preferable to the other methods (*36, 61*).

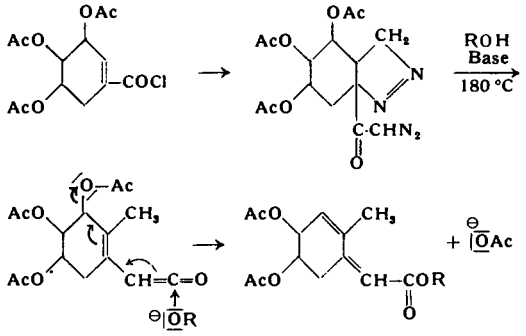
The extension of the Arndt-Eistert synthesis to include the use of higher diazoalkanes has been investigated both by Wilds and Meader (*30*) and by Balenovic and his co-workers (*62*). The possibility of simultaneous α,β-unsaturated ketone formation must then be taken into consideration (*6*). In a large number of cases K. Balenovic and collaborators prepared optically active β-amino acids from N-phthalyl-α-amino acids (*62b, 35a*).

In the presence of α-amino esters, the Wolff rearrangement of α-diazo-γ-N-phthalylamino ketones results in the formation of peptides and β-amino acids (*63*). Similarly, a good yield of optically active triethyl N-trifluoroacetyl-γ-L-glutamyl-L-glutamate was obtained from N-trifluoroacetyl-α-diazo-γ-oxo-L-norvaline ethyl ester in the presence of diethyl glutamate (*64*).



With the exception of α,β-unsaturated acids, the Arndt-Eistert synthesis can also be extended to compounds containing double and triple bonds (65).

According to R. Grewe, the Wolff rearrangement of the diazoketone obtained from triacetylshikimic acid yields a derivative of cyclohexenylideneacetic acid (*66*).



While trifluoroacetic acid can be converted into the homologous 3,3,3-trifluoropropionic acid (*36, 67*), the rearrangement of diazoketones of structure $CF_3—(CF_2)_x—(CH_2)_n—CO—CHN_2$ can only be carried out if $n \geqslant 2$ (*68*).

In a number of unexplained instances, the yields of homologous acids are exceptionally poor, e.g. in the case of 1-diazo-3-phenoxy-2-butanone (*69*).

In sterically hindered diazoketones, the α-keto carbene initially formed was observed to undergo secondary reactions (*70*). Trifluoroacetylcarbethoxycarbene, formed by the irradiation of trifluoroacetyldiazoacetic ester, no longer undergoes a Wolff rearrangement; this is due to the powerful electronegative effect of the trifluoromethyl group. The carbene attacks the solvent in a somewhat novel manner (*50, 71*).

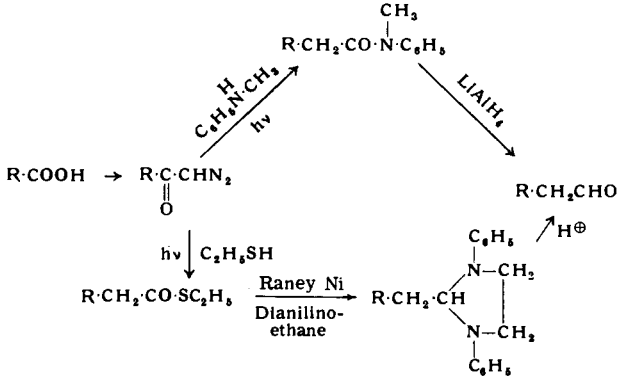
It might also be mentioned that in the reaction between diazoketones and phenylhydrazines, the phenylhydrazides of the homologous carboxylic acids constitute only the secondary product; the osazones of the corresponding α-keto aldehydes are formed in considerably higher yield (*72*).

Homologous Aldehydes and Their Derivatives

The synthesis of homologous aldehydes from carboxylic acids is based on the Wolff rearrangement. Thus Keglevic-Brovet (*73*) describes the conversion of N-phthalyl-L-leucine into β-aminohomoleucine; the acid chloride of the latter is then prepared and converted into the aldehyde by the Rosenmund reaction.

The photolytic Wolff rearrangement in the presence of N-methylaniline represented a substantial simplification (*74*). The N-methylanilides thus formed can be reduced to the aldehydes by means of lithium aluminum hydride (*75*).

Furthermore, diazoketones can be converted into the thiol esters of the homologous carboxylic acids by irradiation in the presence of ethyl mercaptan (*74*). On treatment of these esters with nondeactivated Raney nickel in the presence of 1,2-dianilinoethane, they yield the 1,3-diphenyl-



tetrahydroimidazole derivatives (*76*) of the corresponding aldehydes, which are then readily obtained by decomposition with acid (*77*).

It should be noted that the recently discovered reduction of carboxylic acid dimethylamides with diethoxy aluminum hydride to give aldehydes (*78*) offers a new variant of homologous aldehyde preparation; this is made use of by effecting the irradiation in the presence of dimethylamine.

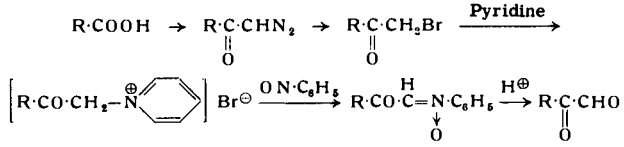
Preparative Methods

N-Methylanilides of homologous acids (*74*). A well-stirred solution (3–5%) of a diazoketone and 2–3 times its quantity of N-methylaniline in absolute benzene is irradiated by means of a cooled immersion lamp (quartz cooler) until the evolution of nitrogen has ceased. The brown coating which forms on the lamp must be removed every 12 hr. The benzene is distilled off, and the residue either crystallizes or can be distilled under high vacuum. It is sometimes preferable to drive as much of the material over as possible with a free flame, and to fractionate afterwards. For the reduction of the N-methylanilides, see ref. (*75*).

Thiol esters of homologous acids (*74*). A solution (3–5%) of a diazoketone and 1.5 times the calculated quantity of ethyl mercaptan (a larger excess should be avoided) in absolute benzene is irradiated until the evolution of nitrogen has ceased (as above). The benzene is distilled off and the residue fractionated *in vacuo*. For conversion of the thiol esters into aldehydes, see ref. (*77*).

Homologous α-Keto Aldehydes and Their Derivatives

If diazoketones are to be converted into α-keto aldehydes, the diazo group must be replaced by an aldehyde group. The diazoketones are first allowed to react with hydrogen halide to give the α-haloketones, and these are then converted into the α-keto aldehydes (*81*, *82*) via the nitrones (*80*) by the method of Kröhnke (*79*).



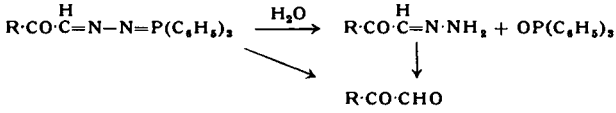
The required pyridinium salts can also be obtained by allowing the diazoketones to react with the pyridine hydrohalide directly (*83*, *83a*).

Diazoketones also undergo a number of reactions as a result of which derivatives of α-keto aldehydes are formed directly. The oldest of these is the reaction with potassium cyanide to give the cyanohydrazones of the α-keto aldehydes (*16*), which yield the semicarbazones and thiosemi-

carbazones of α,β-dicarbonyl compounds with water and H_2S, respectively (*16,84*). Decomposition of these derivatives to give the free α-keto aldehydes cannot be effected with acid.

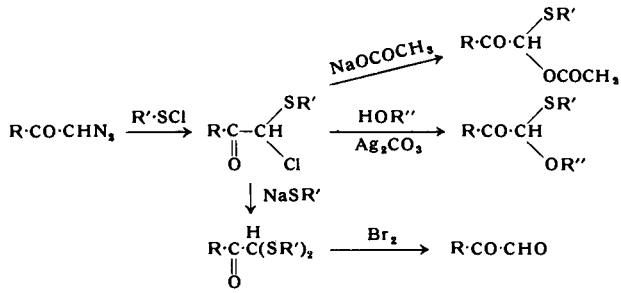
The reduction of some diazomethyl ketones with H_2S afforded the aldehyde hydrazones of α-keto aldehydes (*85,86*).

The products, mentioned earlier, of the reaction between diazoketones and triphenylphosphine are true derivatives of α-keto aldehydes (*17*). The hydrazones obtained on hydrolysis are identical with those formed by the reduction with H_2S (*17*). Both the phosphazines and the hydrazones afford good yields of the free α-keto aldehydes on decomposition with nitrous acid (*87*).



The gaseous products formed during the course of this reaction have not yet been examined in detail. If R is an aromatic ring, the α-keto aldehydes can be isolated and purified as the readily decomposed tetrahydroimidazoles (*76*).

The bifunctional character mentioned earlier of the α-chloro-α-alkyl(or aryl)mercapto ketones (*13*) produced from the reaction between diazoketones and sulfenyl chlorides has considerably widened the preparative scope of the diazoketones (*14*). If the hemimercaptal chlorides of the α-keto aldehydes are allowed to react with sodium acetate, with alcohols in the presence of silver carbonate, or with sodium mercaptide, the acetylhemimercaptals (*88*), monothioacetals (*89*), or the full mercaptals (*13,88–90*), respectively, are obtained; the latter can be converted into the free α-keto aldehydes with bromine (*90*).



In sugar chemistry, this method allowed the first preparation of mercaptals of the osone series (*91*).

α-Keto aldehydes are also obtained by treatment of the α-chloro-α-ethylmercapto ketones with bromine in aqueous acetic acid. This eliminates the additional stage of conversion into the full mercaptal (*92*).

Preparative Methods

3,4,5,6-Tetra-O-acetyl-D-glucosone-1-hydrazone (*86*). (*a*) A stream of H_2S (approximately 100 ml/min) is allowed to pass for 25 hr through a solution of crude 3,4,5,6-tetra-O-acetyl-1-deoxy-1-diazo-D-fructose (960 mg) in ethanol (110 ml) containing ammonium sulfide solution (4 drops), followed by a stream of nitrogen. The solvent is distilled off *in vacuo*, and the residue taken up in benzene/alcohol and filtered. Carbon disulfide is added until crystallization commences, and the solution stored in the refrigerator overnight. Yield, 570 mg; m.p. 158–160.5°C after repeated recrystallization; $(\alpha)_D^{24} = +76°$ ($c = 3.9$, $CHCl_3$).

(*b*) 3,4,5,6-Tetraacetylglucosone-1-triphenylphosphazine (1.24 gm, obtained from 3,4,5,6-tetra-O-acetyl-1-deoxy-1-diazo-D-fructose by the general method of preparation described below) is refluxed for 15 min in 80% ethanol (3 ml) containing glacial acetic acid (0.1 ml). The solution is then allowed to stand at room temperature for 4 hr and in the refrigerator overnight. The crystals which have separated are filtered off and washed with ethanol. Intense cooling and concentration of the mother liquors afford a second fraction; total yield 665 mg (93%). The compound crystallizes in square plates from ethanol and long needles from toluene. M.p. and mixed m.p. of both forms with the product obtained via (*a*) 155–159°C; $(\alpha)_D^{19} = +80.7°$ ($c = 2$, $CHCl_3$).

General preparation of α-keto triphenylphosphazines (*17*). A 30% solution of triphenylphosphine (1.3 moles) in absolute ether is added to a 20% solution of a diazoketone (1 mole) in absolute ether. (In some cases the mixture becomes warm.) The phosphazine begins to crystallize within a few minutes. After storage in the refrigerator for several hours, the crystals are filtered and washed with ether. If the diazoketone is insoluble in ether, the reaction can be carried out in dioxane, ethyl acetate, or a benzene-ether mixture. In such cases the mother liquors still contain considerable amounts of phosphazine, which is then isolated by the addition of absolute ether or concentration. These compounds tend to form strongly supersaturated solutions and crystallization will then only set in following prolonged scratching with a glass rod. α-Keto triphenylphosphazines can be recrystallized from absolute ethanol or a very small quantity of benzene.

Phenylglyoxal (*87*). A solution of sodium nitrite (8 gm) in water (50 ml) is added to a suspension of phenylglyoxaltriphenylphosphazine (20

gm) in acetone (200 ml), and 20% hydrochloric acid (30 ml) added dropwise to the stirred, ice-cooled mixture. The latter is allowed to stand for 30–60 min, until the evolution of gas has ceased, and the acetone then distilled off *in vacuo* at room temperature. The residue is extracted with ether, and the ethereal extract washed with sodium bicarbonate and dried over magnesium sulfate. The solvent is evaporated and the residue distilled at the oil pump, yielding phenylglyoxal (4.6 gm, 70%) as a yellow oil, b.p. 70–80°C/1.2 mm. The distillation residue consists of triphenylphosphine oxide.

α-Chloro-α-ethylmercapto acetone (*13*). A solution of ethanesulfenyl chloride (13.5 gm) in absolute ether (10 ml) is slowly added dropwise to a stirred solution of diazoacetone (11.7 gm) in absolute ether (50 ml) maintained at −60°C. When the reaction is complete the mixture is allowed to stand at room temperature for 2 hr, and the ether evaporated under vacuum. The residual pale-brown liquid is distilled *in vacuo*, b.p. 87°C/14 mm, to yield a pale-yellow oil (15.4 gm, 72%) which has an unpleasant odor and loses HCl on storage.

1-Methoxy-1-ethylmercapto acetone (*89*). Diazoacetone (10 gm) is allowed to react with ethanesulfenyl chloride (12.8 gm) as above, and the ether evaporated *in vacuo*. To the stirred residue, a suspension of silver carbonate (16.5 gm) in absolute methanol (150 ml) is added dropwise; the mixture becomes hot and CO_2 is evolved. After being allowed to stand for some time, the precipitate is filtered off, the methanol evaporated at the water pump and the residue distilled *in vacuo* to give a yellow oil (8.3 gm, 72.8%), b.p. 77°C/11 mm.

1-Acetoxy-1-ethylmercapto acetone (*88*). α-Chloro-α-ethylmercapto acetone (11.3 gm) is added to a solution of anhydrous sodium acetate (6.1 gm) in a mixture of glacial acetic acid (20 ml) and acetic anhydride (20 ml). The mixture is allowed to stand at room temperature for 12 hr, boiled for 15 min and, when cooled, centrifuged to remove the precipitated sodium chloride. The solvent is evaporated under vacuum and the residue is extracted with absolute ether, filtered, and the solvent again evaporated. B.p. 94°C/5 mm; yield, 9.8 gm (75%).

α-Keto aldehyde mercaptals from diazoketones (*90*). The stirred diazoketone, dissolved or suspended in absolute ether and maintained at −20 to 0°C, is allowed to react with the calculated amount of ethanesulfenyl chloride in the absence of moisture. The mixture is allowed to stand at room temperature for several hours, passed through a fluted filter paper, and added dropwise to a stirred ice-cooled suspension of sodium ethyl mercaptide in absolute ether. Stirring is continued for 24 hr, water is added, and the aqueous phase separated and twice extracted

with ether. The combined ethereal solutions are dried over calcium chloride, the solvent evaporated, and the mercaptal distilled at a pressure of 0.01–1 mm or recrystallized. The yields amount to 70–90%.

The sodium mercaptide is prepared from the calculated quantity of finely cut sodium and ethyl mercaptan (10% excess) by stirring in ether for 12 hr (reflux condenser). A larger excess of mercaptan should be avoided.

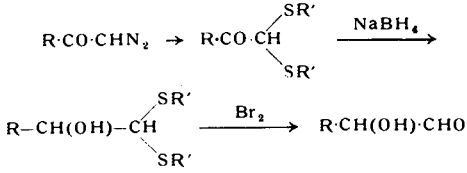
Benzylglyoxal. 1-Phenyl-3-diazoacetone (2 gm, prepared from phenylacetyl chloride) is allowed to react with ethanesulfenyl chloride (1.04 ml) in the manner described. The ether is evaporated and the residue dissolved in glacial acetic acid (15 ml), to which water (3 ml) and concentrated HCl (0.5 ml) have been added. A solution of bromine (0.64 gm) in glacial acetic acid (5 ml) is added dropwise at 45–50°C and the mixture allowed to stand for 12 hr. A saturated solution of sodium bicarbonate is then added until the first crystals begin to separate. The mixture is allowed to stand in the refrigerator for 24 hr, again treated with bicarbonate solution (7 ml), and kept at 0°C for a further 20 hr. The long needles which separate are filtered off and dried in a vacuum desiccator. Yield, 1.2 gm (64.8% calculated with respect to the diazoketone), m.p. 118–119°C (after initial softening) from toluene.

Homologous α-Hydroxy Aldehydes and Their Derivatives

The preparation of homologous α-keto aldehydes also paved the way for the synthesis of the corresponding α-hydroxy aldehydes and their derivatives. K. Balenovic and his co-workers allowed α-keto aldehydes (obtained from diazoketones) to react with orthoformic ester to give the diethyl acetals, and these were converted into the α-hydroxy aldehyde acetals by catalytic hydrogenation (*81*). Decomposition of these substances into the free carbonyl compounds was not described.

The α-keto aldehyde mercaptals obtained by the method discussed in the previous section are readily reduced with $LiBH_4$ in aqueous alcohol (*93*). Treatment with bromine of the α-hydroxy aldehyde mercaptals formed yields the α-hydroxy aldehydes, which sometimes exist as polymers (*93, 94*).

The application of the reactions represented by the above equations to the carbohydrate field gives a new route for the synthesis of aldoses



containing one carbon atom more than the starting aldonic acids (tetraacetylarabonic acid → 3,4,5,6-tetraacetyl-1-deoxy-1-diazofructose → glucose + mannose) (*93*).

Preparative Methods

Lactaldehyde diethyl mercaptal (*93*). Lithium borohydride (0.33 gm) in alcohol (30 ml) and water (4 ml) (solution of the $LiBH_4$ should be effected with vigorous stirring and intense cooling) is added to the solution of methylglyoxal diethylmercaptal (b.p. 58–60°C/0.5 mm, prepared by the method described, 10 gm) in ethanol (50 ml) and water (5 ml), maintained at 0–5°C. The mixture is allowed to stand at room temperature for 12 hr, the gelatinous precipitate is filtered, the solvent is evaporated *in vacuo*, and the residue taken up in ether and again filtered. Vacuum distillation yields a colorless liquid (8.1 gm, 80%), b.p. 117–119°C/14 mm, 79°C/0.6 mm.

Lactaldehyde 2,4-dinitrophenylhydrazone (*93*). Bromine (2 moles) in glacial acetic acid (2 ml) is added dropwise to a stirred solution of lactaldehyde diethyl mercaptal (0.5 gm) in glacial acetic acid (5 ml) and water (2.5 ml). After 1 hr the mixture is diluted with water, buffered to pH5 with sodium acetate, treated with animal charcoal, and filtered. 2,4-Dinitrophenylhydrazine (1.1 moles) in glacial acetic acid containing concentrated hydrochloric acid (1 drop) is added to the clear solution. The yellow precipitate is filtered after 2–3 hr and recrystallized from dilute alcohol to give yellow needles, m.p. 147–148°C, yield 84%.

Homologous α-Keto Acids and Their Derivatives

Balenovic and his collaborators (*95*) prepared homologous α-keto acids via the α-haloketones, which are first converted into the nitrones by the method of Kröhnke (*96, 80*). The nitrones are then treated with NaCN and hydrolyzed to give the α-keto acids:

$$R{\cdot}CO{\cdot}CHN_2 \xrightarrow{HBr} R{\cdot}CO{\cdot}CH_2Br \xrightarrow[2.\ ONC_6H_5]{1.\ \text{Pyridine}} R{\cdot}CO{\cdot}\overset{\displaystyle H}{\underset{\displaystyle O}{C}}{=}N{\cdot}C_6H_5$$

$$\xrightarrow{NaCN} R{\cdot}CO{\cdot}\underset{\displaystyle CN}{C}{=}N{\cdot}C_6H_5 \xrightarrow{H^{\oplus}} R{\cdot}CO{\cdot}COOH + C_6H_5NH_2$$

As mentioned at the beginning, the reaction between diazoketones and diazonium salts results in the formation of the arylhydrazide chlorides of α-keto acids (*11*)

$$R{-}C_6H_5{-}NH{\cdot}N{=}\underset{\displaystyle Cl}{C}{-}CO{-}R$$

which are so versatile in synthetic work.

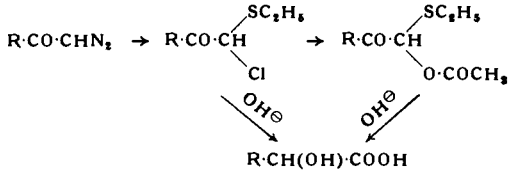
Preparative Method

Benzoylformic acid p-nitrophenylhydrazide chloride (*11*). Pure diazoacetophenone (0.80 gm) is added to a cold methanolic solution of *p*-nitrobenzenediazonium chloride (1.0 gm); the addition results in the immediate evolution of nitrogen. The mixture is allowed to stand for 1 hr and the pale-yellow precipitate is filtered off. Yield, 1.30 gm (79%). M.p. 244–245°C after repeated recrystallization from acetone.

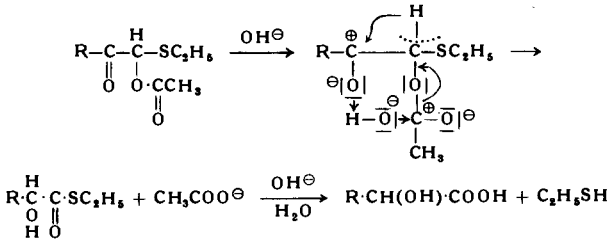
Homologous α-Hydroxy Acids and Their Derivatives

Homologous α-hydroxy acids are formed by the catalytic reduction of the α-keto acids described in the previous section (*95*).

Alkaline treatment of α-chloro-α-alkylmercapto ketones, or better still, α-acetoxy-α-ethylmercapto ketones, provides an entirely different route for the preparation of this class of compounds (*88*).



We interpret the mechanism of this, an intramolecular Cannizzaro-type reaction, as follows:



In this reaction the aldehydic hydrogen atom is displaced as a hydride ion (*97*).

Preparative Method

Mandelic acid (*98*). Ethanesulfenyl chloride (5.8 gm) is added dropwise to an ice-cooled solution of diazoacetophenone (8.8 gm) in absolute ether (70 ml). The solution is allowed to stand for 2 hr and the solvent distilled off under vacuum. The residue is treated with a solution of anhydrous sodium acetate (6.4 gm) in a mixture of glacial acetic acid (27 ml) and acetic anhydride (27 ml), allowed to stand for 12 hr and

boiled under reflux for 2 hr. The solvent is evaporated *in vacuo,* and the residue is shaken with sodium hydroxide solution (50%, 80 ml) for 20 hr. The alkaline solution is twice extracted with ether and acidified with concentrated hydrochloric acid. The mandelic acid thus formed is extracted with ether. Yield, 6.3 gm (69%, calculated with respect to the diazoketone).

Aldehydes and Ketones

Aldehydes

For the sake of completeness, the scheme of Grundmann (*24*) representing the preparation of aldehydes from carboxylic acids containing the same number of carbon atoms is reproduced here.

$$R{\cdot}COOH \rightarrow R{\cdot}CO{\cdot}CHN_2 \rightarrow R{\cdot}CO{\cdot}CH_2{\cdot}O{\cdot}COCH_3 \rightarrow$$

$$R{\cdot}\overset{\overset{H}{|}}{C}{\cdot}CH_2{\cdot}O{\cdot}COCH_3 \xrightarrow[2.\ Pb(OAc)_4]{1.\ Hydrolysis} R{\cdot}CHO + CH_2O$$

$$\overset{|}{OH}$$

Experimental details have been described by B. Eistert (*3*). A list of the aldehydes synthesized by this method has been compiled by Mosettig (*99*).

α-Haloketones

The reaction between diazoketones and hydrohalic acids yields α-haloketones (cf. ref. *3*). During the past few years, the action of hydrofluoric acid on diazoketones has also been studied (*100*). This reaction results in the formation of the expected α-fluoroketones.

$$R{-}CO{-}CHN_2 \xrightarrow{HF} R{-}CO{-}CH_2F$$

The same compounds are also formed from the reaction between acyl fluorides and one mole of diazomethane (*101*).

The α-halo-α-alkyl(or aryl)mercapto ketones, which also belong to the haloketone class, have been discussed earlier.

Preparative Method

1-Fluoro-2-heptanone (*100b*). Hexanonyl chloride (8.0 gm, 0.06 mole) is added dropwise to a well-cooled stirred solution of diazomethane (12.6 gm, 0.3 mole) in ether. Stirring is continued for 2 hr and the ether evaporated. The residue is treated dropwise with anhydrous hydrofluoric acid (5 gm), contained in a polythene bottle and cooled in acetone/Dry Ice. The reaction mixture is gradually allowed to warm up to room temperature and poured on to anhydrous potassium fluoride (20 gm). The liquid

is decanted, and the solid is repeatedly washed with ether. The liquid phase and ethereal extracts are combined and dried over anhydrous potassium fluoride. The solvent is removed and the residue distilled *in vacuo*, b.p. 54°C/13 mm, $n_D^{25} = 1.4048$. Yield, 3.0 gm (38%).

Ketols and Their Derivatives

Ketols and Ketol Esters

Hydrolysis of diazoketones by means of dilute sulfuric acid yields ketols (cf. ref. *3*). If the diazo group is flanked by two carbonyl groups, the acid concentration must be appreciably increased (*102*). As was recently discovered by Eistert and his co-workers, the ketols (in this case mostly enediols) can then be obtained under considerably milder conditions by effecting the hydrolysis in 0.1 *N* H_2SO_4 in the presence of copper powder (*103*).

Diazoketones react with carboxylic acids to give ketol esters (*3*). Copper salts (*104, 105, 107*) and copper (*105*) are recommended as catalysts to accelerate the reaction, which can also be used for the identification of carboxylic acids (*104*).

Thioketol esters are obtained from thiocarboxylic acids in analogous manner (*106*):

$$R{-}CO{-}CHN_2 + HS{-}CO{-}R' \longrightarrow R{-}CO{-}CH_2{-}S{-}CO{-}R'$$

The reaction between diazoketones and glacial acetic acid to give ketol acetates has been applied by Wolfrom in the development of an elegant synthesis of ketoses from aldonic acids, as described in numerous publications (*107*). It should be noted that in a number of instances ketol sulfuric acid ester formation has been observed to result from the reaction between diazoketones and H_2SO_4 (*22, 57*).

The interesting conversion of 21-diazoprogesterone into the ketol phosphoric acid ester (*108*) by means of phosphoric acid has recently again been utilized in the synthesis of indolyl-3-glyoxylmethanol 1-phosphoric acid ester (*109*).

Preparative Method

Identification of carboxylic acids as their phenacyl esters (*104b*). The carboxylic acid (3 mmoles) is dissolved in dioxane (10 ml) contained in a test tube (warm if necessary). *p*-Bromo- or *p*-phenyl-ω-diazoacetophenone (2 mmoles) is added to the solution at room temperature, followed by the addition of cupric chloride (2–4 mg), and the solution is heated until the evolution of nitrogen has ceased. Heating is discontinued when the pale-yellow solution begins to turn brown and a vigorous evolution

of gas sets in. When no more gas is evolved, the solution is again brought to the boil for 1 min and poured into a cooling mixture which consists of water (100 ml), 10% potassium chlorate solution (5 ml), and a few ice cubes. The yellow crystalline ester is washed with water and, in the case of esters of aliphatic acids, recrystallized from dilute alcohol. Esters of aromatic acids are recrystallized from petroleum ether or acetone.

Ketol Ethers

If diazoketones are decomposed in alcohol with copper powder (*10*) or boron trifluoride (*57, 110*) as catalyst, ketol ethers are produced. CuO also catalyzes this reaction in some cases (*111*):

$$R{\cdot}CO{\cdot}CHN_2 + R'{\cdot}OH \xrightarrow[CuO]{Cu;\ BF_3} R{\cdot}CO{\cdot}CH_2{\cdot}OR' + N_2$$

Ketol thioethers are formed in similar manner in the presence of mercaptans.

Preparative Methods

ω-Ethoxyacetophenone (*10*). Diazoacetophenone is dissolved in ethanol, the solution warmed to 50–55°C, and copper powder added. A vigorous evolution of nitrogen immediately sets in and the solution darkens. It is filtered, the alcohol is distilled off *in vacuo*, and the residue fractionated, b.p. 125–127°C/14.5 mm. Yield, 60%.

2′,4-Dimethoxyacetophenone (*57*). Boron trifluoride etherate (0.5 gm) is added to a solution of ω-diazo-*p*-methoxyacetophenone in methanol (10 ml) and ether (100 ml) maintained at −25°C. After 70 min the calculated amount of nitrogen has been evolved. The solvent is removed and the ketol ether crystallizes. It is recrystallized from petroleum ether. M.p. 39.2–40.2°C; yield, 4.2 gm (67%).

α-Amino Ketones

Amino ketones can be synthesized from diazoketones. As discovered by Birkofer (*112*), many diazoketones are converted into α-amino ketones on catalytic reduction:

$$R{\cdot}CO{\cdot}CHN_2 \xrightarrow{3H_2} R{\cdot}CO{\cdot}CH_2{\cdot}NH_2 + NH_3$$

In this reaction, which is essentially applicable to aromatic diazoketones only, the calculated quantity of glacial acetic acid required to neutralize the ammonia and the amino ketone must be added before the hydrogenation commences. If this is omitted, the amino ketone may condense to give a 3,6-dihydropyrazine derivative.

Most processes consist of the initial conversion of the diazoketone into the α-haloketone, and replacement of the halogen atom by an amino group by various methods. The Gabriel method of reaction with potassium phthalimide and removal of the phthalyl residue has proved useful (*113*). The reaction sequence is illustrated by the synthesis of δ-aminolevulinic acid (*114*).

$$\mathrm{ROOC{\cdot}(CH_2)_2{\cdot}COOH} \rightarrow \mathrm{ROOC{\cdot}(CH_2)_2{\cdot}CO{\cdot}CHN_2} \rightarrow \mathrm{ROOC{\cdot}(CH_2)_2{\cdot}CO{\cdot}CH_2Br} \xrightarrow[\text{2. Hydrolysis}]{\text{1. Potassium phthalimide}} \mathrm{HOOC{\cdot}(CH_2)_2{\cdot}CO{\cdot}CH_2{\cdot}NH_2}$$

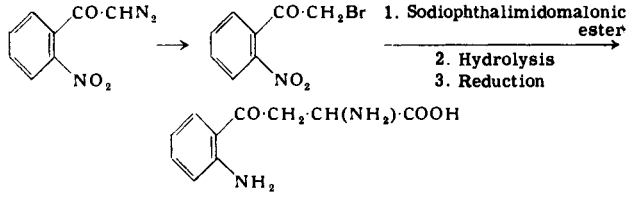
A further possibility is the reaction between the bromoketone and hexamethylenetetramine, followed by decomposition of the adduct with hydrobromic acid (*22*).

A number of publications describe the preparation of N-mono- and disubstituted amino ketones. The decomposition, discussed earlier, of diazoketones in the presence of aniline or piperidine results in the direct formation of such amino ketones (*10*).

An additional method consists of the reaction between bromoketones and secondary amines (*115*).

α-Amino-γ-keto Acids

o-Nitro-ω-diazoacetophenone provided the starting material for the first synthesis of DL-kynurenine, an α-amino-γ-keto acid (*116*).



3-Hydroxykynurenine was synthesized in analogous manner (*117*).

β-Keto Esters

A new synthesis of β-keto esters was recently developed, involving the use of phosphazines. The starting materials are α-diazo-β-keto esters, which are converted according to the following reaction scheme (*118*):

$$\mathrm{R{\cdot}CO{\cdot}Cl + N_2HC{\cdot}COOR'} \rightarrow \mathrm{R{\cdot}CO{\cdot}\underset{\underset{N_2}{|}}{C}{\cdot}COOR'} \xrightarrow{P(C_6H_5)_3}$$

$$\mathrm{R{\cdot}CO{\cdot}\underset{\underset{N{-}N{=}P(C_6H_5)_3}{\|}}{C}{\cdot}COOR'} \xrightarrow{H_2O} \mathrm{R{\cdot}CO{\cdot}\underset{\underset{N{\cdot}NH_2}{\|}}{C}{\cdot}COOR'} \xrightarrow[80-100^\circ]{\text{Pyridine}} \mathrm{R{\cdot}CO{\cdot}CH_2{\cdot}COOR'}$$

Hydrolysis of the triphenylphosphazines, obtained in excellent yield from the reaction between diazo compounds and triphenylphosphine, yields the α-hydrazones of the α,β-diketo esters. Under the influence of the two adjacent carbonyl groups, these compounds undergo a Wolff-Kishner reduction in pyridine or quinoline at temperatures as low as 80–100°C. This method is particularly well suited to the preparation of β-keto esters containing groups unstable to acid or alkali.

Preparative Methods

Trifluoroacetyl-(2-triphenylphosphazine)glyoxylic ester (118). A solution of triphenylphosphine (55 gm) in absolute diisopropyl ether (150 ml) is added to trifluoroacetyldiazoacetic ethyl ester (see p. 419) (40 gm) dissolved in diisopropyl ether (50 ml) and maintained at 0°C. On warming the color turns red and crystallization sets in. The reaction mixture is allowed to stand in the refrigerator for 12 hr, filtered, and recrystallized from benzene-ether. Yield, 81 gm (90%) after working up the mother liquors. Moisture must be excluded in all the operations. M.p. of the phosphazine: 141–143°C.

Trifluoroacetylglyoxylic ester 2-hydrazone (118). The phosphazine (40 gm) is refluxed for 1 hr in 80% methanol (70 ml), which results in the decolorization of the solution. It is allowed to stand for 12 hr, the solvent is removed *in vacuo,* and the residue is dissolved in ether (500 ml) and dried over magnesium sulfate. Anhydrous zinc chloride (32 gm) in ether (500 ml) is then added dropwise to the well stirred solution, and the adduct of $ZnCl_2$ and triphenylphosphine oxide is precipitated. The stirred ethereal solution is treated with water (100 ml) and the precipitate is separated and washed with ether. The aqueous phase is separated and extracted with ether, and the ethereal solutions combined and washed with sodium bicarbonate solution. The solution is dried and the ether evaporated, leaving colorless crystals (17 gm, 97%), m.p. 96–100°C after recrystallization from toluene.

Trifluoroacetoacetic ester (118). The hydrazone obtained (4 gm) in absolute alcohol (5 ml) and quinoline (1 ml) is heated on a boiling water bath for 17 hr. (Addition of boiling stones accelerates the evolution of nitrogen.) The ethanol is distilled off and the residue fractionated through a small Vigreux column at 50 mm pressure. Trifluoroacetoacetic ester (2.2 gm), b.p. 49°C/50 mm is obtained. The distillation residue is dissolved in ether, and shaken three times with 2 N H_2SO_4 and once with sodium bicarbonate solution. Drying and evaporation of the ether allows the isolation of a second fraction (0.5 gm), best accomplished as the copper salt. Total yield 78%.

Methyl Ketones

In diazoketones of structure R—CO—CHN_2, replacement of the diazo group by two hydrogen atoms yields methyl ketones. The reaction may be effected by various methods.

The most widely used method is that of Wolfrom (*119*), which is based on the action of hydriodic acid on diazocarbonyl compounds:

$$R{\cdot}CO{\cdot}CHN_2 \xrightarrow{HI} R{\cdot}CO{\cdot}CH_3$$

Optically active α-aminomethyl ketones were prepared via this route by Balenovic and Thaller (*120*).

Catalytic hydrogenation of diazoketones in the presence of CuO also results in the formation of methyl ketones in certain cases; the yields, however, are unsatisfactory (*112, 121*). Reduction by means of $SnCl_2$ of the α-bromoketones obtained from the diazoketones affords better yields (*23*).

$$R{\cdot}CO{\cdot}CH_2Br \xrightarrow{SnCl_2} R{\cdot}CO{\cdot}CH_3$$

Treatment with dilute alkali of the α-keto aldehyde al-hydrazones obtained from the hydrolysis of α-keto triphenylphosphazines results in the elimination of nitrogen and the formation in 70–90% yield of the methyl ketones (*17*):

$$R{\cdot}CO{\cdot}CHN_2 + P(C_6H_5)_3 \rightarrow R{-}CO{-}CH{=}N{-}N{=}P(C_6H_5)_3 \xrightarrow{H_2O}$$
$$[R{-}CO{-}CH{=}N{-}NH_2] \xrightarrow{OH^{\ominus}} R{\cdot}CO{\cdot}CH_3 + N_2$$

The hydrazones need not be isolated. After the hydrolysis of the phosphazine, the reaction mixture is immediately made alkaline, or the hydrolysis is itself carried out in an alkaline medium. The Wolff-Kishner reduction which occurs exceptionally readily in these cases must be attributed to the influence of the adjacent carbonyl group (*122, 123*).

Methyl ketones can also be obtained by the desulfurization with Raney nickel of the α-keto aldehyde al-mercaptals described earlier (*91*).

$$R{\cdot}CO{\cdot}CH(SR)_2 \xrightarrow{Raney\text{-}Ni} R{\cdot}CO{\cdot}CH_3$$

Preparative Methods

Acetophenone (*119*). Hydriodic acid (47%, 5 ml) is added to diazoacetophenone (2.2 gm) dissolved in chloroform (20 ml). When the evolution of nitrogen has ceased, the solution, now darkened by separated

iodine, is treated with water. The chloroform layer is separated and washed in turn with sodium thiosulfate solution and water. The solution is dried, the chloroform evaporated and the residue distilled, b.p. 200°C. Yield, 1.75 gm (96%).

Phenylacetone (*17*). The triphenylphosphazine (5 gm) obtained from 1-phenyl-3-diazoacetone is refluxed for 2 hr in 80% methanol (40 ml), 2 *N* NaOH (4 ml) is added, and the alkaline solution is immediately steam-distilled. When no more ketone comes over (test with 2,4-dinitrophenylhydrazine) the distillate is extracted with ether, the ethereal layer dried and the solvent evaporated. The residue distills at 104–106°C/13 mm. Yield, 3.55 gm (74%).

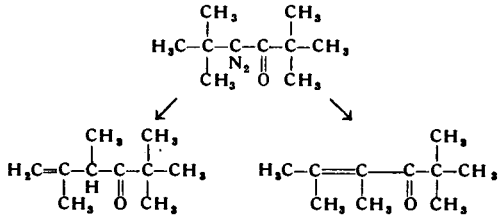
α,β-Unsaturated Ketones

Diazoketones of general formula R—CO—CN_2—CH_2—R undergo photolytic or silver-oxide–catalyzed decomposition to give α,β-unsaturated ketones (*6*).

$$R{\cdot}CO{\cdot}CN_2{\cdot}CH_2{\cdot}R' \xrightarrow[Ag_2O]{h\nu} R{-}CO{-}CH{=}CH{-}R'$$

Purified dioxane has proved suitable as solvent. The decomposition with silver oxide is effected at room temperature, since elevated temperatures favor the Wolff rearrangement.

Sterically hindered diazoketones decompose to form unsaturated ketones, e.g. (*70*):



Preparative Method

Phenyl vinyl ketone (*6*). A suspension of freshly prepared silver oxide (150 mg) in water (25 ml) is added to a solution of benzoyldiazoethane (10 gm) in purified dioxane (80 ml). A continuous evolution of gas soon sets in, and ceases after 2 hr. The silver oxide is removed by filtration, and the solution is concentrated under vacuum until two layers appear. The organic layer is taken up in ether, dried over calcium chloride, and distilled, b.p. 115°C/18 mm. Yield, 72%.

1,2-Diacyl Ethylenes

Decomposition of diazoketones by means of cupric oxide in inert solvents results in the formation of 1,2-diacyl ethylenes.

$$2\ R{\cdot}CO{\cdot}CHN_2 \xrightarrow{CuO} R{-}CO{-}CH{=}CH{-}CO{-}R$$

This reaction, discovered by Grundmann (*6*), has recently been utilized by Ernest and his collaborators (*124–127*) for the synthesis of diketo dicarboxylic esters.

$$ROOC{-}(CH_2)_n{\cdot}\underset{\underset{O}{\|}}{C}{\cdot}CH{=}CH{\cdot}\underset{\underset{O}{\|}}{C}{\cdot}(CH_2)_n{-}COOR$$

The simultaneous decomposition of two diazoketones affords the unsymmetrical 1,2-diacyl ethylene in yields of approximately 20%. A threefold excess of one diazoketone raises the yield to 30–40% (*128*).

Preparative Methods

trans-1,2-Dibenzoylethylene. ω-Diazoacetophenone (1.0 gm) is dissolved in petroleum ether (b.p. 70–80°C, 20 ml) and refluxed for 1 hr with finely powdered cupric oxide (1 gm). The warm mixture is filtered free from cupric oxide, and the solvent is evaporated *in vacuo*. The residue is recrystallized from methanol and gives large yellow needles of the compound (0.48 gm), m.p. 110°C.

Dimethyl docos-11-ene-10,13-dione-1,22-dioate (*125*). Sebacoyl chloride methyl ester (50 gm) dissolved in ether (250 ml) is added dropwise to a stirred, cooled solution of diazomethane (26.8 gm) in ether (2000 ml). The solution is allowed to stand for 12 hr and evaporated under vacuum to a volume of 100 ml. Benzene (600 ml) is added and the remainder of the ether distilled off. CuO (10 gm) is added and the mixture slowly warmed on a water bath. Nitrogen evolution begins at 75°C and ceases after 15 min. The warm mixture is filtered free from cupric oxide, and the solvent evaporated *in vacuo*. The residue is twice recrystallized from methanol, yielding colorless crystals (18.4 gm, 20.3%), m.p. 86–88°C.

1,4-Diketones

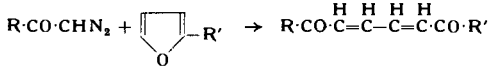
Catalytic hydrogenation of the 1,2-diacyl ethylenes discussed in the previous section yields 1,4-diketones (*124, 125, 127*). PtO_2 or $Pd/CaCO_3$ are recommended as catalysts.

Preparative Method

Dimethyl docosane-10,13-dione-1,22-dioate. Adams catalyst (0.5 gm) is added to the unsaturated dimethyl ester (28.5 gm) described above, dissolved in warm methanol (80 ml), and the mixture subjected to hydrogenation at 20°C and 950 mm pressure (hydrogen uptake 1960 ml). The catalyst is filtered off and the solution evaporated under vacuum. The residue yields colorless crystals (19.3 gm, 68.6%), m.p. 79°C from methanol.

1,4-Diacyl Butadienes

The decomposition of diazoketones with copper powder in the presence of furan derivatives is rather surprising (*105, 129*). J. Novak and F. Sorm succeeded in identifying the products of this reaction as 1,4-diacyl butadienes (*129*).



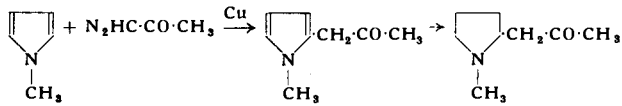
The decomposition of diazoacetone in furan (R′ = H) yields hepta-2,4-dien-6-on-1-al. (The mechanism of this interesting reaction has thus far not been elucidated.)

Preparative Method

Octa-3,5-diene-2,7-dione (*129*). The solution of diazoacetone (5 gm) in α-methylfuran (10 gm) is added dropwise to a boiling suspension of copper bronze (0.5 gm) in the same furan derivative (50 ml) at such a rate that the mixture is maintained at the boiling point. When the evolution of gas has ceased, the catalyst is filtered off, the excess of α-methylfuran distilled, and the residue fractionated *in vacuo*. The fraction boiling at 65–100°/0.5 mm affords a crystalline product which is filtered off and recrystallized from methanol. M.p. 127°C; yield, 3.2 gm (39%).

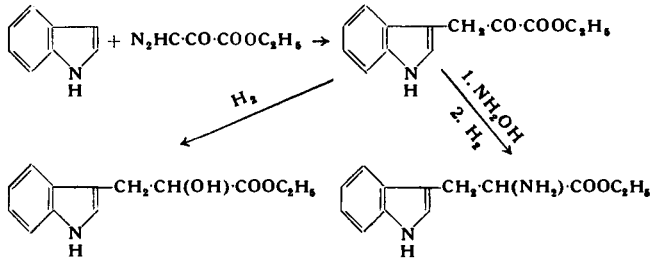
Ketones by Substitution of α-Keto Carbenes

Decomposition of diazoketones in the presence of heterocyclic compounds may result in substitution in the ring. Sorm was the first to report a reaction of this type, when he allowed diazoacetone to react with N-methylpyrrole and obtained N-methyl-2-acetonylpyrrole; this was then reduced to give racemic hygrine (*130*).



Since it was recently proved that the so-called Hess synthesis yields no hygrine (*131*) the reaction depicted above is the first hygrine synthesis.

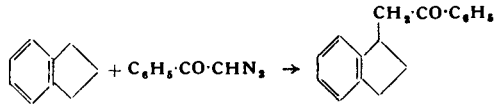
Diazoketones react in similar manner with indole and thiophene to give 3-substituted indole derivatives (*9, 105*) and 2-thienyl ketones (*9*) respectively. Thus diazoacetone yields 2-thienylacetone. The diazo components used include ω-diazo keto esters (*105*). The preparative possibilities offered by diazopyruvic ester are shown in the scheme below.



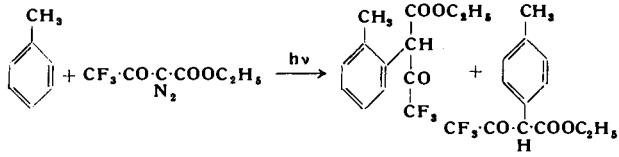
When diazoketones are allowed to react with heterocyclic compounds, it must be borne in mind that the dimerization, described earlier, of the α-keto carbenes to diacyl ethylenes takes place simultaneously with and in competition to the desired reaction. As far as possible, therefore, there should be a constant excess of the heterocyclic component.

α-Keto carbenes attack oxygen-containing ring systems in a different manner, as illustrated by the furan example earlier.

Treibs and Quarg observed yet another substitution reaction when they allowed diazoacetophenone to react with hydrindene in the presence of copper powder. They obtained both 5-benzoylazulene (cf. azulene) and phenacylindene (*8*).



Photolysis of trifluoroacetyldiazoacetic ester in an aromatic solvent results in electrophilic substitution of the aromatic ring (*50, 132*).



No norcaradiene derivative appeared to be formed, nor was any substitution of the CH_3 group observed.

Preparative Method

Ethyl indolylpyruvate (*105*). Crystalline diazopyruvic ester (4.5 gm) is added in small portions to a mixture of indole (5 gm), cyclohexane (15 ml), and copper powder (1 gm) maintained at 85–95°C. As soon as the evolution of nitrogen has ceased the brown reaction mixture is cooled and dissolved in ether. The ethereal extract is chromatographed on neutral alumina and eluted with ether. Fractions of 60 ml are collected. The first two fractions contain indole (m.p. 52°C), the fourth and fifth yield crude ethyl indolylpyruvate (3.15 gm, 49% calculated with respect to the indole used up), which is obtained as colorless needles from ethyl acetate/cyclohexane (1:3). The compound is unstable in solution.

Glycols and Amino Alcohols

Glycols

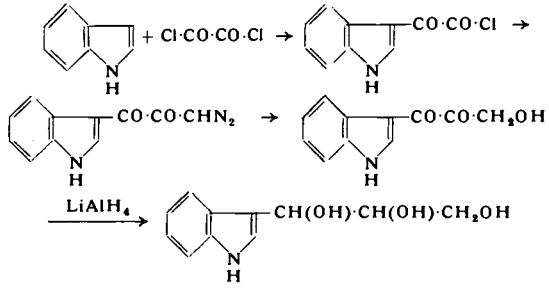
The Grundmann aldehyde synthesis includes, in the intermediate stage, a method for the preparation of glycols (*24*). Ruggli and Knecht obtained derivatives of *m*-phenylene diglycol in a similar manner (*133*).

$$R{-}CO{-}CHN_2 + HO{-}R' \rightarrow R{-}CO{-}CH_2{-}O{-}R' \rightarrow R{-}CH(OH){-}CH_2{-}O{-}R'$$

$R' = H; -CO-CH_3$; Alkyl

The ketol derivatives can be reduced catalytically (*133*) with sodium or aluminum amalgam or with aluminum isopropoxide (*24*).

Balenovic and co-workers have described the preparation of glycols by the reduction of the α-keto aldehydes which they had obtained by the method of Kröhnke (*81*). Not without interest in this connection, is the synthesis of 3-indolylglycerol (*134*).



AMINO ALCOHOLS

The synthesis of α-amino alcohols containing a terminal amino group is readily accomplished by the reduction of the α-amino ketones described earlier. Good yields are sometimes obtained from the direct reduction of diazoketones with $LiAlH_4$ (*121*).

$$R{\cdot}CO{\cdot}CHN_2 \xrightarrow{LiAlH_4} R{\cdot}CH(OH){\cdot}CH_2{\cdot}NH_2$$

Catalytic reduction also affords α-amino alcohols in some cases; considerable side reactions are, however, encountered (formation of hydrazone, methyl ketone, etc.) (*112, 121*). The yields of N-substituted α-amino alcohols by catalytic reduction on the other hand, are appreciably increased by the addition of an aldehyde (*121*):

$$R{\cdot}CO{\cdot}CHN_2 + R{\cdot}CHO \xrightarrow{H_2/PtO_2} R{\cdot}CH(OH){\cdot}CH_2{\cdot}NH{\cdot}CH_2{\cdot}R'$$

The preparation of α-N-dialkylamino alcohols was accomplished as follows: The α-haloketones obtained from the diazoketones were reduced with aluminum isoproproxide to give the halohydrins, and the latter were converted into the desired compounds by direct condensation with secondary amines (*23, 135*).

$$R{\cdot}CO{\cdot}CH_2{\cdot}Cl \xrightarrow[\text{isopropoxide}]{\text{Aluminum}} R{\cdot}CH(OH){\cdot}CH_2{\cdot}Cl \rightarrow \left[R{\cdot}C\begin{matrix}H\\ \\ O\end{matrix}\!\!-\!\!CH_2\right]$$

$$\xrightarrow{HN\begin{matrix}R'\\ R'\end{matrix}} R{\cdot}CH(OH){\cdot}CH_2{\cdot}N\begin{matrix}R'\\ \\ R'\end{matrix}$$

Prostenik and his collaborators (*136*) synthesized enantiomeric sphingines, i.e. α-amino alcohols containing a terminal OH group.

$$H_3C{\cdot}(CH_2)_{15}{\cdot}COCl \rightarrow CH_3{\cdot}(CH_2)_{15}{\cdot}CO{\cdot}CHN_2 \rightarrow$$

$$H_3C{\cdot}(CH_2)_{15}{\cdot}CO{\cdot}CH_2{\cdot}O{\cdot}COCH_3 \xrightarrow[H_2]{C_6H_5CH_2NH_2} CH_3{\cdot}(CH_2)_{15}{\cdot}CH{\cdot}CH_2OH$$

$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad NHCH_2C_6H_5$$

$$\Big\downarrow \begin{matrix}1.\ NH_2OH\\ 2.\ LiAlH_4\end{matrix}$$

$$H_3C{\cdot}(CH_2)_{15}{\cdot}CH(NH_2){\cdot}CH_2OH$$

Preparative Method

1-Phenylethanolamine (*121*). Diazoacetophenone (1.15 gm) in absolute ether (20 ml) is added dropwise to a well stirred solution of $LiAlH_4$ (0.76 gm) in the same solvent. The reaction mixture is allowed to stand for a brief period, decomposed with ice-water, made alkaline, and

thoroughly extracted with ether. The base is removed from the ethereal solution with hydrochloric acid (2%). Evaporation of the acid solution under vacuum results in the crystallization of the hydrochloride (1.21 gm, 93%), m.p. 176–177°C.

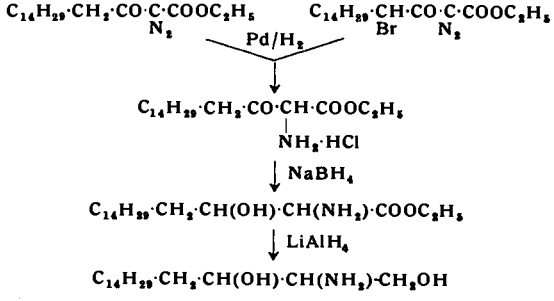
α-Amino-β-hydroxy Acids

Reduction of the α-diazo-β-keto esters obtained from acid chlorides and diazoacetic ester yields α-amino-β-hydroxy esters:

$$R{-}CO{-}CN_2{-}COOR' \xrightarrow{H_2} R{-}CH(OH){-}CH(NH_2){-}COOR'$$

Thus when Birkofer reduced acetyldiazoacetic ester ($R = CH_3$) in aqueous alcohol in the presence of sulfuric acid and PtO_2, he obtained a mixture of DL-threonine and DL-allothreonine (*112*). The reduction of methyl benzoyldiazoacetate ($R = C_6H_5$) in 70% glacial acetic acid, on the other hand, is stereospecific and yields the methyl ester of DL-allophenylserine (*137*).

The reduction of 2-diazopalmitylacetic ester and 2-diazo-3-oxo-4-bromostearic ester to give DL-2-amino-3-oxostearic ester has also been described; the latter was first converted into the corresponding α-amino-β-hydroxy acid with $NaBH_4$, and then into DL-2-amino-1,3-octadecanediol (*138*):



DL-Threo and DL-erythro forms are produced side by side.

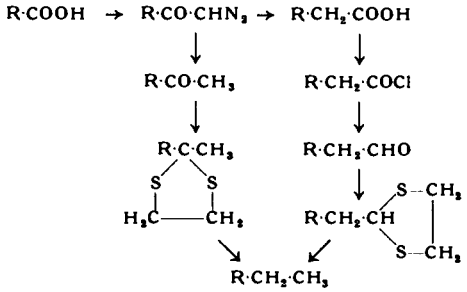
Preparative Method

Methyl ester of DL-*allophenylserine hydrochloride* (*137*). Palladium on charcoal (5%, 0.5 gm) is added to a solution of benzolydiazoacetic ester (10 gm) in acetic acid (70%, 100 ml). The ester is hydrogenated at a pressure of 3 atm until the theoretical amount of hydrogen has been taken up (approximately 5 hr). The catalyst is filtered off, and the solution evaporated to a volume of 35 ml, cooled to 5°C, made alkaline to

litmus with concentrated ammonium hydroxide solution, and extracted ten times with ether (150 ml portions). Hydrogen chloride is passed into the dried ethereal solution, and the hydrochloride is precipitated. The salt is filtered off and dried over KOH. Yield, 9.3 gm (82%), m.p. 182°C (dec.) after recrystallization from methanol-ether.

Hydrocarbons

Keglevic-Brovet (*73*) and Balenovic and his co-workers (*62, 139*) developed two methods for the conversion of carboxylic acids into hydrocarbons (R—COOH → R—CH_2—CH_3). This work arose out of their studies on the determination of the configuration of β-amino acids.

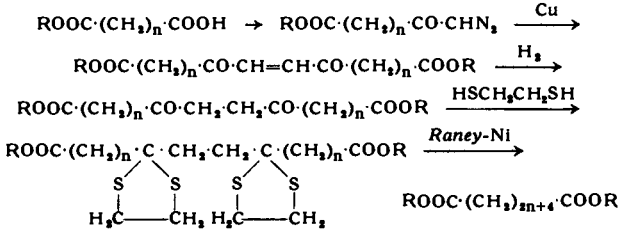


The conversion of the diazoketones into methyl ketones by the process described is effected with hydriodic acid. The acid chlorides are reduced by the Rosenmund-Zetsche method.

This reaction sequence, restricted thus far to amino acids, may well be of general preparative interest.

α,ω-Dicarboxylic Acids

The decomposition of diazoketones to diacyl ethylenes led to the development by I. Ernest and collaborators of a method of synthesizing long-chain α,ω-dicarboxylic acids (*124, 125*).



Sebacoyl chloride methyl ester thus afforded dimethyl docosane-1,22-dioate; conversion of the latter into the monomethyl ester followed by the repetition of the whole reaction sequence resulted in the first prepara-

tion of dimethyl hexatetracontane-1,46-dioate, from which the free acid was liberated (*125*).

Preparative Methods

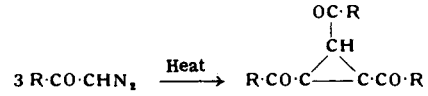
Bisethylenemercaptole of dimethyl docosane-10,13-dione-1,22-dioate (*125*). Anhydrous sodium sulfate (40 gm) and zinc chloride (40 gm) are added to a solution of dimethyl docosane-10,13-dione-1,22-dioate (for preparation, see p. 437) (37.8 gm) and ethanedithiol (28 ml) in dioxane (250 ml). The mixture is allowed to stand for 10 days and extracted with benzene and water. The benzene solution is dried over Na_2SO_4, and both the solvent and the excess of mercaptan are evaporated under vacuum. The solid residue can be recrystallized from methanol/benzene. Yield (including product isolated from the mother liquors), 50.2 gm (98%), m.p. 62–63°C.

Dimethyl docosane-1,22-dioate (*125*). A solution of the above mercaptole (9.7 gm) in methyl alcohol (970 ml) is refluxed for 8 hr with a suspension of Raney nickel (160 ml). The nickel is filtered from the warm mixture and extracted five times with boiling benzene (100 ml portions). The filtrates are combined, the solvent is evaporated, and the residue recrystallized from methanol to yield colorless crystals (5.8 gm, 86.9%), m.p. 72–73°C.

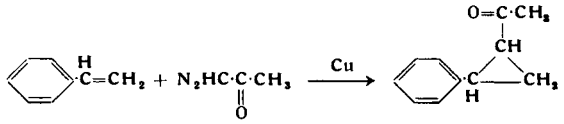
Isocyclic Compounds

Derivatives of Cyclopropane

According to the investigations of Grundmann (*7*), the thermal, noncatalyzed decomposition of diazoketones yields derivatives of cyclopropane:



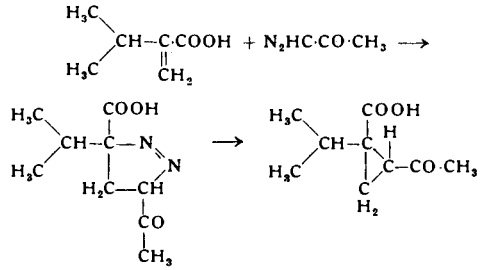
Ketones in the cyclopropane series can also be obtained by the catalytic decomposition of diazoketones in the presence of olefins (*9*).



This reaction can also be extended to include cycloölefines (*9*).

Neither ring enlargement nor norcaradiene derivative formation was observed when the decompositions were carried out in aromatic hydro-

carbons (benzene and anisole). As shown by Guha and Muthanna in connection with the synthesis of umbellulonic acid, diazoketones can add to polarized double bonds to give pyrazoline derivatives; on heating, these are converted into cyclopropanes with elimination of nitrogen (*140*).

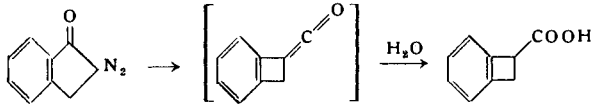


Preparative Method

1-Acetyl-2-phenylcyclopropane (*9*). A solution of diazoacetone (3 gm) in styrene (5 gm) is added dropwise over a period of 1 hr to a mixture of styrene (15 gm) and copper powder (1 gm) maintained at a temperature of 100°C. When the evolution of nitrogen has ceased, the catalyst is filtered off, the unreacted styrene distilled and the residue fractionated under vacuum to yield a colorless oil (2.35 gm, 42%), b.p. 80°C/0.4 mm.

Derivatives of Benzocyclobutene

Like their straight-chain analogs, cyclic diazoketones undergo a Wolff rearrangement when subjected to photolytic decomposition, giving rise in this case to a ring contraction (*141, 142*). Thus diazoindanone derivatives yield benzocyclobutenes (*41, 42, 45*).



The preparation of naphtho-2′,3′,2,3-cyclobutene-1-carboxylic acid and 4′,5′-dimethylene(benzo-1′,2′,2,3-cyclobutene)carboxylic acid was recently effected in a similar manner (*142*).

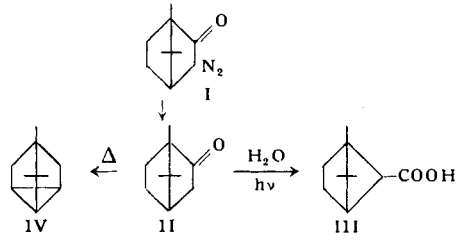
Preparative Method

Benzocyclobutenecarboxylic acid (*41*). The irradiation described is carried out in a glass trough covered by a quartz plate and fitted with a stirrer, thermometer, and cooling coil. A quartz burner (S-700) and reflector are situated above the trough. 2-Diazoindanone (for prepara-

tion, see p. 418) (8 gm) is dissolved in tetrahydrofuran/water (5:1, 660 ml) and irradiated to the extent of 80% for 5 to 6 hr at 20°C. The tetrahydrofuran is distilled on a water bath, and the residue is taken up in ether and repeatedly washed with saturated sodium bicarbonate solution. On acidification of the bicarbonate extract with hydrochloric acid, a yellow-brown oil separates which is dissolved in ether and dried. The ether is evaporated under vacuum, leaving a viscous residue which is repeatedly extracted with petroleum ether (b.p. 40–60°C) by warming under reflux. Evaporation of the petroleum ether yields pale-yellow crystals of the crude acid. Recrystallization from water gives colorless needles, m.p. 75°C. Yield, 25%.

Derivatives of Bicyclo[2.1.1]hexane

If diazocamphor (I) is irradiated with ultraviolet light in the presence of water, the Wolff rearrangement results in ring contraction to the bicylo[2.1.1]hexane derivative III (*144*).



No Wolff rearrangement occurs when the same keto carbene (II) is formed by the thermal decomposition of diazocamphor. Substitution takes place, and pericyclocamphanone (IV) is obtained (*145*).

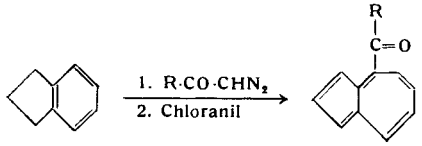
Preparative Method

1,6,6-Trimethylbicyclo[2.1.1]hexane-2-carboxylic acid (*144*). Diazocamphor (1.8 gm) in a mixture of dioxane (70 ml) and water (10 ml) is irradiated by means of a cooled immersion lamp until the evolution of nitrogen has ceased. The solvent is evaporated and the residue taken up in sodium bicarbonate solution and filtered free from undissolved resin. Acidification of the bicarbonate solution precipitates the required acid, which forms small colorless needles on recrystallization from ethyl acetate. Yield, 1.3 gm; m.p. 111°C.

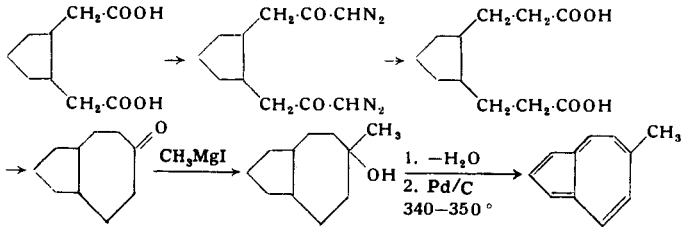
Azulenes

Decomposition of diazoketones in boiling hydrindene in the presence of copper powder results in both the previously mentioned substitution

of the solvent molecule and ring enlargement. If the reaction product is dehydrogenated with chloranil, 5-substituted azulene ketones are formed (*8*).



In order that explosions be avoided, the reaction temperature must be such that the diazoketone, added dropwise, is immediately decomposed. Plattner and Studer describe one synthesis of methylazulene starting from *cis*-cyclopentane-1,2-diacetic acid and involving the Arndt-Eistert method (*146*).

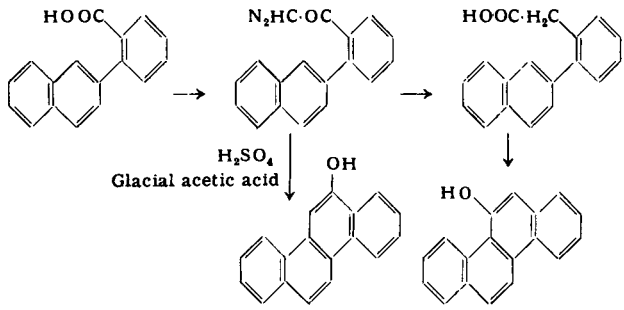


Preparative Method

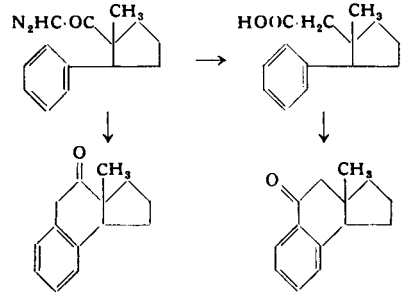
5-Benzoylazulene (*8*). A solution of diazoacetone (3 gm) in hydrindene (50 ml) is slowly added dropwise to hydrindene (250 ml) containing a little copper powder and maintained at the reflux temperature. When the evolution of nitrogen has ceased, chloranil is added in small portions to the solution at 120–130°C until a permanent green color is obtained. The cooled solution is chromatographed on alumina and eluted with an ether-cyclohexane mixture. The residue from the violet-blue fraction is recrystallized from low-boiling petroleum ether to give violet-black needles, m.p. 122–123°C.

Condensed Aromatic and Hydroaromatic Systems

When they allowed a mixture of glacial acetic acid and sulfuric acid to react with the diazoketone obtained from α-chrysenic acid, Cook and Schoental discovered a cyclization which can be utilized for the synthesis of polycondensed hydrocarbons. 2-Chrysenol was formed. The synthesis of 1-chrysenol, accomplished with the aid of the Arndt-Eistert reaction, is also shown (*147*).



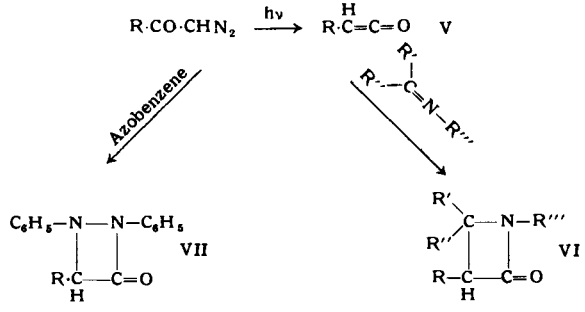
Analogous routes were subsequently followed in the preparation of hydroaromatic compounds containing angular methyl groups (*148*).



Heterocyclic Compounds

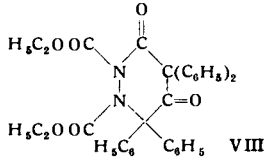
Acetidones (β-Lactams) and 1,2-Diazacyclobutanones

The ketenes initially formed by the Wolff rearrangement resulting from the photolysis of diazoketones will react with Schiff bases to give β-lactams (VI) (*149*).



Irradiation in the presence of azobenzene causes addition of the ketone to the latter, and 1,2-diazo-1,2-diphenylcyclobutanone (III) is obtained (*54, 150*).

When azibenzil is irradiated in the presence of azodicarboxylic ester, a product is formed which is identical with that obtained from two molecules of diphenylketene and one molecule of the azo compound, and which probably possesses structure VIII (*150*).



VIII

In general, photolytically produced carbenes containing electrophilic substituents show little or no tendency to undergo the additions described (*149*).

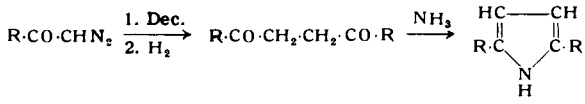
Preparative Methods

1,3,4-Triphenylacetidone (*149*). Diazoacetophenone (0.01 mole) and benzalaniline (0.01 mole) in benzene (100 ml) are irradiated by means of a cooled immersion lamp until the evolution of nitrogen has ceased. The benzene is evaporated *in vacuo* and the residue in chloroform chromatographed on neutral alumina (Wölm, column 15 × 3 cm) until the upper brown zone has reached the last third of the column. The eluate is evaporated and the residue is digested with hot methanol (20 ml) and filtered. Yield, 2.22 gm (74%), m.p. 134°C after recrystallization from butanol.

1,2,3,3-Tetraphenyl-1,2-diaza-4-cyclobutane (*39*). Azibenzil (4.4 gm) and azobenzene (3.5 gm) in absolute ether (170 ml) are irradiated until the evolution of nitrogen has ceased. The ether is evaporated and the yellowish residue recrystallized from methanol to give large colorless crystals (4.5 gm), m.p. 173°C.

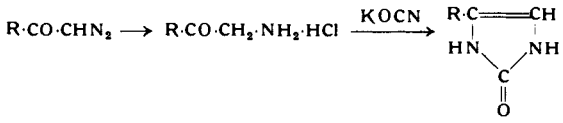
PYRROLES

The preparation, previously described, of 1,4-diketones from diazoketones provides a direct synthesis of pyrroles; this consists in allowing the diketones to react with ammonia, and was carried out by Ernest and co-workers (*124–128*).

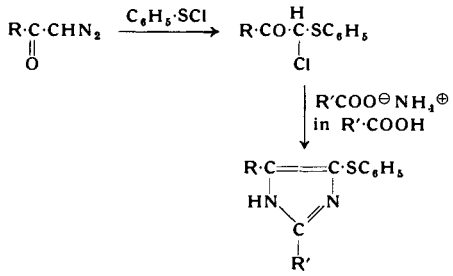


Imidazoles

2-Imidazolones were obtained by du Vigneaud and his collaborators, who allowed α-amino ketones (obtained from diazoketones via the phthalimide method) to react with potassium cyanate (*113*).



The same heterocyclic ring system is formed by the action of liquid carboxylic acids, into which NH_3 has been passed, on α-chloro-α-phenylmercapto ketones (*151*):



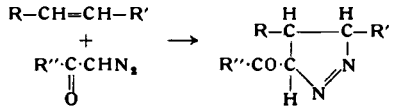
The course of the reaction is not yet clearly understood.

Preparative Method

2-Ethyl-4(5)-methyl-5(4)-phenylmercaptoimidazole (*151*). Ammonia (4.5 gm) is passed into propionic acid (50 ml), α-chloro-α-phenylmercaptoacetone (6 gm) added, and the mixture refluxed for 2 hr. Ammonium chloride is precipitated and the solution becomes dark red. The cooled reaction mixture is diluted with an equal volume of water, treated with animal charcoal to remove the diphenyl disulfide formed, and filtered. The base is precipitated by the addition of aqueous ammonium hydroxide until the mixture is distinctly alkaline, and filtered. Purification can be effected either by recrystallization from alcohol/water (1:2) and treatment with animal charcoal or by sublimation. M.p. 199°C; yield, 2.1 gm (32.3%).

Pyrazoles

Diazo compounds can add to polarized double bonds to form pyrazoline derivatives (*140*).

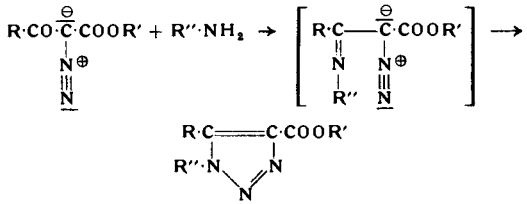


According to Huisgen (*4*), Wolff's (*152*) synthesis of pyrazoles from diazoketones and β-keto esters or β-diketones also proceeds via the addition of the diazo compound to the enol form of the β-diketo compound, followed by the elimination of water.

Triazoles

Diazoketones flanked by two carbonyl groups are capable, on account of their increased possibilities of mesomerism, of undergoing a number of reactions which diazomethyl ketones of structure R—CO—CHN_2 do not undergo. Two such reactions are discussed here and in the following section.

α-Diazo β-keto esters react with ammonia or primary amines to give triazoles (*153*).



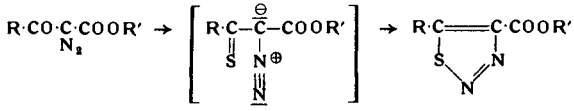
The amine components used include substituted hydrazines and hydroxylamine.

Preparative Method

Ethyl 1-benzyl-5-methyltriazinecarboxylate (*153*). Ethyl acetyldiazoacetate (7 gm) and benzylamine (10 gm) in glacial acetic acid (20 ml) are maintained at 90–100°C for 12 hr. When the reaction mixture is poured into cold sodium carbonate solution, the ester crystallizes out. It is recrystallized from alcohol. Yield, 4 gm; m.p. 79–80°C.

Thiadiazoles

While the action of H_2S on diazomethyl ketones gives the hydrazones of α-keto aldehydes (*84, 85*), that on diazoketones of structure R—CO—CN_2—CO—R′ yields thiadiazoles (*154*).



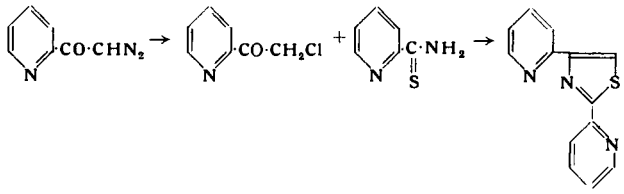
Infrared studies proved that thiadiazoles are true heterocyclic compounds, not diazothioketones (*155*). The band at 4.7–4.9 μ, characteristic of the diazo group, is absent (*156*).

Preparative Method

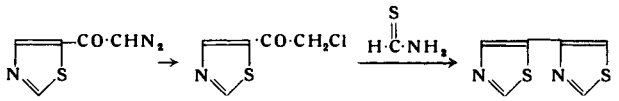
Ethyl phenylthiodiazolecarboxylate (*154b*). Hydrogen sulfide is passed for 24 hr through a solution of benzoyldiazoacetic ester (4 gm) and ammonium sulfide (4% solution, 5 ml) in alcohol (20 ml). The precipitated sulfur is filtered off, the solvent evaporated, and the residue taken up in ether. Evaporation of the ether gives an oil which crystallizes on cooling. Recrystallization from a small quantity of alcohol yields colorless needles or plates, m.p. 42°C.

THIAZOLES

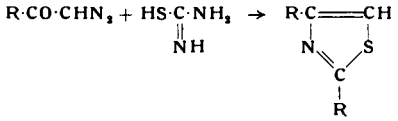
By virtue of their ready conversion into α-haloketones, diazoketones have frequently been used as starting materials in the synthesis of thiazoles. This heterocyclic ring can be obtained from α-haloketones by a number of methods. Erlenmeyer and co-workers prepared 2,4-di(α-pyridyl)thiazole (*157*).



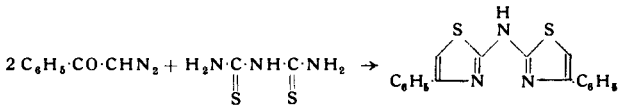
The synthesis of 4,5-dithiazolyl follows a similar course (*158, 159*).



Thiourea is among the thioamides used (*105, 160, 161*). As diazoketones react with thiourea or thioamides directly to form thiazole derivatives, the α-haloketone stage can be omitted (*162*).



Bis(4-phenyl-2-thiazolyl)amine was obtained from diazoacetophenone and thiobiuret (*162*).

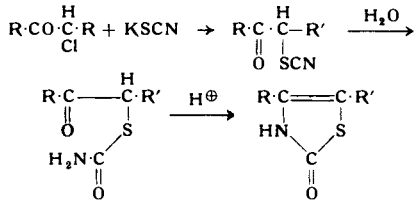


Preparative Method

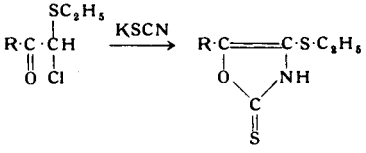
2-Amino-4-phenylthiazole (162). Diazoacetophenone (1.46 gm) and thiourea (2.4 gm) are refluxed for 1 hr in absolute alcohol (20 ml). Part of the solvent is then distilled off, a little water added, and the solution warmed and filtered with animal charcoal. The thiazole crystallizes on cooling.

OXAZOLETHIONES

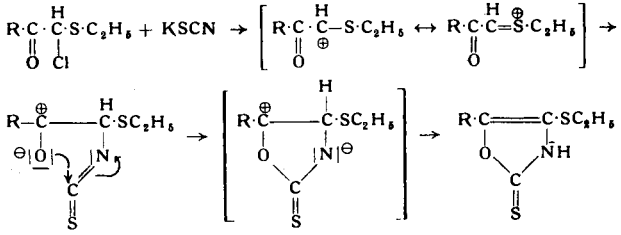
According to the investigations of Hantzsch (*163*), the reaction between α-haloketones and potassium thiocyanate, followed by cyclization in an aqueous acid medium, results in the formation of thiazolones.



This reaction cannot, however, be extended to the α-chloro-α-ethylmercapto ketones obtained from diazoketones and sulfenyl chlorides. If they are allowed to react with potassium thiocyanate, 2-oxazolethiones are formed (*164*).



Whereas compounds of type R—CO—CH_2—X react with KSCN via an S_N2 mechanism to give thiocyanates, α-halo thioethers follow an S_N1



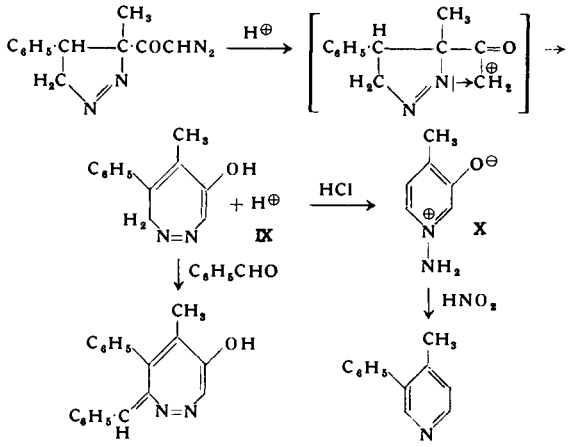
mechanism and yield isothiocyanates which immediately cyclize at the neighboring carbonyl group (*165*).

Preparative Method

5-Methyl-4-ethylmercapto-2-oxazolethione (*164*). α-Chloro-α-ethylmercaptoacetone (10 gm) is added to a warm solution of potassium thiocyanate (8 gm) in acetone (50 ml). A vigorous reaction immediately ensues and KCl is precipitated. The mixture is allowed to stand for 48 hr, filtered, the precipitate washed with acetone, and the solvent evaporated *in vacuo*. The crystalline residue is taken up in ether, filtered free from undissolved KCl, and dried over $MgSO_4$. Evaporation of the ether and repeated recrystallization from ligroin yield colorless needles (9 gm, 72%), m.p. 107–108°C.

1,2-Diazacycloheptatriene and Derivatives of Pyridine

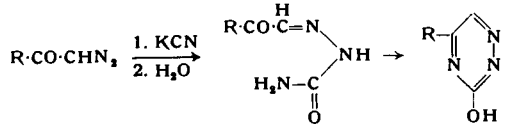
Decomposition with glacial acetic acid of 3-diazoacetyl-3-methyl-4-phenyl-Δ^1 pyrazoline, the diazoketone obtained from α-methylcinnamoyl chloride and diazomethane, gave a new heterocyclic compound which can be converted into a pyridine derivative. The course of the reaction (no preparative details have thus far been published) is shown in the scheme below (*83a*).



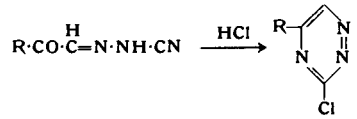
The rearrangement of the 1,2-diazacycloheptatriene derivative IX into the zwitterion X is effected by dissolving in 20% hydrochloric acid and liberating the base X from the precipitated hydrochloride. Compound X can then be converted into 3-hydroxy-4-methyl-5-phenylpyridine with nitrous acid in alcohol.

TRIAZINES

As previously described, the reaction between diazoketones and potassium cyanide yields the cyanohydrazones of the α-keto aldehydes; these react with water or H_2S to give the corresponding semicarbazones or thiosemicarbazones, respectively. These compounds cyclize to *as*-triazines in an alkaline medium (*16*, *83*).



The action of HCl on the cyanohydrazones yields chlorotriazoles:



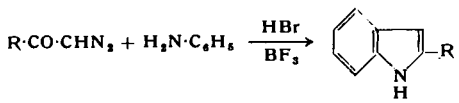
Preparative Methods

Benzylglyoxal monothiosemicarbazone (*83*). A concentrated aqueous solution of KCN (50% excess) is added to a solution of 1-phenyl-3-diazoacetone in the minimum quantity of alcohol. The precipitated potassium salt is filtered off after a few hours and dissolved in a small amount of water. H_2S is passed into the solution until no further precipitate separates; then it is filtered and recrystallized from alcohol. M.p. 162.5–163.5°C; yield, 70%.

3-Mercapto-5-benzyl-as-triazine. The thiosemicarbazone obtained is boiled under reflux for 15 min with aqueous potassium carbonate. On cooling, the solution is neutralized with acetic acid, a little animal charcoal added, and the mixture filtered and acidified with hydrochloric acid. The precipitated product is recrystallized from alcohol; m.p. 169–170°C.

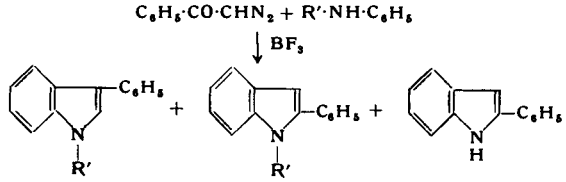
INDOLES

If diazoketones are heated at 180–200°C with aniline and aniline hydrochloride or aniline-BF_3, 2-substituted indoles are obtained in 65–93% yields when the diazoketone is derived from an aromatic acid (R = aromatic) (*166*):

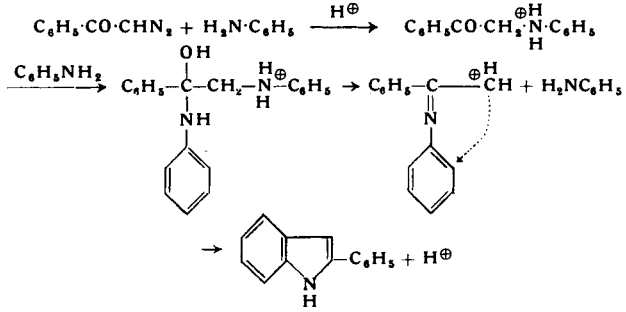


Aliphatic diazoketones (R = aliphatic) afford lower yields. Aromatic diazoethyl ketones, obtained from diazomethane, give 3-methyl-2-aryl indoles in 33–35% yields.

Reaction with secondary aromatic amines in the presence of BF_3 yields a mixture of N-alkyl-2- and -3-aryl indoles and 2-aryl indoles.



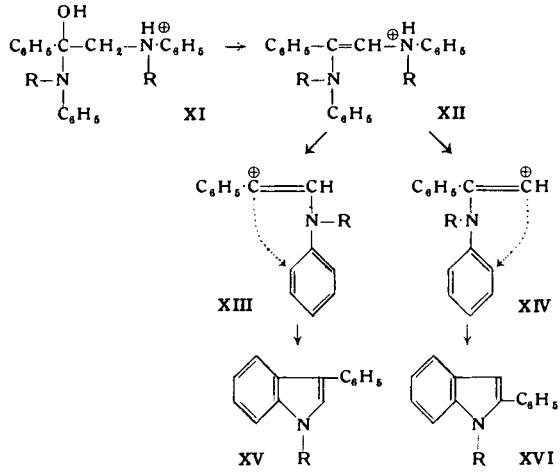
Taking into consideration experiments using C^{14} and Br^{89} (*167*), we would agree with the mechanism proposed by Blades and Wilds and interpret it as follows (H^+ can be replaced by BF_3):



The first step consists in the formation of phenacylanilinium salts [cf. the preparation, discussed earlier, of phenacylpyridinium bromide from diazoacetophenone and pyridine hydrobromide (*82*), and the reaction between diazoacetophenone and aniline in the presence of copper (*10*)]. This is followed by the addition of one molecule of aniline to the carbonyl group. Elimination of water and aniline yields the anil of the phenacyl cation, which itself loses a proton and undergoes ring closure at the position *ortho* to the N=C grouping to give a 2-aryl indole.

In the reaction with secondary aromatic amines the first two steps are identical. Water elimination from the adduct of aniline and the carbonyl compound XI cannot, however, yield the anil, but gives the enediamine XII.

It will readily be seen that elimination of aniline from XII can yield a carbonium ion in two ways (XIII and XIV). By ring closure at the position *ortho* to the nitrogen substituent, these two cations give either



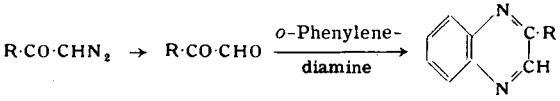
3-aryl indoles (XII → XIII → XV) or 2-aryl indoles (XII → XIV → XVI).

Preparative Method

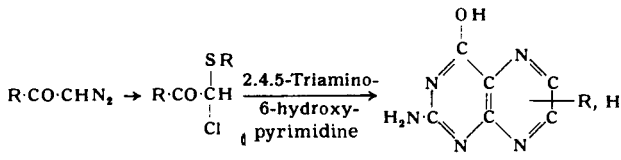
2-Substituted indoles from diazoketones (*166*). The diazoketone (1 gm) and an equimolar quantity of either BF_3-etherate or aniline hydrobromide are heated at 175–200°C for 1 hr in freshly distilled aniline (10 ml). An excess of sodium carbonate is added and the aniline removed by steam distillation. The residue is purified by recrystallization or sublimation.

Quinoxalines and Pteridines

By virtue of the ability of α-keto aldehydes to condense with *o*-diamines, the synthesis of homologous α-keto aldehydes offers a method of preparing derivatives of both quinoxaline and pteridine (*80*).

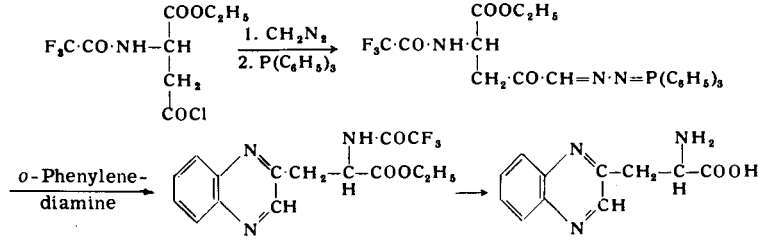


The synthesis of these heterocyclic compounds does not necessitate the use of the free α-keto aldehydes. The identical condensation products are formed from their derivatives, e.g. the α-chloro-α-ethylmercapto ketones, which are far more readily obtained from the diazoketones (*168*):



The reaction between the α-keto-α-halo thioethers and 2,4,5-triamino-6-hydroxypyrimidine to give pteridine derivatives has invariably produced a mixture of the isomers containing the group R in positions 6 and 7 (*168*).

The α-keto triphenylphosphazines discussed earlier also react directly with *o*-diamines to give heterocyclic compounds (*169*), as illustrated by the synthesis of optically active quinoxalylalanine (*170*).



The condensation of the phosphazines with triaminohydroxypyrimidine to give pteridines also yields a mixture of the 6- and 7-isomers. Hydrazine and triphenylphosphine oxide are invariably formed during the course of these reactions.

Preparative Methods

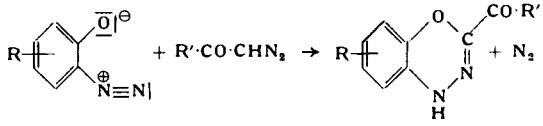
6- and 7-Methylpteridine (*168*). (*a*) 1-Chloro-1-ethylmercaptoacetone (1 gm) is added to a stirred solution of 2,4,5-triamino-6-hydroxypyrimidine sulfate hydrate (1.4 gm) and sodium acetate (1.2 gm) in water (50 ml). Ethyl mercaptan is immediately liberated (odor) and a precipitate separates which is centrifuged off after 5 hr. The compound is dissolved in 0.1 *N* NaOH, reprecipitated with glacial acetic acid, redissolved in boiling sodium acetate solution (250 ml), and treated with a little Fuller's earth. The hot solution is adjusted to pH 3–4 with hydrochloric acid and allowed to cool slowly to yield silky, sparkling microcrystals (34%).

(*b*) 2,4,5-Triamino-6-hydroxypyrimidine sulfate (4 gm) is brought to pH 7 with a saturated solution of barium hydroxide. The same volume of alcohol containing methylglyoxaltriphenylphosphazine (4 gm) is added, followed by glacial acetic acid (3.3 ml), and the mixture boiled

under reflux for 4 hr. It is filtered hot and washed with alcohol and ether. The solid is dissolved in a small quantity of 2 *N* NaOH and filtered into water (500 ml). The solution is brought to the boil and acidified to pH 3–4 with 2 *N* HCl. The precipitate is centrifuged off and washed with alcohol and ether. Yield, 1.3 gm (*169*).

Benzo-4H-1,3,4-oxadiazines

Diazoketones react with quinone diazides to give benzo-4H-1,3,4-oxadiazines (*12*).

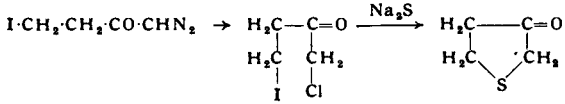


Preparative Method

2-Benzoyl-6,8-dinitrobenzo-4H-1,3,4-oxadiazine. Diazotized picramic acid (1.8 gm) is heated at 60–70°C with a solution of diazoacetophenone (1.25 gm) in dioxane (8 ml) until the evolution of nitrogen has ceased. On standing in the refrigerator, the product (1.52 gm) crystallizes out; a second crop (0.27 gm) is obtained from the mother liquors. Total yield, 78%. Recrystallization from glacial acetic acid affords orange-yellow tangled needles, m.p. 209°C (dec.).

3-Thiophanone

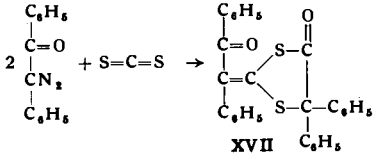
3-Thiophanone was synthesized from iodopropionic acid by Karrer and Schmidt (*171*).



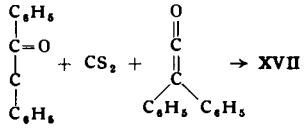
The diazoketone was not isolated, and the ring closure affords yields of 22%.

Derivatives of 1,3-Dithiacyclopentane and -pentene

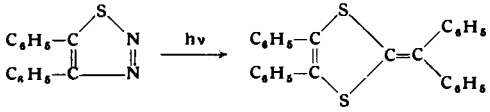
Azibenzil reacts with boiling carbon disulfide to give an excellent yield of a compound whose molecular formula is $C_{29}H_{20}O_2S_2$ (*172*); Yates and Christensen showed this product to be a derivative of 1,3-dithiacyclopentane (*173*).



Compound XVII is probably formed by the addition of one molecule of CS_2 to one molecule of unrearranged α-keto carbene and one of the diphenylketene formed by Wolff rearrangement.



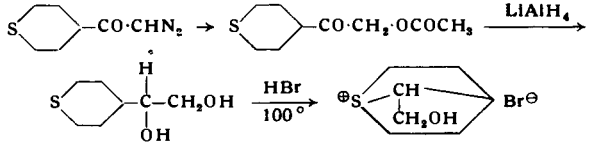
1,4-Dithiafulvenes, derivatives of 1,3-dithiacyclopentene, are formed in the photolysis of thiadiazoles (*155*). As mentioned earlier, the latter are obtained by the action of H_2S on diazoketones containing two adjacent carbonyl groups.



With strong acids, these new compounds form colorless salts possessing a tropylium-type cation.

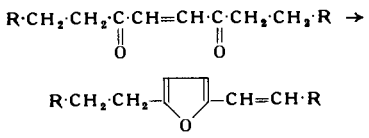
Derivatives of Bicyclo[2.2.1]heptane-1-thionium Bromide

Derivatives of these bicyclic compounds are obtained with the aid of diazoketones (*174*).



Derivatives of Furan

During the course of investigations into the decomposition of diazoketones to give diacyl ethylenes, Ernest and his co-workers discovered a new reaction of these compounds. Under the action of mineral acid, α,β-unsaturated 1,4-diketones undergo water-elimination and isomerization and are converted into unsaturated 2,5-disubstituted furans (*175*).



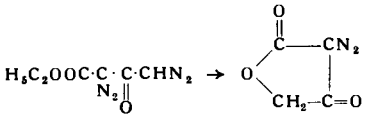
The catalytic effect of HCl is greater than that of other mineral acids.

Preparative Method

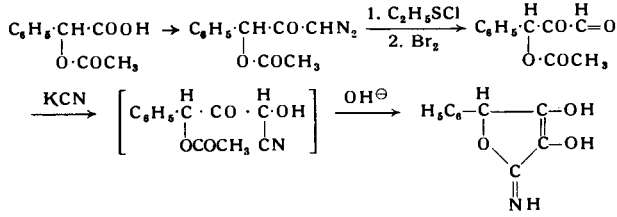
5-Phenethyl-2-styrylfuran (*175*). 1,8-Diphenyloct-4-ene-3,6-dione (1 gm), obtained by the decomposition of 1-diazo-4-butan-2-one (itself obtained from hydrocinnamic acid) with CuO in benzene, is dissolved in 99.8% acetic acid (75 ml) containing hydrogen chloride (0.178 gm). The mixture is allowed to stand at 20°C for 90 min and the solvent is distilled off *in vacuo*. The pale yellow oily residue is dissolved in ether and shaken with hydrochloric acid. The ether is dried and evaporated, and the residue chromatographed on alumina (activity III). Elution with cyclohexane and evaporation of the solvent afford a colorless oil which soon solidifies. M.p. 50–51°C; yield, 715 mg (70%).

Derivatives of Tetronic Acid

If 1,3-bisdiazoacetoacetic ester, mentioned earlier, is treated with dilute sulfuric acid, only the terminal diazo group is attacked. Spontaneous ring closure yields diazotetronic acid, which thus becomes readily accessible (*51*).



Application of the homologous α-keto aldehyde synthesis resulted in the preparation of 4-phenyl-2-hydroxytetronimide (*92*), obtained by Dahn via a completely different route (*176*).



Preparative Methods

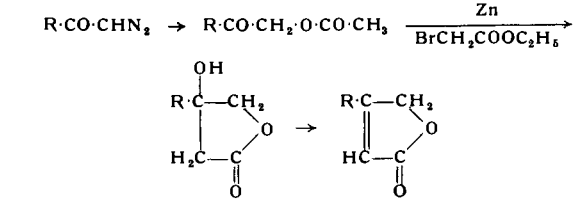
1,3-Bisdiazoacetoacetic ester (*51*). Diazomalonyl chloride ethyl ester (5 gm) in absolute ether (10 ml) is slowly added dropwise to a well-

cooled solution of diazomethane (prepared from 16 gm nitrosomethylurea). The solution is allowed to stand for 2 hr and the ether evaporated *in vacuo*. The residual oil soon crystallizes, and is recrystallized from ether at —40°C to yield fine yellow needles, m.p. 53°C.

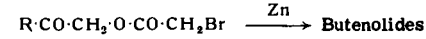
Diazotetronic acid (*51*). 1,3-Bisdiazoacetoacetic ester (5 gm) is added to 2 *N* sulfuric acid (40 ml), which becomes slightly warm. When the evolution of nitrogen has ceased, the mixture is extracted several times with methylene dichloride, the organic layer dried over sodium sulfate and the solvent evaporated. The crystalline residue is recrystallized from alcohol. Yield, 2.65 gm (76.5%), m.p. 93°C.

Butenolides

Diazoketones have frequently been used in the synthesis of butenolides. One method consists of a Reformatski reaction between bromoacetic ester and ketol acetates (*177, 178*).

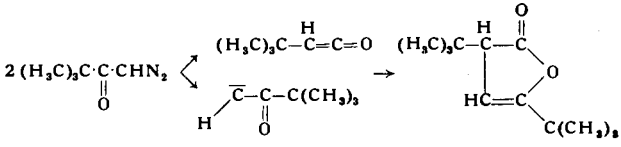


Alternatively, the diazoketones are allowed to react with bromoacetic acid to give the ketol bromoacetates, which are then treated with zinc (*179*).



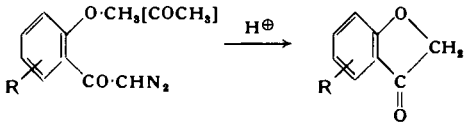
This last step can only be accomplished if bromoacetic ester is added. Since even so the yields are highest when 0.75 equivalent of the ester is added, it appears doubtful whether an intramolecular ring closure does in fact take place.

The photolysis of diazomethyl *tert*-butyl ketone gives α,γ-di-*tert*-butyl-$\Delta^{\beta,\gamma}$-butenolide; the formation of the latter can be thought of as resulting from the addition of a ketene (produced by a rearrangement) to an unrearranged α-keto carbene (*70*):

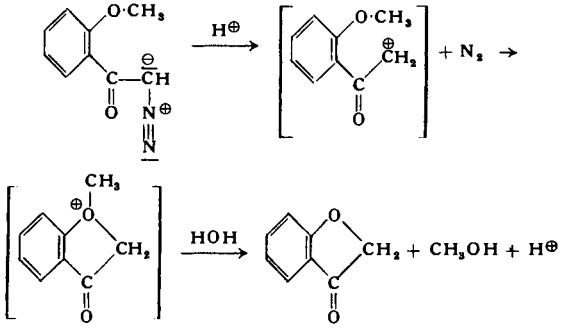


Derivatives of Coumarone

o-Methoxy- and *o*-acetoxydiazoacetophenones are converted into coumarone derivatives by the action of protons (*179, 180;* cf. *3*).



The mechanism of this reaction, which is catalyzed by traces of HCl, was elucidated by Bose and Yates (*181*).



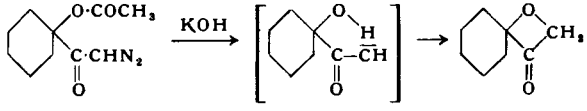
If the phenolic OH group is protected by an acetyl group, acetic acid is formed instead of methanol.

Preparative Method

Coumarone (*181*). Hydrochloric acid (0.1 *N*, 0.1 ml) is added dropwise to a stirred suspension of *o*-methoxy-ω-diazoacetophenone (1 gm) in water (5 ml). A further quantity of HCl (0.1 ml) is added after 1 hr, and the precipitate filtered off after 3 hr, by which time the continuous evolution of gas has ceased. Yield, 0.65 gm (86.5%); m.p. 97°C; sublimation raises the m.p. to 100–101.5°C.

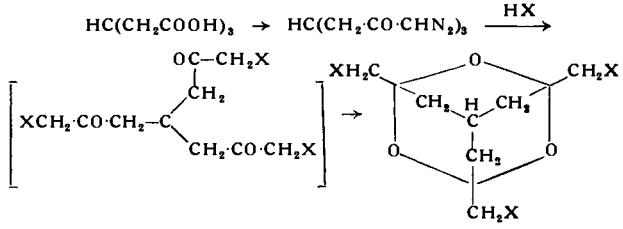
1-Oxaspiro[3.5]nonan-3-one

The above-mentioned formation of coumarone derivatives bears some analogy to the cyclization which occurs when 1-acetoxy-1-diazoacetylcyclohexane is treated with alcoholic KOH to yield 1-oxaspiro[3.5]-nonan-3-one (*182*).



Derivatives of 2,4,9-Trioxaadamantane

An elegant synthesis of the 2,4,9-trioxaadamantane ring system was devised by Stetter and Stark (*183*).

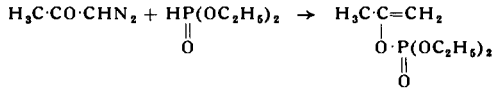


The compound, m.p. 128–129°C, formed in the reaction between the trisdiazoketone and HBr, is volatile, undergoes no carbonyl reactions, and exhibits no carbonyl bands in the infrared spectrum. The trioxaadamantane structure must therefore be assigned to it.

Miscellaneous Reactions

Reaction Between Diazoketones and Diethyl Phosphite

The action of diethyl phosphite on diazoacetone in the presence of triethylamine, followed by the decomposition with silver oxide of the adduct formed, results in the formation of the diethyl enol phosphate of acetone (*184*).



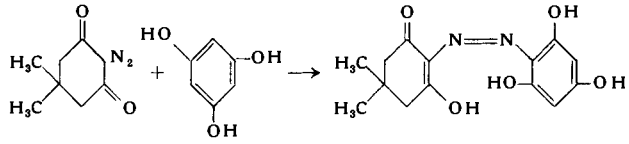
Preparative Method

Diethyl isopropenyl phosphate (*184*). Triethylamine (5 ml) is slowly added to a stirred mixture of diazoacetone (8.4 gm) and diethyl phosphite (13.8 gm). The mixture is warmed at 70°C for 2 hr, and a freshly prepared suspension of Ag_2O in a little dioxane added, which results in the immediate evolution of nitrogen. When no more gas is evolved, more silver oxide is added, the mixture is briefly boiled, shaken with charcoal, and filtered. The solvent is evaporated and the residue fractionated *in vacuo*. B.p. 94–95°C/11 mm; yield, 8 gm (41%).

Coupling Reactions of Diazoketones

Coupling reactions like those undergone by aromatic diazo compounds had not been encountered in the case of diazoketones until recently, when

Severin (*19, 185*) succeeded in effecting a reaction of this type. An azo compound is rapidly formed when diazodimedone is allowed to react with phloroglucinol in an alkaline medium.



Diazoacetylacetone, diazoacetoacetic ester, and other aliphatic diazo compounds undergo similar reactions with phenols which couple readily.

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