THE ORGANIC CHEMISTRY OF DRUG SYNTHESIS
Volume 2

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The Organic Chemistry of Drug Synthesis

VOLUME 2

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A WILEY-INTERSCIENCE PUBLICATION

JOHN WILEY AND SONS, New York • Chichester • Brisbane • Toronto

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Library of Congress Cataloging in Publication Data:

Lednicer, Daniel, 1929-
The organic chemistry of drug synthesis.

"A Wiley-Interscience publication."
1. Chemistry, Medical and pharmaceutical.
2. Drugs. 3. Chemistry, Organic. I. Mitscher, Lester A., joint author. II. Title.

RS421.L423 615'.191 76-28387
ISBN 0-471-04392-3

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

It is our pleasure again to dedicate
a book to our helpmeets: Beryle and Betty.

"Has it ever occurred to you that medicinal chemists are just like compulsive gamblers: the next compound will be the real winner."*

*R. L. Clark at the 16th National Medicinal Chemistry Symposium, June, 1978.

Preface

The reception accorded "Organic Chemistry of Drug Synthesis" seems to us to indicate widespread interest in the organic chemistry involved in the search for new pharmaceutical agents. We are only too aware of the fact that the book deals with a limited segment of the field; the earlier volume cannot be considered either comprehensive or completely up to date. Because the earlier book did, however, lay the groundwork for many of the structural classes or organic compounds that have proven useful in the clinic, it forms a natural base for a series that will, in fact, be comprehensive and up to date. This second volume fills some of the gaps left by the earlier work and describes developments in the field up to the end of 1976. More specifically, we have included literature and patent preparations for

those compounds granted a USAN* generic name prior to and including 1976 that did not appear in Volume I.

In assembling the first volume, we faced an apparently staggering mass of material. It seemed at the time that attempts to be inclusive would lead to an undigestible compendium. In order to keep the reader's interest, we chose instead to be selective about material to be included. Specifically, the first volume deals predominantly with organic compounds actually used in the clinic. It is, of course, well known that many compounds die in various stages of clinical trials, either from lack of effect, lack of superiority over existing drugs, or the presence of disqualifying side effects. Particularly since 1962, sponsoring companies have become much more demanding in the standards to be met by a drug before undertaking the cost involved in the clinical work leading to an NDA.† For that reason, this period has seen a large increase in the number of compounds that have been granted generic names but have failed to achieve clinical use. Many such failed analogues were omitted from the previous volume. Since we now intend to make the series comprehensive, and since those analogues do have heuristic value, we have chosen to violate chronology and include them in the present volume. Volume 2 thus goes beyond simple updating.

*United States Adopted Name

†New Drug Application

The organization of the material by chemical classes used earlier has been retained since it provided a convenient method for lending coherence to the subject matter. However, changes in emphasis of research in medicinal chemistry have led us to change the organization of the individual chapters. The small amount of new work devoted to some structural types (e.g., phenothiazines) that formed large units in the earlier book failed to provide sufficient material to constitute a chapter here; what material was available has simply been included under some broader new heading. As was the case previously, syntheses have been taken back to commonly available starting materials as far as possible. An exception to this rule will be found in the section on steroids. Many of the compounds described are corticoids, that are the products of intricate multistep syntheses. In the earlier volume, we described the preparation of some quite highly elaborated corticoids using plant sterols as starting materials. Many of these corticoids are used for preparation of compounds in this volume. Since there seems little point in simply reiterating those sections, a starting material is judged to be readily available if its preparation is described in the first volume. The reference will be to that book rather than to the original literature.

We have endeavored, too, to approach biological activity in the same fashion as we did earlier. The first time some therapeutic indication occurs will be the occasion for a concise simplified discussion

of the disease state and the rationale for the specific method of drug therapy. Biological activities are noted for each generic compound at the same time as its preparation. It will be emphasized again that the activities quoted are those given by the authors; this book is not intended as a critical text in pharmacology.

"Organic Chemistry of Drug Synthesis, Volume 2" is addressed to the same audience as was Volume 1: graduate students in medicinal and organic chemistry, as well as practitioners in the two fields. This book also assumes that the reader will have a good understanding of synthetic organic chemistry and at least a rudimentary knowledge of biology.

Finally, we express our sincere appreciation to several individuals who contributed time and talent to this project. Ms. Carolyn Kelly patiently typed the many versions of the manuscript, including the final camera-ready copy, in the midst of the press of her daily responsibilities. Sheila Newland drew the structural formulae, and John Swayze read the entire manuscript and made several useful suggestions to help clarify the text and reduce the number of typos. Ken McCracken and Peggy Williams were extremely helpful in guiding us through the intricacies of the IBM "Office System 6".

Daniel Lednicer — Evansville, Indiana
Lester A. Mitscher — Lawrence, Kansas
January, 1980

Contents

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Monocyclic and Acyclic Aliphatic Compounds

1. CYCLOPENTANES

a. Prostaglandins

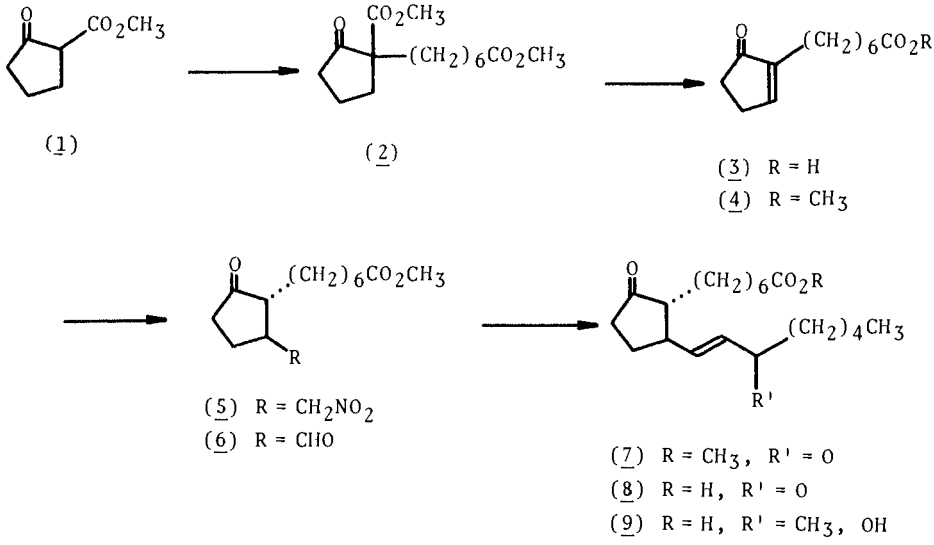
When realistic quantities of the natural prostaglandins became available, their extreme potency and wide-ranging biological activities were discovered and visions of therapeutic application in the regulation of fertility, control of ulcers, blood pressure, bronchial asthma, and many other conditions led to a torrent of chemical and biological studies which currently measures about four papers daily, and at least one a week dealing with synthesis alone. Initial chemical emphasis lay in developing efficient syntheses of the natural substances to solve the supply problem. Presently, the emphasis has shifted to preparation of analogues which are intended to be less expensive, more selective in their action, and longer lasting. The five drug candidates in this

section are significant representatives of the hundreds of such analogues available.

The naturally occurring prostaglandins, E_1, E_2 and A_1, have potent antisecretory activity when given parenterally and have been suggested for use in treatment of gastric ulcers. Unfortunately, these natural compounds have relatively poor oral activity and rapid metabolism makes their action short-lived. Molecular manipulation proved that an oxygen atom at C_{11} was not necessary for bioactivity but these compounds also lacked the desired oral activity. This problem was solved by a study of the metabolizing enzymes and by borrowing an artifice from steroid chemistry (*viz*-methyl testosterone, Volume I). The most rapid metabolic deactivating reaction is oxidation to the bioinert C_{15}-oxo prostaglandins. Converting the latter to a tertiary methyl carbinol led to the desired orally active gastric antisecretory agents.

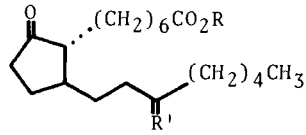
Starting with 2-carbomethoxycyclopentanone (*1*), t-BuOK catalyzed alkylation of methyl ω-bromoheptanoate gave diester *2* which was then hydrolyzed and decarboxylated. The conjugated double bond was then introduced by a bromination-dehydrobromination sequence to give versatile prostaglandin synthon *3*. Esterification to *4* was followed by conjugate addition of sodio nitromethane to give *5*. Nitroketone *5* was converted to the sodium salt of the corresponding nitronic acid with sodium in methanol and this was hydrolyzed with icecold dilute H_2SO_4 to ketoaldehyde *6*. This sequence is the Nef reaction. Wittig

reaction of this sodio dimethyl-2-ketoheptyl phosphonate gave *7*.[1,2] Ester hydrolysis to *8* followed by careful reaction with methyl magnesium bromide produced the orally active bronchiodilator, *doxaprost (9)*.[2] *Doxaprost*, at least as originally prepared, is conformationally undefined at C_{15} and is probably a mixture of R and S isomers.



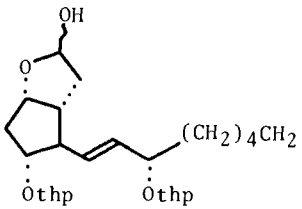
Enzymic studies demonstrated that the 15-dehydrogenase was also inhibited by saturation of the C_{13} double bond and *deprostil (12)* embodies this chemical feature as well.[3] Catalytic hydrogenation of *7* produced *10* which was hydrolyzed to *11* and reacted with methyl magnesium bromide in ether. As above, careful control of conditions allowed the organometallic reagent to add selectively to the

less hindered side chain carbonyl to produce the orally active potent gastric antisecretory agent, *deprostil (12)*. Interestingly, studies with resolved *12* showed that the unnatural epimer at C_{15} was more potent.



(10) R = CH_3, R' = O
(11) R = H, R' = O
(12) R = H, R' = CH_3, OH

Introduction of an allene function in place of an olefinic double bond is not commonly employed by medicinal chemists, although such derivatives are occasionally used as progestational steroids. It is interesting, therefore, that the presence of this synthetic feature is consistent with typical prostaglandin biopotency.[4] In this case, the well-known Corey-lactol synthon, *13*, was reacted with dilithio pent-4-yn-1-ol to give acetylenic carbinol *14* which was protected by esterification with acetyl chloride to give *15*. Treatment of *15* with $LiMe_2Cu$ led to allene *16*. The mechanism of this curious reaction is not clear. Possibly the reagent forms an organometallic derivative of the acetylene moiety with expulsion of the acetate group and double bond migration as a consequence. When this sequence was applied in earlier papers to terminal acetylenes (*e.g., J. Am. Chem. Soc., 91, 3289 (1969)*), terminal



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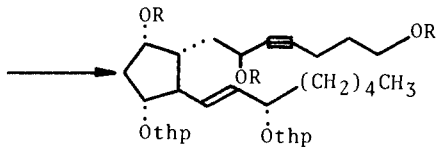
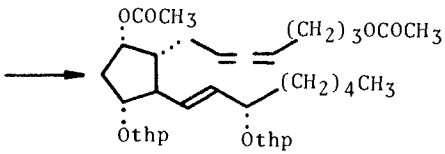


(14) R = H
(15) R = $COCH_3$



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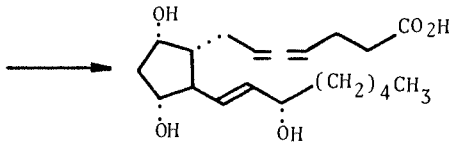


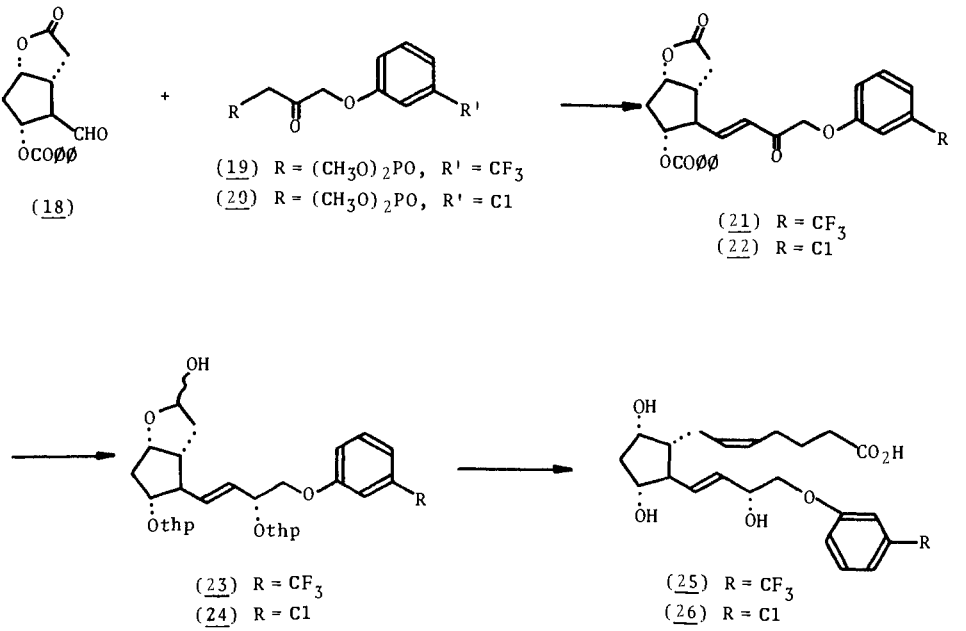
(17)

methylation accompanied allene formation and loss of the acetoxy group. Careful alkaline hydrolysis of allene *16* preferentially cleaved the terminal primary ester. The resulting alcohol was then oxidized to the carboxylic acid with Jones' reagent. Saponification under more strenuous conditions removed the remaining acetate group and acid treatment removed the thp ethers. There is thus obtained *prostalene (17)*, which has been described as a bronchodilator and hypotensive agent.

Animal husbandry requires the careful selection and management of breeding stock and a prize stud is an economically valuable asset. The expensive service fee makes it very important that the female be in estrus at the time of mating. In order to

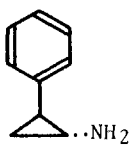
optimize the breeding process, two prostaglandin analogues have recently been marketed which are potent luteolytic agents used to regularize or synchronize estrus in horses. The inclusion of an aryloxy residue in place of the last three carbons of the aliphatic moiety at the methyl terminus of the prostaglandins greatly increases activity and apparently decreases metabolic deactivation.

The synthesis begins with *18*, a well-known prostaglandin synthon first developed by Corey.[5] This is condensed with the appropriate phosphonate ylide reagents (*19* or *20*) which are themselves prepared by reaction of the appropriate ester or acid chloride of an aryloxyacetic acid with the anion of the dimethyl methylphosphonate. The resulting *trans*-eneone (*21* or *22*) is reduced with zinc borohydride, the p-phenylphenylester serving to give preferential reduction to the 15α-ols. The ester is then hydrolyzed with K_2CO_3/MeOH and the two alcoholic functions are protected as the tetrahydropyranyl ethers. Reduction with diisobutylaluminum hydride at -78°C produces lactols *23* and *24* and their C_{15} epimers. Reaction with the Wittig reagent from 5-triphenylphosphonopentanoic acid and acid catalyzed removal of the protecting groups followed by chromatography gives *fluprostenol (25)* and *cloprostenol (26)*,[6] respectively. These compounds are several hundred times more potent by injection than prostaglandin $F_{2\alpha}$ as luteolytic agents, although striking species differences are observed.



b. Other Cyclopentanoids

Clinical success with the monoamine oxidase inhibitor and amphetamine analogue *tranylcypromine (27)* led to an exploration of the effect of ring size on activity.[7] It was found that an interesting dissociation of properties could be achieved and the best of the series, *cypenamine (30)*, is an antidepressant without significant MAO inhibitory activity. One of the more convenient syntheses[8] makes use of the finding that hydroxylamine-O-sulfonic acid is soluble in diglyme and therefore is suitable for conversion of organoboranes from hindered and unhindered olefins into the corresponding amines. 1-Phenylcyclopentene



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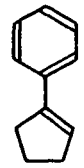

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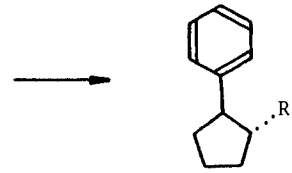


(29) R = B

(30) R = NH_2

(28) is hydroborated to *29* in the usual way with borohydride and BF_3. Addition of H_2NOSO_3H followed by acid hydrolysis completes the synthesis of *cypenamine (30)* with excellent regio and stereospecificity. The reaction sequence is a net *cis* anti-Markownikoff addition of the elements of NH_3 to *28*.

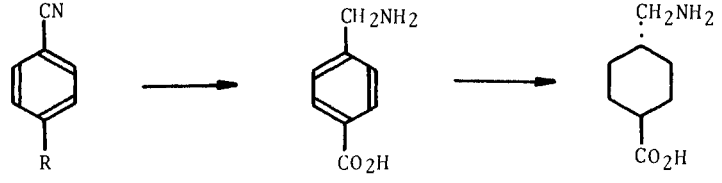
2. CYCLOHEXANES

a. Cyclohexane and Cyclohexene Carboxylic Acids This subgroup is classified strictly for chemical convenience because their pharmacological properties are unrelated to one another.

Clotting of blood is, of course, one of the more significant ways in which the body protects itself from excessive blood loss after injury. After the healing takes place, the clot, which is a three-dimensional polypeptide, is broken down by proteolytic enzymes such as fibrinolysin or plasmin. In some pathological states, fibrinolysis is hyperactive and inhibitors have a hemostatic value.

Plasmin does not occur in free form but is generated as needed from an inactive precursor, plasminogen. The active of plasminogen to plasmin is a proteolytic event and can be inhibited by ω-

aminocarboxylic acids having a structural or spatial resemblance to lysine. One such agent is *p-aminomethylbenzoic acid (33)* and its reduction product *tranexamic acid (34)*.[9] First p-cyanotoluene *(31)* is oxidized to the carboxylic acid *(32)* with CrO_3; then reduction of the nitrile group with Raney cobalt in the presence of liquid ammonia produces p-aminomethylbenzoic acid *(33)*. Reduction of the aromatic ring of

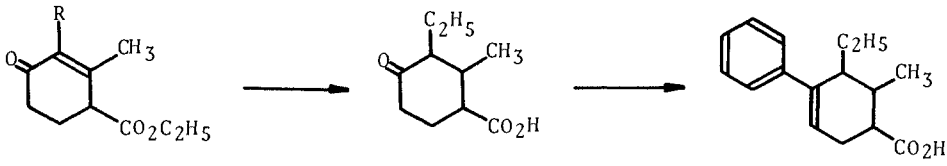


(31) R = CH_3
(32) R = CO_2H

(33) (34)

33 with a platinum catalyst produces mainly the *cis* isomer. Upon heating under nitrogen at 315-325°, isomerization occurs to the *trans*-analogue *(34)* which possesses all of the hemostatic activity.

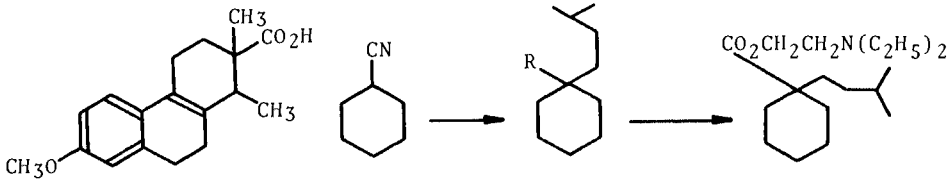
Many substances other than estrone possess estrogenic activity and some of these bear only little formal resemblance to the natural hormone. Many years ago, doisynolic acid *(39)*, a steroid degradation product, was shown to have such activity. Over the years many simple compounds have been synthesized following the idea of molecular dissection. One of these is *fenestrel (38)*.[10] Hageman's ester *(35)* is alkylated to *36* by t-BuOK and ethylbromide. The regioselectivity observed is generally



(35) R = H
(36) R = C_2H_5

(37)

(38)



(39)

(40)

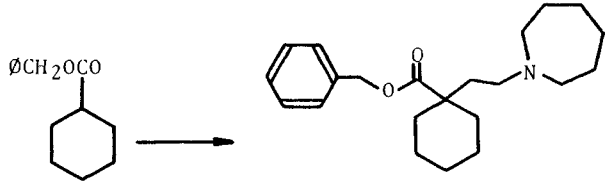
(41) R = CN
(42) R = CO_2H

(43)

regarded to be a consequence of the greater reactivity of the enolate at C_2 over the other possible enolates (at C_4 and C_6). The double bond is reduced with hydrogen and a palladium catalyst and saponification produces *37* of unspecified stereochemistry. Treatment with phenyl magnesium bromide followed by dehydration with tosic acid in acetic acid leads to the estrogen, *fenestrel (38)*. Presumably, the double bond remains tri- rather than tetrasubstituted in this case because of the steric interactions this latter case would engender between the ethyl and phenyl groups. The stereochemistry of *fenestrel* is complex so formula *38* implies no stereochemical meaning.

A smooth muscle relaxant apparently of the antimuscarinic type whose actions, therefore, are somewhat reminiscent of atropine, is *isomylamine* *(43)*.[11] Its synthesis begins with the sodamide catalyzed alkylation of cyclohexyl nitrile *(40)* with 1-bromo-3-methylbutane and the resulting nitrile *(41)* is hydrolyzed to the acid *(42)* with HBr in acetic acid. Alkylation of the sodium salt of this acid using β-chloroethyldiethylamine leads to the desired *43*.

Coughing is a useful physiologic device utilized to clear the respiratory tract of foreign substances and excessive secretions. Coughing, however, does not always serve a useful purpose but can rob the patient of sleep. A number of agents are available to suppress this. Many of these are narcotic and have an undesirable abuse potential. One of the agents available which is claimed to be nonnarcotic is *amicibone* *(45)*.[12] The synthesis involves base-catalyzed alkylation of benzyl cyclohexanecarboxylate *(44)* with β-hexamethyleneiminoethyl chloride a reaction which may go through an aziridinium intermediate.



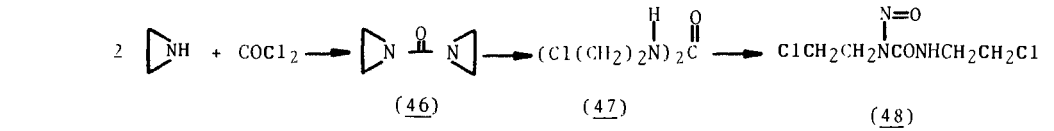
(44) (45)

b. Cyclohexylamines

Although substantial strides have been made toward the chemotherapeutic control of cancer, much remains to be accomplished with respect to broadening of activity spectrum, decreasing host toxicity, increasing remission time, etc., of the various chemotherapeutic agents available. Lacking an all-encompassing rationale upon which to build a drug design program, many potentially useful leads have emerged from directed screening efforts. The nitrosoureas *carmustine (BCNU, 48)*, *lomustine (CCNU, 58)* and *semustine (MeCCNU, 56)* are cases in point belonging to the group of cytotoxic alkylating agents.

Cell multiplication requires the rapid synthesis of functional DNA. Those cells which are dividing most rapidly, for example, cancer cells, are particularly sensitive to agents which disrupt this process. The alkylating agents alkylate the purine and pyrimidine bases and so convert them to unnatural compounds. This has the consequence of stopping DNA synthesis and/or inhibiting transcription of the genetic code from DNA. Normal host cells generally spend time in a resting stage where they are less damaged by these cytotoxic agents. Tumor cells, by contrast, are almost always in an active phase of the cell cycle. Following up a lead discovered at the Cancer Chemotherapy National Service Center, it was ultimately shown that unsymmetrical N-nitrosoureas are quite potent alkylating agents and several are now in clinical trial.

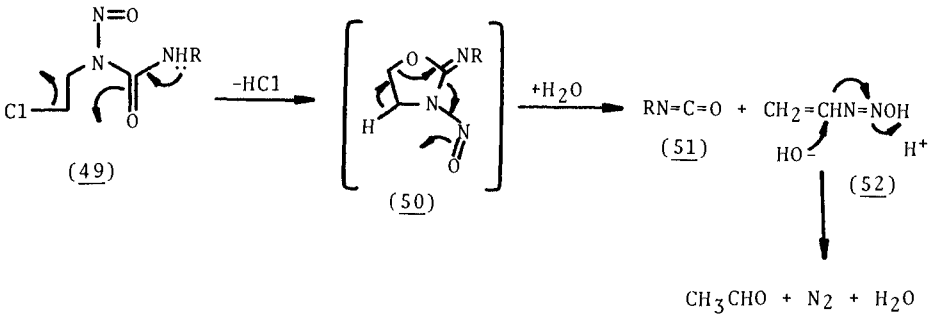
BCNU is synthesized[13,14] by treating phosgene with ethyleneimine without the addition of a base to take up the HCl liberated. Reaction of the intermediate urea *(46) in situ* with hydrogen chloride serves to open the aziridine rings to afford *sym*-bis-2-chlorethylurea *(47)*. This is nitrosated with sodium nitrite in formic acid to give *BCNU (48)*.

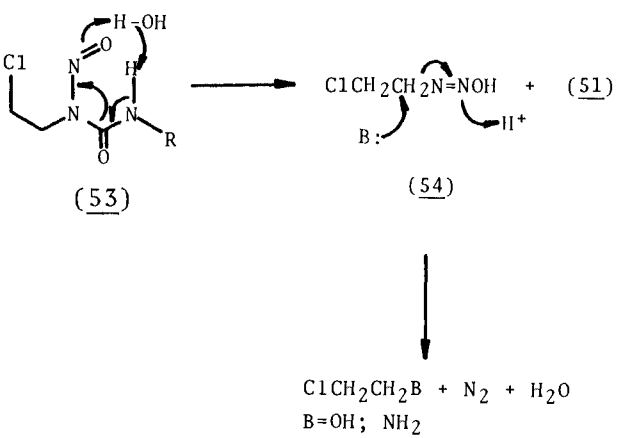


(46) (47) (48)

On standing in water under various conditions, two main modes of degradation occur and these are rationalized as follows.

The nonnitrosated nitrogen of *49* supplies electrons for an intromolecular displacement of Cl to give intermediate imino ether *50* which collapses to isocyanate *51* and highly reactive *52* which latter fragments, ejecting nitrogen and capturing OH to produce acetaldehyde, after enolization. In the second mode, a cyclic fragmentation process *(53)* leads to isocyanate *51* and N-hydroxy-2-chloroethylazine *(54)* which undergoes fragmentation, losing nitrogen and capturing OH (to give 2-chloroethanol) or NH_3 (to give 2-chloroethylamine). As 2-chloroethylamine is a known source of aziridine, this substance has potential alkylating activity. Also, ejection





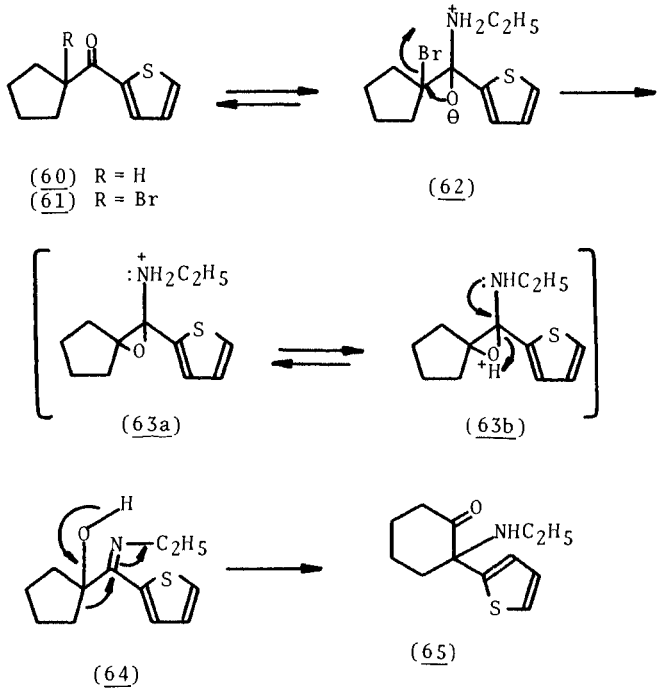
of nitrogen from *52* to *54* leads to electron deficient species which react with nucleophiles. The isocyanate *(51)* also adds nucleophiles. Thus, it is not certain at this stage which of these is the most responsible agent for the bioactivity or whether the antitumor properties are a blend of these.

The reader has noted that unsymmetrical ureas can nitrosate on either nitrogen and that these decomposition modes enable one to assign structure to the products. This, in fact, also has preparative significance and both *lomustine (CCNU, 58)* and its methyl analogue *semustine (MeCCNU, 56)* are made in this way.[14] In the *semustine* synthesis, *BCNU (48)* is decomposed in the presence of two equivalents of *trans*-4-methylcyclohexylamine to give an 84% yield of unsymmetrical urea *55*--probably *via* the trapping of intermediate isocyanate *51* (R = CH_2CH_2Cl). Nitrosation with $NaNO_2/HCO_2H$ produces *semustine (56)* contaminated with some of the alternate nitroso analogue. Use of cyclohexylamine in this reaction sequence leads to *lomustine (58)* instead. There is some evidence to suggest that *in vivo* 4-hydroxylation to *59* may be of great importance in the activity of *lomustine*.

(55) R = CH_3
(57) R = H

(56) R = CH_3
(58) R = H
(59) R = OH

A more complex cyclohexylamine, *tiletamine (65)*, is a useful anesthetic in that injection leads to loss of consciousness without an untoward decrease in blood pressure or heart rate and without undue respiratory depression. Its synthesis[15] begins with



(60) R = H
(61) R = Br

(62)

(63a) (63b)

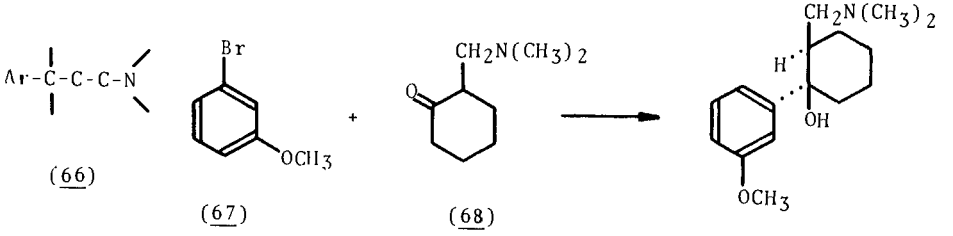
(64)

(65)

bromination of α-thienylcyclopentylketone *(60)* to give *61*. Reaction with ethylamine appears to involve carbonyl addition to *62* followed by epoxy formation *(63ab)* and then rearrangement to ethylimine *64* after proton loss. It is, of course, apparent that bromide *61* could not undergo a Favorskii rearrangement. Thermolysis of *64* results in a ring expansion and formation of *tiletamine (65)*. The close structural relationship between *tiletamine* and *ketamine*[16] is probably not coincidental.

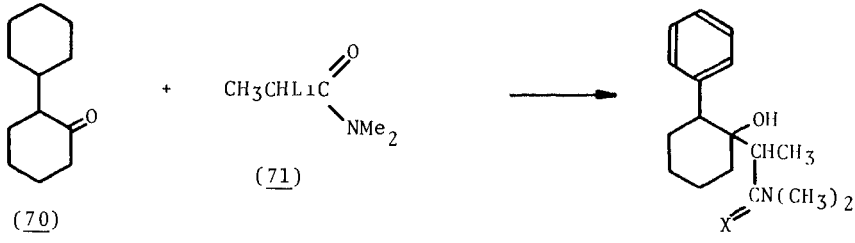
c. Miscellaneous

The molecular dissection embodied in the morphine rule *(66)* has served as a useful empirical guide for the synthesis of analgesic agents even though a number of significant agents fit the rule poorly. Briefly, the morphine rule suggests that substances containing an aromatic ring attached to a quaternary carbon which is in turn separated from a tertiary amine by two carbons might be active. One such is *tramadol (69)*. It is synthesized[17] by reacting the Grignard reagent prepared from m-methoxybromobenzene *(67)* with 2-dimethylaminomethylenecyclohexanone *(68)*, itself obtained by Mannich reaction on cyclohexanone, to give *tramadol (69)*. The isomers are separated by fractional crystallization of the HCl salts.



(66) (67) (68) (69)

A closely related analgesic which does not fit into the morphine rule is *nexeridine (73)*. In this case,[18] 2-phenylcyclohexanone *(70)* is reacted with the lithium salt of N,N-dimethylpropionamide *(71)* to give tertiary alcohol *72*. Reduction of the latter with lithium aluminum hydride gives *nexeridine (73)*.



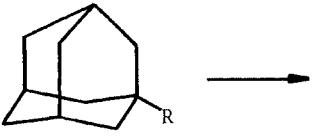
(70) (71) (72) X = O (73) X = H_2

3. ADAMANTANES

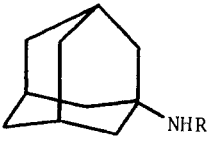
The adamantane moiety is of medicinal chemical interest because of its inertness, compactness relative to lipid solubilizing character, and symmetry. Considerable interest, therefore, was engendered by the finding that *amantadine (78)* was active for the chemoprophylaxis of influenza A in man. There are not many useful chemotherapeutic agents available for the treatment of communicable viral infections, so this finding led to considerable molecular manipulation. The recent abrupt end of the National Influenza Immunization program of 1976 prompted a new look at the nonvaccine means for prophylaxis or treatment of respiratory tract infections due to influenza A, especially in that the well-known antigenic shift or drift of the virus obviates usefulness of the vaccine but not *amantadine*.

The synthesis[19] begins with the halogenation of adamantane *(74)* with bromine to give *76* or chlorine and $AlCl_3$ to give *75*. The four bridgehead positions

are identical and surprisingly reactive. Reaction

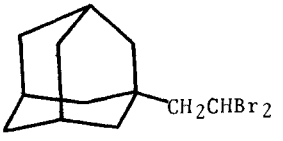


(74) R = H
(75) R = Cl
(76) R = Br



(77) R = $COCH_3$
(78) R = H

of *76* with acetonitrile in sulfuric acid leads through an apparent SN_1 reaction to amide *77* which is hydrolyzed by base to give *amantadine (78)*. A similar antiviral agent, *rimantadine (83)*, is also useful for treatment of respiratory diseases due to type A influenza virus. It is synthesized[20] from



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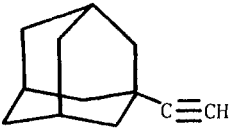

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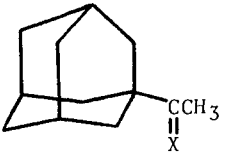
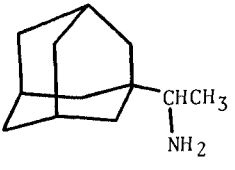


(81) X = O
(82) X = NOH



(83)

adamantyl bromide *(76)* by $AlBr_3$ catalyzed addition of vinylbromide to give 79 which is then dehydrohalogenated by heating with KOH to give acetylene *80*. Hydration to methyl ketone *81* is achieved by HgO-catalyzed reaction with sulfuric acid. After oxime formation *(82)* lithium aluminum hydride reduction leads to *rimantidine (83)*.

The high lipophilicity of adamantyl moieties suggests that drugs containing them might pass into tissues of high lipid content or cross the blood-brain barrier. Indeed *carmantadine (85)* is active against the spasms associated with Parkinson's disease. *Amantadine (78)* reacts[21] with methyl 2,4-dibromobutyrate to give ester *84* which can be hydrolyzed with aqueous barium hydroxide to complete the synthesis of *carmantidine (85)*.

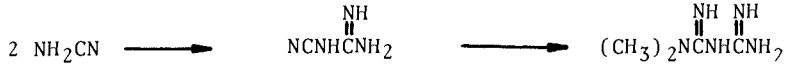
(84) R = CH_3
(85) R = H

4. NONCYCLIC ALIPHATICS

Many of the biguanides have oral hypoglycemic activity, and *metformin (87)* is such an antidiabetic agent. Cyanamide has a highly reactive nitrile function because of the electropositive NH_2 group

attached and at pH 8-9 self-adds to form "dicyanamide" *(86,* for which cyanoguanidine would be a better name). Fusion with dimethylamine[22] leads efficiently to *metformin (87)* by addition to the nitrile function. *Metformin* is closely related to *buformin.*[23]

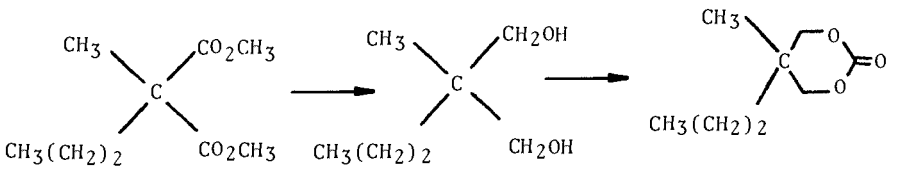
The discovery and clinical acceptance of *meprobamate,* and the relative chemical accessibility of this group of compounds has led to intensive exploration of 1,3-biscarbamates. It was found that



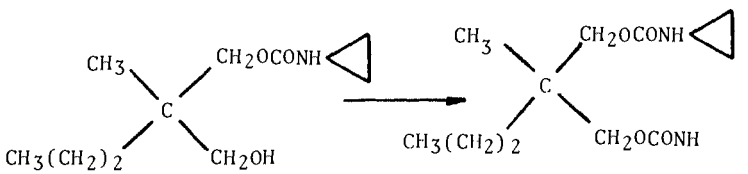
(86) (87)

substitution of one of the NH hydrogens by an alkyl group changed the emphasis of the biological response from muscle relaxant and anticonvulsant to centrally acting muscle relaxant whose action differs somewhat from *meprobamate. Carisoprodol* was the best member of one of these series and *lorbamate (92)* is its cyclopropyl analogue. The chief synthetic problem to be overcome was the differentiation of the two primary alcohol groups of *89,* readily accessible by lithium aluminum hydride reduction of the appropriate di-substituted malonate *(88).* This was solved[24] by an ester exchange reaction with diethylcarbonate to give *90* which produced carbamate *91* on reaction with

cyclopropylamine. Ester exchange of *91* with ethyl carbamate led efficiently to *lorbamate (92)*, a useful muscle relaxant.

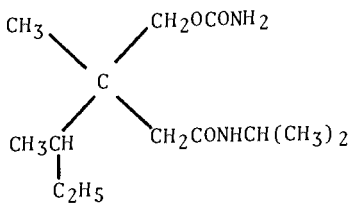


(88) (89) (90)



(91) (92)

Relatively simple variants of this basic scheme led to the minor tranquilizers *nisobamate (93)*[25] and *tybamate (94)*.[26]



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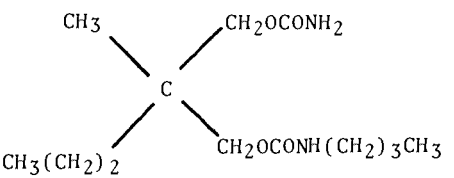

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2

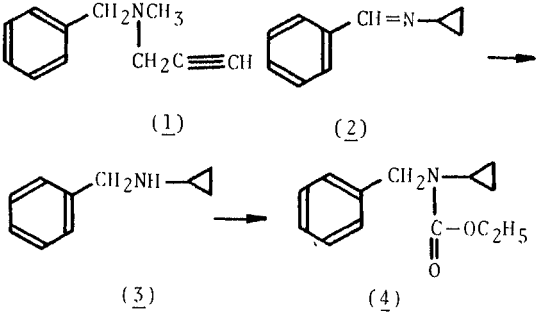
Derivatives of Benzyl and Benzhydryl Alcohols and Amines

As will become apparent in a perusal of this book, organic molecules owe their biological activity to a variety of structural features. Sometimes a set of activities is associated with the structural backbone of a molecule. For example, most prostanoids share certain biological properties despite some changes in functionality; the same will be noted later for steroids. Some biological activities are associated with a specific arrangement of structural subunits; e.*g.*, β-adrenergic blocking agents tend to be derivatives of aryloxypropanolamines. Some activities are quite directly associated with a specific functionality; no better example of this exists than the host of guanidine-containing sympathetic blocking agents. Sometimes, however, no such discernable

relationship can be detected between activity and structure. Such classes are often marked by widely divergent activities. Derivatives of benzyl- and benzhydrylamines and alcohols fall into this latter category.

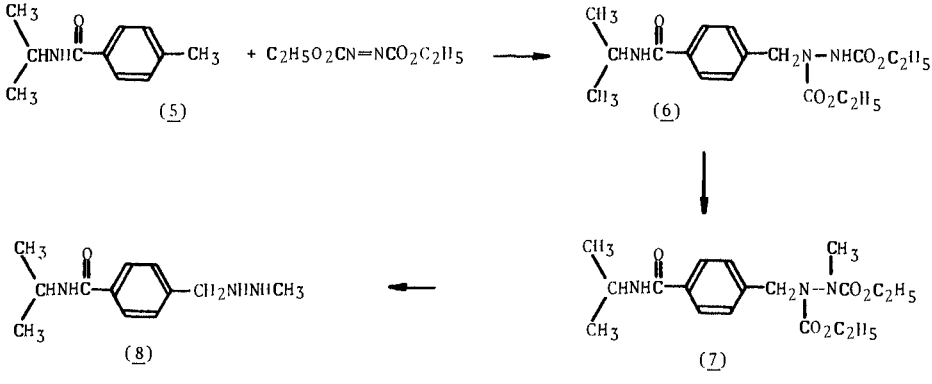
1. Derivatives of Benzylamine

In the course of some work aimed at delineation of the structure-activity relationships of the antidepressant monoamine oxidase (MAO) inhibiting drug *pargyline (1)*, it was noted that activity was consistent with quite wide modification of the substitution on nitrogen. One of the best drugs to emerge from this study is *encyprate (4)*. Hydrogenation of the Shiff base from benzaldehyde and cyclopropylamine *(2)* gave the secondary amine *(3)*. Treatment of this with ethyl chloroformate afforded the MAO inhibitor *encyprate (4)*.[1,2]



A derivative of benzylhydrazine, *procarbazine (8)*, exhibits antineoplastic activity. In an interesting insertion-type sequence, reaction of the p-toluamide *(5)* with ethyl azodicarboxylate leads directly to the substituted hydrazine *(6)*. It is not unlikely that the first mole of the diazo compound

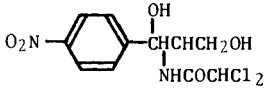
oxidizes the benzylic methyl group to an anion or radical anion; addition of that to a second mole of diazo compound would give the observed product *(6)*. Methylation by means of sodium hydride and methyl iodide proceeded at the less hindered amide to give *(7)*. Acid hydrolysis of the carbethoxy groups leads finally to *(8)*.[3]



An important feature of the antibiotic *chloramphenicol (9)* is the presence of the dichloroacetamide function. Inclusion of this amide in a simpler molecule, *teclozan (15)*, leads to a compound with antiamebic activity. Whether this is cause and effect or fortuitous is unclear. The synthesis begins with alkylation of the alkoxide derived from ethanolamine *(10)* with ethyl iodide to give the aminoether *(11)*. Reaction of α,α'-dibromo-p-xylene *(12)* with 2-nitropropane in the presence of base leads to dialdehyde *(13)*. The reaction probably proceeds by O-alkylation on the nitropropyl anion

followed by bond reorganization and subsequent hydrolysis of the resulting enol ether. Reductive alkylation of the dialdehyde with aminoether *(11)* gives diamine *(14)*. Acylation by means of dichloroacetyl chloride affords *teclozan (15)*.[4]

The presence of the dichloroacetamide grouping is apparently not an absolute requirement for anti-



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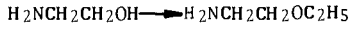

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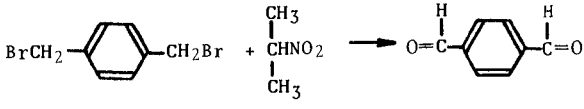

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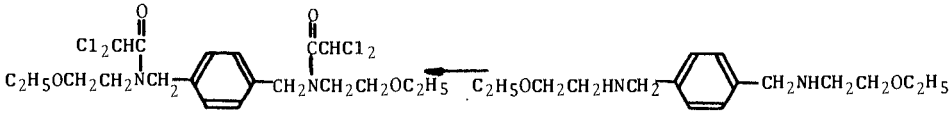
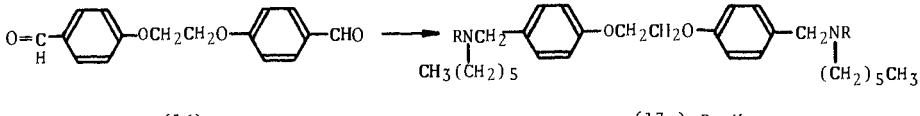


(15) (14)

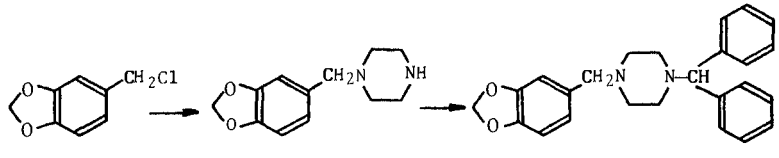
amebic activity. In one pertinent example, reductive alkylation of dialdehyde *(16)* with n-hexylamine affords *17a* and Eschweiler-Clark methylation of *17a* by heating with formaldehyde in formic acid then leads to the antiamebic drug *symetine (17b)*.[5]



(16) (17a) R = H (17b) R = CH_3

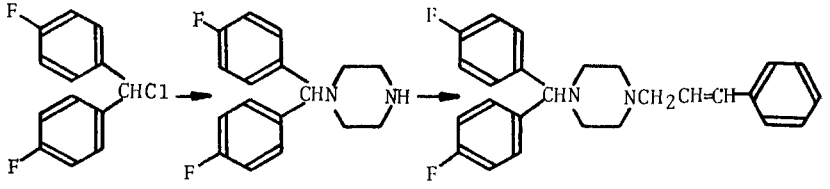
2. Benzhydrylamine Derivatives

Attachment of piperazine nitrogen directly to a benzhydryl carbon leads to a pair of compounds which show vasodilator activity, and which should be useful in disease states marked by impaired blood circulation. Reaction of piperonyl chloride *(18)* with a mixture of piperazine and piperazine dihydrochloride leads to the monoalkylation product *(19)*. (It may be supposed that the mixture of free base and salt equilibrates to the monobasic salt, thus making the second amine less nucleophilic.) Alkylation of *19* by means of benzhydryl chloride then affords the coronary vasodilator *medibazine (20)*.[6]



(18) (19) (20)

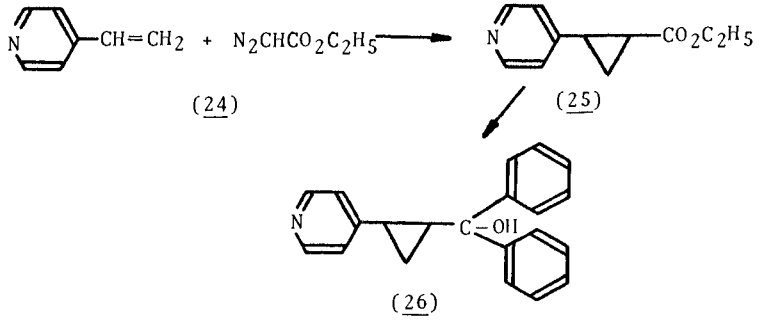
In an analogous sequence, condensation of piperazine with 4,4'-difluorobenzhydryl chloride gives the monoalkylation product *(22)*. Reaction of *22* with cinnamyl bromide affords *flunarizine (23)*.[7] *Flunarizine* is also a coronary vasodilator.



(21) (22) (23)

3. Benzyhydrol Derivatives

Cyprolidol (26), a highly modified benzhydrol derivative, is reported to exhibit antidepressant activity; it is of note that this agent bears little structural relation to either the MAO inhibitors or tricyclic antidepressants. Addition of the carbene from



(24) (25)

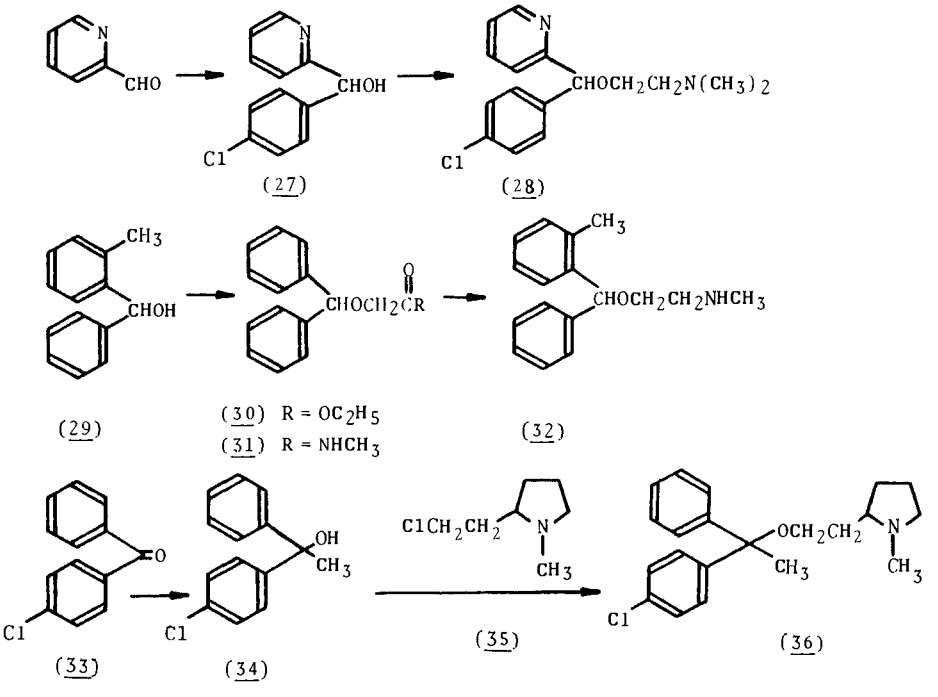
(26)

decomposition of ethyl diazoacetate to 4-vinylpyridine gives the cyclopropane *(25)* (stereochemistry unspecified). Condensation of the ester with phenylmagnesium bromide affords *cyprolidol (26)*.[8]

Basic ethers of benzhydrols are among some of the better known antihistaminic compounds. The earlier volume describes well over a dozen of these drugs. However, research in the area of allergy has recently shifted away from compounds which antagonize the action of histamine to drugs that intervene in earlier stages of the allergic reaction. The basic ethers are therefore represented here by but a few entries. In the preparation of *rotoxamine (28)*, reaction of pyridine-2-carboxaldehyde with the Grignard reagent formed from p-bromochlorobenzene gives the carbinol *(27)*; alkylation with N,N-dimethylchloroethylamine and optical resolution gives *rotoxamine (28)*, the levorotatory form of *carbinoxamine*.[9]

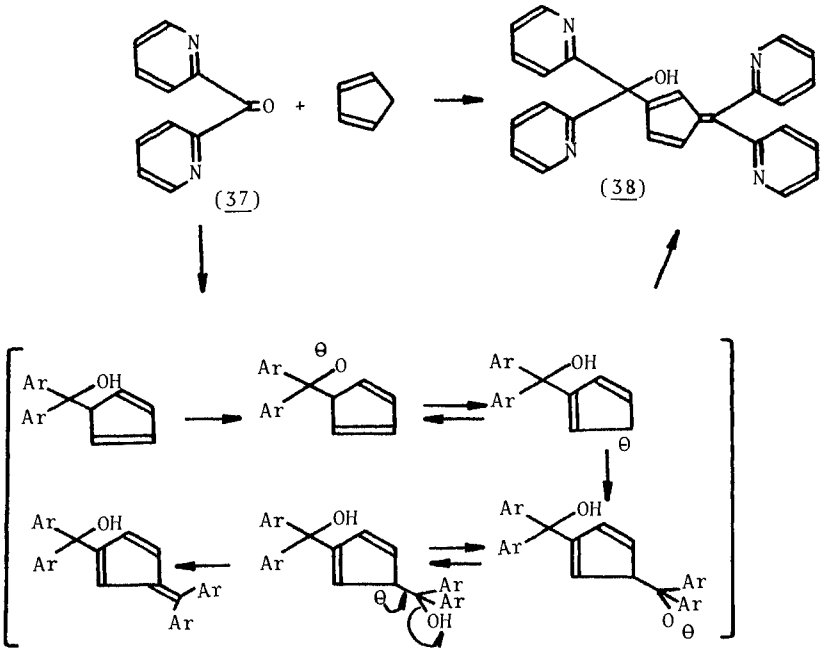
A slightly more complex scheme is required for preparation of an antihistaminic agent bearing a secondary amine, e.*g.*, *tofenacin (32)*. In the synthesis of *tofenacin*, alkylation of the benzhydrol *(29)* with ethyl bromoacetate affords the alkoxy ester *(30)*; saponification followed by conversion to the methylamide gives *(31)*, which is reduced with lithium aluminum hydride to complete the synthesis of *32*.[10]

Antihistaminic properties are well known to be preserved even when nitrogen is included in a ring, such as in *clemastine (36)*. Synthesis of *36* is begun by reaction of 4-chlorobenzophenone *(33)* with



methyl magnesium bromide to give the carbinol *(34)*. Alkylation of *34* with the chloroethyl pyrrolidine *(35)* then yields *clemastine (36)*.[11]

Arrhythmias, that is, disturbances in the regular timed beating of the heart, often result in life-threatening situations, since the pumping efficiency of the heart is directly related to its rhythmic synchronous contractions. Much activity has thus been expended in searching for drugs which abolish irregularities of the beat without compromising other aspects of cardiac function. One apparently



quite complex compound which exhibits such activity is, in fact, the product of a relatively simple reaction: condensation of cyclopentadiene with bis(2-pyridyl)ketone *(37)* in the presence of base affords directly *pyrinoline (38)*.[12] The condensation can be rationalized by a scheme such as that shown.

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3

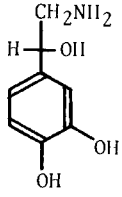
Phenylethyl and Phenylpropylamines

1. PHENYLETHYL AND PHENYLPROPYLAMINES

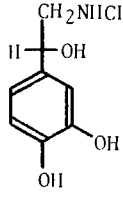
a. Those With a Free ArOH Group

The autonomic nervous system controls tissues and organs whose functions are largely automatic, *i.e.*, not requiring conscious effort for activation. Norepinephrine is the accepted neurotransmitter at the nerve endings and the motor endplate in the sympathetic branch of the autonomic nervous system. Administration of norepinephrine *(1)* mimics the effect of stimulation of these nerves, causing responses such as vasoconstriction, increased heart rate, relaxation of the ileum, contraction of the uterus in pregnant animals, and relaxation of the lung and bronchial muscles. Synthetic substances eliciting some of these responses are called sympathomimetic agents, and a wide variety are known. More recently, adrenergic agents (another synonym for

sympathomimetic agents) have been functionally divided into those acting at α-receptors-- those mainly associated with excitatory processes such as vasoconstriction--and at β-receptors--those mainly associated with inhibitory processes such as vasodilatation. Pharmacological agents which block each of these receptor groups (antagonists) are predominantly used in classifying the drugs. A finer subdivision of the β-receptors into β_1--which are involved in certain heart muscle and intestinal smooth muscle responses--and β_2--which are involved in certain other smooth muscles such as bronchi, uterus and blood vessels--has been found extremely useful. *Isoproterenol (2)* is the archetypal β-agonist, having strong activity against both β_1 and β_2 receptors. Generally, the R-configuration at the benzylic carbon is required for maximal potency amongst the agonists and antagonists of this type.



(1)



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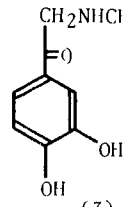


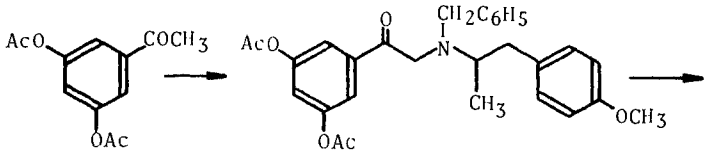
(3)

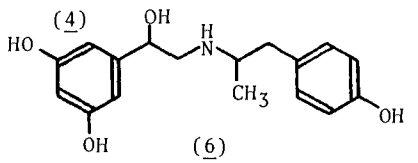
One can infer correctly from the foregoing that increased bulk on the nitrogen generally increases selectivity toward the β-receptors. Further, a

catechol ring or a system electronically equivalent to it is needed for optimum activity, especially at the β-receptors, while alkyl branching in the ethanolamine side chain generally decreases potency.

The chemistry of most of the drugs in this family is quite simple, accounting in part for the very large number of analogues which have been made. The foundation for the chemistry in this series was laid long ago by Stolz[1] in his classic synthesis of the ophthalmic agent *adrenalone (3)* in which he reacted catechol with chloroacetyl chloride and then displaced the reactive chlorine atom with methylamine to complete the synthesis. Borohydride reduction would have given epinephrine (adrenaline).

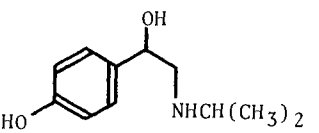
This process, or simple variants of it, is used to prepare many drugs. For example, one method for the synthesis of *fenoterol (6)*, a bronchodilator, starts with sidechain bromination of m-diacetoxy-





(4) (6)

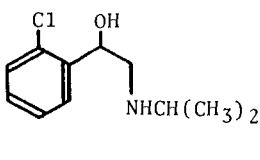
(5)



(7)

acetophenone *(4)* and then displacement of halogen by 1-(p-methoxyphenyl)-2-N-benzylaminopropane to give *5*.[2] Hydrogenation removes the benzyl group, whose function was to prevent overalkylation. Next, HBr cleaves the ether and ester groups, and either catalytic or hydride reduction completes the synthesis of *6*. Separation of diastereoisomers was achieved by fractional crystallization.

Analogous methods are used to prepare the ophthalmic agent *deterenol (7)*;[3] the bronchodilators *clorprenaline (8)*[4] and *isoetharine (9)*;[5] the vasodilators *bamethan (10)*[6] and *ifenprodil (11)*;[7] and the smooth muscle relaxant *ritodrine (12)*.[8]



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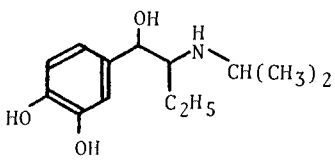

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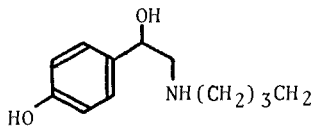

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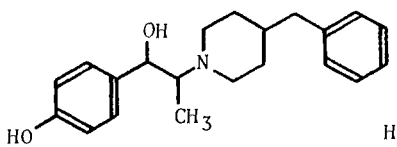

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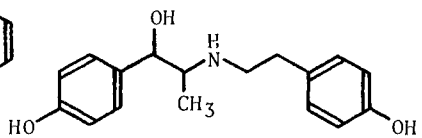
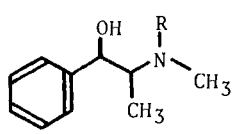


(12)

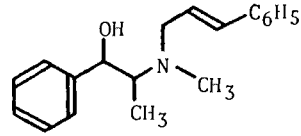
Direct alkylation of the appropriate arylethanolamine is, of course, widely used as, for example, in treatment of *ephedrine (13a)* with ethyl iodide to give the adrenergic agent, *etafedrine (13b)*,[9] or with cinnamyl chloride to give the muscle relaxant, *cinnamedrine (14)*.[10] Likewise, alkylation

of β-hydroxyphenethylamine with 2-chloropyrimidine gives *fenyripol (15)*, also a muscle relaxant.[11]

The Mannich reaction can also be used to add an alkyl group in the condensation of ℓ-norephedrine *(16)* with formaldehyde and m-methoxyacetophenone to give *oxyfedrine (17)*, a coronary vasodilator.[12]



(13a) R = H
(13b) R = C_2H_5



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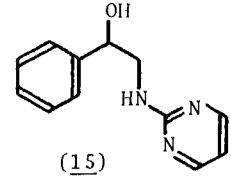

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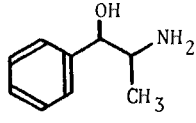

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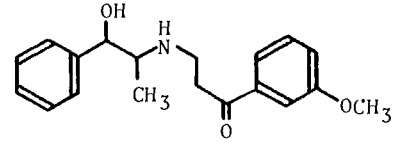
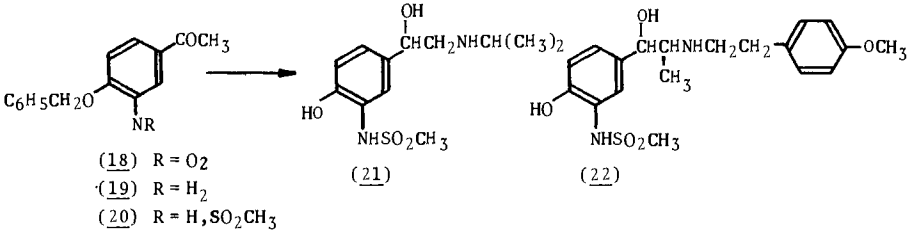


(17)

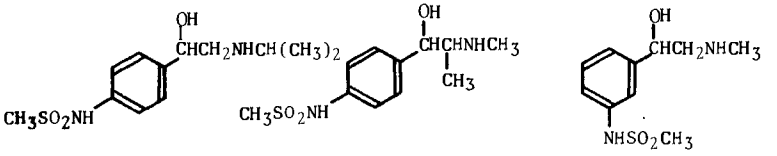
A departure from the catechol pattern of the natural neurotransmitters was achieved following application of the fact that arylsulfonamido hydrogens are nearly as acidic as phenolic OH groups. Nitration of p-benzyloxyacetophenone gave *18* which was reduced to *19* with Raney nickel and hydrazine, and in turn reacted with mesyl chloride to give sulfonamide *20*. Methanesulfonate *20* was then transformed to *soterenol (21)*, a clinically useful bronchodilator, in the

usual way.[13] The analogue *mesuprine (22)* was made by a slight variation in this scheme.[13] The β-blockers *sotalol (23)* and *metalol (24)*[14] are made in essentially the same fashion. These agents *(23* and *24)* owe their activity to their capacity to occupy β-adrenergic receptors without triggering the normal



(18) R = O2
(19) R = H2
(20) R = H,SO2CH3

(21) (22)

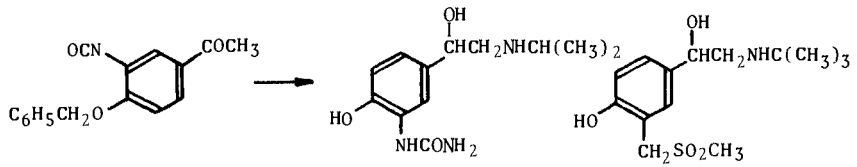


(23) (24) (25)

physiological response. The resemblance of *23* and *24* to the normal agonist helps them serve as antagonists. Greater coverage of β-blockers will be found in Chapter 5.

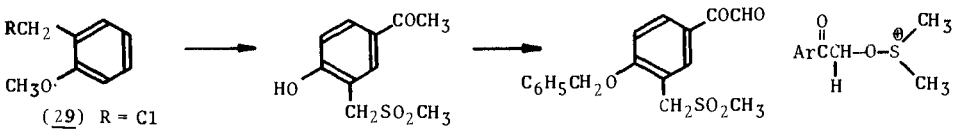
Amidephrine (25), an adrenergic agent very closely related to *metalol*, finds use as a bronchodilator.[15] *Carbuterol (27)*, another bronchodilator, is made by reacting 3-amino-4-benzyloxyacetophenone with phosgene to give isocyanate *26*. Subsequent

treatment of *26* with ammonia produces a urea derivative, which is converted to *carbuterol* by the familiar bromination, amine displacement and reduction sequence.



(26) (27) (28)

It is evident that some leeway is available in the substituents tolerable in the m-position. The bronchodilator *sulfonterol (28)* is descended from this observation.[16] Chloromethylanisole *(29)* is reacted with methylmercaptan to give *30*, and the newly introduced group is oxidized to the methylsulfonyl moiety of *31* with hydrogen peroxide. Ether cleavage, acetylation and Fries rearrangement of the phenolic acetate produces *32*, which is next brominated with pyrrolidinone hydrobromide tribromide and then oxidized to the glyoxal *(33)* with dimethyl sulfoxide.

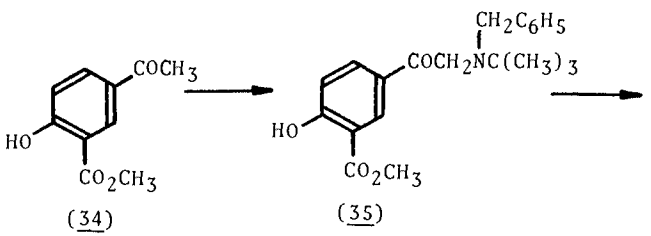


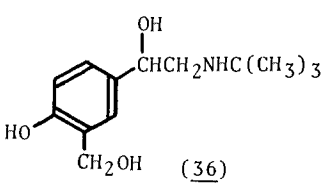
(29) R = Cl
(30) R = SCH_3
(31) R = SO_2CH_3

(32) (33) (33a)

The last reaction perhaps involves an intermediate such as *33a* which expells a proton and dimethyl sulfide. Formation of the Schiff's base with t-butylamine, reduction with sodium borohydride and hydrogenolysis of the benzyl ether produces *sulfonterol (28)*. Despite the fact that the methylene hydrogen of *sulfonterol* must be much less acidic than of the corresponding urea proton on *carbuterol* or the sulfonamide proton on *soterenol*, good bio-activity is retained.

That even further leeway is possible is shown by the utility of the saligenin analogue *albuterol (36)* as a bronchodilator.[17] One of the several syntheses starts by Fries rearrangement of aspirin followed by esterification to *34* which is then brominated and reacted with benzyl t-butylamine to give *35*. Hydride reduction reduces both carbonyls, and hydrogenolysis of the benzyl group completes the synthesis. Presumably, chelation, believed to be significant in the molecular mode of action of the catecholamines, can still take place with *albuterol*.

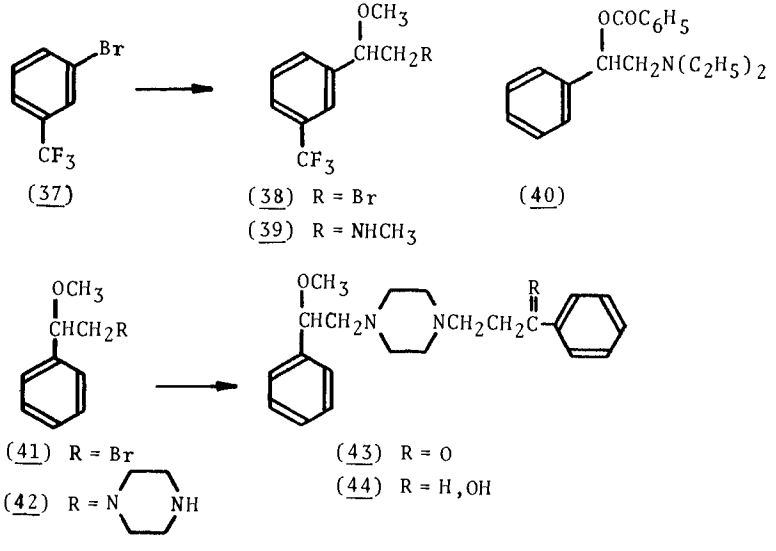




b. Those Agents With An Acylated or Alkylated ArOH Group

Once again we come upon a chemical classification that has no pharmacological significance. The three drugs in this small group cause widely different biological responses.

Reaction of the Grignard reagent prepared from m-trifluoromethylbromobenzene *(37)* with methyl-1,2-dibromoethylether leads to alkoxy bromide *38*, which is then reacted with methylamine to give the anorexic agent *fludorex (39)*.[18]



(37)

(38) R = Br

(39) R = $NHCH_3$

(40)

(41) R = Br

(42) R = N NH

(43) R = O

(44) R = H,OH

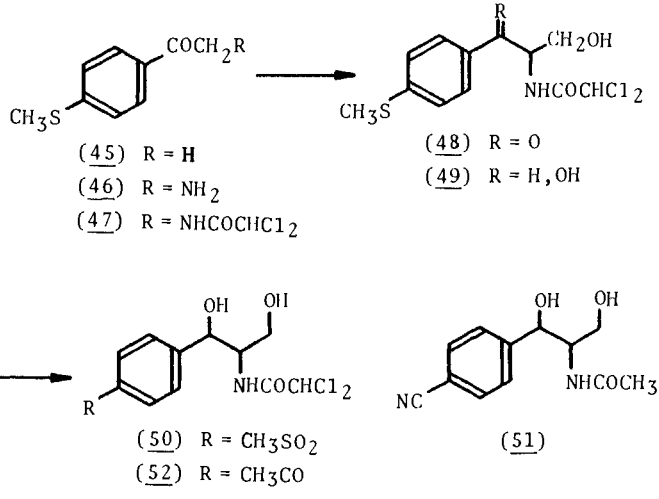
The gastric anticholinergic agent, *elucaine (40)*, is synthesized by reaction of styrene oxide with diethylamine, followed by esterification with benzoyl chloride.[19] In a similar fashion, *eprozinol*

(44), a bronchodilator, is synthesized by adding the elements of CH_3OBr to styrene, by reaction with t-butylhypobromite in methanol, to give *41*. This is next reacted with piperazine to give *42*. A Mannich reaction with formaldehyde and acetophenone leads to ketone *43*, and reduction with borohydride completes the synthesis of *eprozinol*.[20]

2. 1-PHENYL-2-AMINOPROPANEDIOLS

Chloramphenicol was the first orally active, broad-spectrum antibiotic to be used in the clinic, and remains the only antibiotic which is marketed in totally synthetic form. Its initial popularity was dampened, and its utilization plummeted when it was found that some patients developed an irreversible aplastic anemia from use of the drug. Of the hundreds of analogues synthesized, none are significantly more potent or certain to be safer than *chloramphenicol* itself. Two analogues have been given generic names and fall into this chemical classification. It was found early in the game that activity was retained with p-substituents, and that electron withdrawing substituents were best. The synthesis of *thiamphenicol*[21] *(50)* begins with p-thiomethylacetophenone *(45)*, which is brominated and then reacted with hexamethylenetetramine to give *46*, which is in turn converted to amide *47* by reaction with dichloroacetyl chloride. Reaction with formaldehyde and bicarbonate introduces the hydroxymethyl function of *48*, and subsequent Meerwein-Pondorff-Verley reduction with aluminum isopropoxide gives

49. The p-SCH_3 function was oxidized to the methylsulfonyl group of racemic *thiamphenicol (50)* with peracetic acid. The drug has been resolved by saponification of *49*, treatment with an optically active acid, reamidation and oxidation. Closely related *cetophenicol (52)* is synthesized from the p-cyano analogue *51* by reaction with methyl lithium followed by amide exchange to give *52*.[22]



(45) R = H
(46) R = NH_2
(47) R = $NHCOCHCl_2$

(48) R = O
(49) R = H,OH

(50) R = CH_3SO_2
(52) R = CH_3CO

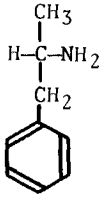
(51)

3. PHENYLETHYLAMINES

Phenylethylamines lacking the β-hydroxy group of norepinephrine *(1)* and related neurotransmitters are much more lipophilic. They exert a much more pronounced central--as opposed to peripheral--sympathomimetic effect. Their action is, however, not direct. It is generally accepted that these agents function at least in part by liberating endogenous catecholamines from storage sites. These, then, exert their characteristic actions. It will be recalled that amphetamine is used clinically for appetite suppression, as an euphoriant-antidepressant, as a nasal decongestant, to improve psychomotor performance, to treat drug depression, in treating children with minimal brain dysfunction (hyperkinesis) and so on. Insomnia, anxiety and, especially with large doses, occasionally psychotomimetic activity are undesirable side effects. Removal of side effects or greater selectivity of action is, as usual, the objective of molecular manipulation in this drug class.

Amphetamine (53) is the prototype drug in this group. One significant objective of molecular manipulation in this group is to retain the appetite depressant activity without significant central stimulation. This is as yet unrealized. Some of the drugs prepared with this purpose in mind are discussed in this section. Reductive alkylation of the nitrogen atom of amphetamine with β-chloropropionaldehyde produces the anorexic agent *mefenorex (54)*.[23] The

Schiff's base of amphetamine with chloral, *amphecloral (55)*, is a single molecule combination of a stimulant -anorexic and a sedative.[24] Presumably, *in vivo* hydrolysis releases the sedative, chloral, to combat the excitant action of amphetamine with the intended retention of the anorexic action.



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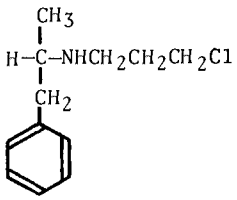

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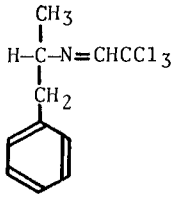
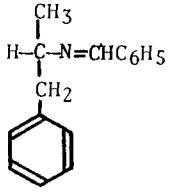


(55)

The psychotropic (stimulant) action of *amphetaminil (57)* may be intrinsic or due to *in vivo* hydrolysis of the α-aminonitrile function--akin to a cyanohydrin--to liberate amphetamine itself. It is synthesized by forming the Schiff's base of amphetamine with benzaldehyde to give *56*, and then nucleophilic attack on the latter with cyanide anion to form *amphetaminil (57)*.[25]



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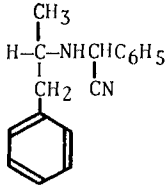
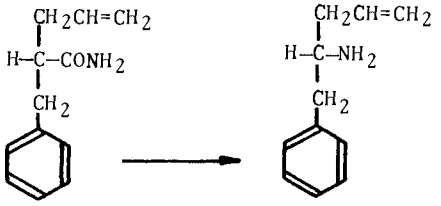


(57)

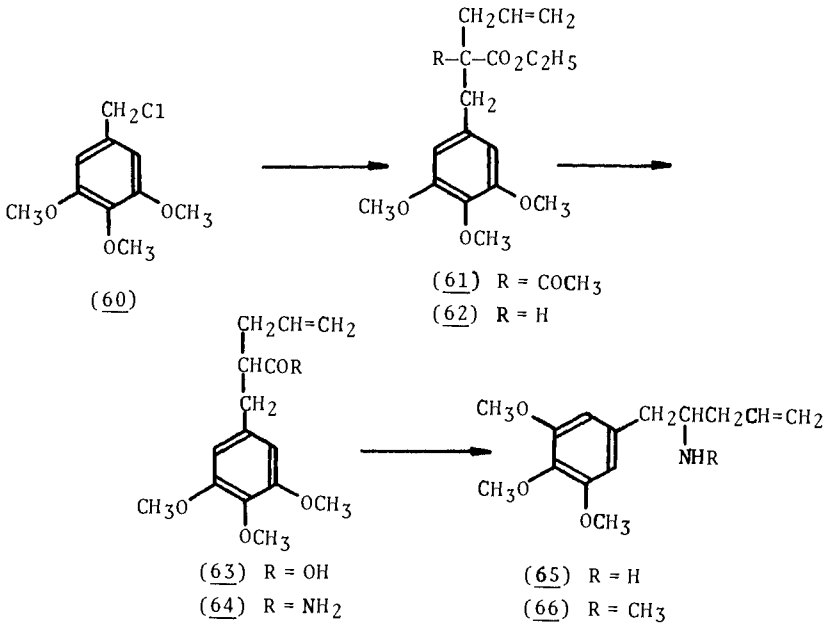
The alkyl terminus of the side chain need not be methyl for retention of activity. *Aletamine (59)*

is such an agent. It is prepared by the Hofmann rearrangement of α-allyl-β-phenylpropionamide *(58)*.[26]



(58) (59)

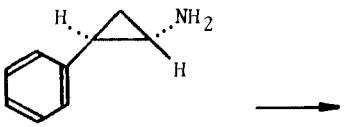
The action of monoamine oxidase in terminating the bioactivity of primary amines in this class is inhibited by their conversion to secondary amines, which are not substrates for this enzyme. Greater selectivity of action, for reasons that are obscure, is often seen when a trimethoxyphenyl moiety is present in the drug. Such considerations may have played a role in the design of *trimoxamine (66)*, an antihypertensive agent.[27] The synthesis starts with trimethoxybenzyl chloride *(60)*, which is alkylated with the anion from ethyl allylacetoacetate and NaH to give *61*, which is cleaved to ester *62* with sodium ethoxide *via* a retro-Claisen reaction. Saponification to acid *63* is followed by conversion to a mixed anhydride by means of ethyl chlorocarbonate. Treatment with ammonia gives amide *64*. Hoffman rearrangement with NaOBr gives *65*, which is converted to the secondary amine *66* by reaction with ethyl chlorocarbonate, followed by lithium aluminum hydride reduction.



Drugs most often react with biopolymers called receptors in order to exert their pharmacological effects and the receptors are optically asymmetric and should therefore require a most favorable configuration and conformation for maximal activity. Thus, there has been much interest in preparation of rigid analogues both for their utility in mapping receptors and because it was felt that an intrinsically correct fit would maximize intrinsic potency. One drug designed with these considerations in mind is *rolicyprine (68)*, an antidepressant.[28] This drug is most probably a latentiated form (prodrug) of the free amine, *tranylcypromine (67)*. Restriction of the primary amino group into a rigid ring system decreases its conformational possibilities enormously.

Use of the relatively small cyclopropane ring drastically reduces the potential for deleterious steric bulk effects and adds only a relatively small lipophilic increment to the partition coefficient of the drug. One of the clever elements of the *rolicyprine* synthesis itself is the reaction of d,l-*tranylcypromine (67)* with L-5-pyrrolidone-2-carboxylic acid (derived from glutamic acid) to form a highly crystalline diastereomeric salt, thereby effecting resolution. Addition of dicyclohexylcarbodiimide activates the carboxyl group to nucleophilic attack by the primary amine thus forming the amide *rolicyprine (68)*.

Dopamine (69) is a well-known neurotransmitter which interacts with many receptors in the central



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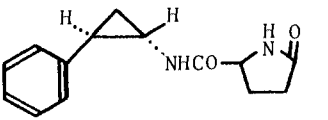

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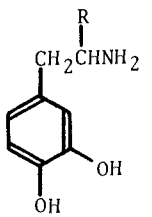
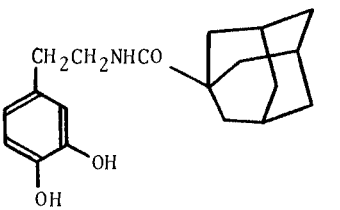


(69) R = H

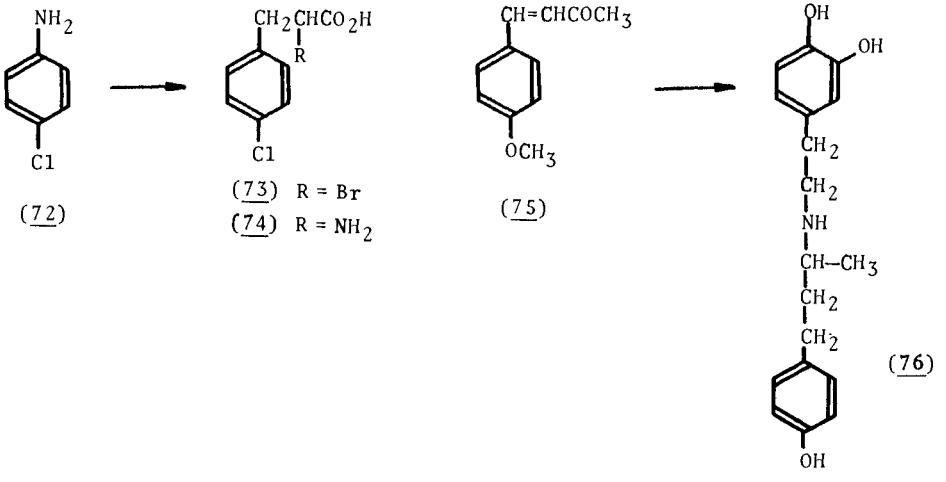
(70) R=CO_2H



(71)

nervous system. In Parkinsonism, a fine tremor and muscular rigidity is present which finds its biochemical basis in low levels of dopamine in certain regions of the CNS. Administration of dopamine itself is insufficient to overcome this defect, as it cannot efficiently penetrate the blood-brain barrier. Before the discovery that the corresponding amino acid, *DOPA (70)*, which efficiently entered the brain, was converted enzymatically to *dopamine*, and thereby constituted effective therapy, various means were employed to attempt such central delivery. One of these used the lipophilicity of adamantoyl analogues. *Dopamine* was reacted with the acid chloride of adamantane-1-carboxylic acid to give *dopamantine (71)*, an anti-Parkinsonian agent.[29]

A relatively old compound, p-*chlorophenylalanine (74)*, is able to penetrate the blood-brain barrier into the CNS and serves as a serotonin inhibitor. Interestingly, it increases copulatory behavior in



(72)

(73) R = Br

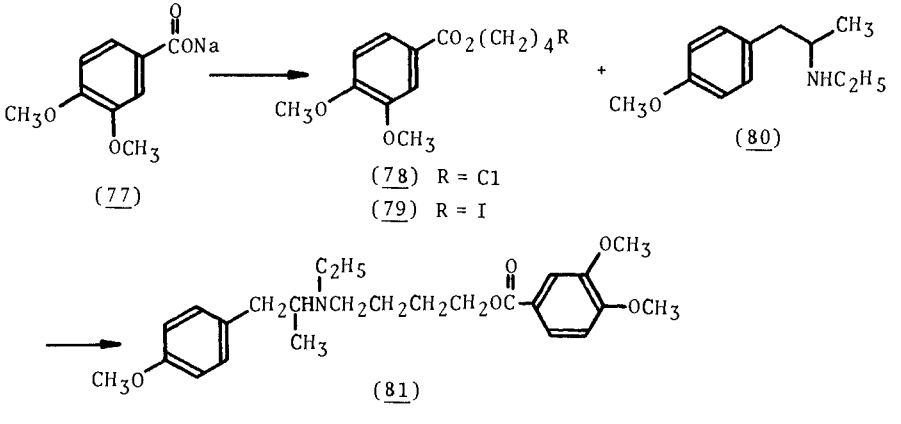
(74) R = NH_2

(75)

(76)

experimental animals, as does testosterone, and has achieved some notoriety on this ground. One of the syntheses begins by diazotization of p-chloroaniline *(72)*, followed by Meerwein reaction with cuprous bromide and acrylic acid to give 2-bromopchloro-hydrocinnamic acid *(73)*; which is then reacted with ammonia to give p-*chlorophenylalanine (74)*.[30]

Dobutamine (76), on the other hand, is a *dopamine* derivative which does not act centrally, but is of interest because of its coronary vasodilator properties. Such drugs are potentially of value in treatment of angina pectoralis. Further, it is now undergoing extensive clinical trials as an inotropic agent for use in heart failure. Its synthesis is effected by Raney nickel catalyzed reduction of methyl p-methoxyvinylphenylketone *(75)* to its dihydro analog followed by reductive alkylation with β-(3,4-dimethoxyphenyl)ethylamine. The ether groups are cleaved with HBr to complete the synthesis of *76*.[31]



(77)

(78) R = Cl

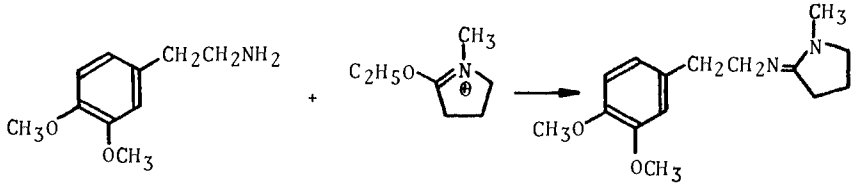
(79) R = I

(80)

(81)

Mebeverine (81), a smooth muscle relaxant, is prepared, *i.a.*, by reacting sodium 3,4-dimethoxybenzoate *(77)* with 1,4-dichlorobutane to form chloroester *78* which is in turn transformed to the corresponding iodide *(79)* on heating with NaI in methylethyl ketone. Alkylation of 2-ethylamino-3-p-methoxyphenylpropane *(80)* with *79* leads to *mebeverine (81)*.[32]

Mixidine (84), an amidine related to *dopamine (84)*, has coronary vasodilator properties. It is prepared by reaction of β-(3,4-dimethoxy)phenethylamine *(82)* with the ethylimino derivative of N-methyl-2-pyrrolidone *(83)* in an apparent addition-elimination sequence.[33]

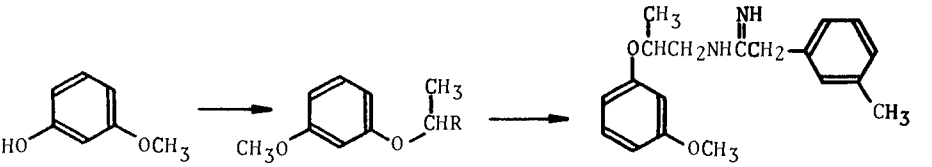


(82) (83) (84)

b. Miscellaneous

Xylamidine (87) is an amidine which serves as a serotonin inhibitor. This agent is prepared by alkylation of m-methoxyphenol with α-chloropropionitrile, KI and potassium carbonate in methylethyl ketone to give *85*, which is in turn reduced with

lithium aluminum hydride to give the primary amine *86*. When *86* is treated with m-tolylacetonitrile in the presence of anhydrous HCl, the synthesis is completed.[34] Alternately, one can react primary amine *86* with m-tolylacetamidine under acid catalysis to produce *xylamidine*.



(85) R = CN
(86) R = CH_2NH_2

(87)

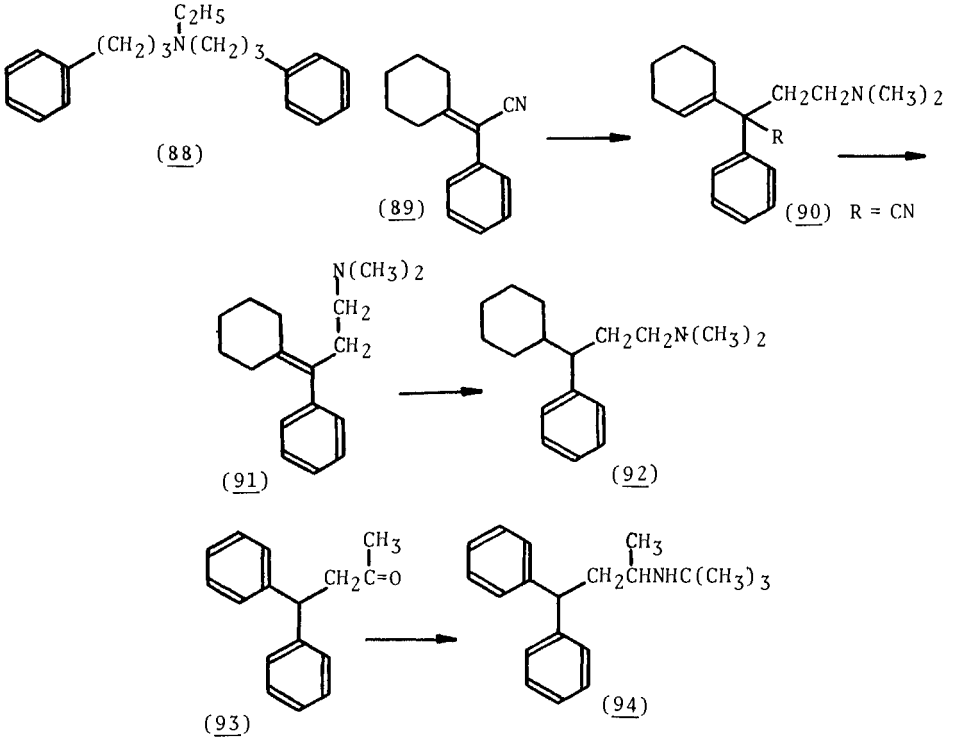
4. PHENYLPROPYLAMINES

The drugs of this group also have widely different pharmacological properties, indicating the general absence of a common pharmacophoric moiety in the group.

Alverine (88) is an anticholinergic agent prepared by reductive alkylation of ethylamine with two equivalents of phenylpropionaldehyde.[35]

Alkylation of cyclohexylidinephenylacetonitrile *(89)* with 2-chloroethyldimethylamine, using NaH as base, gives nitrile *90*. Note that the product results from alkylation of the enolate which results in a double bond shift. This product *(90)* is transformed to unsaturated amine *91* on heating with HCl.

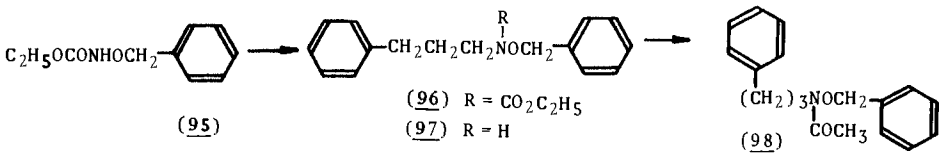
Catalytic hydrogenation of the double bond then produces *gamfexine (92)*, an antidepressant.[36]



Reductive amination of methyl 2,2-diphenylethyl ketone *(93)* with t-butylamine in formic acid leads to *terodiline (94)*, a coronary vasodilator.[37]

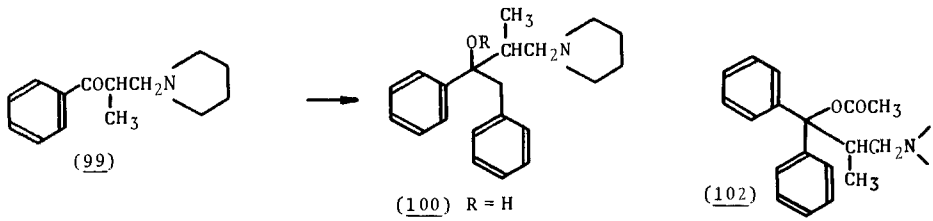
The relationship between serum cholesterol levels and cardiovascular disease remains suggestive, despite intensive research into the subject. In any case, agents which can lower serum cholesterol levels are of therapeutic interest. *Beloxamide (98)*,

an N-benzyloxyacetamido derivative, is such an hypocholesterolemic agent. It is synthesized by alkylating N-carbethoxyhydroxylamine with benzyl bromide, using sodium ethoxide. The resulting carbamoyl ester *(95)* is alkylated again, this time with 3-phenylpropyl bromide and sodium ethoxide to give *96*, which is then cleaved to the alkylated O-benzylhydroxylamine derivative *97*. Reaction with acetyl chloride completes the synthesis of *beloxamide*.[38]



(95) (96) R = $CO_2C_2H_5$ (97) R = H (98)

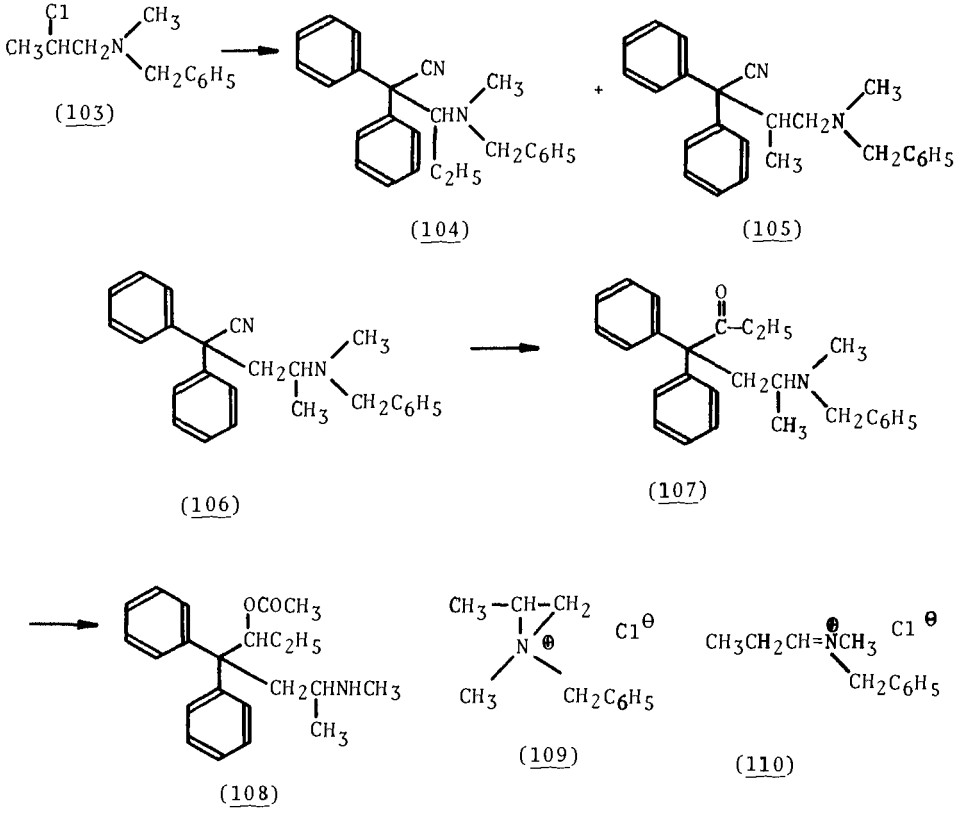
A *propoxyphene*-like analgesic which obeys the empirical morphine rule is *pyrroliphene (101)*. A Mannich reaction involving *pyrrolidine*, formaldehyde and propiophenone gave amino ketone *99*, which was converted to tertiary carbinol *100* by reaction with benzyl magnesium chloride; reaction with acetyl



(99) (100) R = H (101) R = $COCH_3$ (102)

chloride completed the synthesis.[34] It is gratifying that *pyrroliphene (101)* retained the desired bioactivity as its synthesis was apparently impelled by the observation that the initial target compounds (*e.g., 102*) were not very stable chemically.

A somewhat related analgesic, *noracymethadol (108)*, is an active metabolite of *acetylmethadol*.



It can be synthesized from methyl benzyl 2-chloropropylamine *(103)* by sodium amide induced alkylation of 2,2-diphenylacetonitrile to give a mixture of amines *104*, *105* and *106*. Amines *105* and *106* are the expected products of nucleophilic attack on the presumed intermediate asymmetric aziridinium *109*. Amine *104* can be rationalized by assuming dehydrohalogenation and rearrangement of the resulting enamine to the charged iminium ion *(110)* which would rapidly add the nucleophile to give the observed product. In any event, treatment of nitrile *106* with ethyl magnesium bromide, followed by hydrolysis, produced intermediate ketone *107*. This was reduced to the secondary carbinol with lithium aluminum hydride and acetylated before catalytic debenzylation of the amine using palladium on carbon catalyst.[40] Given the nature of the initial alkylation reaction, it is doubtful that this is a practical synthesis.

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4

Arylalkanoic Acids and Their Derivatives

1. ANTIINFLAMMATORY ARYLACETIC ACIDS

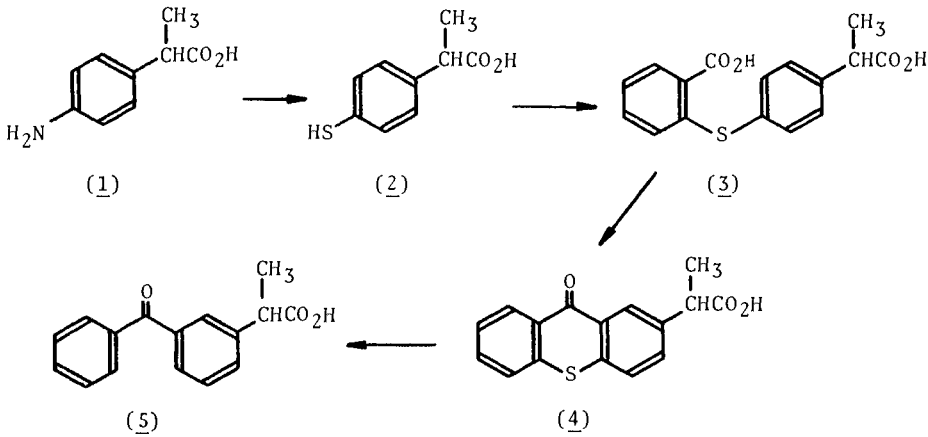
Inflammation is an intimate part of every organism's apparatus for dealing with injuries imposed by the environment. Under normal circumstances, the complex sequence of events characterizing inflammation ceases soon after the environmental challenge stops. Not infrequently, however, the inflammatory process, once started, continues despite the fact that the original triggering event has passed. The incident swelling and pain is familiar to all. Treatment of chronic or persistant inflammation has gone through some clearly recognizable cycles. From about the turn of the century, the standard drug therapy for treatment of this syndrome has consisted of *aspirin* or another of the simpler aromatics, such as *antipyrine* and *acetaminophen*. The layman chooses these materials for self-administration. Use of

these drugs for severe conditions is, however, limited by their relatively low activity--particularly in treatment of the inflammation due to arthritis--and the incidence of side effects when used at higher doses. The discovery of the antiinflammatory activity of *cortisone* and related corticosteroids quickly led to common prescription of these potent drugs for a wide variety of inflammatory conditions. This widespread use uncovered the host of endocrine effects the corticoids elicit upon chronic administration. This phenomenon required the more selective use of these compounds.

Quite recently, a series of arylacetic acid derivatives has come into clinical use as potent antiinflammatory agents. In general, these compounds show profiles of activity quite similar to *aspirin*, and though as a rule they are more active and are less likely to cause or exacerbate gastric ulcers. Many of these compounds have been shown to be effective in the treatment of arthritis. Since they apparently work by a mechanism different from that of the corticosteroids and are structurally unrelated, they have no corresponding endocrine effects.

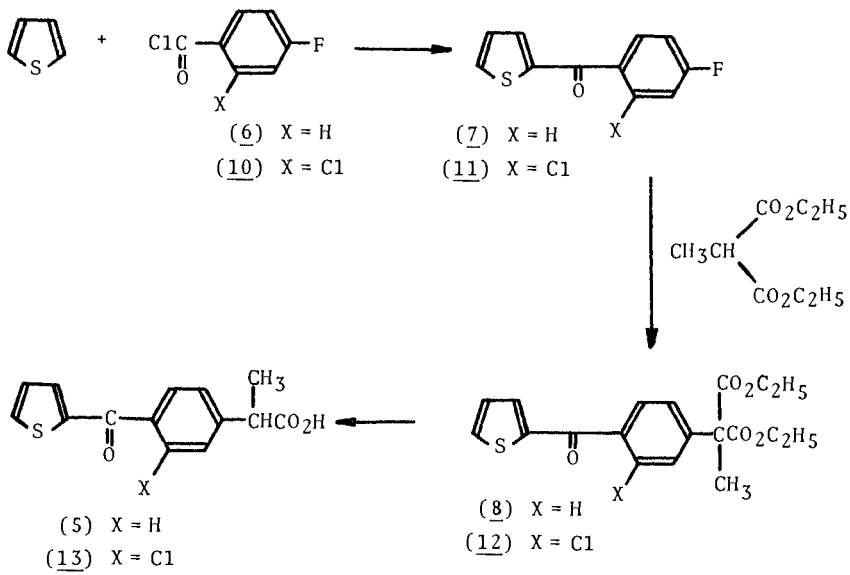
An interesting example of this class of nonsteroidal antiinflammatory agents is *ketoprofen (5)*. It is synthesized by reaction of the diazonium salt from amine *1* with potassium ethyl xanthate, followed by alkaline hydrolysis to afford thiophenol *2*. Reaction of the sodium salt of *2* with 2-iodobenzoic acid results in formation of the corresponding bisarylsulfide *via* nucleophilic aromatic substitution.

Friedel-Crafts cyclization of the dibasic acid gives thiaxanthone *4*. Note that the symmetry of this intermediate assures formation of a single product. Desulfurization by means of Raney nickel leads, finally, to the antiinflammatory agent, *ketoprofen (5)*.[1]



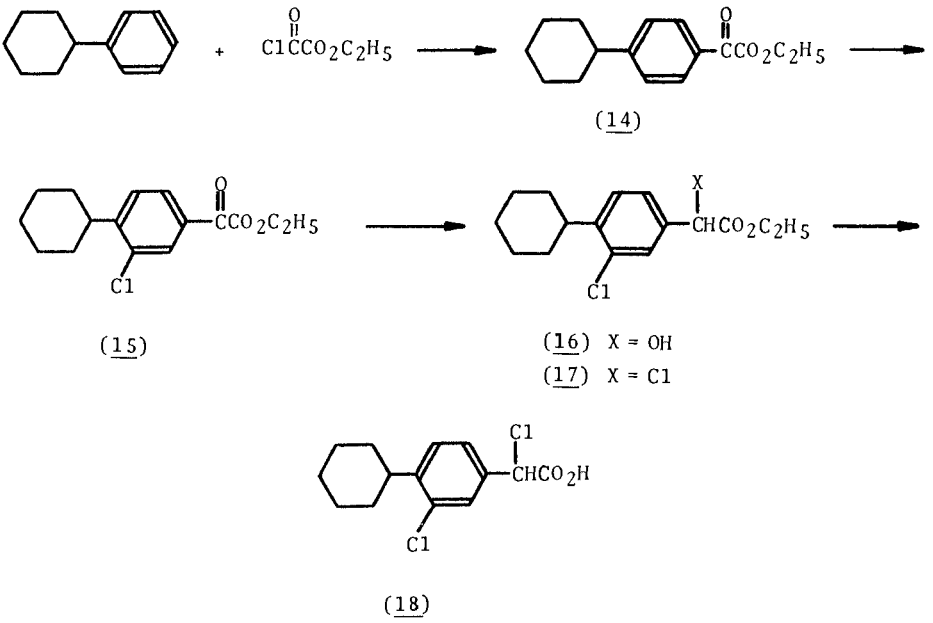
Quite a different route is employed to prepare heterocyclic analogues of *5*. For example, acylation of thiophene with p-fluorobenzoyl chloride *(6)* affords ketone *7*. Nucleophilic aromatic substitution with the enolate from diethyl methylmalonate gives the diester *8*. Saponification, followed by decarboxylation, gives *suprofen (9)*.[2,3] A similar sequence starting with the more highly substituted acid chloride *(10)* affords *cliprofen (13)*.[2,3]

Structure-activity studies in the phenylacetic acid antiinflammatory series have shown that inclusion of a methyl group on the benzylic carbon usually leads to maximal activity. It is of note that this



group can be replaced, in at least one case, by chlorine. Acylation of phenylcyclohexane with ethyl oxalyl chloride affords the glyoxylic ester *14*. Chlorination proceeds *meta* to the carbonyl group to give *15*.[4] Reduction of the keto moiety gives the corresponding mandelate *16*, which reacts in turn with thionyl chloride to replace the hydroxyl group by chlorine to give *17*; ester hydrolysis affords *fenclorac (18)*.[5]

In a similar vein, the keto bridge in *5* can be replaced by oxygen with retention of activity. Reduction of acetophenone derivative *19* by means of sodium borohydride leads to the corresponding alcohol *(20)*. Reaction with phosphorus tribromide gives *21*. Displacement of the halide with cyanide gives



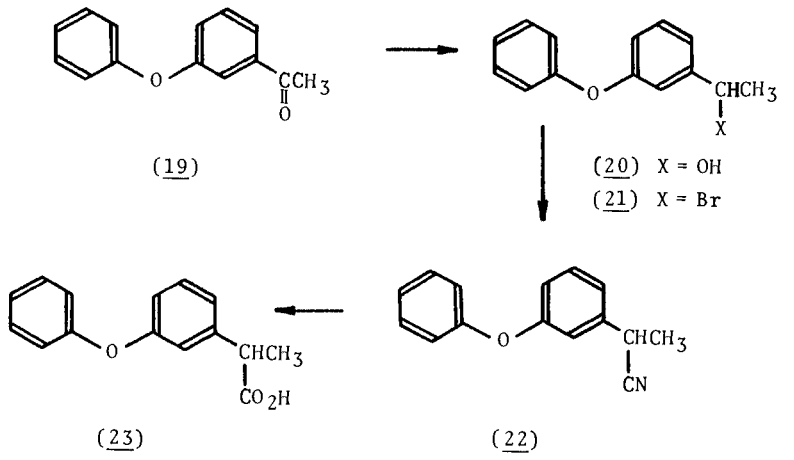
(14)

(15)

(16) X = OH
(17) X = Cl

(18)

substituted acetonitrile *22*, whose saponification affords the antiinflammatory acid, *fenoprofen (23)*.[6]



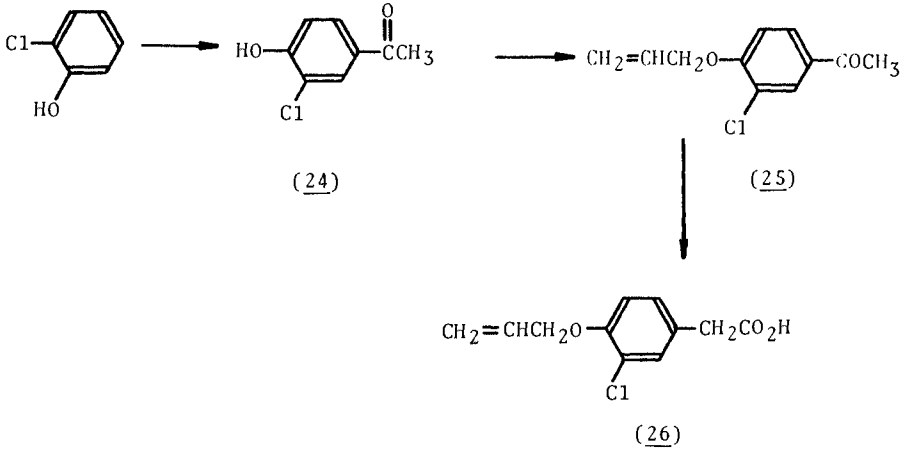
(19)

(20) X = OH
(21) X = Br

(23)

(22)

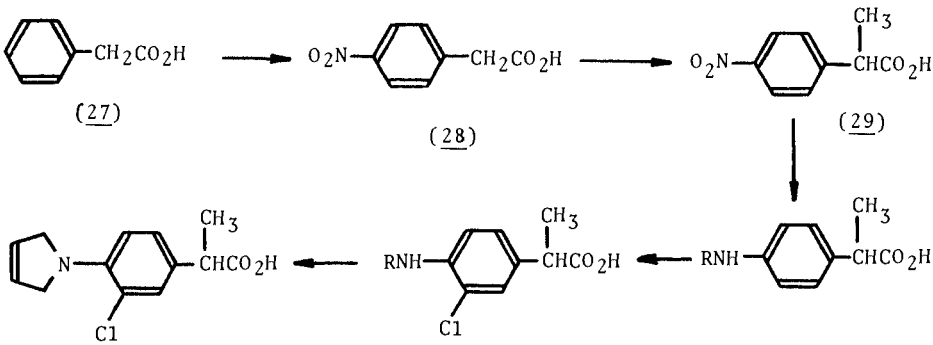
Alclofenac (26)[7] represents one of the more extreme simplifications in this class of anti-inflammatory agents. The general method for preparation of related compounds[8] starts with acylation of ochlorophenol to give *24*. Alkylation of the phenolic group of *24* with allyl bromide affords the corresponding ether *(25)*. Willgerodt reaction on the acetophenone results in transposition of the side chain and oxidation to the acid to give *alclofenac (26)*.



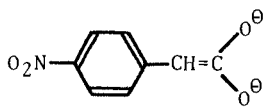
(24) (25) (26)

Inclusion of basic nitrogen in the p-position is also compatible with antiinflammatory activity in this series. Nitration of phenylacetic acid *(27)* affords *28*. Methyl iodide alkylation of the enolate prepared from *28* using two equivalents of sodium hydride gives *29*. This appears to involve an Ivanov intermediate *(28a)*. Catalytic reduction of the

nitro group leads to the corresponding aniline *(30)*. Acetylation to *31*, followed by reaction with chlorine, serves to introduce the desired aryl halogen atom. Removal of the acetyl group, followed by cyclo-alkylation of the primary aniline *(33)* with 1,4-dibromo-2-butene affords *pirprofen (34)*.[9]



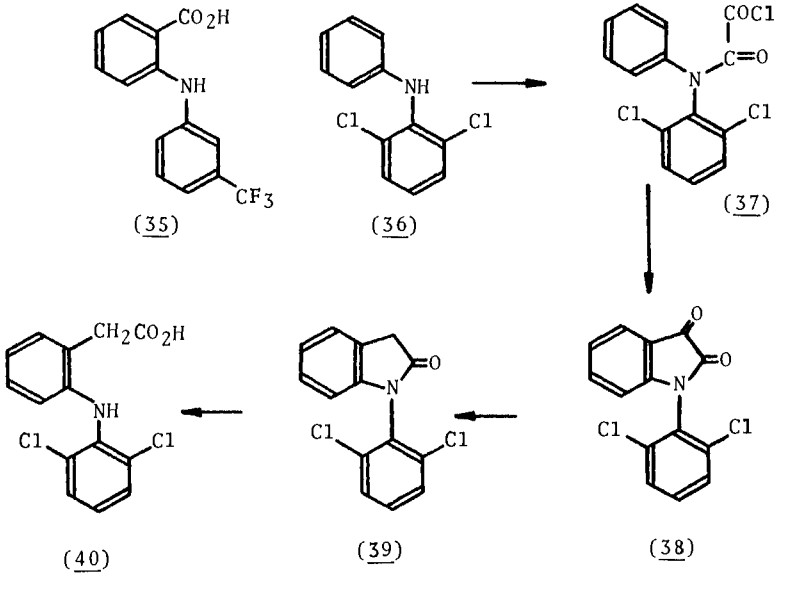
(27) (28) (29) (30) R = H (31) R = $COCH_3$ (32) R = $COCH_3$ (33) R = H (34)



(28a)

Anthranilic acid derivatives, such as *flufenamic acid (35)*, constitute another effective series of non-steroidal antiinflammatory agents. Homologation

of the acid function in that series would of course lead to the arylacetic acid series. It is of note that one such hybrid compound, *diclofenac (40)*, does in fact exhibit antiinflammatory activity. In an interesting synthesis, the diphenylamine *36* is first condensed with oxalyl chloride to give the oxanilic acid chloride *37*. Friedel-Crafts cyclization under quite mild conditions gives the isatin *38*. Reduction of the keto group by means of the Wolff-Kishner reaction gives lactam *39*, whose hydrolysis affords *diclofenac (40)*.[10]



2. DIARYL AND ARYLALKYL ACETIC ACIDS: ANTICHOLINERGIC AGENTS

Acetylcholine is the neurotransmitter amine of the parasympathetic autonomic nervous system. A host of bodily responses, such as gastric secretion, intestinal motility, and constriction of the bronchi, depend on cholinergic transmission. Quite some time ago it was discovered that responses due to activation of the cholinergic system can be antagnoized by *atropine (41)*. Experience with this natural product foreshadowed the shortcomings of most subsequent anticholinergic drugs. That is, these agents, as a class, show little selectivity for a given organ system. They tend to ablate all responses mediated by the parasympathetic nervous system. This lack of selectivity leads to a set of side effects, such as dryness of the mouth, blurred vision, and CNS effects, which are quite predictable as extensions of the pharmacology. As has been detailed elsewhere, numerous SAR studies have reduced the requirements for anticholinergic activity to an ester of a benzilic acid with an alcohol related to ethanolamine; esters of cyclic aminoalcohols tend to be more active than the acyclic counterparts.

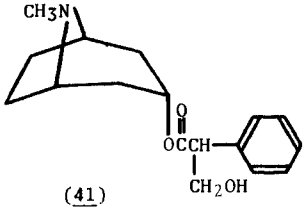
Clinical trials of some of the more potent tertiary amines revealed these to exhibit marked psychotomimetic activity.[11] Much subsequent work thus dealt with the quaternary salts which do not reach the central nervous system. Many of the uses of anticholinergic drugs involve "topical" application (e.*g.*, interior of the stomach, intestine or bronchi);

the drugs could thus in principle show a clinically useful effect without first being absorbed parenterally. In addition, quaternization, while greatly inhibiting absorption, should assure that the drug will not cross the blood-brain barrier.

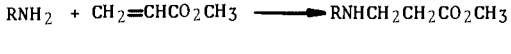
Preparation of the quaternary anticholinergic agent *benzilonium bromide (47)* is begun by conjugate addition of ethylamine to methylacrylate, giving aminoester *42*. Alkylation of *42* with methyl bromoacetate leads to diester *43*, which is transformed into pyrrolidone *44* by Dieckmann cyclization, followed by decarboxylation. Reduction of *44* by lithium aluminum hydride leads to the corresponding aminoalcohol *(45)*. Transesterification of alcohol *45* with methyl benzilate leads to *46*. *Benzilonium bromide (47)* is obtained by alkylation of ester *46* with ethyl bromide.[12]

In a similar sequence, reaction of ketoester *52* with 2-thienylmagnesium bromide gives a modest yield of the benzilic ester *53*. Transesterification of this with aminoalcohol *51*, prepared analogously to *45* by starting with methylamine, gives, after quaternization with methyl bromide, *heteronium bromide (54)*.[12]

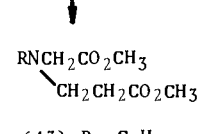
Similarly, lactam formation of diethyl glutamate *(55)* leads to ethyl pyroglutamate *(56)*. Reduction by means of lithium aluminum hydride gives the aminoalcohol *57*, which is then N-methylated to give *58*. Treatment with thionyl chloride leads to the chloroamine *59* and displacement of halogen (possibly *via* an aziridinium intermediate) with sodium benzilate



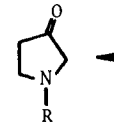
(41)



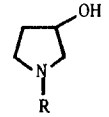
(42) R = C_2H_5
(48) R = CH_3



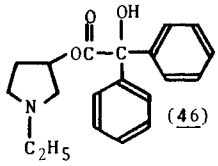
(43) R = C_2H_5
(49) R = CH_3



(44) R = C_2H_5
(50) R = CH_3



(45) R = C_2H_5
(51) R = CH_3



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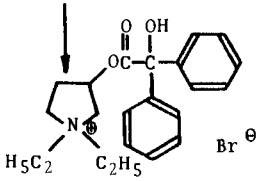

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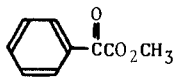

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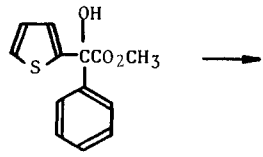
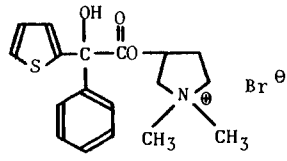
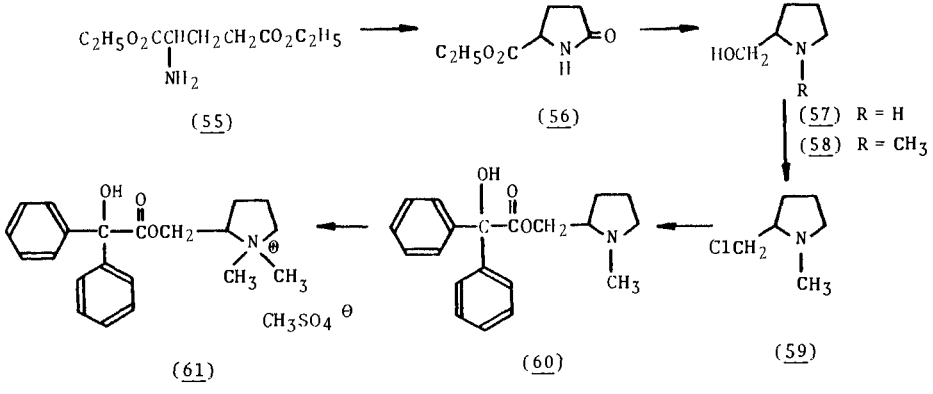


(53)

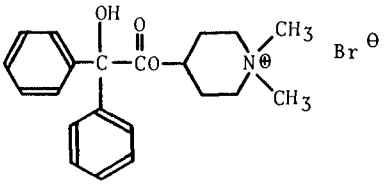


(54)

affords *poldine (60).*[13] Alkylation of *60* with dimethyl sulfate gives *poldine methylsulfate (61),* in which the two-carbon bridge between quaternary N and O is preserved by placing a methylene in the -position of the pyrrolidine nucleus.



Benzilate esters of piperidinols, as well as those of acyclic aminoalcohols, show similar anticholinergic activity. For example, ester interchange between methyl benzilate and N-methyl-4-piperidinol, followed by quaternization of the resulting ester with methyl bromide, gives *parapenzolate bromide (62).*[14] In analogous fashion, ester interchange between methyl benzilate and N-ethyl-N-n-propylethanolamine yields *benapryzine (63).*[15]



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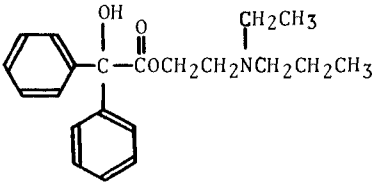
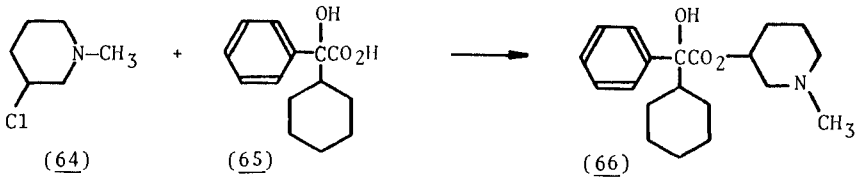


(63)

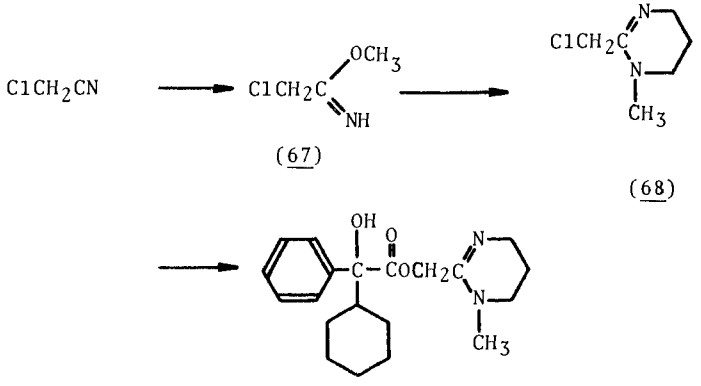
Biological activity in this series shows considerable tolerance for modification in the ester moiety as well. Esters in which one of the aromatic rings is fully reduced still show good anticholinergic activity. One such agent, *propenzolate (66)*, is prepared by displacement of halogen from N-methyl-3-chloropiperidine *(64)* by the sodium salt of acid *65*.[16]



(64) (65) (66)

In yet a further variation on this scheme, the basic center in the molecule can be present as an

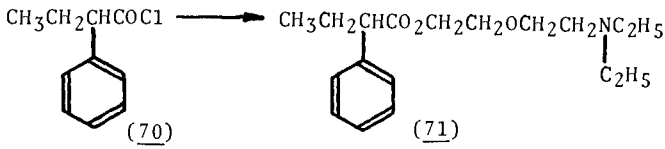
amidine. In the synthesis of *oxyphencyclimine (69)*, reaction of chloroacetonitrile with methanol and hydrogen chloride leads to the corresponding iminoether *67*. Condensation of *67* with N-methyl propylenediamine gives the corresponding tetrahydropyrimidine *(68)*. Displacement of the halogen with the sodium salt of *65* affords *oxyphencyclimine (69)*.[17]



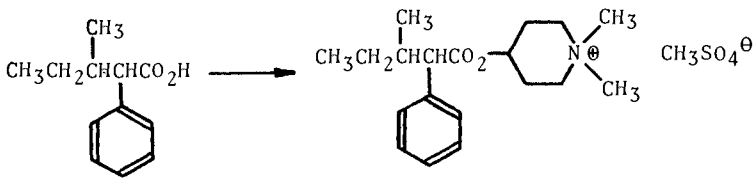
(67) (68) (69)

Omission of the hydroxyl group and one of the cyclic hydrocarbons from the acid moiety is apparently not inconsistent with biological activity. Thus, the ester from 2-phenylbutyryl chloride and diethylaminoethoxyethanol, *butamirate (71)*, shows antispasmodic activity. In analogous fashion, reaction of the acid chloride from *72* with N-methyl-4-piperidinol, followed by quaternization, gives *pentapiperium methylsulfate (73)*.[18]

Apparently, minor chemical modifications of the benzilcarboxylic acid containing molecules led to a compound which shows surprising analgesic activity. Condensation of N-methylphenethylamine *74* with

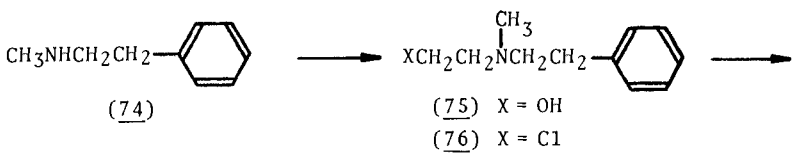


(70) (71)

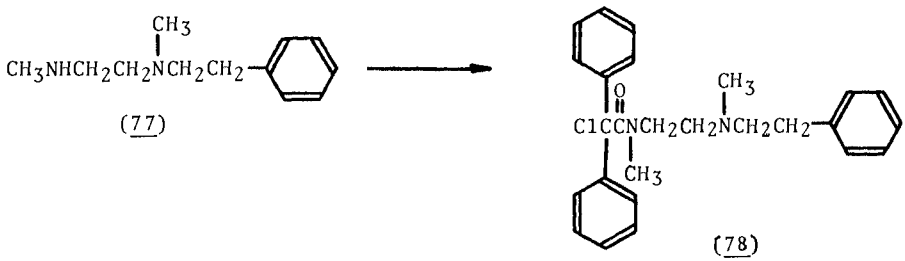


(72) (73)

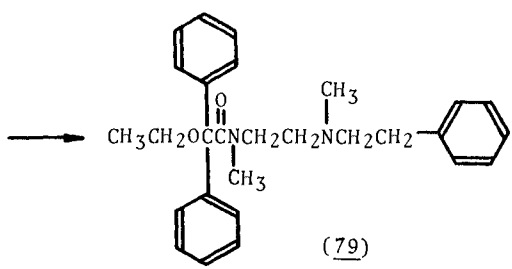
ethylene oxide gives aminoalcohol *75*; which is then



(74) (75) X = OH (76) X = Cl



(77) (78)

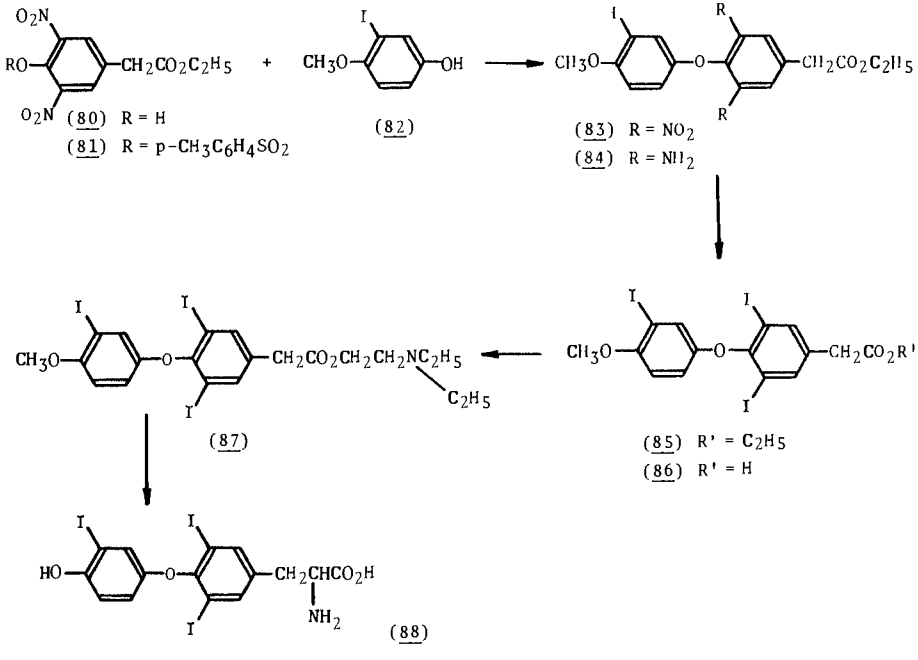


(79)

converted to the halide (*76*) by means of thionyl chloride. Reaction with methylamine leads to the key diamine *77*. Acylation of the diamine with chlorodiphenylacetyl chloride (to *78*), followed by displacement of the benzylic halogen by sodium ethoxide, affords the analgesic agent *carbiphene* (*79*).[19]

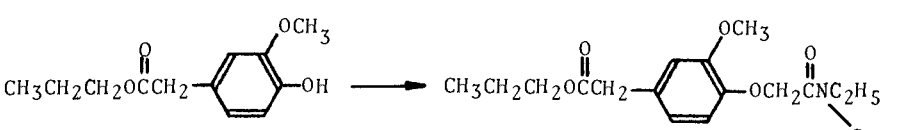
3. MISCELLANEOUS ARYLALKANOIC ACIDS

It has been known for some time that *thyroxine*, and related compounds such as *liothyronine* (*88*) are effective in lowering serum cholesterol. The normal metabolic activity of this class of thyroid active compounds has precluded their use as hypocholesterolemic agents.



A program aimed at preparation of analogues of thyroxine which would maximize their effect on lipids resulted in the preparation of *thyromedan (87)*. This agent, interestingly, proves also to have good thyromimetic activity. In the synthesis of *87*, reaction of the substituted phenylacetate *80* with tosyl chloride leads to the corresponding tosylate *(81)*. Reaction of that intermediate with the salt from phenol *82* results in aromatic nucleophilic displacement of the highly activated tosylate to afford the diphenyl ether *83*. The nitro groups are then reduced catalytically to give diamine *84*. Diazotization, followed by Sandmeyer reaction with sodium iodide, affords the desired triiodo intermediate *85*. Saponification affords the acid *(86)*, and reaction of the sodium salt of the acid with 2-chlorotriethylamine gives *thyromedan (87)*.[20]

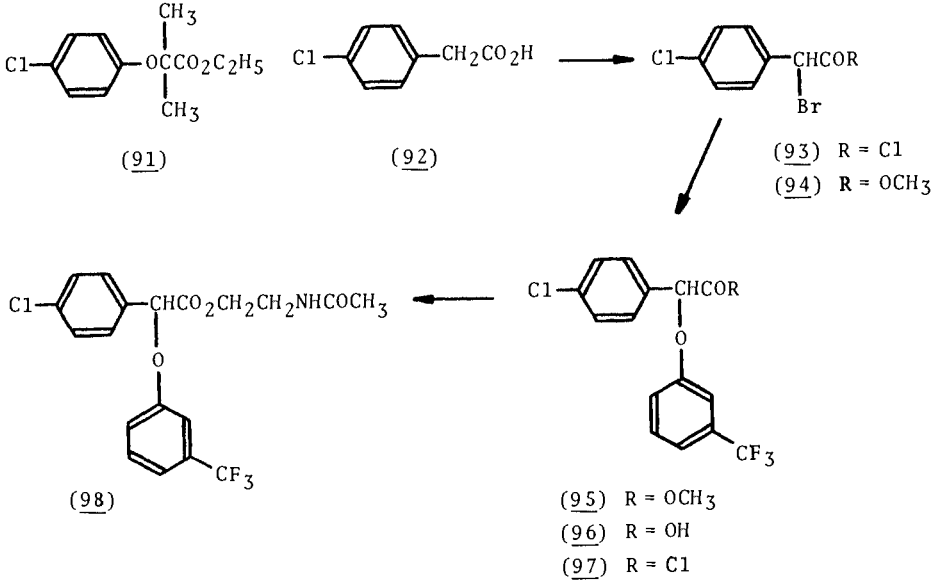
A highly-substituted phenylacetic acid derivative shows activity as a shortacting narcotic and as an injectable general anesthetic. This agent, *propanidid (90)*, is obtained by alkylation of phenol *89* with N,N-diethylchloroacetamide.[21]



(89) (90)

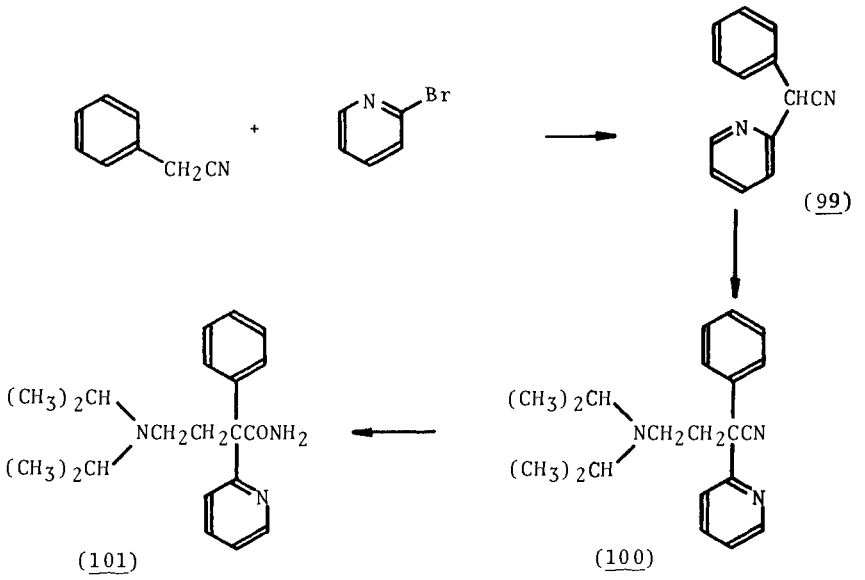
Clofibrate (91) has been in clinical use for several years as a serum triglyceride lowering agent. This drug is an important hypocholesteremic

agent also, blocking cholesterol biosynthesis. Appearance of this agent on the market occasioned intensive work in many laboratories aimed at discovering additional compounds with this activity. A distantly related analogue, *halofenate (98)*, was, in fact, found to be effective. In addition, however, clinical trials revealed this analogue to have marked concomitant uricosuric activity; that is, the drug promotes excretion of uric acid. In order to synthesize *halofenate*, acid *92* is first converted to the acid chloride by means of thionyl chloride; bromination affords the α-halo derivative *93*. This is then allowed to react with methanol to give the corresponding methyl ester *(94)*. Displacement of bromine with the anion from *meta*-trifluoromethylphenol leads to ester *95*. The ester is then hydrolyzed and

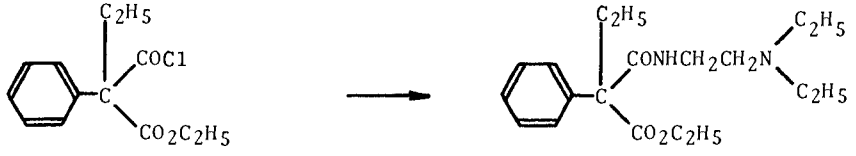


the product *(96)* is converted to the acid chloride *(97)*. Acylation of N-acetylethanolamine with *97* yields *halofenate (98)*.[22]

A disubstituted butyramide, *disopyramide*, distantly related to some acyclic narcotics interestingly shows good antiarrhythmic activity. Alkylation of the anion from phenylacetonitrile with 2-bromopyridine yields *99*. Alkylation of the anion from the latter with N,N-diisopropyl-2-chloroethylamine leads to the amine *100*. Hydration of the nitrile in sulfuric acid affords *disopyramide (101)*.[23]



Finally, reaction of the half acid chloride of malonate *102* with N,N-diethylethylenediamine gives the muscle relaxant *fenalamide (103)*.[24]



(102) (103)

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5

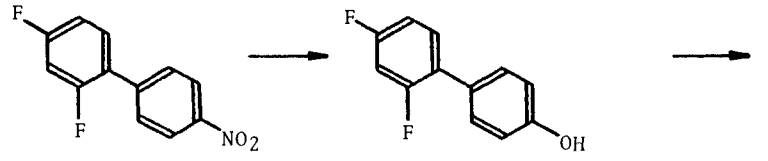
Monocyclic Aromatic Compounds

The benzene ring per se does not impart any particular pharmacological response to a drug. It is widely held that its planarity, its ability to bind to tissue receptors by Van der Waals and charge transfer mechanisms, and, particularly, its ability to serve as a conductor of electrons within a substance serve as modulators, enhancing or diminishing the intensity of response to a molecule that is otherwise inherently bioactive.

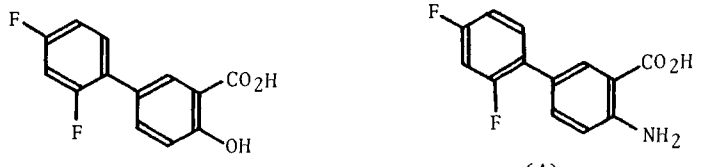
1. DERIVATIVES OF BENZOIC ACID

a. Acids

Salicylic acid analogues are often active as non-steroidal antiinflammatory agents because they interfere with biosynthesis of prostaglandins. *Diflunisal (3)* appears to be such an agent. It is synthesized from the nitrobiphenyl *1* by catalytic reduction to

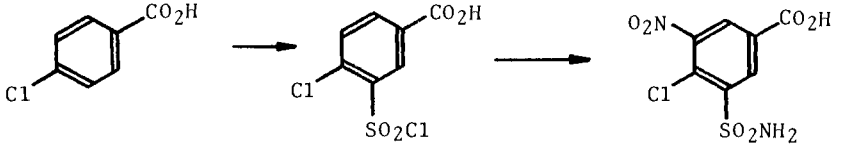


(1) (2)



(3) (4)

the aniline, diazotization, and heating in aqueous acid to give phenol *2*. This is carboxylated using K_2CO_3 and carbon dioxide to give *diflunisal*.[1] Alternatively, the corresponding anthranilic acid derivative *4* is diazotized, then hydroxylated by heating in dilute sulfuric acid to give *diflunisal*.[2]



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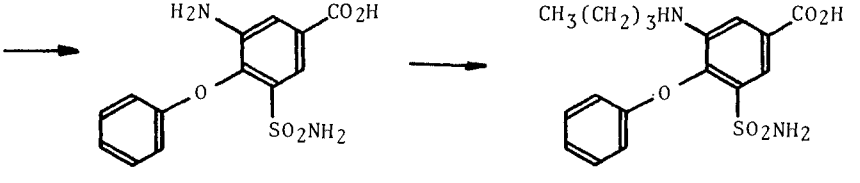


(7) (8)

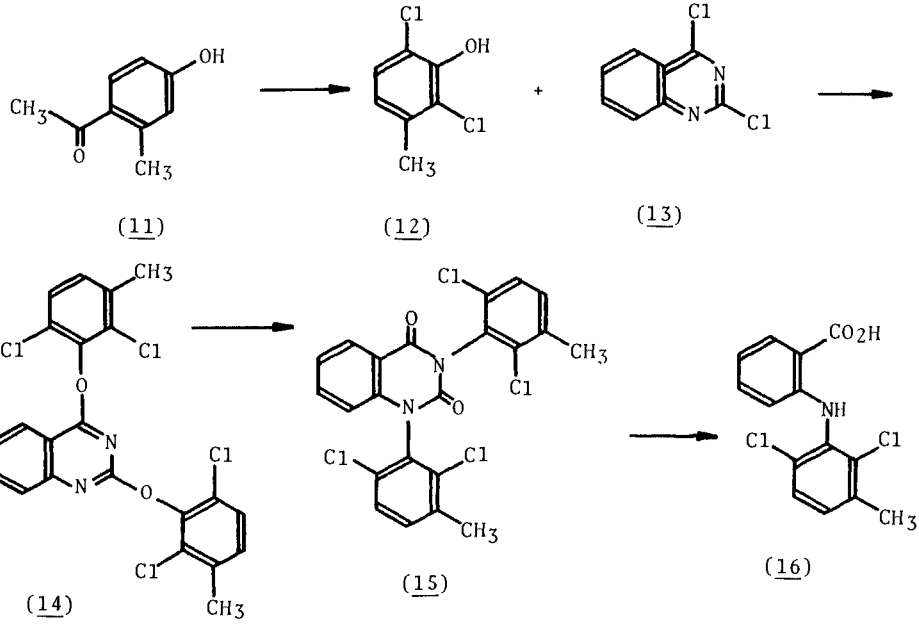
Many benzenesulfonamides have diuretic properties, particularly those having two such functions situated meta to one another. To some extent a carboxyl group can serve in place of one of the sulfonamido groups. *Bumetanide (8)* is such a substance. Chlorosulfonation of p-chlorobenzoic acid leads to *5*, which is nitrated, and then converted to sulfonamide *6* with ammonia. The chloro group of *6* is now highly activated toward nucleophilic aromatic substitution, facilitating reaction with phenoxide. Subsequent catalytic reduction in the presence of LiOH produces amino acid *7*. Next, treatment with butanol and sulfuric acid not only forms the butyl ester but monoalkylates the amino function. Saponification of the ester group leads to *bumetanide (8)*, a diuretic agent possessing 40-fold greater activity in healthy adults than *furosemide*.[3]

Tibric acid (10), interestingly, has the m-carboxysulfonamido functionality but its activity is expressed, instead, as suppression of serum triglyceride levels. In its reported preparation, chlorosulfonic acid treatment converts 2-chlorobenzoic acid to chlorosulfonate *9*, which readily forms the hypolipidemic agent *tibric acid (10)* on reaction with 3,5-dimethylpiperidine.[4]

(9) (10)

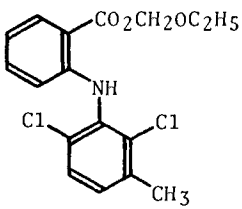
b. Anthranilic Acid and Derivatives

N-Aryl anthranilic acids are frequently found to have antiinflammatory activity and have been studied extensively to maximize potency and decrease side effects (gastric irritation, ulcers, etc.). These compounds are often synthesized by reacting an ortho-halobenzoate salt with a suitably substituted aniline. This procedure failed, perhaps because of steric hindrance, in attempting to synthesize *meclofenamic acid (16).*[5] The successful synthesis begins by



treating 2-methyl-4-hydroxy acetophenone *(11)* with NaOCl, which both ortho-chlorinates adjacent to the phenolic OH and effects a haloform reaction. Decarboxylation leads to the chlorinated meta cresol *12.* When *12* is converted to its sodium salt with NaH in DMF

and then treated with 2,4-dichloroquinazoline *(13)*, two molecules of the phenol react with the heterocycle to give the nucleophilic aromatic substitution product *14*. When heated, *14* undergoes an O to N-aryl rearrangement (Chapman Rearrangement) to give *15*. Upon saponification, carbon dioxide and 2,5-dichloro-3-methylaniline are lost and *meclofenamic acid (16)* results. Reaction of sodium meclofenamate with ethylchloromethyl ether in acetone gives *etoclofene (17)*, which is also active as an antiinflammatory agent. *Etoclofene* reportedly causes less gastrointestinal irritation than *meclofenamic* acid to which it is presumably converted after passage through the stomach.[6]



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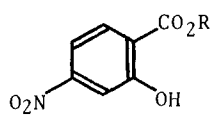
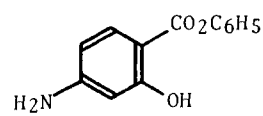


(18) R = H
(19) R = C_6H_5

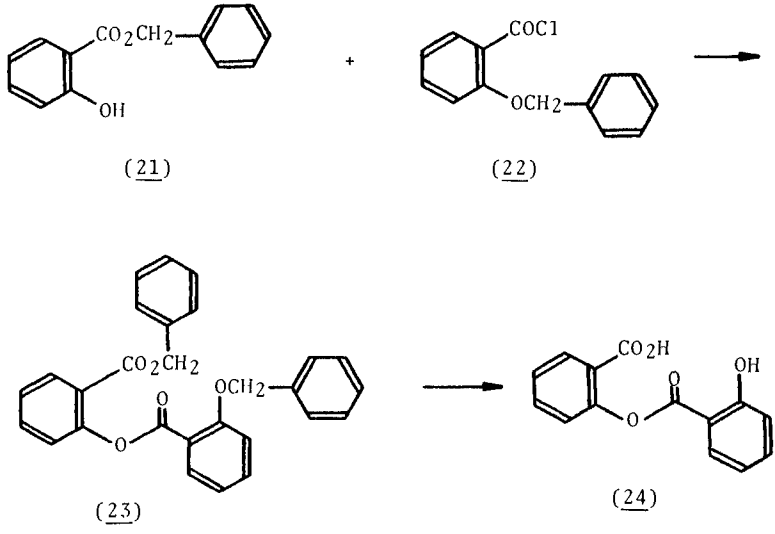


(20)

One of the mainstays in the treatment of tuberculosis is *paraaminosalicylic acid (PAS)*. It is not, however, a pleasant drug to take. *Phenyl aminosalicylate (20)* was synthesized from 4-nitrosalicylic acid *(18)* by esterification of its acid chloride with phenol to give *19*, which is converted to the desired product *(20)* by reduction with Raney nickel catalyst.[7] *Phenyl aminosalicylate* was intended to be more acceptable to patients than *PAS*.

Unquestionably, the most frequently used analgesic is *aspirin*. The reader will recall that *aspirin* is

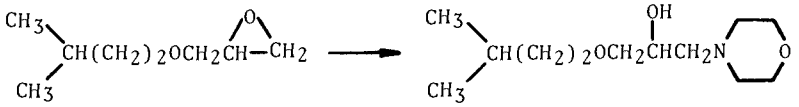
regarded as a latentiated form of salicylic acid and is intended to minimize as far as possible the irritation of the gastrointestinal tract that salicylic acid would otherwise cause. *Salsalate (24)* represents another approach to this problem in which self-esterification has been used to serve the same purpose. Direct self-condensation is difficult to control, although low temperature treatment of salicylic acid with PCl_3 does work. A more stepwise procedure involves the condensation of benzyl salicylate *(21)* with the acid chloride of salicylate benzyl ether *22* to produce protected dimer *23*. Catalytic hydrogenolysis removes the benzyl groups and completes the preparation of *salsalate (24)*.[8]



(21) (22) (23) (24)

Esterification of certain aromatic acids with β-aminoethanol and propanol derivatives frequently results in molecules that show local anesthetic

activity; and some of these derivatives also have an antiarrythmic action on the heart. *Amoproxan (27)* is such an agent. It can be synthesized by reacting epichlorohydrin with 3-methylbutanol and BF_3 to give epoxide *25*. This, then, is reacted with morpholine to give alcohol *26*, which is then reacted with 3,4,5-trimethoxybenzoyl chloride to complete the synthesis of *amoproxan (27)*.[9]



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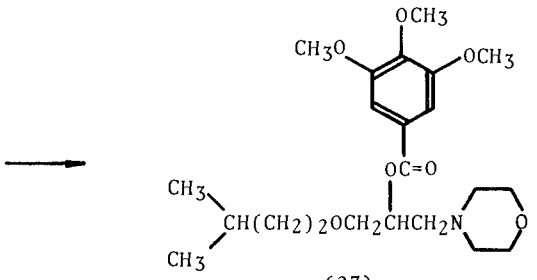
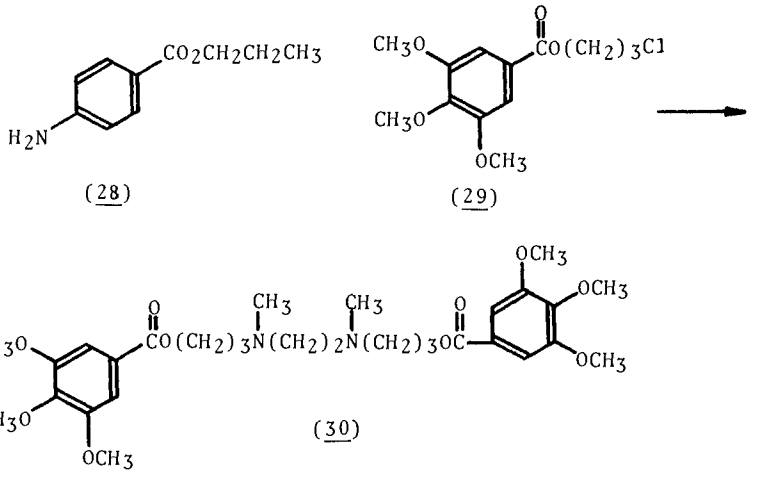


(27)

Risocaine (28) manages to retain local anesthetic activity even without having a "basic ester" moiety.[10] Its synthesis follows classic lines involving esterification of p-nitrobenzoic acid with thionyl chloride followed by reaction with propanol, and then catalytic reduction to complete the scheme.



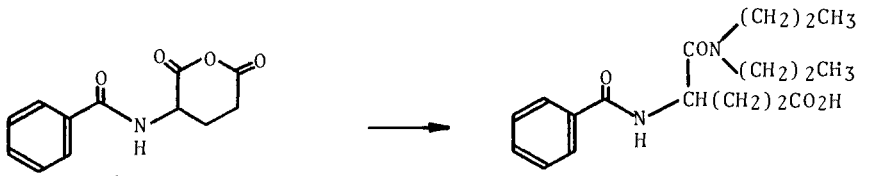
Vasodilators may be of value in the treatment of conditions resulting from insufficient blood flow through tissues. One such agent incorporating a bis-basic ester moiety is prepared by reacting 3,4,5-trimethoxybenzoyl chloride with 3-chloropropanol to give *29*, and condensing two molar equivalents of this with N,N'-dimethylethanediamine to give *hexobendine (30)*.[11]

c. Amides

As one would anticipate, the time honored Schotten-Baumann reaction and its variants are the key steps in putting this group of substances together. Their intrinsic interest to the medicinal chemist depends upon their pharmacological properties and, in some cases, preparation of some of the less common benzoic acid analogues.

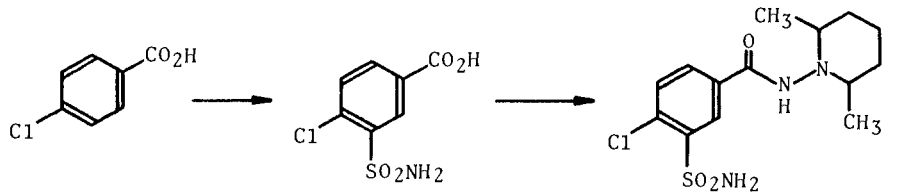
Anticholinergic agents play a role in management of ulcers by decreasing the secretion of gastric acid

mediated by the neurohormone acetyl choline. *Proglumide (32)* is synthesized from the benzoyl amide of glutamic anhydride derivative *31* by reaction of the more activated carbonyl with dipropylamine.[12]



(31) (32)

The diuretic *clopamide (35)* is synthesized from p-chlorobenzoic acid *(33)* by chlorosulfonation and subsequent ammonia treatment to give *34*. This is converted to its acid chloride with thionyl chloride and reacted with the desired hydrazine derivative



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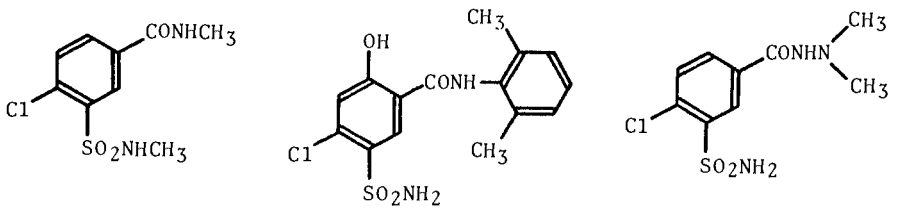
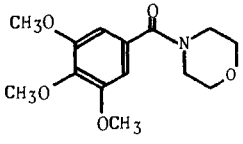


(36) (37) (38)

(itself prepared by lithium aluminum hydride reduction of N-nitroso-2,6-dimethyl piperidine) in a Schotten-Baumann reaction to give *clopamide*.[13] The related diuretics *diapamide (36)*,[14] *xipamide (37)*,[15]

and *alipamide (38)*[16] are made by simple variants on this scheme.



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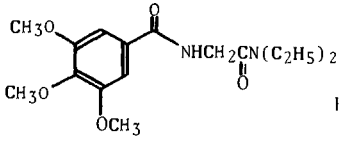

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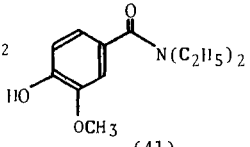

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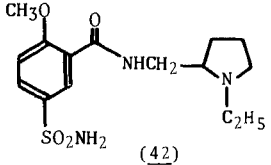

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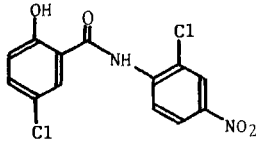

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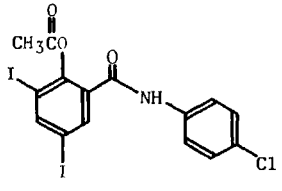
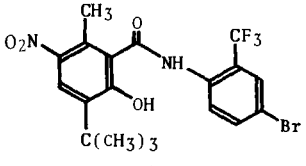


(44)

The sedatives *trimetozine (39)*,[17] and *tricetamide (40)*,[18] the CNS stimulants *ethamivan (41)*,[19] and *sulpiride (42)*,[20] the antihelmintic agents *niclosamide (43)*,[21] *clioxanide (44)*,[22] and *bromoxanide (45)*,[23] the coccidiostat *alkomide (46)*,[24] and the antiarrhythmic agent *capobenic acid (47)*[25] are all made from the corresponding benzoic acids in obvious ways.



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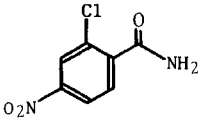

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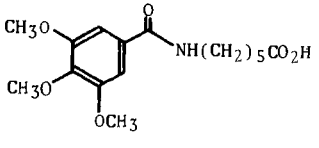
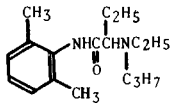


(47)

2. DERIVATIVES OF ANILINE

The clinical success of hindered acetanilide derivatives, such as *lidocaine*, of course, resulted in the synthesis of many analogues. Branching in the acid moiety is consistent with activity as demonstrated by the local anesthetic properties of *etidocaine (48)*[26] and a formally cyclized analogue, *dexivacaine (49)*.[27] *Etidocaine* is prepared from 2,6-dimethylaniline by sequential reactions with 2-bromobutyryl chloride and ethylpropylamine. The preparation of *dexivacaine* follows the same pattern. However, in this case, resolution by crystallization of its quinic acid salt was carried out, whereupon it was found that the S-enantiomer was the longer acting.



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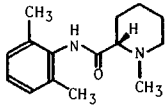

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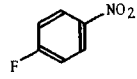

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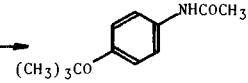
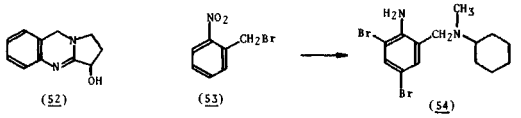


(51)

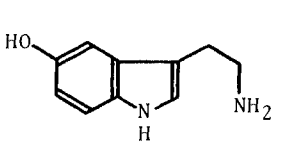
Acetanilide is a well-established analgesic agent. It is perhaps not suprising then that *butacetin (51)* has such activity; however, it appears to have been synthesized while searching for antitubercular agents. The synthesis proceeds from 4-fluoronitrobenzene *(50)* via a nucleophilic aromatic displacement reaction with potassium tert-butoxide, followed by Raney nickel reduction and acetylation.[28]

A molecular dissection of the alkaloid *vasicine (52)* ultimately resulted in the expectorant and mucolytic agent *bromhexine (54)*.[29] The synthesis starts with displacement of halogen on 2-nitrobenzyl-bromide *(53)* by N-methyl cyclohexylamine, followed by Raney nickel and hydrazine reduction of the nitro group. Bromination in acetic acid then affords *bromhexine*.



(52) (53) (54)

Serotonin (55) is a putative neurotransmitter, especially in the central nervous system, and has a number of peripheral effects as well. There have been numerous attempts to associate disturbances in serotonin catabolism and anabolism with mental disease, and antagonists have been prepared as an aid to investigation of these theories and as potential therapeutic agents. *BAS (56)* is one such inhibitor and its structural similarity to *55* makes it understandable that it should be such. On the other hand, *cinanserin (58)* is 157 times more potent as a serotonin inhibitor than *56*, and its structural relationship to either *55* or *56* is much less obvious. This underscores one of the more frustrating features of deliberate drug design--that the best analogues occasionally differ strikingly in structure from the lead molecule so that success requires an unsatisfying amount of semirandom molecular manipulation and a very close liason with the pharmacologist into whose hands the drugs are placed for evaluation. In any



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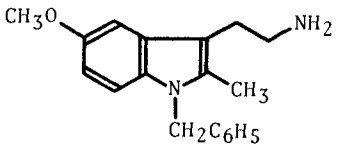

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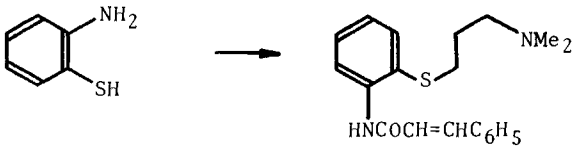
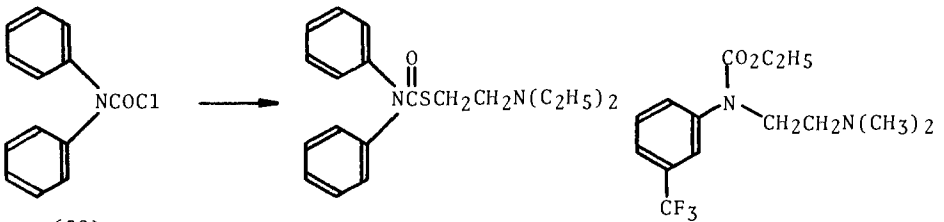


(57) (58)

event, *cinanserin* is synthesized from 2-aminothiobenzene *(57)* by S-alkylation using N,N-dimethyl-3-chloropropylamine and $NaOCH_3$, followed by reaction with cinnamoyl chloride to give *58*.[30]

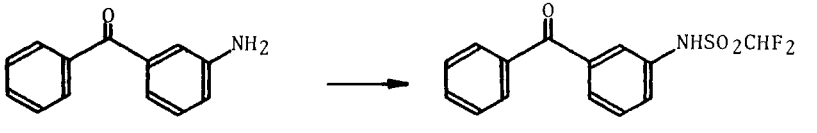


(59) (60) (61)

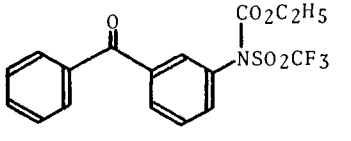
Phencarbamide (60)[31] is a structural analogue of acetylcholine which acts as an anticholinergic agent, possibly by serving as a false agonist. It is made by reacting N,N-diphenylcarbamoyl chloride *(59)* with 2-mercapto-N,N-diethylethamine.

Flubanilate (61) has central nervous stimulating activity and is synthesized conveniently from N-(2-dimethylamino)ethyl-3-trifluoromethylaniline by reaction with ethylchlorocarbonate.[32]

A number of aminobenzophenone derivatives possess nonsteroidal antiinflammatory activity. Illustrative is *diflumidone (63)*. Its synthesis involves treatment of 3-aminobenzophenone *(62)* with difluoromethanesulfonic anhydride in the presence of triethylamine.[33]



(62) (63)



(64)

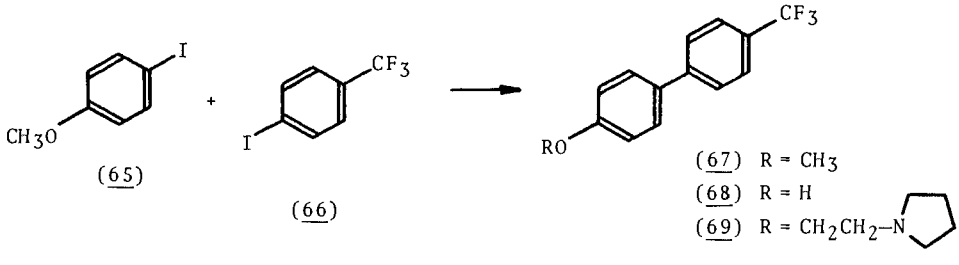
The closely related antiinflammatory agent *triflumidate (64)* can be prepared by abstracting the now acidic NH proton of the trifluoromethyl analogue of *63* with sodium hydroxide and reacting the resulting anion with ethyl chlorocarbonate to give *64*.[34]

3. DERIVATIVES OF PHENOL

a. Basic Ethers

The chemical fragment, OCCN=, occurs very frequently in drugs, perhaps deriving some inspiration from

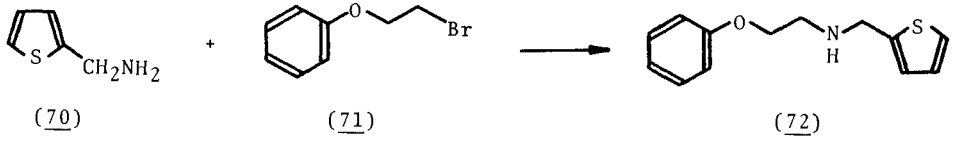
acetyl choline. The fact that drugs containing this unit do not possess some common pharmacological property suggests that the function is involved in transport rather than being a pharmacophore. Several agents containing this moiety are described in this section. *Boxidine (69)* has hypolipidemic properties.[35]



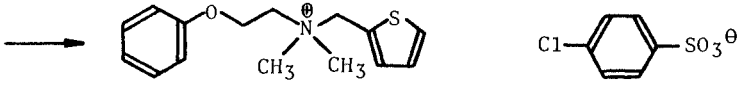
It was synthesized from p-iodoanisole *(65)* by copper-catalyzed coupling with p-trifluoromethyliodobenzene *(66)* to give the expected statistical mixture from which unsymmetrical product *67* could be separated. Ether cleavage with HBr and HOAc gave *68;* this was then alkylated with the aziridinium ion derived from N-(2-chloroethyl)pyrrolidine, using NaH as base, to complete the synthesis of *boxidine (69).*

The quaternary ammonium salt *73, thenium closylate,* is an anthelmintic agent. Many substances of this general type are effective by interfering with nervous conduction, and thereby muscle tone, of intestinal worms. This allows their expulsion, not always in the dead state. The synthesis[36] proceeds from 2-thienylamine *(70)* by monoalkylation with 2-phenoxyethyl bromide *(71)* to give secondary amine *72.*

This is converted by methyl iodide to the quaternary salt which is converted to the p-chlorobenzene sulfonate salt *(73)* for pharmacological purposes.

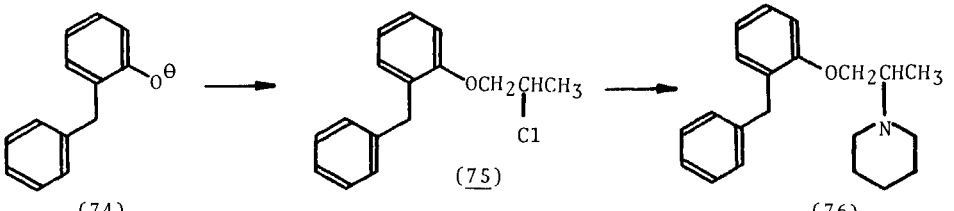


(70) (71) (72)



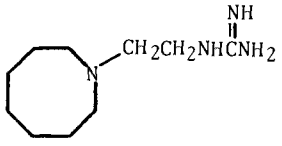
(73)

When 1,2-dichloropropane is reacted with o-benzylphenoxide ion *(74)*, halide *75* results, which is then converted to the antitussive agent *benproperine (76)* on treatment with piperidine.[37]



(74) (75) (76)

Guanethidine (77) was the first of a series of antihypertensive agents which act by interfering with adrenergic transmission. It was subsequently found that simple substitution of the guanidine function onto a nucleus with appropriate lipophilicity almost invariably affords such sympathetic inhibitors.



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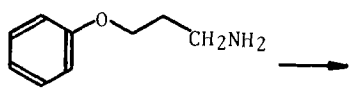

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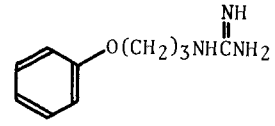

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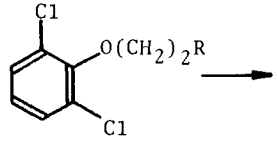
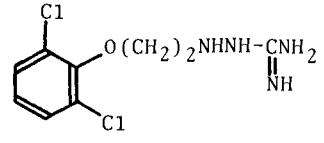


(80) R = Br
(81) R = $NHNH_2$

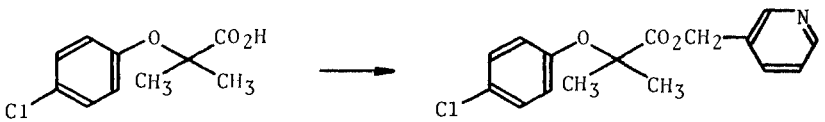


(82)

Thus, for example, guanidine analogues *guanoxyfen (79)* and *guanochlor (82)* also possess antihypertensive activity. *Guanoxyfen* is synthesized[38] by base-catalyzed condensation of phenol with chloroacetonitrile, followed by hydride reduction to amine *78*. The guanido function is introduced by reaction with S-methylthiourea to give *guanoxyfen (79)*. When 2-(2,6-dichlorophenoxy)ethyl bromide *(80)* is reacted with hydrazine to give *81*, and this is reacted with S-methylthiourea, *guanochlor (82)* results.[39]

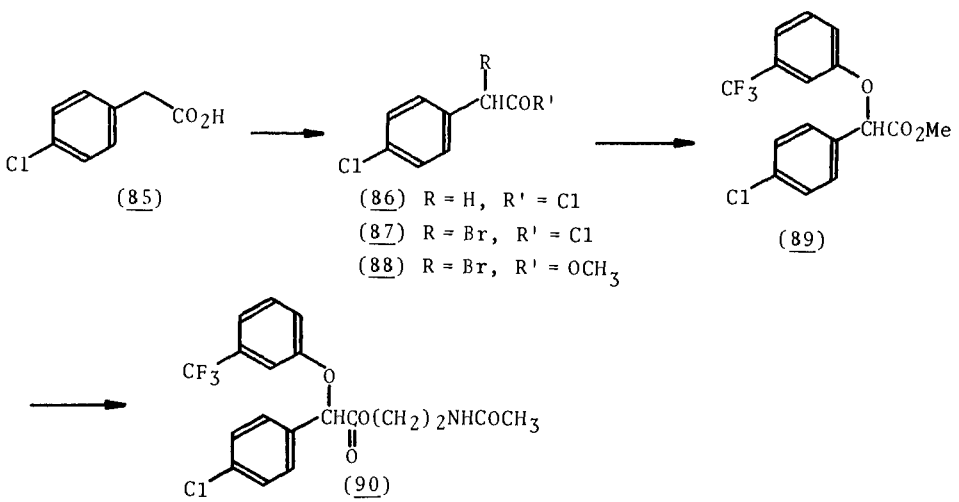
b. Phenoxyacetic Acids

The clinical success of *clofibrate* has naturally led to the synthesis of numerous analogues intended for use as hypocholesterolemic agents. One of these, *clofenpyride (84)*, is synthesized readily from p-chlorophenoxy-2,2-dimethylacetic acid *(83)* by conversion to the acid chloride and reaction with 3-hydroxymethylpyridine.[40] Substitution of a single aromatic



(83) (84)

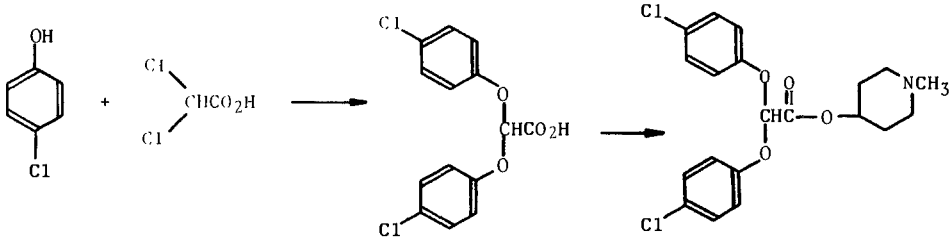
ring in the place of the gem-dimethyl groups of *84* is compatible with activity. Interestingly, the resulting molecule, *halofenate (90)* is also reported to show uricosuric activity. Conversion of p-chlorophenylacetic acid *(85)* to its acid chloride *(86)* activates the benzylic methylene group to bromination with molecular bromine, and the resulting mixed dihalide *(87)* is reacted with methanol to give ester *88*. Nucleophilic halide displacement with the sodium salt of m-trifluoromethylphenol gives intermediate *89*, which is saponified with KOH, converted to the acid



(85) (86) R = H, R' = Cl
(87) R = Br, R' = Cl
(88) R = Br, R' = OCH_3
(89) (90)

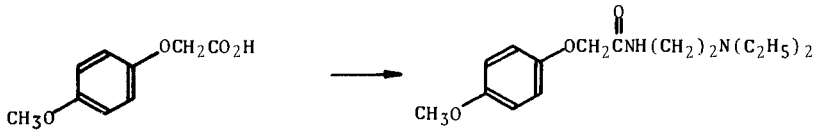
chloride with thionyl chloride, and then esterified with N-acetylethanolamine to give *halofenate (90)*.[41]

Insertion of a second aryl ether oxygen function is also consistent with hypocholesterolemic activity. Burger et al. have published an early and apparently general synthesis of such compounds.[42] In the specific case of *lifibrate (92)*, bis-(4-chlorophenoxy) acetic acid *(91)* is converted to the acid chloride with thionyl chloride, and then reacted with N-methyl piperidine-4-ol to give the desired basic ester *92*.



(91) (92)

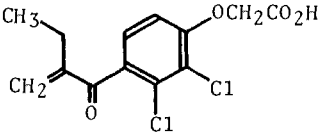
A seemingly simple variation on these structures results in central stimulant activity instead. p-Methoxyphenyloxyacetic acid *(93)* is reacted with N,N-diethylethanolamine via the acid chloride to give *mefexamide (94)*.[43]



(93) (94)

The diuretic properties of *ethacrynic acid (95)* were at one time attributed to its role as a Michael

acceptor. The enone was believed to react with SH groups on enzymes in the kidney. This interesting view was weakened by the discovery that some related molecules which do not possess this structural feature



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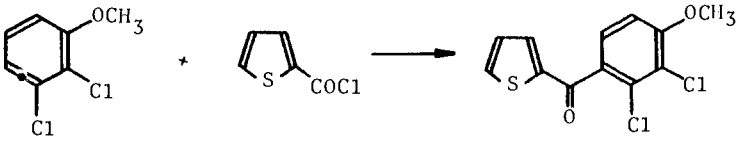
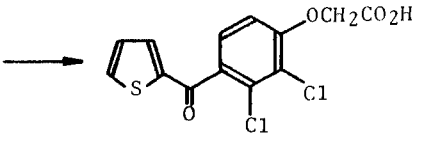


(96) (97)



(98)

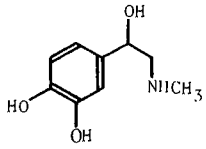
still possess marked diuretic activity. An analogue of *ethacrynic acid* is synthesized by condensing 2,3-dichloromethoxybenzene *(96)* with the acid chloride of thiophene α-carboxylic acid to give *97*. Ether cleavage with $AlCl_3$, followed by sodium salt formation, etherification with ethyl chloroacetate, and then saponification gives *ticrynafen (98)*.[44]

c. Ethers of 1-Aminopropane-2,3-diol

There has been enormous interest recently in the pharmacological properties of selective β-adrenergic blocking agents following the clinical success of *propranolol*. That the many pharmacological responses elicited by norepinephrine and epinephrine in various tissues are the consequence of macromolecular receptor substances of slightly different specificities has been known for some time. Such differences are often most conveniently demonstrated through use of selective inhibitors, and functional classifications of such receptors are usually made on that basis. Ahlquist devised a system of receptor classification based largely upon whether excitatory or inhibitory responses followed administration of adrenergic agents.[45] The α-receptor was associated generally with excitatory responses (vasoconstriction, uterine and nictating membrane stimulation) while the β-receptor was associated with inhibitory responses (vasodilation, inhibition of uterine muscle).

While the physiological responses following β-receptor stimulation are many, those most prominent are those on the cardiovascular system and on the smooth muscles of the bronchial tree. Subsequently, a lack of faithful parallelism between the cardiac and bronchial effects led Lands *et al.*[46] to propose a further subdivision of the β-receptors into β_1, which stimulates cardiac muscle and lipolysis, and β_2, which relaxes bronchioles and influences the vasculature and shows metabolic effects. Epinephrine *(99)*

is an archetypal adrenergic agent stimulating α, β_1, and β_2 receptors.



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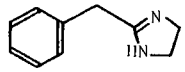

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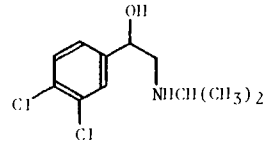

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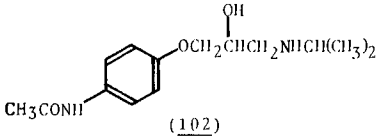

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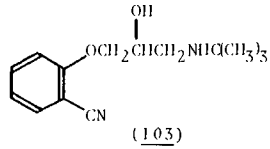

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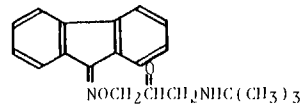

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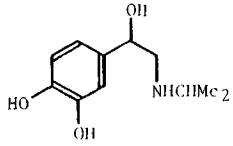

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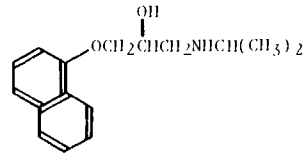


(105)

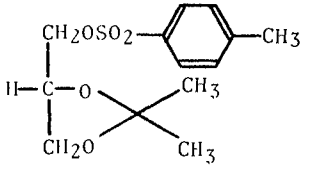
Some specific antagonists of interest in classifying receptors are *tolazoline (100,* α-receptor antagonist), *dichloroisoproterenol (101,* β-receptor antagonist), *practolol (102,* $\beta_1$receptor antagonist), and *bunitrolol (103,* $\beta_2$receptor antagonist). Recently described compound *103a* departs from the previous structural norm and possesses strong $\beta_2$receptor blocking selectivity. These classifications are rendered somewhat difficult because few of these agents are completely selective and may have additional pharmacological properties, such as varying degrees of intrinsic sympathomimetic agonist action.

Isoproterenol (104) is an important agent for classification because of its selective β-receptor agonist activity. It is of special interest that its chronotropic (increase in heart rate) and inotropic (increase in force of contraction) effects exceed that of epinephrine; it is also used in the management of mild to moderate asthma due to its bronchodilating effect, resulting in increased vital capacity of the lungs.

It is in this context that *propranolol (105)* and its myriad analogues need to be judged. Administration of *105* leads to a decrease in heart rate, cardiac contractile force and myocardial oxygen consumption. These drugs often have some intrinsic adrenergic sympathomimetic activity which leads, i.a., to an increase in airway resistance of little consequence to most patients but of potential danger to asthmatics. Another factor of interest is a direct action on cell membranes, affecting their responsiveness to electrical stimulation and, in isolated atria, decreasing spontaneous frequency, maximal driving frequency, contractility and increasing the electrical threshold. In contrast to the β-blocking action, these "local anesthetic" actions are nonstereospecific. Whether these local anesthetic actions are important in antiarrhythmic action is being debated.

The therapeutic use of these agents is in control of cardiac arrhythmias, angina pectoris, and in essential and renovascular hypertension. The various ancillary activities lead to side effects and much

effort has been expended to refine out these extraneous responses. It is not universally agreed whether some intrinsic sympathetic activity (I.S.A.) is desirable or not and, if so, how much a drug should have.



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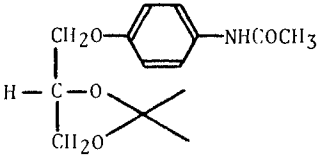

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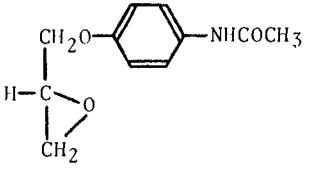

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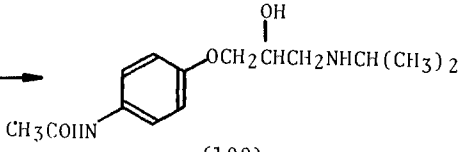

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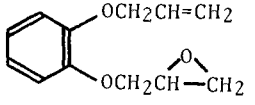

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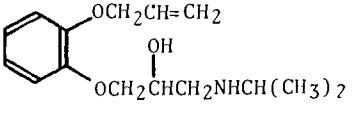
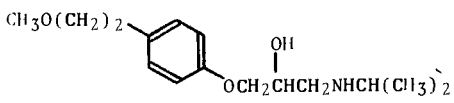


(111)

The means used to prepare these agents can be illustrated by the following examples. *Practolol (109)*[47] gives less clinical bronchoconstriction in some patients than propranolol because its receptor action is more selective. Serious occasional toxicity not related to β-blockade has led to its withdrawal from clinical use. A synthesis is available which relates the absolute configuration of the more potent

optical isomer to (+)-lactic acid. The glycerol derivative *106* is available from D-mannitol and retains the optical activity as the two primary alcohol functions are differentially protected. Displacement with sodium p-acetamidophenoxide gives *107* which is deblocked with dilute acid, selectively reacts at the primary alcohol function with one molar equivalent of tosyl chloride and pyridine, then treated with NaOH in dimethylsulfoxide to yield epoxide *108*. Epoxide opening with isopropylamine leads to optically active *practolol (109)*, showing that the l-compounds are related to R-(-)-epinephrine.

The synthesis of *oxprenolol (111)* follows a similar course.[49] Epoxide *110*, readily synthesized by reaction of the sodium salt of pyrocatechol monoallylether with epichlorohydrin, is reacted either with isopropylamine or with HCl (to form the intermediate halohydrin) followed by isopropylamine.



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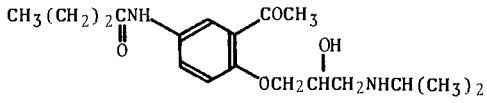

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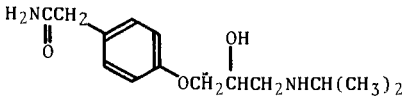

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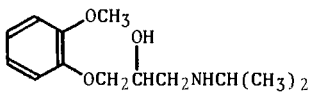
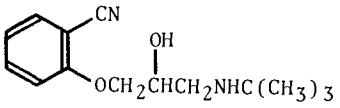


(115)

Metoprolol (112),[50] *acebutolol (113)*,[51] *atenolol (114)*,[52] and *moprolol (115)*[23] are all closely related

and made by this basic route or simple variations of it.



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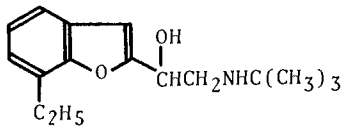

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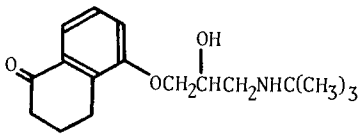

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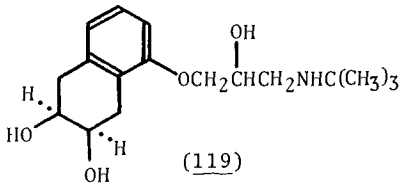

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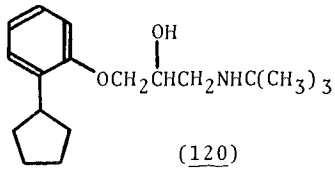

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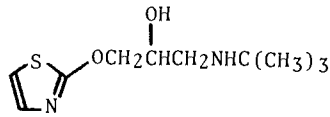
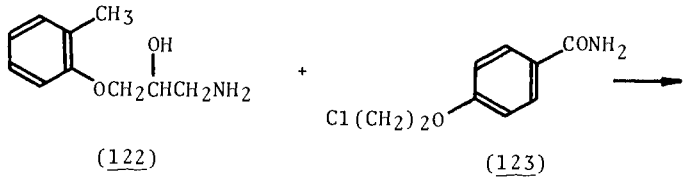


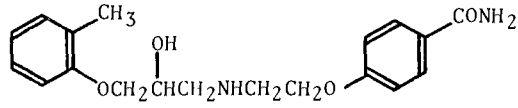
(121)

Replacement of isopropylamine by tert-butyl amino often results in an increase in potency. This substitution is used in the β-blockers *bunitrolol (116)*,[54] *bufuralol (117)*,[55] *bunolol (118)*,[56] *nadolol (119)*,[57] and *phenbutalol (120)*.[58] *Tazolol (121)*[59] whose structure is similar, is not a good β-blocker, possessing substantial ISA.[59]

Substitution of groups other than i-propyl or t-butyl on nitrogen also leads to active compounds. Primary amine *122* is reacted with p-(β-chloroethoxy)-benzamide *(123)* to give the β-blocker, *tolamolol (124)*.[60]



(122) (123)

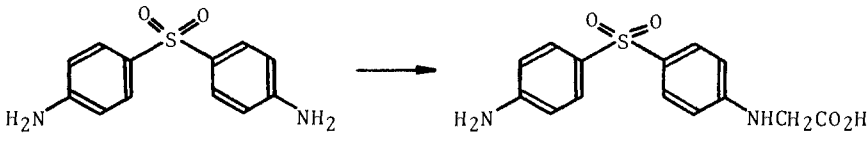


(124)

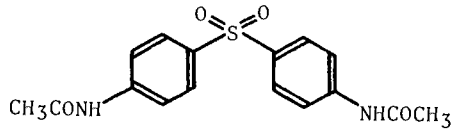
4. ARYLSULFONES AND SULFONAMIDES

a. Sulfones

Until the development of the antibacterial sulfones, Hanson's Disease (leprosy) remained a potentially horrible affliction, treated with largely ineffective ancient remedies. The antibacterial sulfonamides do not do well against this disease and, interestingly, the sulfones which are effective, are not very useful



(125) (126)



(127)

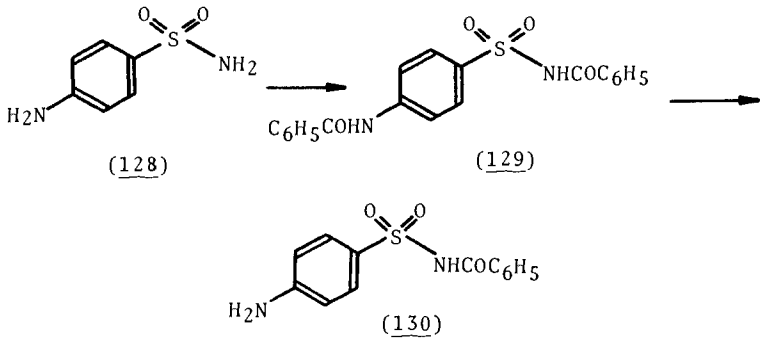
against most other bacterial infections. *Dapsone (125)* is such an agent. It is somewhat inconvenient to administer to patients because of its rather low water solubility. In the search for more easily administered drugs, *125* was reacted with bromoacetic acid to give *acediasulfone (126)* which can be administered as a water soluble salt.[61]

Acedapsone (127), which is conveniently prepared by acetylation of *dapsone*, was intended to be a prodrug.[62] Leprous patients being treated with *dapsone* were observed to have a lower incidence of malaria and *acedapsone* was made to capitalize on this observation. It, indeed, has both antileprotic and antimalarial activity.

b. Sulfonamides

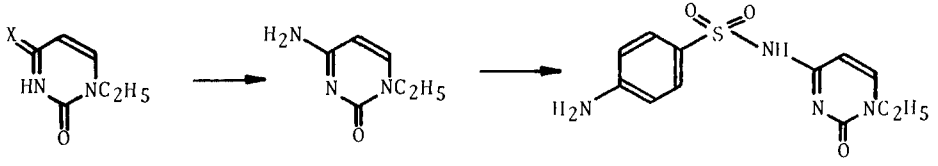
Because of bacterial resistance and unacceptable side effects in some patients, the antibacterial sulfonamides no longer enjoy the clinical vogue they once had. Still, their cheapness, undeniable efficacy in susceptible infections, and the hope of overcoming their deficiencies leads to a continuing interest despite thousands having been synthesized to date. Some of the more significant agents not included in Volume I of this work follow.

Generally, N_1-acylsulfonamides are less effective than those having a single N_1-aryl group. One such acyl analogue, *sulfabenzamide (130)* is prepared simply from *sulfanilamide (128)* by bisbenzamide formation (to *129)* using benzoyl chloride and pyridine, followed by partial saponification.[63]



(128) (129) (130)

The classic syntheses of the antibacterial sulfonamides involve reaction of the appropriate arylamine with an acid addition salt of p-amino-benzenesulfonyl chloride, or p-nitrobenzenesulfonyl chloride followed by reduction. Chemical interest largely resides in preparation of the corresponding arylamines. For the synthesis of *sulfacytine (134)*, N-ethyl uracil *(131)* was converted to its thioamide *(132)* by reaction with phosphorous pentasulfide. The newly introduced sulfur is then displaced with ammonia in methanol to give *133*. Standard reactions complete

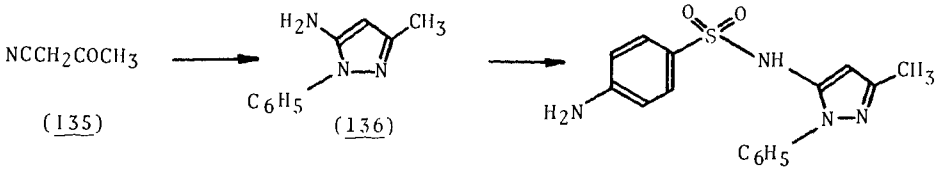


(131) X = O
(132) X = S

(133) (134)

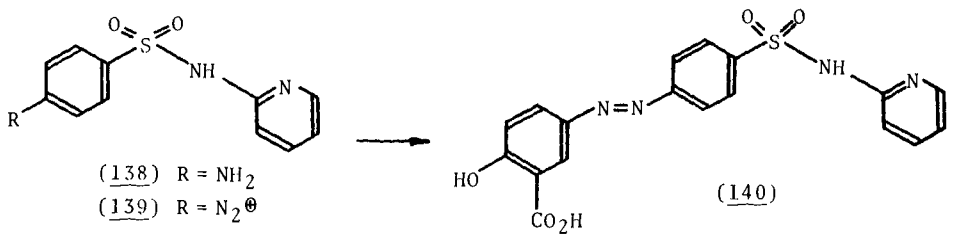
the synthesis of *134*.[64] Reaction of cyanoacetone *(135)* with phenylhydrazine gives the corresponding *pyrazole (136)*, which is then converted to *sulfazamet (137)* in the usual way.[65] An antibacterial agent promoted for use in ulcerative colitis is made by

diazotization of *sulfapyridine (138)* and coupling of the diazonium salt *(139)* with salicylic acid to give *sulfasalazine (140)*.[66]



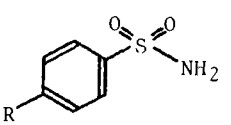
(135) (136) (137)

Mafenide (142) was synthesized in part to see whether the p-amino group of the classical sulfonamides had to be attached directly to the ring for efficacy as an antibacterial agent. The answer is apparently yes.[67] Reduction of p-cyanobenzenesulfonamide *(141)* produces *mafenide*, which is not a clinically useful antibacterial agent.



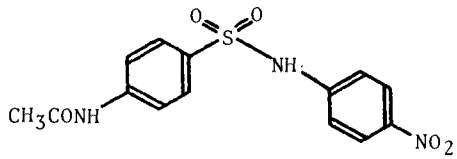
(138) R = NH_2
(139) R = $N_2^{\oplus}$

(140)

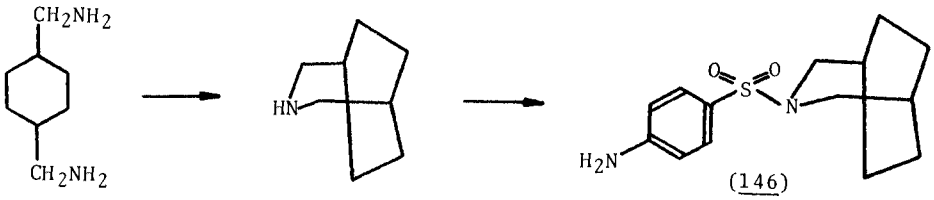


(141) R = CN
(142) R = CH_2NH_2

Coccidiosis is an economically significant respiratory disease of fowl. During the course of studies directed toward antimalarial agents, *sulfanitran (143)* was prepared and found to be a coccidiostat. It is prepared conveniently by reaction of p-acetoamidobenzenesulfonyl chloride with p-nitroaniline in acetic acid.[68]

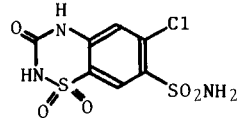


(143)



(144) (145) (146)

Benzenesulfonamides having two substituents on N_1 usually have poor antibacterial potency. Such is the case with *azabon (146)*. This central stimulant is prepared in the usual fashion from 3-azabicyclo-[2.2.2]nonane *(145)*, which is itself prepared by pyrolysis of aliphatic diamine *144*.[69]



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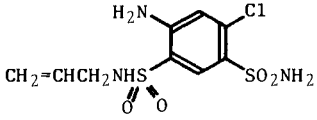

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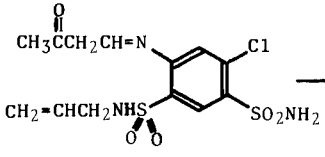

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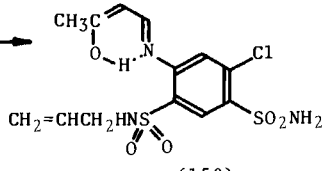

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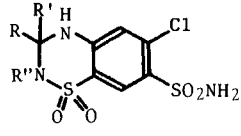


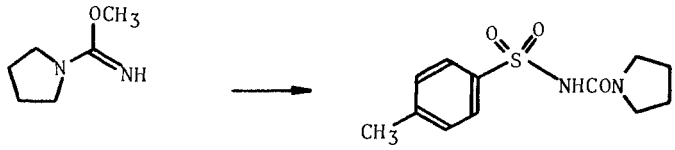
(151)

Ambuside (149), a diuretic, is prepared from cyclic urea derivative *147* by allylation of the more acidic NH group with allyl bromide by means of NaH, followed by hydrolytic ring opening to give 2-allylsulfamyl-5-chloro-4-sulfamylaniline *(148)*. This is in turn treated in acid with 2-ketopropionaldehyde dimethylacetal to give the Schiff base *ambuside (149)*.[70] The enolanil form *(150)* of *ambuside* shows some similarity to the open form of some of the cyclic thiazide diuretics *(151)* which have been speculated to be the active form of these molecules.

c. Sulfonylureas

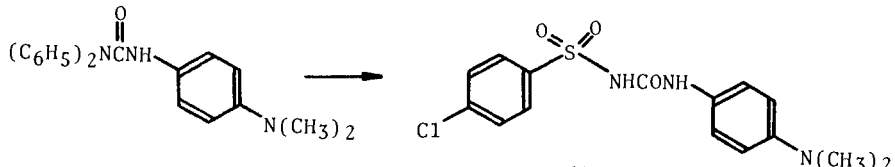
Linear descendants of the antimicrobial sulfonamides, the orally active sulfonylureas continue to be of interest as alternatives to insulin injections in patients with adult-onset diabetes. *Tolpyrramide (153)* is synthesized from unsymmetrical O-methylurea

derivative *152* and tosyl chloride, followed by mild acid treatment to cleave the O-methyl group.[71]



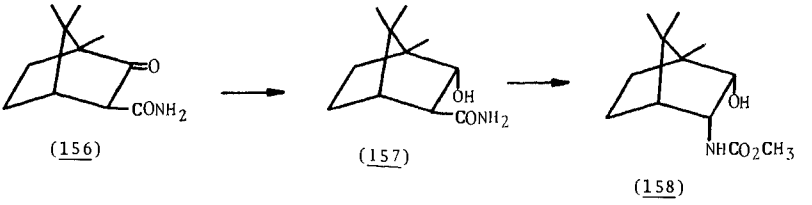
(152) (153)

Glyparamide (155) is made by displacement of the best leaving group of unsymmetrical urea *154* with sodio p-chlorobenzenesulfonamide.[72] *Glibornuride (159)* is an endo-endo derivative made from camphor-

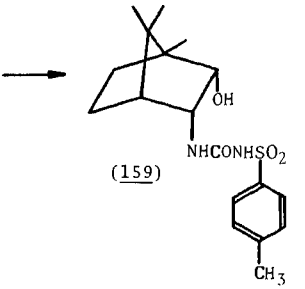


(154) (155)

3-carboxamide *(156)* by borohydride reduction (exo approach) (to *157*), followed by a Hoffman reaction to carbamate *158*, followed by displacement with sodio-tosylamide to give *glibornuride*.[73] *Glyoctamide (160)* is the tosylamide of cyclooctylurea.[74] *Glipizide (163)* is synthesized from 5-methylpyrazine-2-carboxylic acid *(161)* and 4-(2-aminoethyl)benzene sulfonamide to give sulfonamide *162*, which forms *glipizide (163)* on reaction with cyclohexylisocyanate and base in acetone.[75]



(156) (157) (158)



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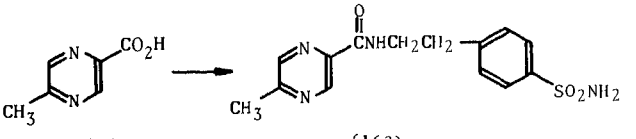
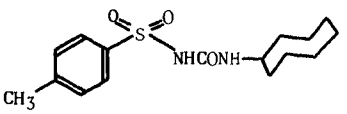


(161) (162)



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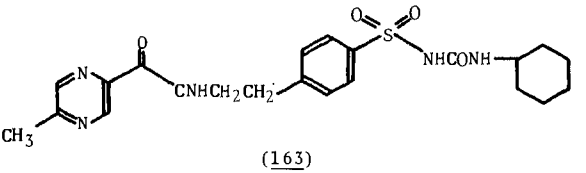

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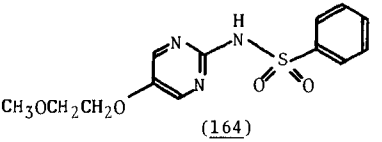


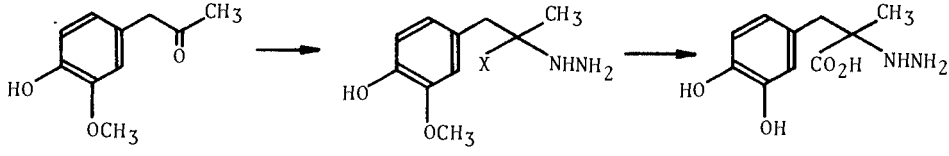
(164)

Though *glymidine (164)* does not contain a sulfonylurea moiety, this function is probably fulfilled by the aminopyrimidine nucleus, which can be considered to be the cyclized equivalent. It is formed simply by reaction of the corresponding alkoxyaminopyrimidine with benzene sulfonyl chloride.[76]

5. FUNCTIONALIZED BENZENE DERIVATIVES

a. Alkyl Analogues

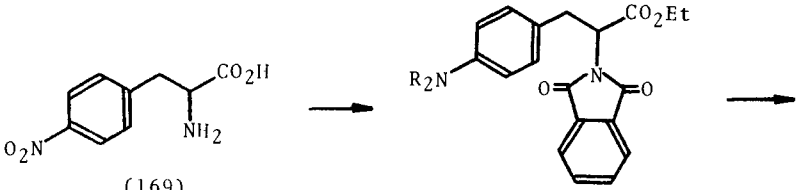
Parkinson's Disease has been fairly convincingly demonstrated to be the manifestation of a deficit of brain dopamine. Administration of this biogenic amine is ineffective in alleviating the symptoms of this disease since the drug fails to cross the blood-brain barrier. Some success has been achieved by administering the amino acid precursor of dopamine: dihydroxyphenylalanine (DOPA). Though this last substance does penetrate the brain, its activity is limited by prior degradation-starting with decarboxylation in the periphery. A compound which would inhibit the enzyme which catalyzes this first step, DOPA decarboxylase, should permit more efficient utilization of DOPA. A compound very closely related structurally to the substrate for the enzyme fulfills this function. *Carbidopa 168* was designed for this purpose. Carbidopa's synthesis begins with a modified Strecker reaction using hydrazine and potassium cyanide on arylacetone *165* to give *166*. This is then hydrolyzed with cold HCl to give carboxamide *167*.



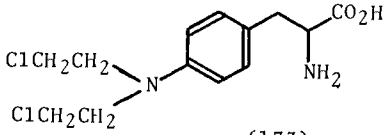
(165) (166) R = CN (168)
(167) R = $CONH_2$

More vigorous hydrolysis with 48% HBr cleaves the amide bond and the arylether group to produce *carbidopa (168)*.[77] There is some evidence that *carbidopa* has some anti-Parkinsonian activity in its own right. If this is confirmed, then its mode of action will be different from that for which the drug was designed and prepared.

Another aminoacid-like drug is the antineoplastic agent *melphalan (173)*. Tumor cells spend less time in resting phases than normal cells so at any given time, they are more likely to be metabolically active than most normal host cells. The rationale behind incorporating an alkylating function in a molecule resembling a primary cellular metabolite was to get a greater safety margin by fooling tumor cells into taking up the toxin preferentially. p-Nitrophenylalanine *(169)* was converted to its phthalimide analogue by heating with phthalic anhydride, and this was converted to its ethyl ester *(170)*. Catalytic reduction produced the aniline *(171)*. Heating in acid with ethylene oxide led to *172*, which was converted to the bischloride with phosphorous oxychloride, and the protecting groups were removed by heating in hydrochloric acid to give *melphalan (173)*.[78]

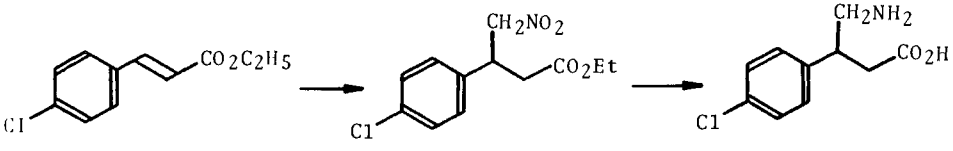


(169) (170) R = O (171) R = H_2 (172) R = CH_2CH_2OH



(173)

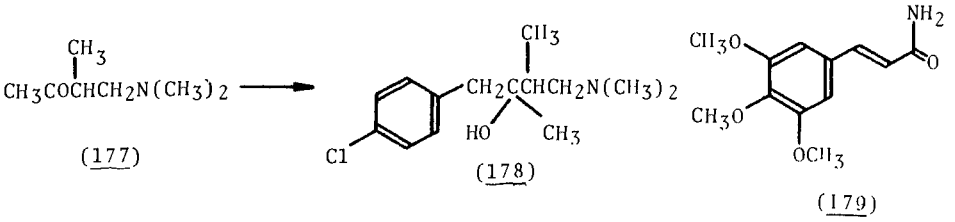
Baclofen (176), a muscle relaxant and hypnotic, is synthesized from ethyl p-chlorocinnamate *(174)* via the Triton B catalyzed Michael addition of nitromethane (to *175)* followed by Raney nickel reduction and saponification. *Baclofen* is formally a GABA (gamma-aminobutyric acid) analogue.[79]



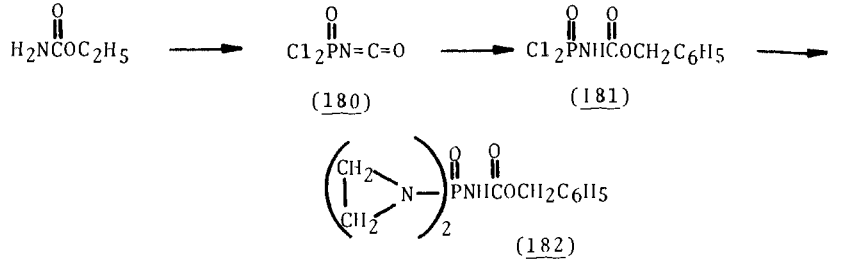
(174) (175) (176)

Reaction of p-chlorobenzylmagnesium chloride with the Mannich product from 2-butanone *(177)* produces the antitussive agent, *clobutinol (178)*.[80] The tranquilizer *cintriamide (179)* is prepared most

conveniently by a simple Shotten-Baumann reaction of the acid chloride.[81] For reasons that are not very clear, the 1,2,3-trimethoxybenzene moiety is frequently associated with CNS activity.

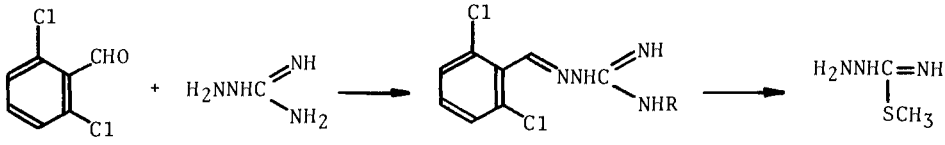


Very reactive nitrogen mustards and aziridine-containing molecules are usually too toxic for general therapeutic use, but find use in neoplastic disease. *Benzodepa (182)* is such an agent. Treatment of ethyl carbamate with phosphorous pentachloride leads to cyanate *180* which readily adds benzyl alcohol to produce carbamate *181*. Displacement of the active



chlorines with ethyleneimine leads to the very reactive *benzodepa (182)*.[82] It was previously known that carbamates and bisaziridininylphosphinyl agents had antitumor properties, so it was natural to combine both moieties in a single molecule to see if synergism would develop.

As noted above, guanido-containing drugs often exhibit antihypertensive activity. Interposition of an additional nitrogen atom is consistent with activity. There is some evidence to suggest that these hydrazines owe their activity to a mechanism different from the guanidines. One such derivative was originally synthesized to be a herbicide.[83] Hydrazone formation



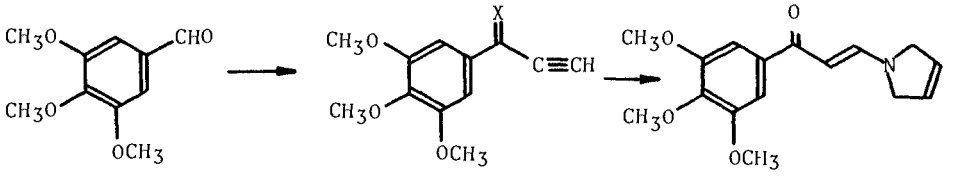
(183)

(184) R = H
(185) R = OH

(186)

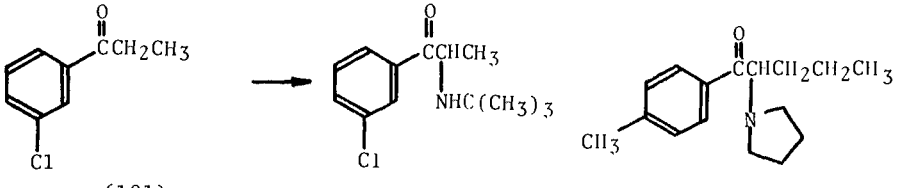
between 2,6-dichlorobenzaldehyde and hydrazinyl guanidine *183* leads efficiently to *guanabenz (184)*. The closely related analogue *guanoxabenz (185)* is prepared in the analogous fashion using the hydrazinyloxyguanidine derivative prepared by reacting thiomethylimine *186* with hydroxylamine and then with 2,6-dichlorobenzaldehyde.[84]

A group of arylalkylketones containing a basic substituent in the side chain shows CNS activities. *Roletamide (190)* is a hypnotic agent. It is prepared from 3,4,5-trimethoxybenzaldehyde *(187)* by addition of sodium acetylide (to give *188*), followed by Jones oxidation of ethynylarylketone *189*. Michael addition of pyrrolidine-3-ene leads to *roletamide (190)*.[85]



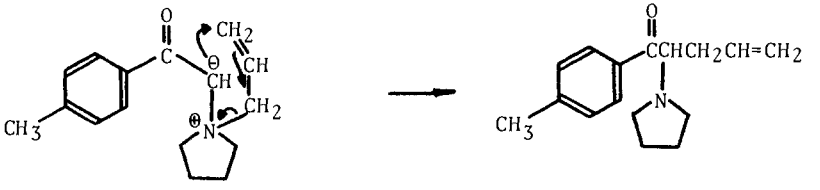
(187) (188) X = H, OH (189) X = O (190)

Reaction of m-chlorobenzonitrile with ethyl Grignard reagent produces ethylarylketone *191*. Bromination in methylene chloride followed by displacement of the α-bromoketone moiety with t-butylamine leads to the antidepressant agent *bupropion (192)*.[86] While the closely related central stimulant *pyrovalerone (193)* can also be made simply by reacting the requisite α-haloaralkylketone with pyrrolidine, a



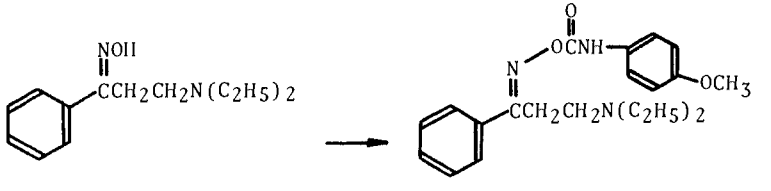
(191) (192) (193)

more interesting synthesis goes through quaternary amine *194* which undergoes a Stevens rearrangement on treatment with base to provide intermediate *195*, which is hydrogenated to *pyrovalerone*.[87] This mechanistic interpretation is supported by studies with unsymmetrical olefins wherein it is seen that the double bond migrates on conversion of *194* to *195*.



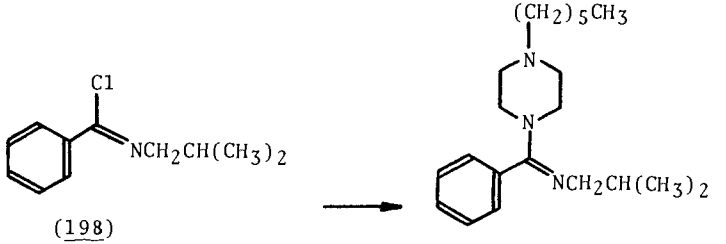
(194) (195)

Conversion of a ketone to a highly substituted imine interestingly leads to a compound which shows analgesic activity, *anidoxime (197)*. Phenyl 2-diethylaminoethyl ketone is converted to its oxime *(196)* in the usual way, and this is converted to *anidoxime* by reaction with p-methoxyphenylisocyanate.[88]



(196) (197)

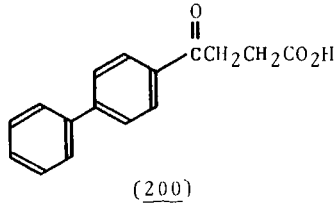
An arylamidine found subsequently to have antiarrythmic activity was actually synthesized in the hope of producing a hypoglycemic agent. Iminochloride *198* is prepared from the corresponding benzamide and the chlorine is displaced with n-amylpiperidine to produce *bucainide (199)*.[89] To posit a similarity to



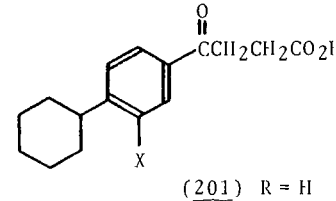
(198) (199)

the well-established antiarrythmic benzamide procainamide and its congeners is perhaps not too fanciful.

While some arylaliphatic acids are established as antiinflammatory agents, it is interesting to note that some arylketones share this activity. *Fenbufen (200)* is prepared simply by a Friedel-Crafts acylation of biphenyl with succinic anhydride.[90] The same reaction using cyclohexylbenzene leads to *201*.



(200)

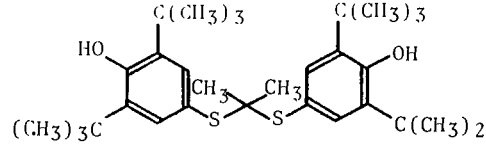


(201) R = H
(202) R = Cl

Chlorination enhances activity and is accomplished by treatment of *201* with chlorine in methylene chloride catalyzed by aluminum chloride. The nonsteroidal antiinflammatory agent *bucloxic acid (202)* results.[91]

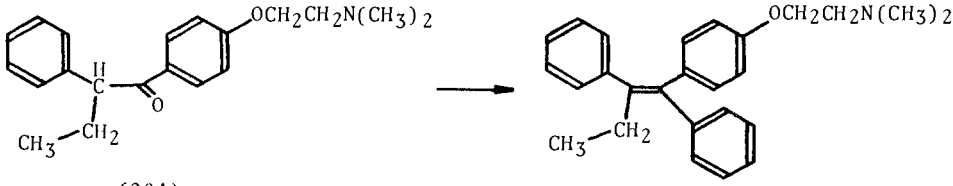
b. Miscellaneous Derivatives

Reaction of 2,6-ditertiarybutyl-4-thiolphenol with acetone leads to the dithioketal *probucol (203)* which has hypolipidemic activity.[92]



(203)

Some tumors are estrogen-dependent and the use of an antiestrogen has therapeutic value. One such antineoplastic agent appears to be patterned after *clomiphene*. Complex aryl ketone *204* is treated with phenyl magnesium chloride and the resulting tertiary



(204) (205)

carbinol is dehydrated. The resulting isomers are separated to give *tamoxifen (205)*. Structural assignment amongst the isomers is performed by pmr measurements.[93]

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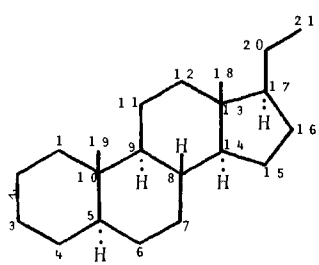
6
Steroids

Early interest in steroid chemistry centered about cholesterol, the bile acids, and the cardiotonic glycosides, but a dramatic expansion took place in the 1930s with the discovery of steroidal sex hormones and the adrenal cortical hormones. As each of the major steroid structures was elucidated, efforts were bent toward developing synthetic methods for their preparation. The impetus for this work was variously to provide amounts of compound sufficient for more detailed pharmacology and clinical application, to prepare orally active analogues, to prepare substances of intrinsic non-hormonal pharmacological activity, and, in some cases, to provide compounds that would antagonize the action of endogenous hormones.

The large number of entries outlined in this chapter might mislead the casual reader into assuming that these represent a correspondingly large number

of drugs in actual clinical use. This is in fact not so: the majority of commercial steroid drugs are to be found in the first volume of this work. The medicinal chemistry and pharmacology of synthetic steroids was a field of intensive concentration for the better part of two decades; numerous compounds were thus produced which showed enough clinical promise to be assigned a generic name, but for one reason or another, most failed to find a place on the drugstore shelf. The fact that so many of these compounds do have generic names indicates that they have interesting activity in various animal assays, and have shown sufficient clinical promise to merit inclusion in this work.

The numbering system and normal stereochemistry of the steroids of interest to this chapter are as follows:

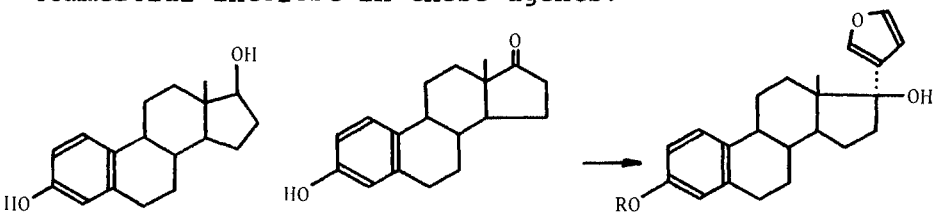


This stereochemical pattern is taken for granted in the following structures with only departures being detailed.

1. ESTRANES

The prototype for the estrane series is the female sex hormone *estradiol* (*1*). Estrogens have important

applications as replacement therapy for hormone-deficient states found in menopausal and post-menopausal women for the treatment of menstrual irregularities, failure of ovarian development, and in treatment of prostatic carcinoma, etc. These compounds also constitute an essential ingredient for the oral contraceptives. It is important to recall that when the synthetic work was done, the Pill was as yet untainted by any shadow and was regarded as an unmitigated boon. There seemed, in fact, to be good reasons for developing new estrogens of greater potency and specificity. It is only fairly recently that there have been serious questions raised about the safety of long-term treatment with exogenous estrogenic compounds, resulting in a lessening commercial interest in these agents.

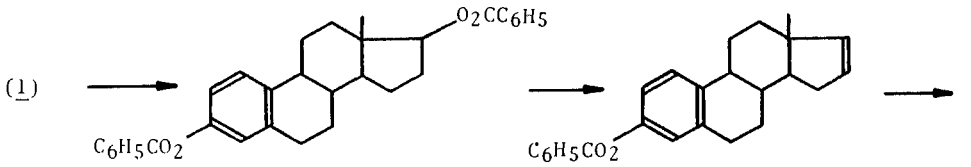


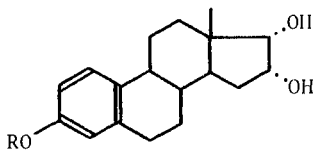
(1) (2) (3) R = H (4) R = $COCH_3$

Reaction of estrone *(2)* with an excess of the lithium reagent from 3-iodofuran gives intermediate diol *3*. The stereochemical assignment follows from the well-known propensity of steroids for attack from the less-hindered backside (α) of the molecule. Acylation of *3* with acetic anhydride then affords the estrogen *estrofurate (4)*.[1]

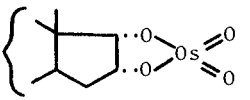
One of the routes for metabolism of the natural estrogens involves oxidation at the 16-position. The resulting compounds (estriols) show paradoxical endocrine activities in animal models. Thus, although these metabolites show estrogenic activity in their own right, they can to some extent block the action of concurrently administered estradiol. The unnatural estriol analogue *epimestrol (8)* shows this kind of activity.

One of the routes to *epimestrol* begins with acylation of estradiol with benzoyl chloride to give the dibenzoate *5*. Pyrolysis of the ester leads to formation of the 16,17-olefin. Hydroxylation by means of osmium tetroxide affords the cis-diol *7* due to the intermediacy of the cyclic osmate ester *(6a)*; attack of the reagents from the α side insures formation of the 16,17α-diol.[2] Saponification is followed by alkylation of the phenolic hydroxyl group with dimethyl sulfate in the presence of base to afford *epimestrol (8)*.[3]



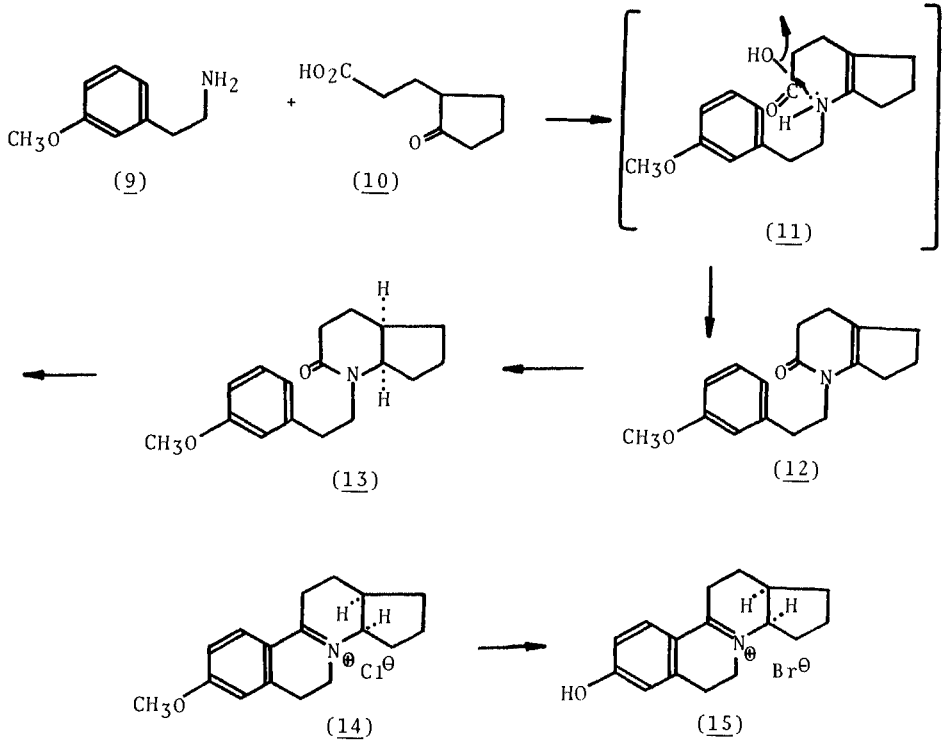


(7) R = H
(8) R = CH_3



(6a)

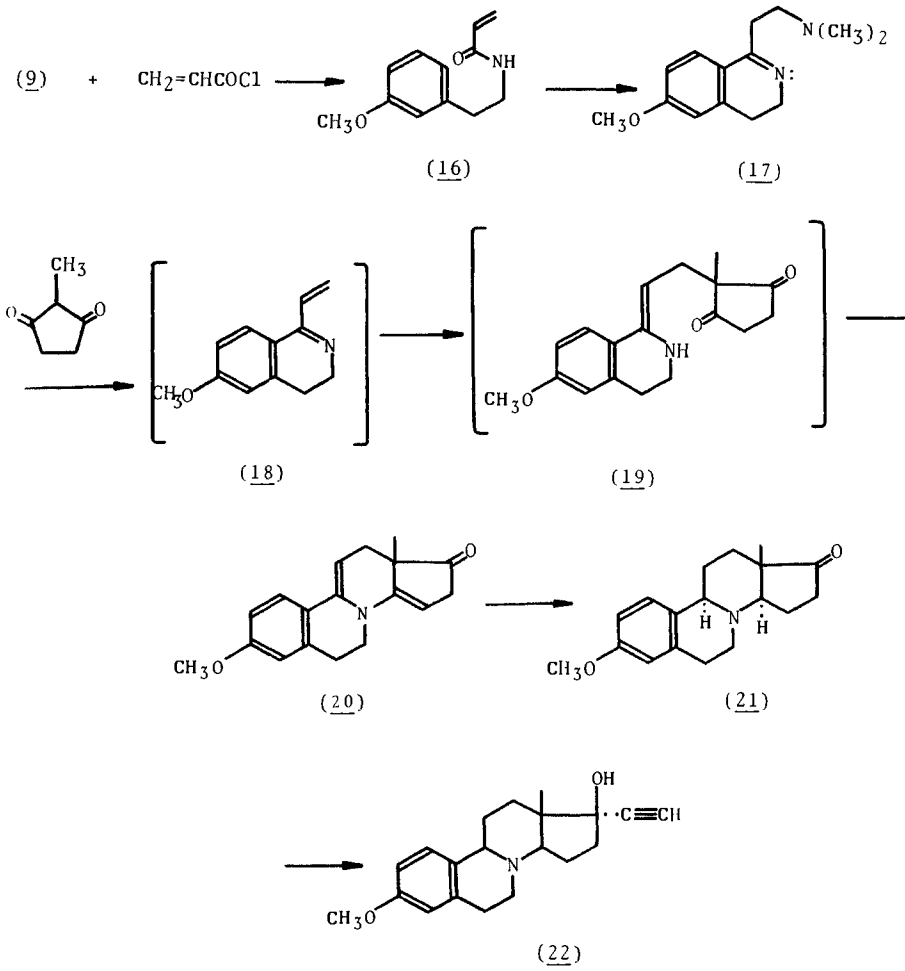
Replacement of a ring carbon by a heteroatom, such as nitrogen, has proven a fruitful modification in many classes of medicinal agents. The resulting analogues often possess the same qualitative activity as the parent compound. Although this strategy has been applied extensively to the steroids, it has not met with overwhelming success. Two cases of substitution by N in which interesting activity was obtained both contain the heteroatom at the 8-position. Such derivatives are most conveniently prepared by total synthesis. For example, condensation of the substituted phenethylamine *9* with 2-cyclopentanonepropionic acid *(10)* affords directly the bicyclic lactam *12*, as a mixture of isomeric eneamides. Though the precise order of the steps is not clear, the reaction can be rationalized as proceeding via enamine *11*; enamide formation will then give the observed products. Catalytic reduction affords the lactam with the expected *cis* ring junction *(13)*. Cyclization by means of phosphorus oxychloride then gives the tetracyclic quaternary salt *(14)*. Treatment with hydrobromic acid serves both to cleave the methyl ether and to replace the counterion by bromide. There is thus obtained *quinodinium bromide (15)*.[4] This compound interestingly exhibits antiarrhythmic rather than hormonal activity, possibly in part because of lack of D-ring functionality required for estrogen receptor activation.



(9) (10) (11) (12) (13) (14) (15)

The scheme used to prepare the direct 8-aza-analogue *21* of estrone bears at least formal similarity to the Torgov-Smith steroid total synthesis sequence. Acylation of the phenethylamine *9* with acryloyl chloride gives amide *16*. Michael addition of dimethylamine followed by Bischler-Napieralski cyclodehydration gives the dihydroisoquinoline, *17*. Reaction of the heterocycle with 2-methylcyclopentane-1,3-dione in the presence of pyridine leads directly to tetracyclic intermediate *20*.[5] The first step in this transformation probably consists in formation of the olefin *18* by elimination of dimethylamine. Michael addition of the anion from the cyclopentane-

dione gives a transient intermediate such as *19*. Reaction of the enamine nitrogen with one of the carbonyl groups leads to the corresponding cyclized dieneamine *20*. Catalytic reduction leads to stereoselective introduction of hydrogen at both C-9 and

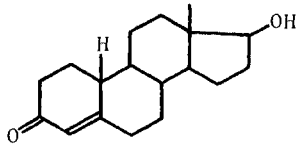


C-14 from the α face. It should be noted that except for the methyl group at C-13, *20* is quite flat; it is not unreasonable to assume that adsorption to the catalyst will take place at the face opposite that substituent, thus leading to the observed stereochemistry. The product is, of course, racemic. Reaction of *20* with lithium acetylide completes the synthesis of *estrazinol (22)*.[6] It is of note that, in contrast to *15*, this compound shows activity as an estrogen.

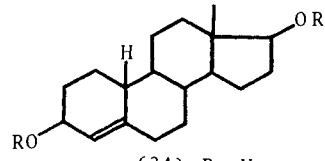
Reduction of the aromatic A ring of the estratrienes and appropriate substitution at the 17--position leads to compounds that show either androgenic or progestational activity. These 19-nor steroids tend to have much better oral activity than their 19-methylated counterparts. Orally active androgens have found some use both in replacement therapy for androgen deficiency and as agents which will reverse protein loss in various pathological wasting diseases (as anabolic agents). Some controversial use is also found in increasing the body mass of professional athletes. By far the largest clinical application for the orally active progestins is as a component part of oral contraceptives.

Reduction of 19-nortestosterone *(23)*[7] with sodium borohydride leads to a mixture of isomers consisting largely of the 3β-alcohol *(24)*; the lack of stereospecificity can be traced back to the relative remoteness of that 3-position from chiral centers which could direct the incoming reagent. Acylation of diol *24* with acetic anhydride in the presence of

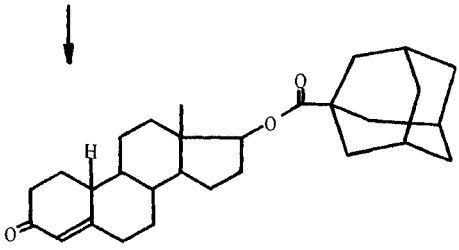
sodium acetate affords the anabolic agent *bolandiol diacetate (25).*[8]



(23)



(24) R = H
(25) R = CH_3CO

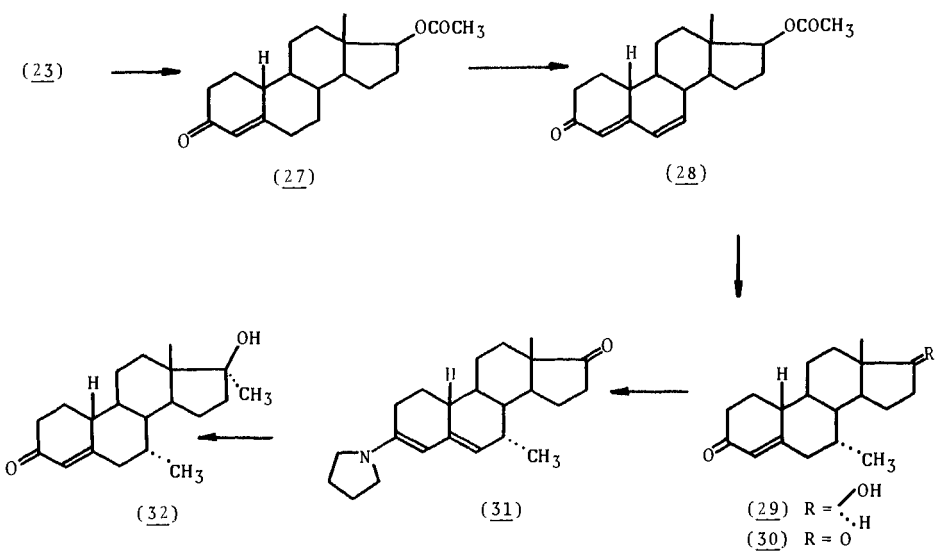


(26)

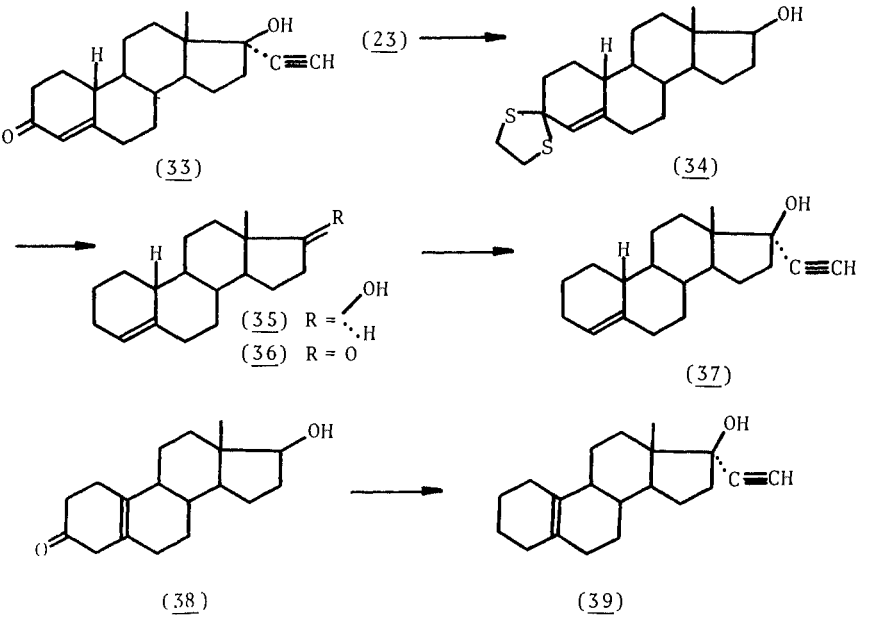
A fairly common strategy for converting a drug to an agent which is excreted more slowly and may be longer acting pharmacologically consists of the preparation of a very lipophilic derivative. This is then administered by subcutaneous or intramuscular injection in an oil solution. The drug or its hydrolysis product then slowly leaches out of that oily depot to provide long-lasting levels in the blood. Reaction of 19-nortestosterone with adamantoyl chloride affords the longacting anabolic agent *bolmantalate (26).*[9] There is some evidence to suggest that this ester is not a prodrug, but has hormonal activity in its own right.

The presence of a 7α-methyl group has been found to potentiate anabolic activity. Acetylation of 19-nortestosterone affords the corresponding 17-acetate

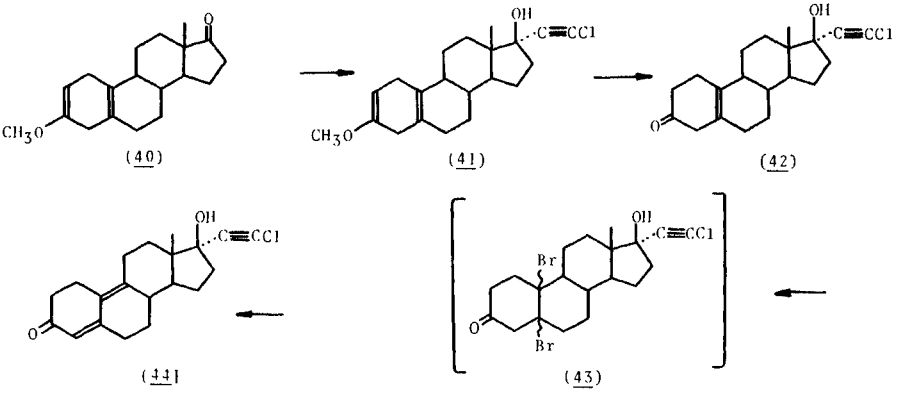
(27). Treatment of this compound with chloranil results in dehydrogenation at C-6,7 and thus formation of the 4,6-diene-3-one moiety. Reaction of 28 with methyl Grignard reagent in the presence of cuprous bromide leads to conjugate (1,6) addition from the bottom face of the molecule with concomitant loss of the ester function from C-17 to give the 7α-methyl derivative *(29)*. Oxidation of the alcohol at C-17 then affords diketone *30*. Condensation of that product with pyrrolidine leads, because of the highly hindered nature of the ketone at C-17, to selective formation of the 3-enamine *(31)*. Addition of methylmagnesium bromide followed by hydrolysis of the enamine function gives *mibolerone (32)*.[10] This last has, interestingly, recently been introduced as a canine oral contraceptive.



The formal replacement of the methyl group at C-17 by ethynyl leads, in the 19-*nor* series, from compounds which show androgenic activity to agents active as progestins. The prototype for this series, and in fact the compound used most widely in oral contraceptives, is *norethindrone (33)*. It is of note that the analogue missing the ketone at C-3 retains this activity. Condensation of ethane dithiol with 19-*nor*-testosterone affords the corresponding thioketal *(34)*. Desulfurization with sodium in liquid ammonia affords *35*. Oxidation affords the 17-ketone; reaction with lithium acetylide gives the progestin *cingestol (37)*.[11] A similar scheme on the isomeric deconjugated ketone *38* (obtained by hydrolyzing the enol ether product from the Birch reduction of estradiol methyl ether under mild conditions) gives *tigestol (39)*.[12]

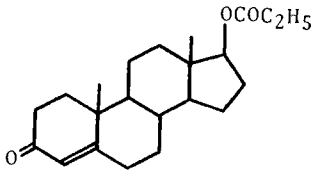


An unusual variation on this theme involves a compound containing both extended conjugation involving the bond connecting rings AC and a haloacetylene moiety. Reaction of ketone *40*[13] with the anion obtained by treatment of *cis* 1,2-dichloroethylene with methyl lithium affords chloroacetylene *41*. This reagent can be generated either by formation of the organometallic agent by abstraction of a proton followed by loss of hydrogen chloride from the adduct or, more likely, by elimination of HCl from the ethylene followed by formation of the lithium reagent from the resulting acetylene. Hydrolysis of the enol ether under mild conditions (acetic acid) affords the unconjugated ketone *42*. Treatment of that compound in pyridine with bromine leads to the potent oral progestin *ethynerone (44)*.[14] This last reaction can be rationalized by assuming that the first step consists of addition of bromine to the double bond at C-5,10 (*43*); double dehydrohalogenation will give the observed product. It is interesting to observe that *44* does not enolize to give an aromatic A ring.

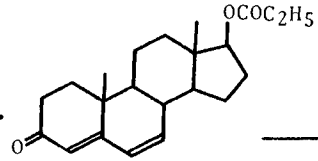


(40) (41) (42) (44) (43)

The potentiation observed in the 19-*nor* androgens by inclusion of a C-7 methyl group is observed even in the presence of the 17-ethynyl function. Dehydrogenation of testosterone propionate (*45*) by means of chloranil gives the corresponding 4,6-diene (*46*). Conjugate addition of methyl magnesium bromide leads to the 7α-methyl derivative *47* along with the 7β-epimer. Treatment of the major product with DDQ leads in this case to the cross-conjugated 1,4-diene. It is likely that the direction of this second dehydrogenation is mandated by the presence of the methyl group at C-7; this group may hinder the approach of reagent to the center which would lead to the alternate diene. The intermediate is then saponified and alcohol at C-17 oxidized (*48*). Elimination of the angular methyl group at C-19 with consequent aromatization is achieved by treatment of the diene with lithium in the presence of diphenyl;[15] there is thus obtained 7α-methyl estrone (*49*).[16] Methylation of the phenolic hydroxyl group followed by reduction of the 17-ketone gives *50*. Birch reduction affords the corresponding 2,5(10)-diene (*51*). The hydroxyl at 17 is then oxidized by means of cyclohexanone and aluminum isopropoxide (Oppenauer oxidation) to give back the 17-ketone (*52*). Addition of lithium acetylide proceeds to give the 17α-ethynyl derivative (*53*). Hydrolysis of the enol ether under mild conditions leads to the unconjugated ketone. There is thus obtained the anabolic agent *tibolone* (*54*).[17]



(45)



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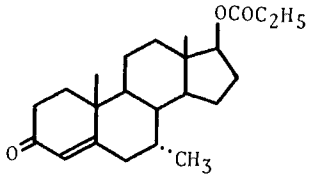

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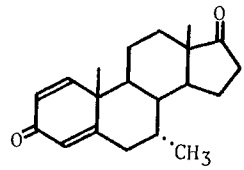

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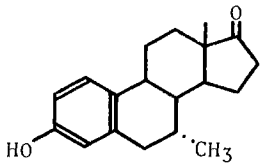

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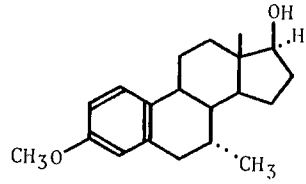

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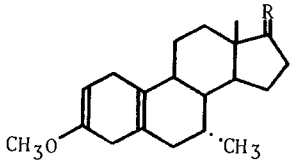
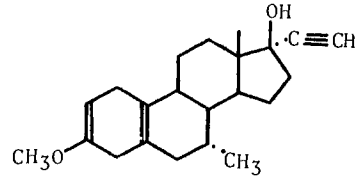


(51) R = OH, H

(52) R = O



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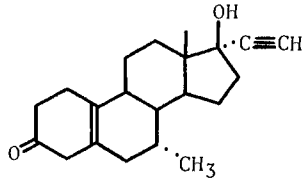
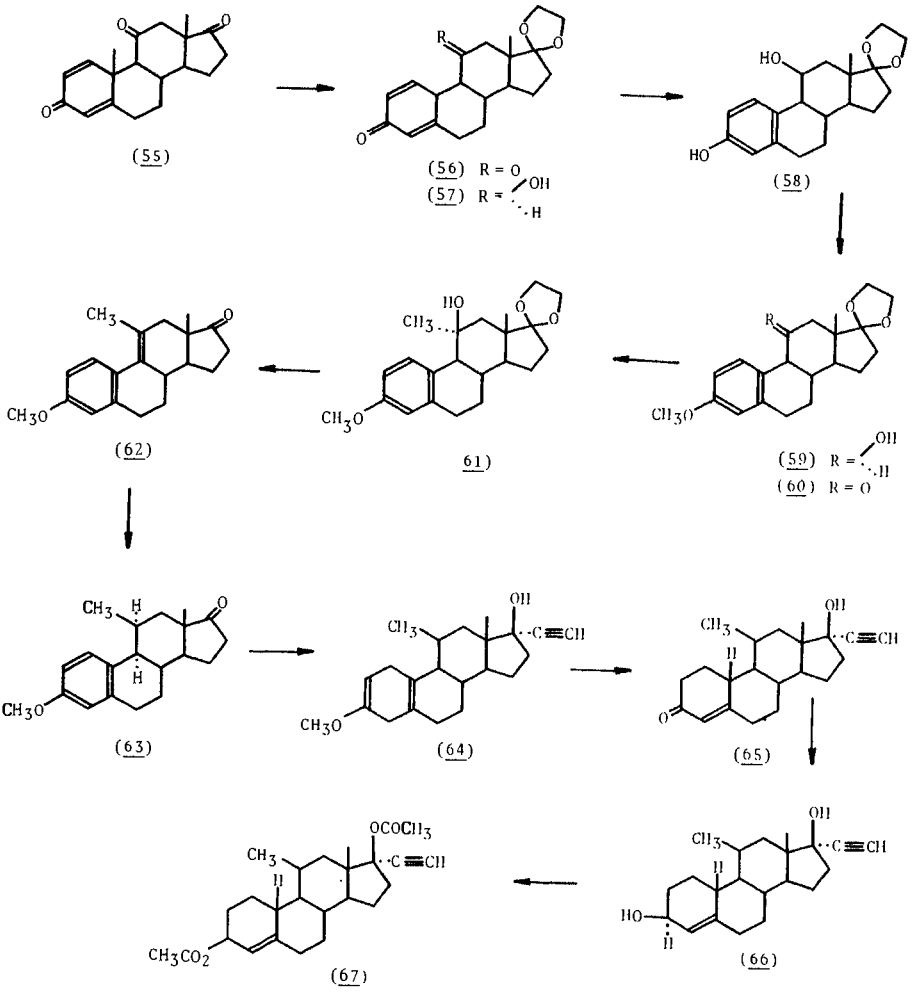
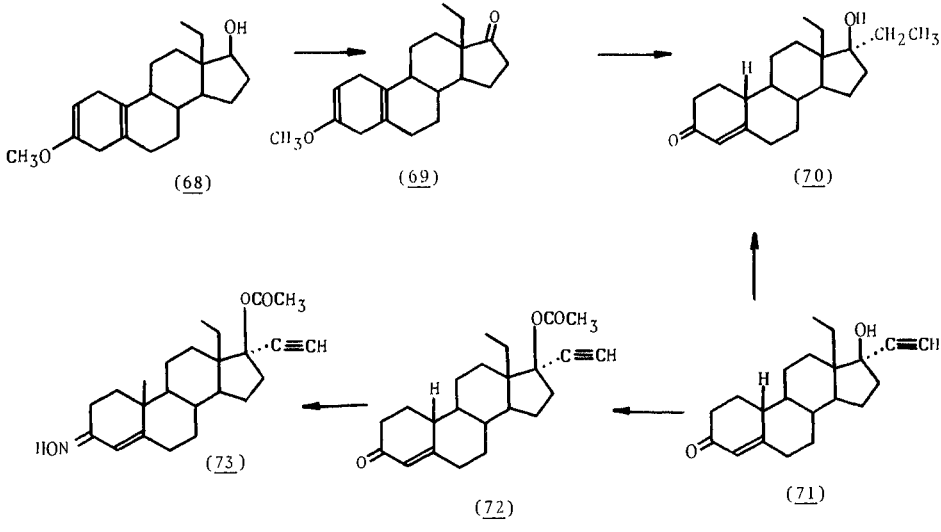


(54)

Inclusion of a methyl group at the difficultly accessible 11-position also proves compatible with oral progestational activity in the 19-nor series. Preparation of an agent incorporating this feature starts with the 1,4-diene *(55)*, corresponding to adrenosterone.[18] Due to the sterically hindered nature of the carbonyl at C-11 and the low reactivity of that at C-3, ketalization proceeds selectively at C-17 *(56)*; reduction of the 11-keto group by means of lithium tri-t-butoxyaluminum hydride gives intermediate *57*. Aromatization by means of the lithium radical anion from diphenyl gives intermediate *58*.[19] Methylation of the phenol *(59)* followed by oxidation of the alcoholic hydroxyl at C-11 affords *60*. Addition of methyl Grignard reagent to that carbonyl group serves to introduce the 11-methyl group *(61)*. It is of note that the corresponding reaction in the 19-methylated (androstrane) series proceeds with extreme reluctance. Deketalization gives the corresponding 17-ketone and acid catalyzed dehydration, followed by catalytic reduction of the olefin *(62)*, gives the intermediate containing the 11β-methyl group *(63)*. That molecule is then subjected to the standard carbonyl reduction, Birch reaction, oxidation, ethynylation and, finally, hydrolysis sequence (see *50* to *53*). Hydrolysis of the enol ether under more strenuous conditions than was employed with *53* gives the conjugated ketone *65*. The carbonyl group is then reduced to afford the corresponding 3β-alcohol *(66)*. Exhaustive acetylation affords the potent oral progestin *methynodiol diacetate (67)*.


(55)
(56) R = O
(57) R = OH, H
(58)
(59) R = OH, H
(60) R = O
61)
(62)
(63)
(64)
(65)
(66)
(67)

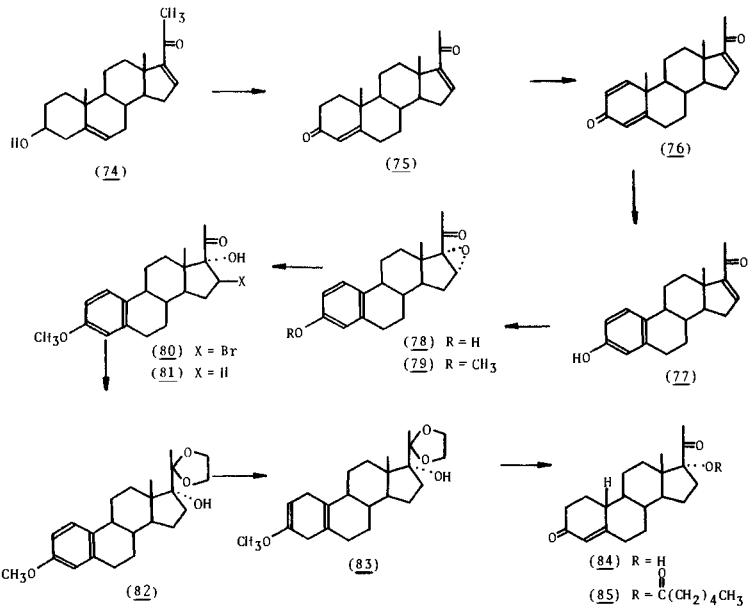
Elaboration of a commercially viable route for total synthesis of 19-*nor* steroids led to the introduction of the totally synthetic product *norgestrel (71)* as the progestational component of an oral contraceptive. As was observed in the "natural" 19-*nor*-compounds, reduction of the 17-ethynyl group to 17-ethyl affords compounds with androgenic/anabolic activity. Oppenauer oxidation of the total synthesis intermediate *68*[22] leads to the corresponding ketone. Reaction with ethylmagnesium bromide gives the expected condensation product. It is of note that reaction is much slower than in the 13-methyl series. Hydrolysis with strong acid affords *norbolethone (70)*.[21] The same compound can be obtained by selective reduction of the ethynyl moiety of *norgestrel (71)*.



In much the same vein, acetylation of optically active *d-norgestrel* by means of acetic anhydride and tosic acid gives the 17-acetate *(72)*. Reaction with hydroxylamine hydrochloride in pyridine affords the orally active progestin *dexnorgestrel acetime (73)*.[23]

The prevalence of 17-ethynyl carbinols among the orally active 19-nor progestins can lead to the impression that this is a necessary group for activity. The good potency shown by a compound that possesses the 17-hydroxy 17-acetyl moiety more characteristic of the 19-methyl progestins indicates that the structure-activity relationship is not quite that narrow. One such compound, *gestonorone caproate (85)* is prepared by oxidation of 16-hydropregnenolone *(74)*[24] to afford the conjugated ketone *75*. This is then converted to the aromatic A-ring phenol *77* by the standard dehydrogenation-aromatization scheme (see *47* to *49*). Epoxidation of the double bond at C-16 by alkaline peroxide gives the 16α,17α-oxide *78*. Methylation of the phenol affords the corresponding ether *(79)*. *Trans-diaxial opening of the oxide by means of hydrogen bromide gives the bromohydrin 80;* halogen is then removed reductively by means of zinc in acetic acid *(81)*. The carbonyl group at C-20 is next protected against the reductive conditions of the subsequent step by conversion to its ethylene ketal *(82)*. Birch reduction leads in the usual way to the enol ether *(83)*. Treatment with strong acid serves to remove both the 20-ketal and the enol ether at C-3, leading to conjugated ketone *84*. Treatment of this last intermediate with caproic anhydride and tosic acid affords

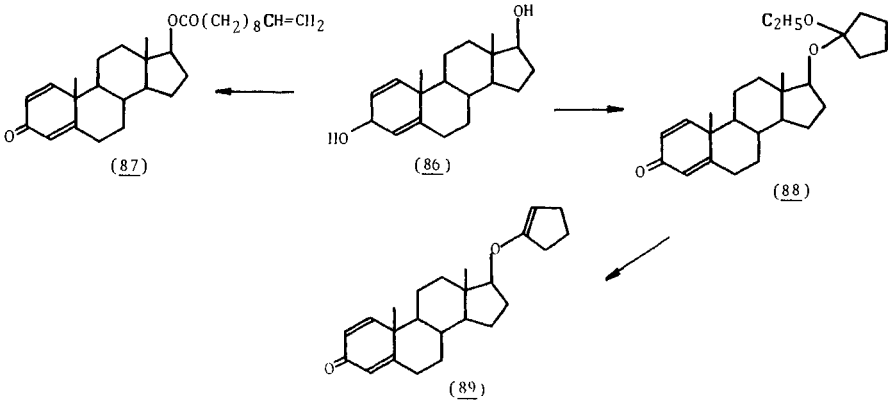
gestonorone caproate (85).[25] The caproate function not only contributes lipophilicity but, presumably, Newman-type hinderence to saponification.



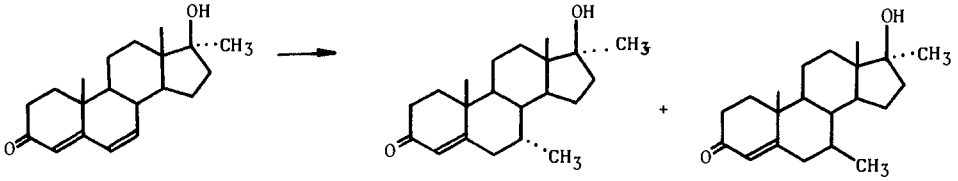
2. ANDROSTANES

Additional unsaturation at C-1,2 is well known to potentiate the action of both androgens and corticoids. The former tend, however, to show poor oral activity in the absence of an alkyl group at the 17-position. Thus, they tend to be used mainly as injectable agents. As mentioned above, esterification with a fatty chain leads to agents with long duration of action. Thus, esterification of *86*[26] with the acid chloride from undec-10-enoic acid gives the injectable anabolic agent *boldenone 10-undecylenate (87).*[27] An

enol ether, interestingly, can serve a similar pharmacological purpose. Thus, acetal interchange of *86* with the diethyl acetal from cyclopentanone gives *88;* pyrolysis leads to elimination of ethanol and formation of *quinbolone (89).*[28]

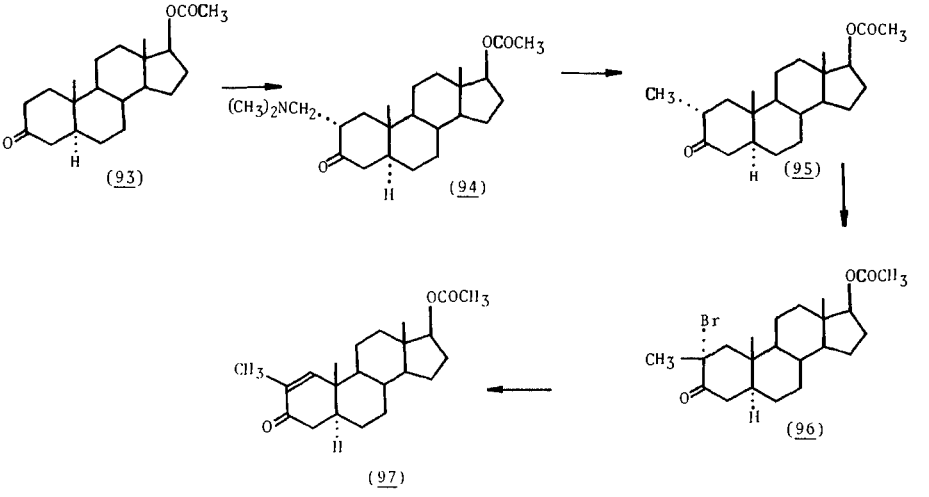


Neoplasms involving gonadal tissues are often dependent on sex hormones for growth. Depriving the cancerous growth of hormonal stimulation frequently slows its development. The past few years have seen considerable application of hormone antagonists as antineoplastic agents for treatment of such hormone-dependent cancers. *Bolasterone (91)* is known to be a potent anabolic/androgenic agent; its 7β-isomer, *calusterone*, has found some use in the treatment of cancer. As originally prepared, conjugate addition of methylmagnesium bromide to diene *90* affords a mixture of *91 and 92* with the former predominating. *Calusterone (92)* was separated by chromatography and fractional crystallization.[29]

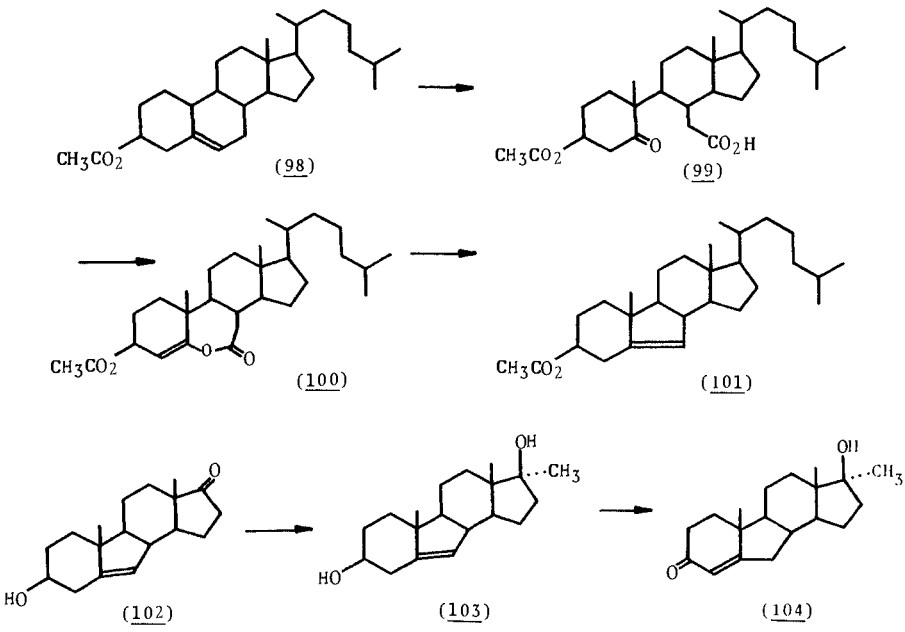


(90) (91) (92)

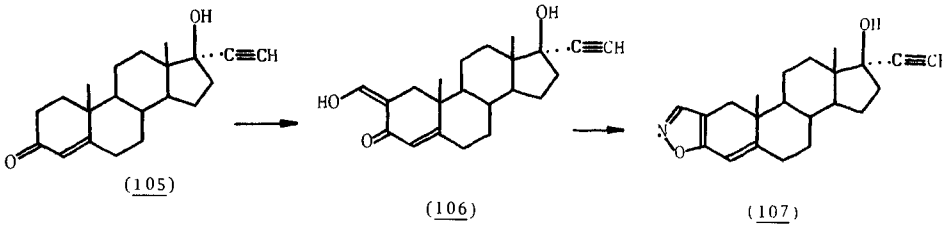
Formal isomerization of the double bond of testosterone to the 1-position and methylation at the 2-position provides yet another anabolic/androgenic agent. Mannich condensation of the fully saturated androstane derivative *93* with formaldehyde and dimethylamine gives aminoketone *94*. A/B-trans steroids normally enolize preferentially toward the 2-position, explaining the regiospecificity of this reaction. Catalytic reduction at elevated temperature affords the 2α-methyl isomer *95*. It is not at all unlikely that the reaction proceeds via the 2-methylene intermediate. The observed stereochemistry is no doubt attributable to the fact that the product represents the more stable equatorial isomer. The initial product would be expected to be the β-isomer but this would experience a severe 1,3-diaxial non-bonded interaction and epimerize via the enol. Bromination of the ketone procéeds largely at the tertiary carbon adjacent to the carbonyl *(96)*. Dehydrohalogenation by means of lithium carbonate in DMF affords *stenbolone acetate (97)*.[30] This product is readily separable from a number of by-products by the fact that it forms a water-soluble bisulfite adduct.



Contraction of the B-ring of the orally active androgen 17-methyltestosterone, interestingly, leads to a compound with antiandrogenic activity. The general method for preparation of such ring contracted analogues was first developed using cholesterol acetate *(98)* as a model. Oxidation by means of chromium trioxide affords keto acid *99* as the principal product; this is then converted to the enol lactone *100* by means of acetic anhydride. Pyrolysis of that enol lactone at 200°C gives the ring contracted condensation product *101*.[31] The analogous 17-ketone *102* is used as starting material for the antiandrogen. Reaction with an excess of methylmagnesium bromide affords the 17-methylcarbinol *103*; Oppenauer oxidation affords *benorterone (104)*.[32]

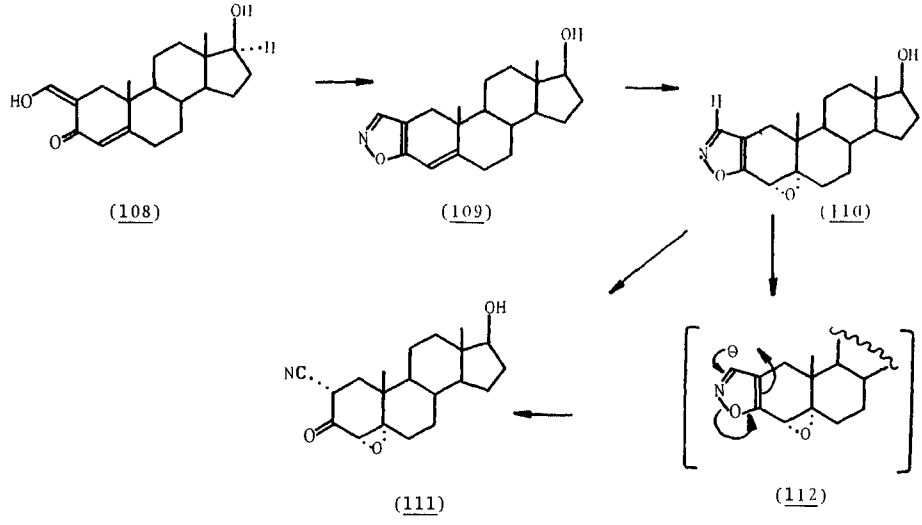


Fusion of a heterocyclic ring onto the A-ring of ethynyltestosterone leads to a compound with hormone antagonistic activity. Such agents find some use in those cases where either the given hormone is present in excessive amounts by malfunction of the particular endocrine gland or where it is desirable to suppress hormonal stimulation of some end organ. Condensation of 17-ethynyl testosterone *(105)* with ethyl formate in the presence of sodium methoxide gives the corresponding 2-hydroxymethylene derivative *(106)*. Reaction of that intermediate with hydroxylamine leads to the pituitary suppressant agent *danazol (107)*.[33]



(105) (106) (107)

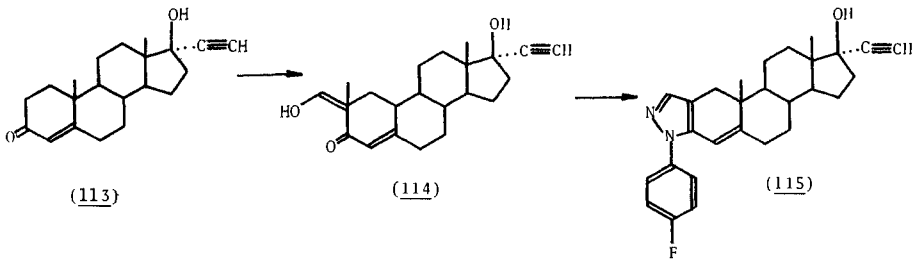
A somewhat related sequence leads to *trilostane (111)*, a compound that inhibits the adrenal gland; more specifically the agent blocks some of the metabolic responses elicited by the adrenal hormone ACTH in experimental animals. Reaction of the hydroxymethylene derivative *108*, obtained from testosterone, with hydroxylamine gives the corresponding isoxazole *(109)*. Oxidation of the C-4,5 double bond by means



(108) (109) (110) (111) (112)

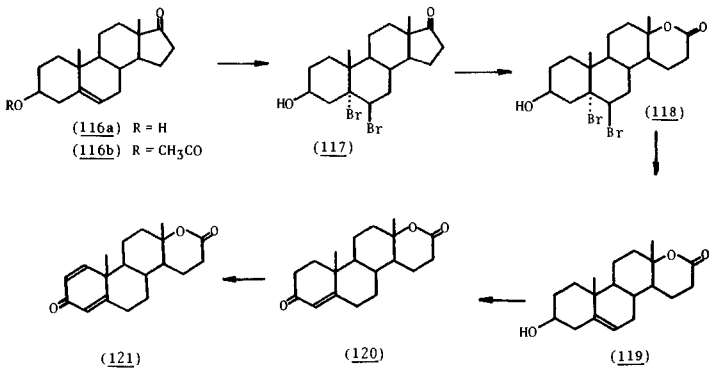
of mCPBA proceeds from the less hindered side to give the α-epoxide. Treatment of the intermediate *110* with sodium methoxide leads to scission of the heterocycle and formation of the corresponding cyanoketone *111*. It is of interest that the epoxide is apparently inert to these conditions; the nitrile is of course readily epimerized, and thus assumes the more stable α (equatorial) conformation. There is thus obtained *trilostane*.[34] The ring opening can be rationalized by assuming first formation of the anion *112*; electrocyclic rearrangement as shown gives the enolate anion of *111*.

Fusion of a heterocyclic ring onto the A-ring of a molecule which shows mainly progestational activity leads to an antiinflammatory agent; this finding does not seem to have been followed up to any extent. Condensation of 17-ethynyl testosterone *(113)* with ethyl formate in the presence of base gives the corresponding 2-hydroxymethyl derivative *(114)*. Reaction of that with p-fluorophenylhydrazine affords the antiinflammatory pyrazolone *nivazol (115)*.[35]



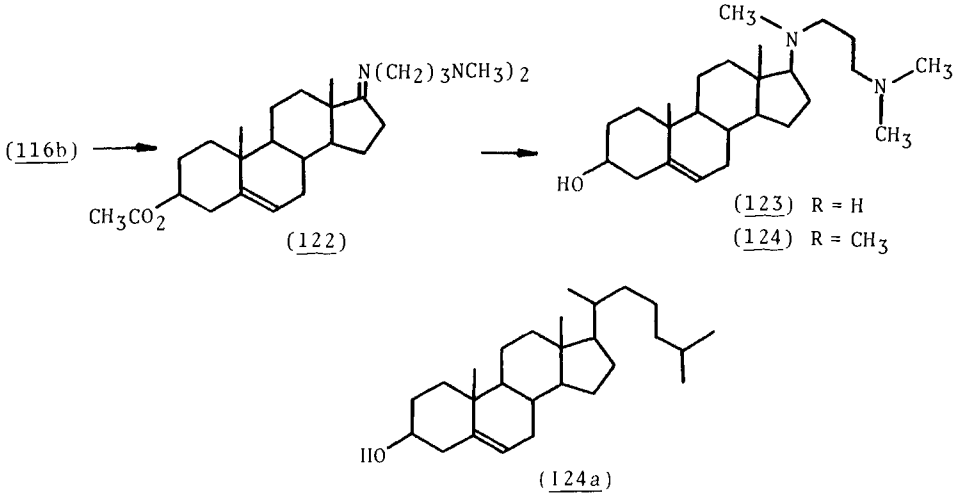
(113) (114) (115)

The antineoplastic agent *testolactone (121)* appears to be obtained commercially by microbiological transformation of either testosterone or progesterone. The compound can be obtained synthetically, albeit in low yield, starting from dehydroepiandrosterone *(116a)*. Addition of bromine serves to protect the double bond as the dibromide *(117)*. Oxidation with peracetic acid gives the Baeyer-Villiger product *118*. The unsaturation at 5,6 is then restored by treatment of the dibromide with sodium iodide *(119)*. This is oxidized to the conjugated ketone *120* under Oppenauer conditions. (A real source of confusion exists in the fact that *120* bears the trivial chemical name testolactone while the same generic name is used to denote *121*.) Previous work, particularly on cortical steroids, had shown that inclusion of additional unsaturation in the A ring at 1,2 leads to a significant increase in potency. Selenium dioxide is a fairly specific reagent for achieving this transformation, and such treatment of *120* affords *testolactone (121)*.[36]



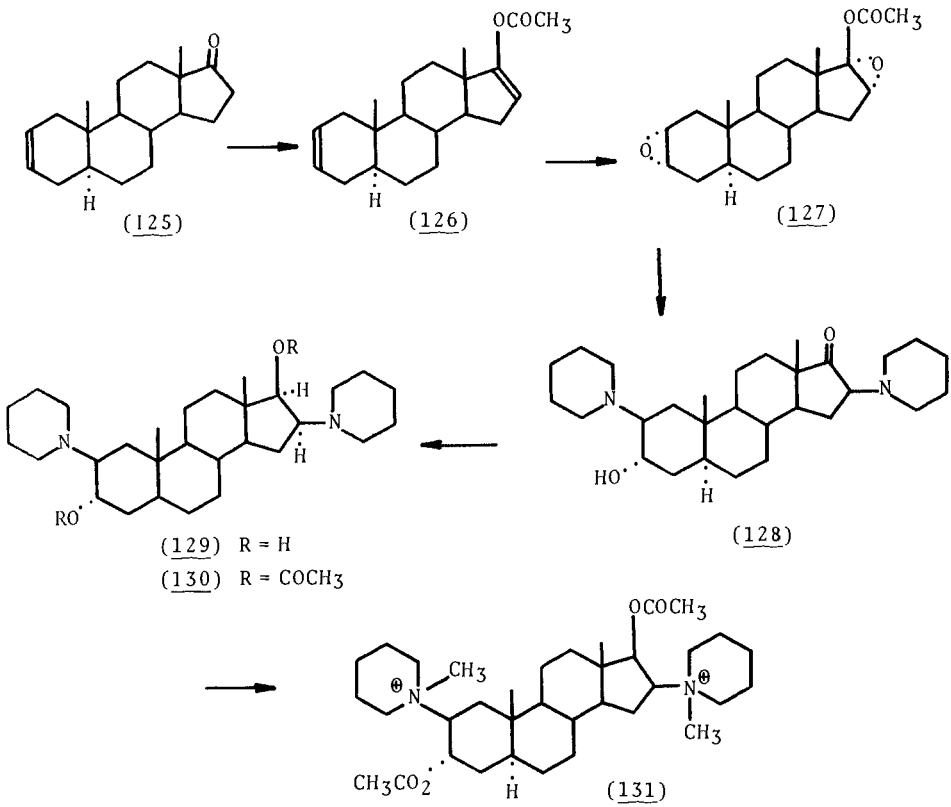
It has been known for many years that elevated levels of serum cholesterol are associated with atherosclerosis, although the cause-effect relationship remains unproven. A rather straightforward therapeutic regimen intended for prevention or arrest of the progress of this disease involves lowering levels of serum cholesterol in the high-risk population. Since a good part of the physiological cholesterol load is provided by endogenous synthesis, agents that inhibit this process should lower cholesterol levels in the serum as an adjunct to dietary precautions, although a compensatory increase in endogenous synthesis can combat this artifice. One approach to this therapeutic goal consists in providing false substrates for enzyme systems involved in cholesterol biosynthesis. Substitution of heteroatoms for carbon has served to provide such enzyme antagonists in other fields. The strategy in the case at hand calls for a cholesterol analogue containing nitrogen in the side chain. Shiff base formation between dehydroepiandrosterone acetate *(116b)* and 3-dimethylaminopropylamine affords imine *122*. Reduction (lithium aluminum hydride) proceeds to give predominantly the β-amine *(123)*. Further methylation by means of formic acid and formaldehyde (Eschweiler-Clark reaction) leads to *azacosterol (124)*.[37] Though the compound does lower serum cholesterol in experimental animals it is not used clinically in man. The drug, not unexpectedly, severely limits cholesterol availability in avian species. Since egg formation in birds is dependent on an abundant supply of cholesterol, *azacosterol* is, in

fact, an effective avian chemosterilant. A glance at the formula of cholesterol *(124a)* clearly shows the bioisosterism used in the design of *124*.



The crude toxin *curare*, used by South American Indians to lend authority to their blow gun darts, proved, because of its neuromuscular blocking activity, to be of interest to surgeons. Structural analysis of the mixture led to the erroneous conclusion that the active agents possessed a pair of quaternary nitrogen atoms with definite spacing because of the rigid molecular framework. Following the rationale based on this belief led to a number of curarelike synthetic agents in which the spacing is provided by aliphatic chains; it is readily apparent that the rigid network provided by a steroid would provide more accurate location of the charged centers. The synthesis of one of these starts with conversion of *125* (probably

obtained by dehydration of the corresponding 3-hydroxy compound) to the enol acetate *(126)*. Epoxidation proceeds as expected from the α side to give the bis epoxide *(127)*. Both regio- and stereochemistry of the subsequent reaction with piperidine are dictated by the diaxial opening propensity of oxiranes; the hemiacetal-like function left at C-17 spontaneously reverts to the ketone to give *128*. Reduction of that ketone proceeds in the usual manner to afford *129*. Acetylation of the hydroxyl groups *(130)*, followed by quaterization with methyl bromide gives *pancuronium bromide (131)*.[38]



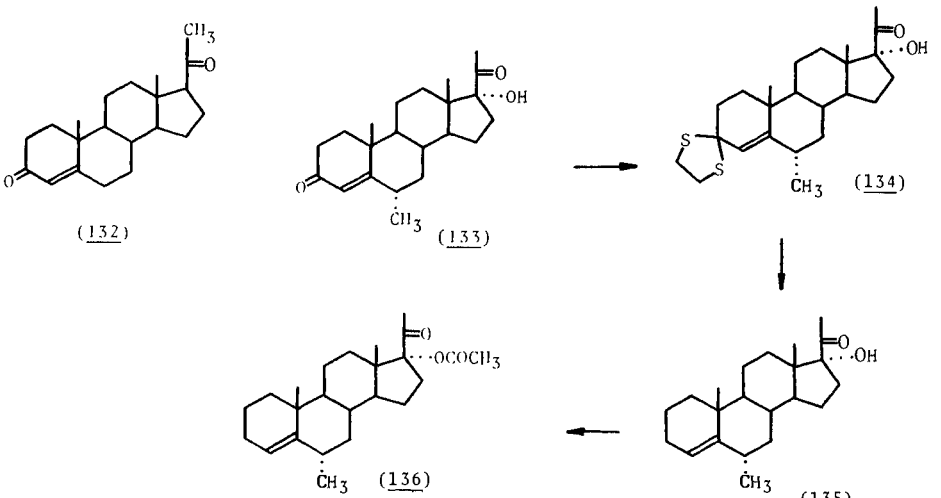
3. PREGNANES

a. 11-Desoxy Derivatives

Progesterone, *132*, is, of course, the prototype pregnane. This natural steroid plays an important role in females in the intricate endocrine chain of events involved in reproduction. In essence, progesterone is one of the steroid hormones directly involved in the timing of ovulation. Very high levels of progesterone are present in early pregnancy, elaborated biosynthetically by a structure on the ovary (the corpus luteum), and this inhibits ovulation in the gravid female to prevent a superimposed pregnancy. It is this observation that gave initial direction to the development of the oral contraceptives. As with the estrogens, much of the work described below was carried out before a shadow fell on this class of drugs. In addition, there was some evidence from human trials that a potent progestin could provide contraceptive activity in the absence of added estrogen. Although the efficacy was somewhat lower than for the combination Pill, the treatment avoided the use of the suspect estrogenic component. The finding that many potent progestins cause tumerous lesions in the beagle on long-term administration effectively laid this class of drugs to rest as far as large-scale usage is concerned. It can be argued quite reasonably that this effect is restricted to the beagle, but expert opinion is divided and use has subsided.

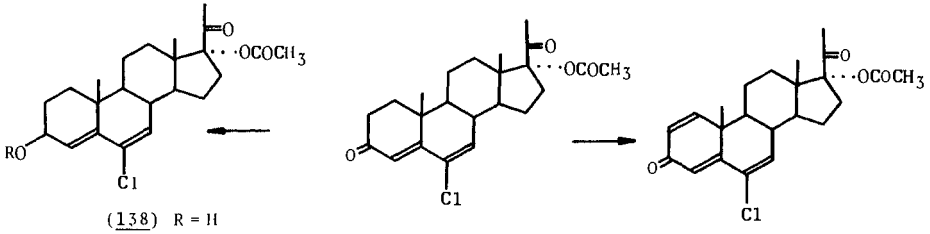
As described earlier, oral activity can be achieved in the progestins by either removing the 19-

methyl group or inclusion of an acyloxy group at the 17-position. It is of interest that removal of the oxygen function at C-3 is compatible with biological activity in both series (see *37*, *39*, this Chapter). Thus, the 3-desoxy analogue of *medroxyprogesterone acetate* shows very similar activity to the parent substance. Reaction of medroxyprogesterone *(133)*[39] with ethanedithiol gives the corresponding thioketal *(134)*. Desulfurization by means of Raney nickel leads to the 3-desoxy steroid *(135)*. Treatment with acetic acid in the presence of trifluoroacetic anhydride completes the synthesis of *angesterone acetate (136)*.[40]



Chlormadinone acetate (137),[41] is an extremely potent orally active progestin. Treatment of this compound with basic sodium borohydride serves to reduce the ketone at C-3 to the corresponding 3-carbinol (*138*; the regioselectivity is presumably due

to the more hindered environment about the 20-ketone). Acetylation affords *clogestone (139)*.[42] Further dehydrogenation of the A ring of *chlormadinone* by means of selenium dioxide affords *delmadinone acetate (140)*.[43]



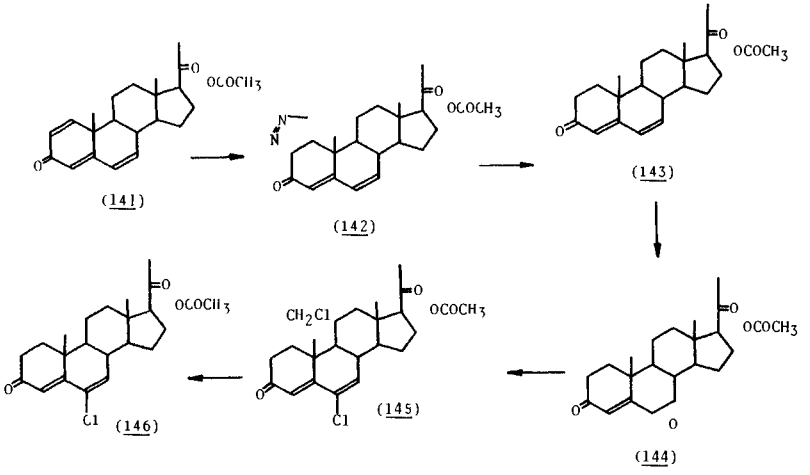
(138) R = H
(139) R = $COCH_3$

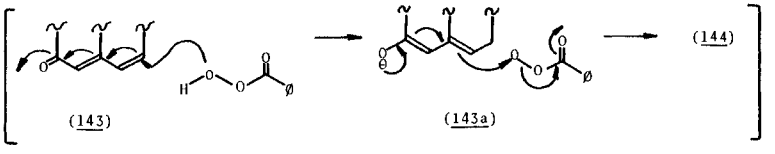
(137)

(140)

Fusion of a cyclopropyl ring onto the 1,2-position of *chlormadinone* gives a compound which, interestingly, shows mainly antiandrogenic activity. Preparation of *cyproterone acetate (146)* starts by reaction of triene *141* (obtainable from 17-acetoxy-progesterone[44] by sequential dehydrogenations at C-5,6 and C-1,2) with diazomethane affords the pyrazoline *(142)*. Pyrolysis leads to the cyclopropyl derivative *(143)* by loss of nitrogen.[45] Oxidation by means of perbenzoic acid gives the C-6,7 epoxide *(144)*. Regioselectivity in this reaction is probably due to conjugate addition of peracid from the α side followed by electron backflow and ejection of benzoate as shown in *143a*. Reaction of that intermediate with hydrogen chloride serves to open both the oxirane and cyclopropyl rings. The intermediate chlorohydrin is not observed as it undergoes spontaneous dehydration

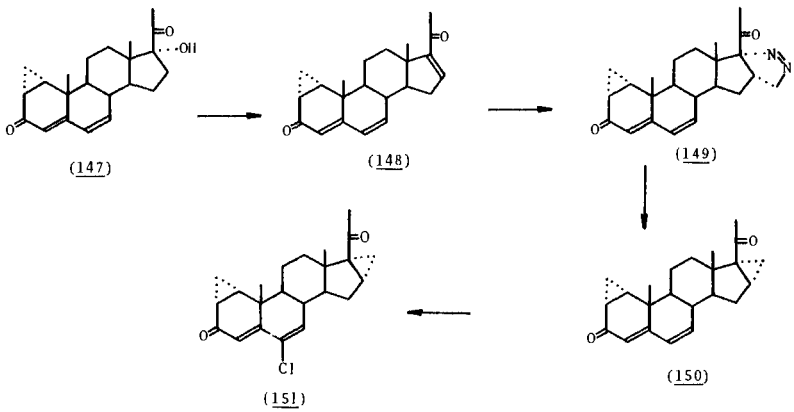
to *145*. Treatment of the chloromethyl derivative with collidine serves to reform the cyclopropyl ring; the reaction very probably goes by internal alkylation of the anion generated by the base at the 2-position. There is thus obtained *cyproterone acetate (146)*.[46]



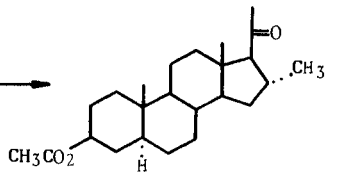


Inclusion of an additional fused cyclopropane ring at C-16,17 gives a compound in which progestational activity is said to predominate. Saponification of the acetate in *143* gives the corresponding 17-alcohol *(147)*. Heating in refluxing quinoline results in dehydration with formation of the 16,17-olefin *(148)*. Reaction with diazomethane gives

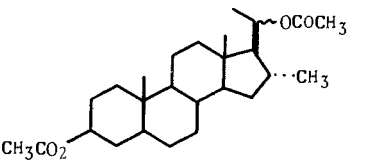
the pyrazoline *(149)*, which on heating in acid affords the biscyclopropyl derivative *(150)*. This compound is then taken on to the 6-chloro analogue by a sequence identical to that used to prepare *146*. There is thus obtained the progestin *gestaclone (151)*.[47,48]



Substitution by a methyl group at the 16-position is known to have a marked potentiating effect in the corticosteroid series. Combination of such a group with the unsaturated 6-chloro group in the progesterone series affords an extremely potent progestin. One route for preparation of the starting material for this drug consists in first introducing the 17-hydroxyl. Thus, the ketone at C-17 in the progesterone derivative *152* (obtainable from the corresponding pregnenolone *165)* is converted to the enol acetate *(153)*. The next step in this so-called Gallagher chemistry consists in conversion of the enol double bond to the epoxide to give *154*. Hydrolytic ring opening gives initially the hydroxy hemiacetal acetate; this quickly goes on to the hydroxy ketone *(155)*.

(165) → 

(152)



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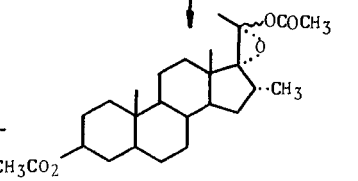

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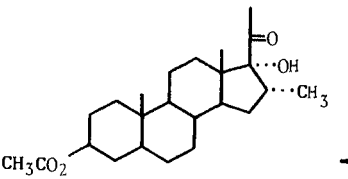

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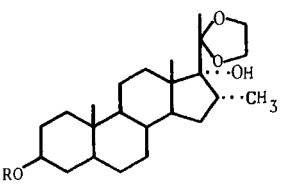
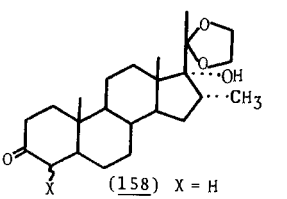
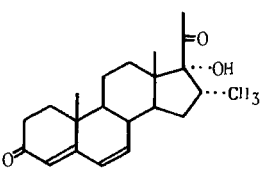


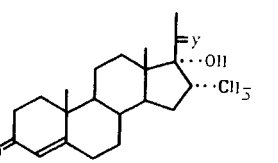
(156) R = CH_3CO
(157) R = H



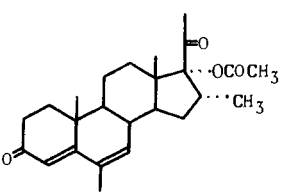
(158) X = H
(159) X = Br



(162) R = H
(163) R = $COCH_3$



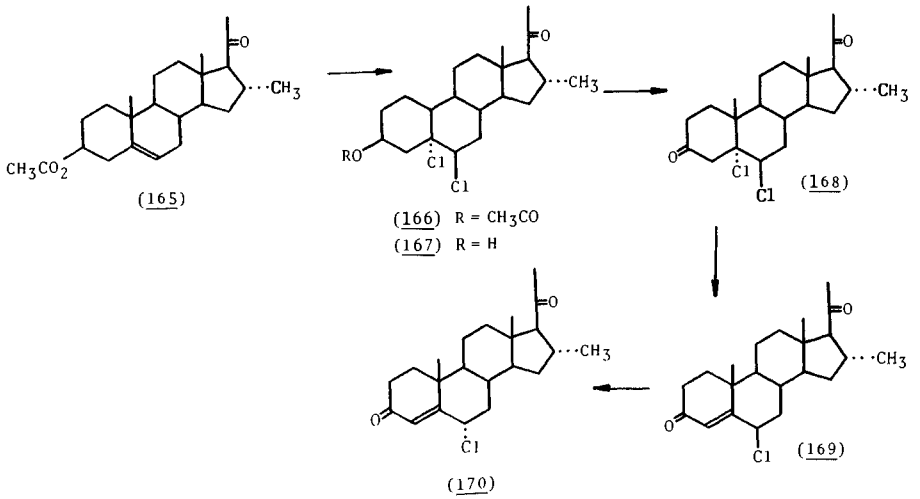
(160) y = O, O
(161) y = O



(164)

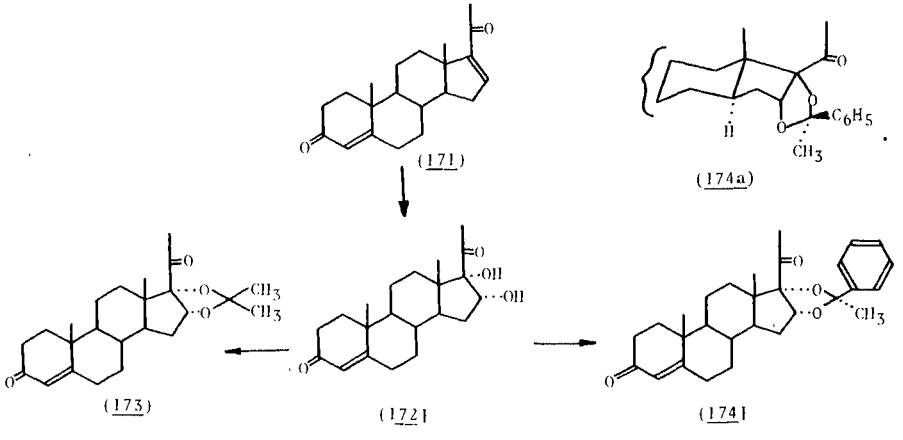
After protection of the C-20 keto group as the dioxolane *(156)*, the 3-acetyl group is saponified and the resulting alcohol *(157)* is oxidized to the ketone *(158)*. Bromination *(159)* followed by dehydrobromination introduces the required 4-ene-3-one functionality *(160)*; removal of the ketal would then afford the required starting material *(161)*. Heating of *161* in the presence of chloranil then introduces the desired unsaturation at C-6,7. A sequence identical to that used to prepare *146* (epoxidation; hydrogen chloride) is then used to introduce the 6-chlorine atom[50] and the progestin *clomegestone acetate (164)* results.

The analogue of *164* lacking unsaturation at C-6 and oxygen at C-17 unexpectedly shows antiestrogenic rather than progestational activity. Pregnenolone analogue *165*[49] is starting material for this analogue as well. Chlorination of the double bond by means of chlorine in pyridine affords the dihalo derivative *166*. The stereochemistry is best rationalized by assuming chloronium ion formation on the less-hindered α-side followed by diaxial opening of that ring by chloride ion. Oxidation of the alcohol *(167)* affords the 3-keto derivative *(168)*, and reaction of that with sodium acetate leads to dehydrochlorination, yielding the enone *(169)*. Exposure of that intermediate to mild acid isomerizes the halogen substituent to the more stable equatorial 6α-position and produces *clometherone (170)*.[51]



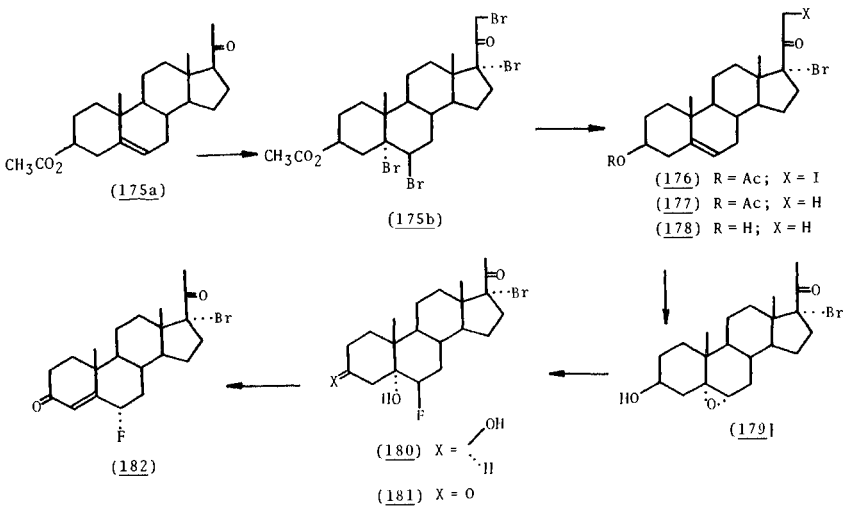
Yet another observation that carries over from the corticoids to progestins is the potentiation observed by formation of acetonides from the 16,17-glycols. It is of note in this case that the parent glycol itself fails to show activity in the standard progestational assay. Treatment of the progesterone derivative *172* (available by oxidation of 16-dehydropregnenolone *(171)* with potassium permanganate) with acetone affords the 16,17-cyclic acetal *algestone acetonide (173);*[52] in the same vein, reaction with acetophenone yields *algestone acetophenide (174).*[53] Although formation of the latter involves the creation of a new chiral center, only one isomer is in fact isolated from the reaction. Since acetal formation is accomplished under thermodynamic conditions, the more stable isomer involving the least steric crowding

should prevail. It has been proposed that the configuration of *174* is that which carries the aromatic ring oriented away from the steroid molecule *(174a)*. Earlier work had shown that the presence of the 17-hydroxyl substituent is crucial for oral activity in the 21-carbon progestin series; progesterone itself



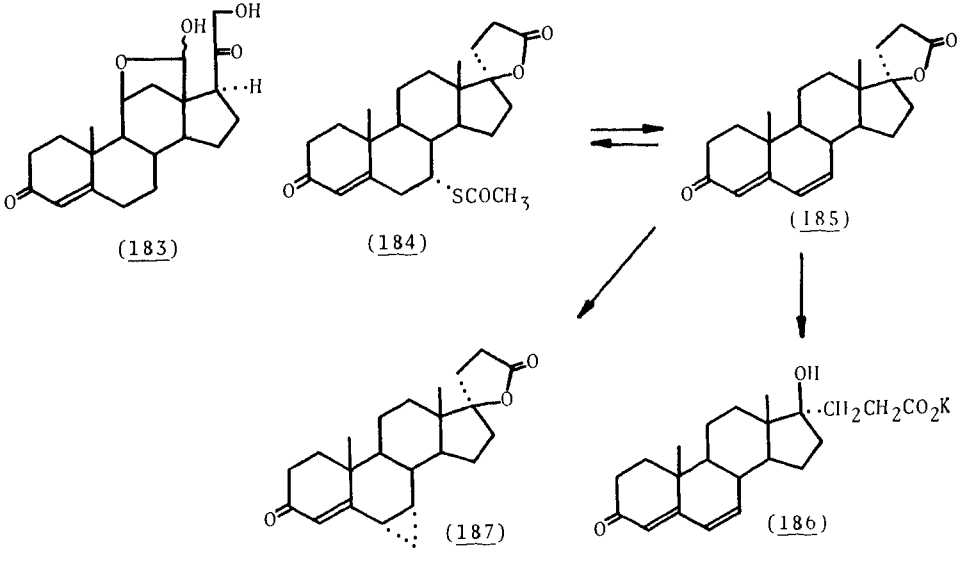
shows poor activity on oral administration. This key group can be replaced by halogen with retention of oral activity. Bromination of pregnenolone acetate *(175a)* in acetic acid gives the tetrabromide *175b*. Treatment with sodium iodide leads to both elimination of the 5,6-dibromide grouping and displacement of the α-keto halide at C-21 by iodine; there is obtained dihalide *176*. Reduction of the haloketone with bisulfite gives the methylketone *177*;[54] the selectivity is probably due to both the greater reactivity of iodine and the greater steric accessibility of

that group. Saponification to *178* followed by treatment with peracid gives the 5,6-oxide *179*. Diaxial ring opening of the oxirane with HF leads to the *trans*-fluorohydrin *180*. Oxidation of the hydroxyl at C-3 by means of Jones reagent then affords hydroxyketone *181*. Treatment of this last with acid serves both to generate the enone, by dehydration of the tertiary carbinol, and to invert the fluoro group at C-6 to the more stable equatorial, 6α-configuration. There is thus obtained *haloprogesterone (182)*.[55]



Aldosterone *(183)* is one of the key steroid hormones involved in regulation of the body's mineral and fluid balance. Excess levels of this steroid quickly lead to marked retention of sodium chloride, water and, often as a consequence, hypertension. The aldosterone antagonist *spironolactone (184)*[56] has proven of great clinical value in blocking the effects

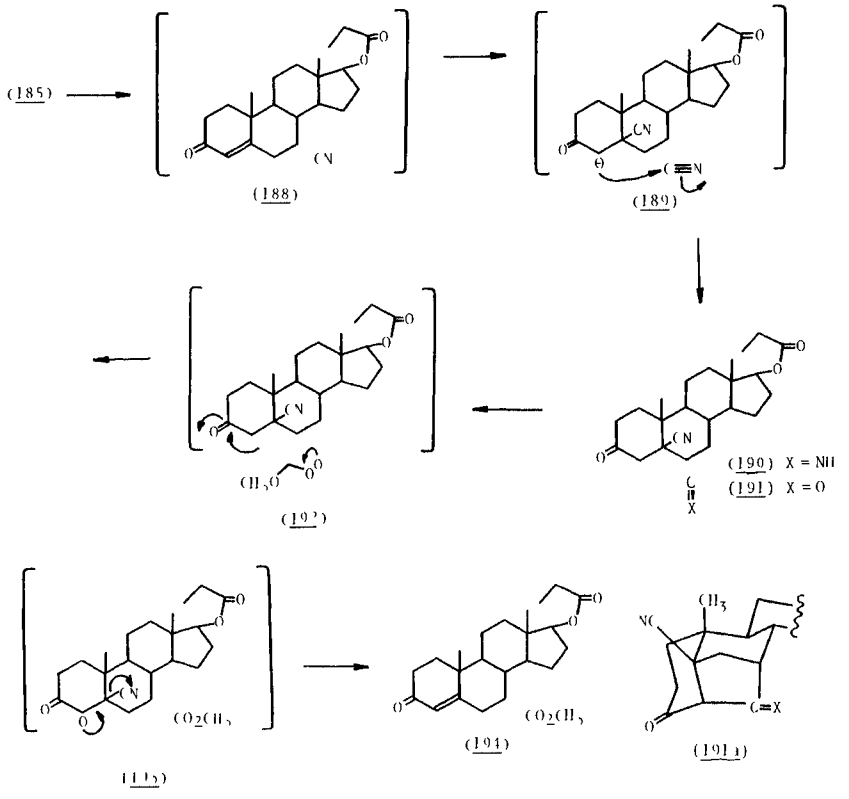
of hyperaldosteronism. In addition, the drug has proven an effective diuretic and antihypertensive agent even in those cases where no gross excesses of aldosterone can be demonstrated. It is of note that the immediate chemical precursor of *spironolactone (184)*, diene *185* was in fact found to be one of the active metabolites of that drug in the body. The diene, *canrenone (185)* now constitutes a drug in its own right. Both this and the following aldosterone antagonists are also available in the form of the potassium salt of the ring-opened hydroxy acid; in this case, *potassium canrenoate (186)*.



Cyclopropanation of the 4,6-diene function proceeds selectively at the 5,6-double bond. Thus, reaction of *185* with the ylide from trimethyl sulfonium iodide and sodium hydride, in DMSO, affords predominantly the α-cyclopropyl compound *(187)* accompanied

by traces of the β-isomer. The lactone constitutes the diuretic-antihypertensive *prorenone*;[57] the ring-opened salt is known as *potassium prorenoate*.

Introduction of a carbomethoxy moiety at C-7 should afford a nonreversible counterpart of *184*. To effect this, addition of cyanide to the extended conjugated system in *185* leads to addition of two moles of the nucleophile; there is obtained the unusual bicyclic intermediate *190*. The reaction may be rationalized by assuming that addition occurs initially at the terminus of the system to give *188* as expected. This, however, under the reaction conditions chosen, undergoes addition of the second mole of cyanide which, of necessity, goes through anion *189*; reaction of the negative charge at C-4 with the nitrile at C-7 would lead to the observed product *(190)*. This can only happen following β-addition of cyanide. Hydrolysis of the imine function proceeds to give diketone *191*. A conformational drawing *(191a)* shows that the molecule is by no means as strained as the planar projection would suggest. Reaction of *191* with methoxide reverses the formation of the additional ring. The reaction sequence probably starts by addition of methoxide to the carbonyl group *(192)*; collapse of the alkoxide anion gives the intermediate anion *193*, which neutralizes itself by facile elimination of the excellent leaving group, cyanide. There is thus finally obtained *mexrenone (194)*;[58] the salt is known as *potassium mexrenoate*.



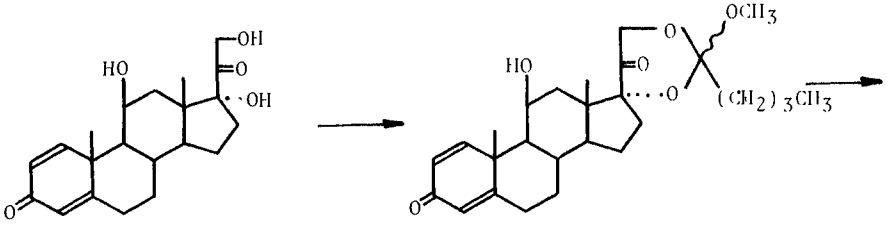
b. 11-Oxygenated Pregnanes

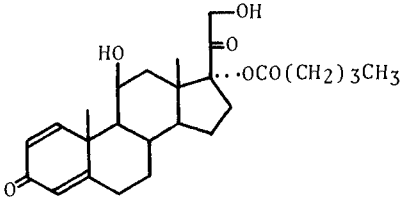
The story of the discovery of the utility of cortisone as an antiinflammatory agent has been told often enough not to need full repetition here.[59] In brief, cortisone is one of the more important hormonal steroids elaborated by the adrenal cortex; this steroid is intimately involved in the regulation of a host of biological processes such as, for example, regulation of glucose utilization and mineral balance. Administration of doses far in excess of those required for hormonal

action were found to alleviate the symptoms of a multitude of conditions marked by inflammation. When used for this purpose, the normal hormonal effects are undesirable. These side effects are, however, seen to be natural extensions of the hormonal action. Immediately following this discovery, an enormous effort was mounted in the laboratories of the pharmaceutical industry aimed at separation of the anti-inflammatory activity of these molecules from their hormonal activities. The most visible outcome of this work was a tremendous increase in the milligram potency achieved by various structural modifications. Drugs were produced that, in addition, had changed hormonal spectra; some such steroids had more pronounced effects on glucose metabolism ("glucocorticoids"), whereas others were more effective in changing mineral balance ("mineralocorticoids"). Despite this, no steroid truly devoid of hormonal activity rewarded these efforts. The full realization of the clinical deficiencies of the corticoids, coupled with the increasing availability of non-steroidal antiinflammatory agents, has led to a great decrease in routine use of these drugs in medical practice. It is for that primary reason that the compounds discussed next failed to have greater medical and economic impact. It is of note that this work represented an unparalleled effort on the part of medicinal chemists, both as to the complexity of the molecules involved and the length of the synthetic schemes utilized. In some ways this foreshadowed the current prostaglandin programs, both in the goal

(splitting of activities) and in chemical sophistication (in fact, the same names often appear as authors in the late steroid papers and early prostaglandin publications).

As has been mentioned, preparation of esters of the C-17 hydroxyl group of selected progestins affords compounds with prolonged action. Similar chemical treatment of a corticoid would almost certainly lead to an ester of the sterically more accessible primary alcohol at C-21. In an interesting method for achieving esterification of the more hindered and less reactive tertiary 17-hydroxyl, *prednisolone (195)*[59] is converted to a mixture of the diasteromeric cyclic ortho esters *(196)* by ester interchange with trimethyl ortho-pentanoate. Acid-catalyzed dioxolane ring opening proceeds by protonation of the more



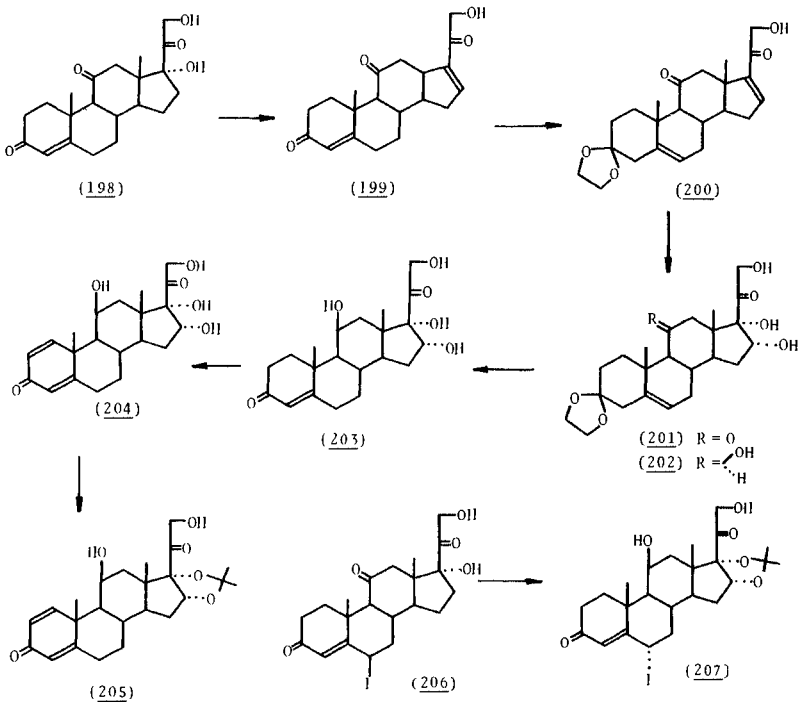


(197)

sterically accessible oxygen attached to the 21-position. There is thus obtained *prednival (197)*.[60] It is of interest that *197* rearranges to the 21-ester on heating, representing an O-to-O acyl migration.

It was found quite early in the steroid effort that inclusion of several groups, which singly potentiated activity had an additive effect; for example, a cortisone derivative that included both the unsaturation at C-1,2 and a methyl group at C-6 would be more potent than the derivative that possessed either group alone. Much of the chemical strategy thus devolved on designing routes which would permit the inclusion of combinations of potentiating groups.

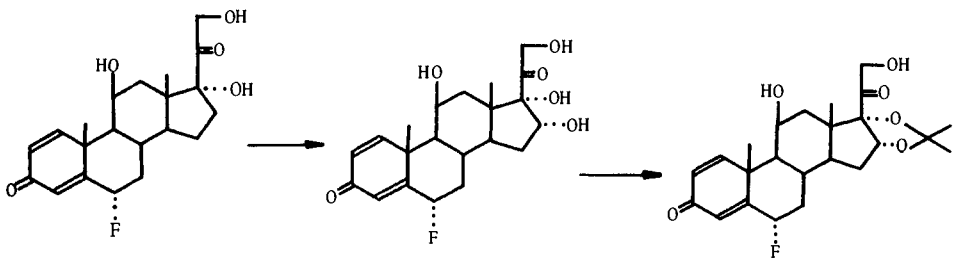
Dehydration of cortisone *(198)* affords the diene *199*. This is then converted to ketal *200*. The selectivity is due to hindrance about both the 11- and 20-carbonyl groups. The shift of the double bond to the 5,6-position is characteristic of that particular enone. Treatment of protected diene *200* with osmium tetroxide results in selective oxidation of the conjugated double bond at C-16,17 to afford the *cis*-diol *(201)*. Reduction of the ketone at C-11 *(202)* followed by hydrolysis of the ketal function gives the intermediate *203*.[61a] Selenium dioxide has been found empirically to dehydrogenate such 3-keto-4-ene steroids to the corresponding 1,4-dienes. (See, for example, *120-121* and *137-140*.) Thus in the case at hand, reaction of *203* with selenium dioxide gives the diene *204*.[61b] Reaction of the *cis*-diol function with acetone forms the cyclic acetal and, thus, the corticoid *desonide (205)*.[62]



An analogous sequence starting with 6β-fluorocortisone *(206)*,[63] but omitting the selenium dioxide dehydrogenation, affords *flurandrenolide (207)*.[64]

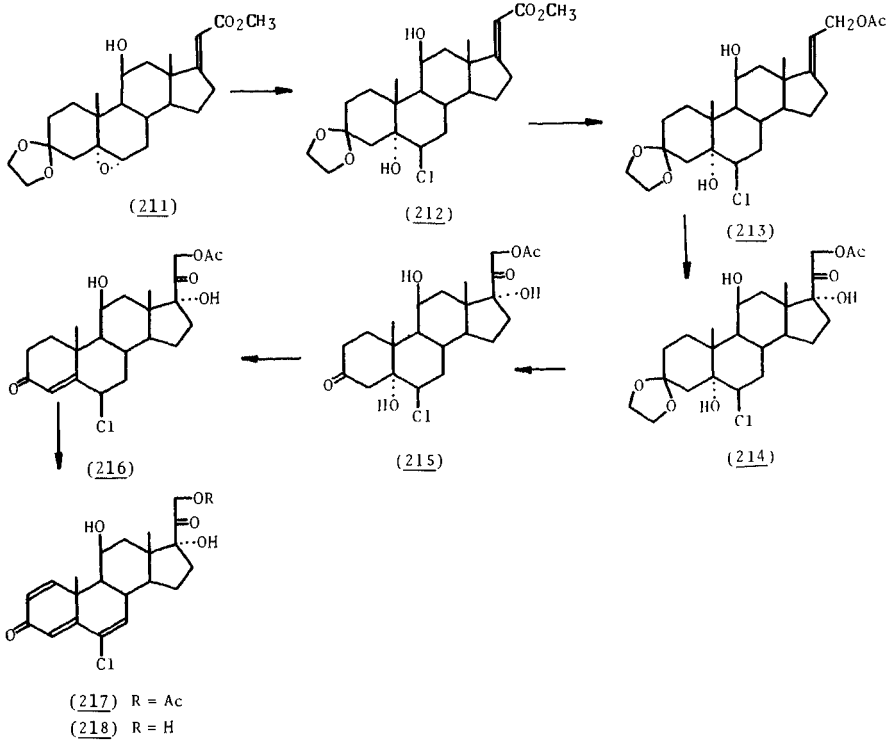
Microbiological oxidation has proven of enormous value in steroid chemistry, often affording selective means of functionalizing remote and chemically inactivated positions. It will bear mentioning that the 11-oxygen for all commercially available corticoids is in fact introduced by such a reaction carried out on plant scale. Preparation of the 1-dehydro analogue of *207* involves biooxidation to introduce the 16-hydroxyl. Incubation of 6α-fluoroprednisolone

(208)[63] with *Streptomyces roseochromogenes* effects α-hydroxylation at the 16-position *(209)*. Reaction with acetone affords the corticoid *flunisolide (210)*.[65]



(208) (209) (210)

The 6-chloro-6-dehydro moiety apparently has a similar potentiating effect on corticoids as it does on progestins. One scheme for preparing the requisite starting 6-chloro compound begins with the opening of oxide *211* with hydrogen chloride to give halohydrin *212*. Reduction of the 21-ester function by means of lithium aluminum hydride, followed by acetylation, gives *213*. Transformation of the 17,20-olefin to the requisite hydroxyketone grouping is achieved by a combination of osmium tetroxide and N-morpholine oxideperoxide (NMOP) treatments. The reaction sequence presumably starts by hydroxylation of the olefin via the osmate ester; the secondary alcohol at C-20 is then further oxidized to the ketone by the NMOP. The latter also served to reoxidize the osmium reagent from the dioxide to the tetroxide, allowing that expensive and toxic reagent to be used in catalytic quantities. Deketalization *(215)* followed by acid



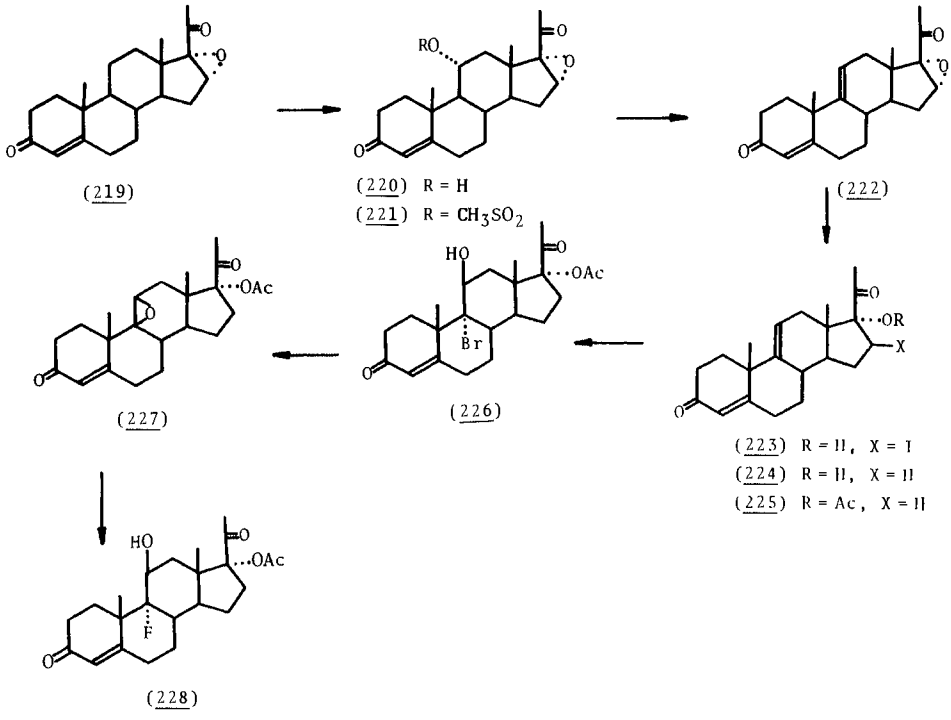
(211) (212) (213) (214) (215) (216)

(217) R = Ac
(218) R = H

catalyzed dehydration affords the conjugated ketone *(216)*.[63] The remaining unsaturation at C-1 and C-6 is then introduced either by sequential treatment with selenium dioxide and chloranil or under special conditions with chloranil alone. Saponification of the acetate affords the corticoid *cloprednol (218)*.[66]

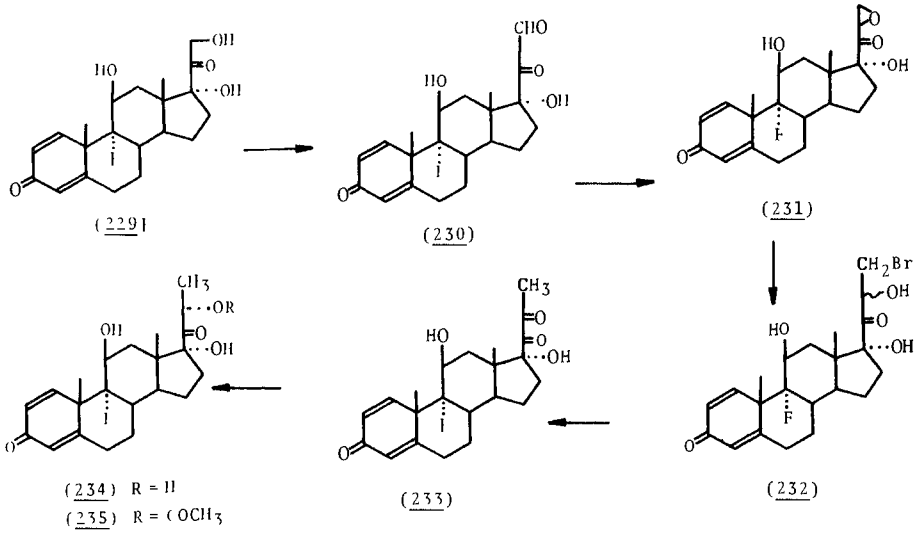
Although oxygenation at C-11 seems to be required for activity in the corticoid series, the presence of that function is not incompatible with progestational activity.[67] Thus, perhaps surprisingly in view of some corticoids discussed below, mere lack of the hydroxyl group at C-21 seems, in at least one case,

to give a compound which exhibits progestational activity. Microbiological oxidation of diketone epoxide *219* by means of *Rhizopus nigricans* affords the corresponding 11α-hydroxy derivative *(220)*. Dehydration of this via the mesylate *(221)* gives the 9,11-olefin *(222)*. Ring opening of the oxirane moiety by means of hydrogen iodide gives the halohydrin *223*. Treatment with zinc in acid serves to remove the halogen reductively *(224)*; the 17-hydroxy group is then acetylated by means of acetic anhydride in the presence of tosic acid to give *225*. The 11β-hydroxy-9α-halo function is associated with most potent corticoids; the manner of introduction used in this case well illustrates the relatively standard sequence used to incorporate this function. Addition of the elements of HOBr to the double bond is usually accomplished by N-bromosuccinimide in aqueous base. Both regio- and stereospecificity are no doubt guided by the initial formation of the 9α,11α-bromonium ion, followed by nucleophilic diaxial opening to give *226*. Treatment of the bromohydrin with base leads to the formation of the β-oxide *(227)* by intramolecular displacement of halogen by the neighboring alkoxide ion. Addition of hydrogen fluoride to the oxide proceeds with diaxial opening to afford the 9α-fluoro-11β-hydroxy functional array. In the case at hand there is formed the progestin *flurogestone acetate (228)*.[69] This drug has been in use for controlling the estrus cycle in domestic animals under the name Equamate®.



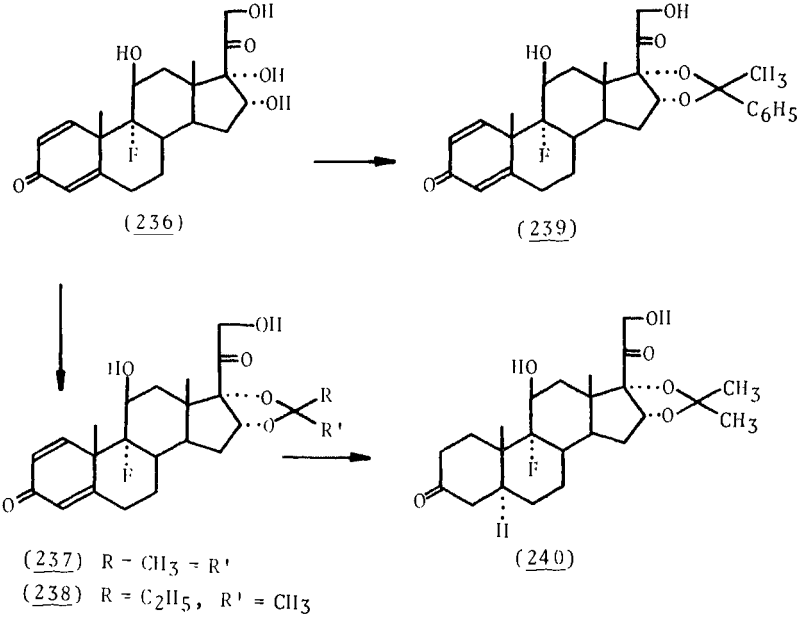
The presence of an additional carbon atom on the dihydroxyacetone side chain is quite compatible with antiinflammatory activity. Oxidation of 9α-fluoprednisolone *(229)*[70] by means of cupric acetate affords the corresponding 21-aldehyde *(230)*. Addition of diazomethane to the aldehyde serves to lengthen the side chain as the epoxide *231*. Opening of the oxirane ring with hydrogen bromide occurs regioselectively to give the 22-bromo derivative *(232)*. Heating of the bromohydrin leads to loss of hydrogen bromide with formation of the alpha diketone *(233)* (this reaction

can be rationalized as loss of HBr to give the enol followed by ketonization). Reduction of the side chain diketo alcohol by means of yeast proceeds both regio and stereospecifically to give the derivative containing the 21α-hydroxyl group *(234)*. Acetylation under mild conditions then affords the antiinflammatory steroid *fluperolone acetate (235)*.[71]



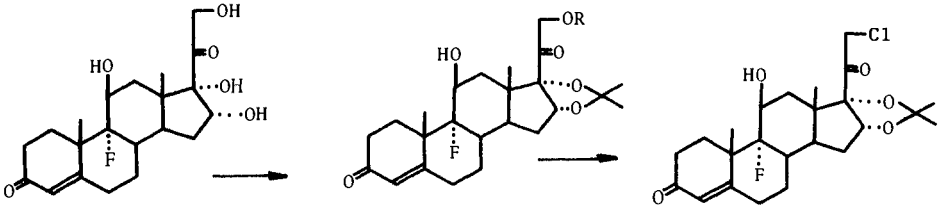
The potentiating effect of the 16-hydroxyl group in the corticoid series has been mentioned previously. The acetonide of such a steroid, *triamcinolone (237)*, is in fact one of the more widely used corticosteroids. The nature of the group used to form a ketal apparently has only relatively minor influence on biological activity. Reaction of the 16,17-glycol *236*[72] with 3-butanone yields *amcinafal (238)*;[73] in the same vein condensation with acetophenone leads to *amcinafide*

(239).[73] The ketal stereochemistry is not specified. Unsaturation in the A ring has been usually assumed to be necessary for biological activity; the reader will have noted the high prevalence of 1,4-dienes. It is interesting therefore to note that the analogue possessing a fully saturated A ring is apparently quite active in its own right. Thus, catalytic reduction of *237* affords the corticoid *drocinonide (240)*.[74]



It is of interest that there exists a considerable amount of flexibility as to the substituent at C-21 in the acetonide series. For example, formation of the acetonide from *241*[72] affords intermediate *242*. Reaction with methanesulfonyl chloride gives the corresponding mesylate *(243)*. Displacement

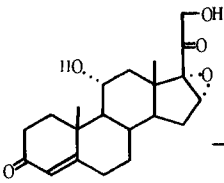
of the ester with lithium chloride in DMF gives the corticoid *halcinonide (244)*.[75]



(241) (242) R = H (243) R = SO_2CH_3 (244)

The C-21 substituent can in fact be dispensed with entirely. Perhaps because *descinolone acetonide (254)* predates *244* by better than a decade, the synthetic sequence reported for its preparation is quite complex. Although *descinolone (253)* could in principle be prepared in a few steps from some currently available starting materials, such as *241*, the original synthesis is presented for its heuristic value.

Epoxyketone *245* is readily available from 16-dehydropregnenolone via several steps, including a crucial microbiological 11α-hydroxylation. Dehydration of *245* gives the 9,11-olefin *246*. The alcohol at C-21 is then converted to the mesylate *(247)*, and this is reduced to give the methyl ketone *(248)*. The olefin is then converted to the 9α-fluoro-11β-hydroxy array *(250)* by the standard sequence [addition of HOBr, closure to the oxirane *(249)*, opening with HF]. Note that the reactivity of the epoxides in *249* is



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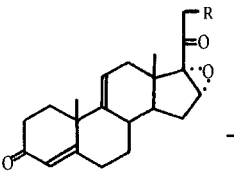
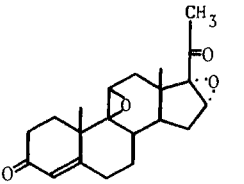


(246) R = OH
(247) R = OSO_2CH_3
(248) R = H



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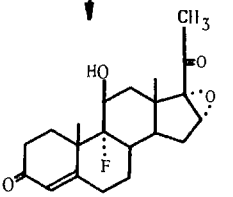

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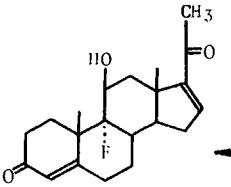

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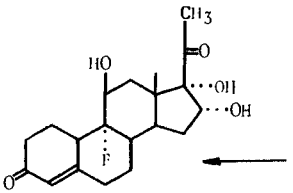

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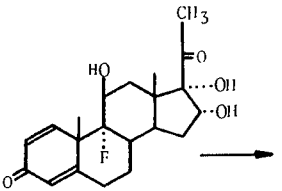

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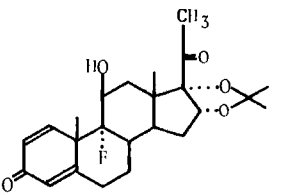

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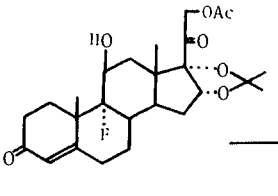

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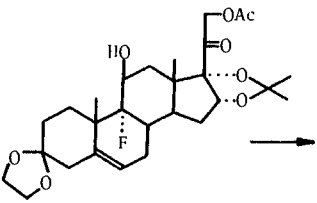

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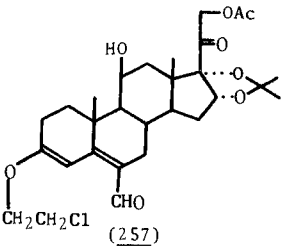


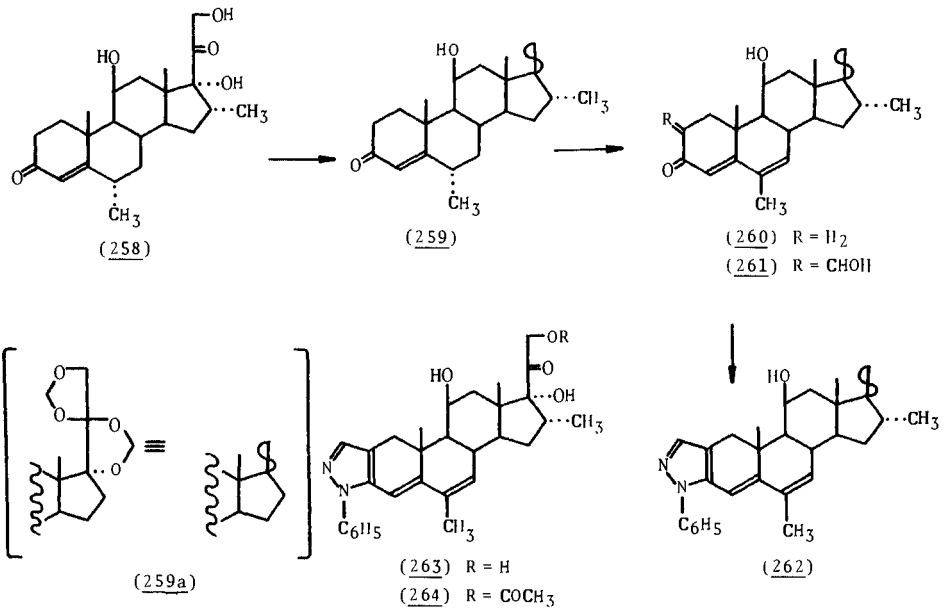
(257)

sufficiently different so that reaction occurs regioselectively at C-9,11. The remaining major transformation is the establishment of the 16α,17α-glycol function; this cannot be readily achieved from *250* since this would demand the *cis*-opening of an oxirane. Deoxygenation of the epoxide with chromous chloride gives back the 16,17-olefin *(251)*. In effect the epoxide has been used in this sequence as a protecting group for an olefin. Hydroxylation with osmium tetroxide gives the desired glycol *(252)*; microbiological dehydrogenation (using *Nocardia corallina*) serves to introduce the double bond at C-1 *(253)*. Reaction with acetone finally affords *descinolone acetonide (254)*,[76] an antiinflammatory agent.

Although the Vilsmeier reaction is known best in aromatic systems, aliphatic olefins also undergo formylation. Synthesis of *formocortal (257)* involves such a step. Formation of the monoketal of *255* involves the 3-ketone function with the familiar concomitant shift of the double bond to C-5,6. Reaction of *256* with phosphorous oxychloride and DMF involves first formylation at the 6-position; opening of the ketal to the enol ether by the HCl produced in the Vilsmeier reaction would afford a hydroxyethyl side chain at C-3. This is no doubt converted to a chloroethyl group by excess oxychloride. There is thus obtained the antiinflammatory agent *formocortal (257)*.[77]

As is the case with other classes of steroids, inclusion of nitrogen atoms into corticoids has met with only limited pharmacological success. Compounds

containing a pyrazole ring fused onto the A ring have, however, shown sufficient activity to merit generic names. Synthesis of the requisite intermediate for its incorporation starts with the protection of the dihydroxyacetone side chain. Reaction of *258* with formaldehyde gives the internal double acetal *259*. (This bismethylenedioxyether-protected *(259a)* function is known as BMD for short.) Dehydrogenation by means of chloroanil proceeds in the usual way to give the 4,6-diene *(260)*. Formylation with ethyl formate and sodium hydride leads to *261*.

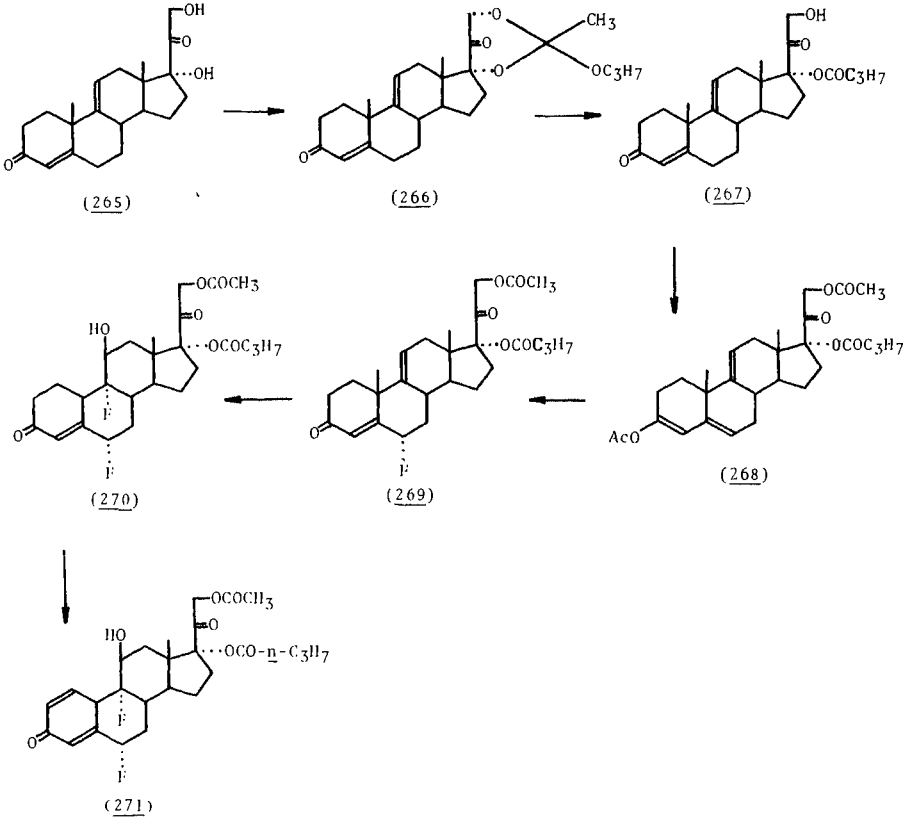


Condensation with phenylhydrazine results in phenylpyrazole *262*. The regiospecificity results from intermediate phenylhydrazone formation of the more

reactive aldehyde function. The sequence is completed by deprotection of the cortical side chain by acid hydrolysis *(263)*, followed by acetylation of the 21-hydroxy group. There is thus obtained the corticoid *cortivazol (264)*.[78]

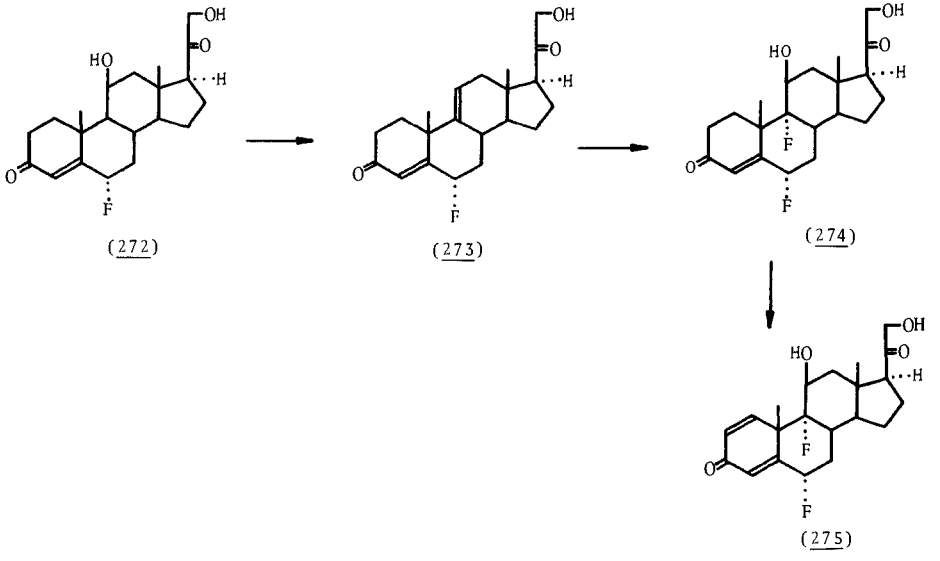
Inclusion of halogen, particularly fluorine, at either the C-6 or C-9 positions in the cortisone molecule is well known to increase potency. Combination of these potentiating groups in the same molecule in general leads to an additive influence on potency. The synthesis of one such compound, *diflupredna*te *(271)*, starts with a scheme analogous to that used to prepare *197*. The C-17,21 diol *265* is first converted to the cyclic ortho-ester *(266)* by means of methyl ortho-butyrate. Cautious hydrolysis affords the 17-butyrate ester *(267)*. Exhaustive acetylation leads to reaction not only at C-21, but formation of the enol acetate at C-3 as well *(268)*. Reaction of that intermediate with perchloryl fluoride ($FClO_3$) leads to halogenation at the terminus of the electron-rich diene system. Work-up gives a mixture of the epimeric 6-fluoro compounds; equilibration in acid provides the more stable equatorial 6α-isomer *(269)*. The 9,11-diene is then taken on to the 9α-fluoro-11β-hydroxy function by the standard reaction sequence *(270)*. Dehydrogenation by means of DDQ completes the synthesis of *diflupredna*te *(271)*.[79]

Omission of the 17-hydroxyl group in the 6,9-dihalo compounds apparently does not lead to loss of biological activity. Dehydration of the 6α-fluoro-17-desoxy intermediate *272*[80] by means of NBS in pyridine



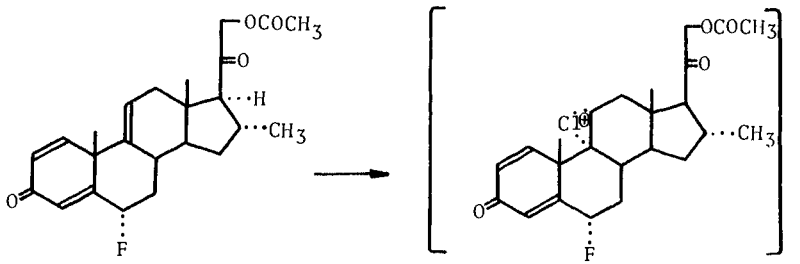
leads to the 9,11-olefin *(273)*. This is then converted to the halohydrin by the standard sequence. Microbiological dehydrogenation of the A ring leads to the 1,4-diene. There is thus obtained the antiinflammatory steroid *diflucortolone (275)*.[81]

Although the most common substituent found at the C-9 position in the commercially available corticoids is fluorine, the initial observation of the

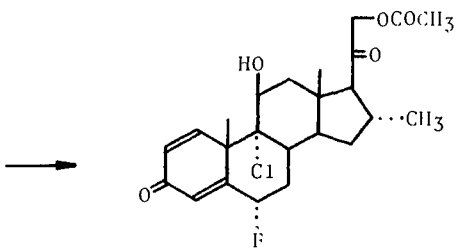


(272) (273) (274) (275)

potentiating effect of halogen was in fact made with chlorine at that spot. It is thus of interest to note that one of the more recent 17-desoxy-6,9-dihalo cortocoids contains chlorine at C-9. Starting material for that compound is 16-methyl steroid *276*.[82] In distinct contrast to previous work, the desired halohydrin is introduced in a convenient single step rather than by the usual three-step sequence. Thus, reaction of the olefin with tertiary butyl hypochlorite in the presence of perchloric acid affords directly the 9α-chloro-11β-hydroxy function and, thus, *clocortolone (277)*, an antiinflammatory agent. It is not unlikely that the actual reagent is HOCl; attack on the 9,11-olefin by Cl^+ would occur from the less hindered side to give the 9α,11α-chloronium intermediate. Attack of OH to give diaxial ring opening would lead to the observed halohydrin.

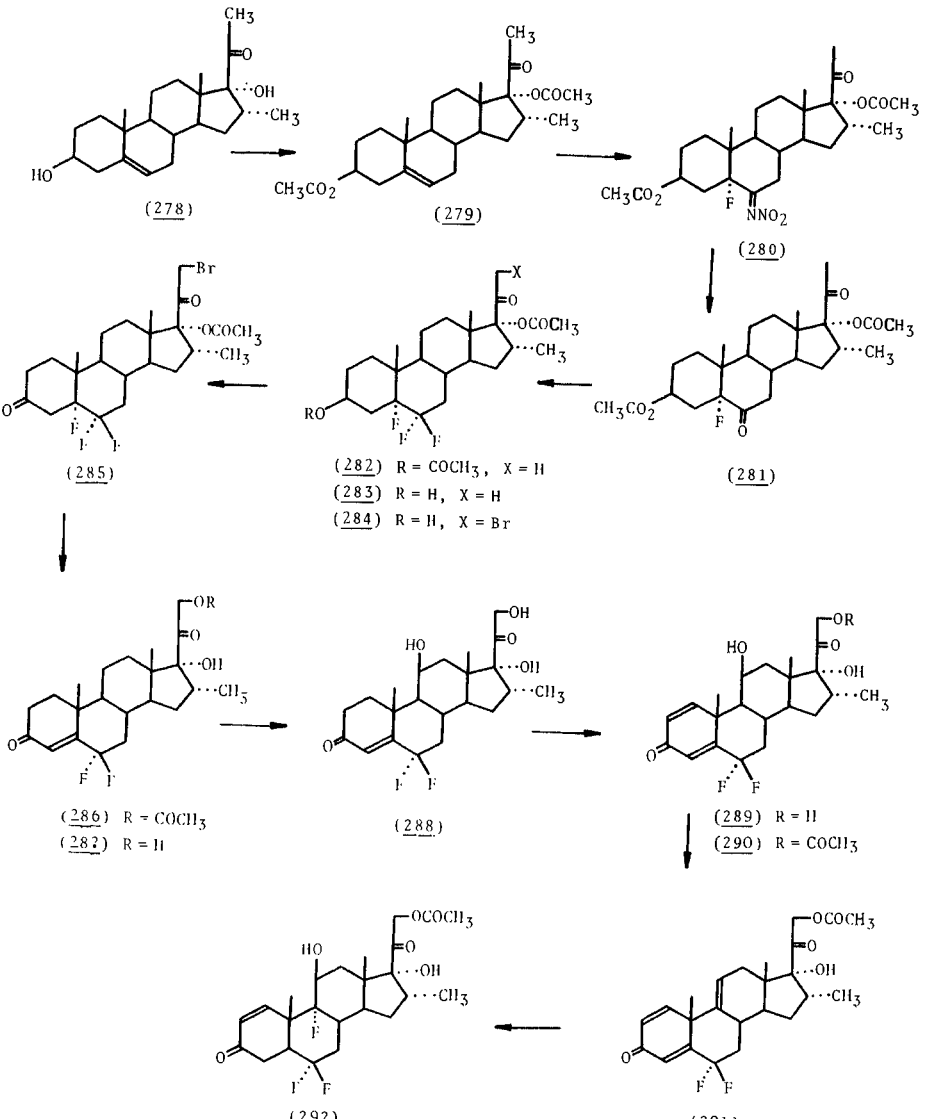


(276) (276a)



(277)

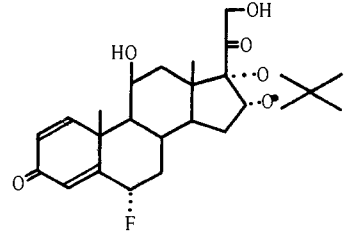
The scheme required to prepare the potent trifluoro corticoid *cormethasone acetate (292)* illustrates the synthetic complexities involved in some of this work. Sequential acetylation of the pregnenolone derivative *278* with first acetic anhydride in pyridine and then acetic anhydride in the presence of tosic acid affords diacetate *279*. Reaction of that intermediate with nitrosyl fluoride results initially in addition of the reagent to the 5,6-olefin moiety to afford the fluoro oxime; reaction with a second mole of reagent at nitrogen gives the nitroimine derivative *280*; passage over alumina serves to hydrolyze the imine function to the corresponding 6-ketone *(281)*.



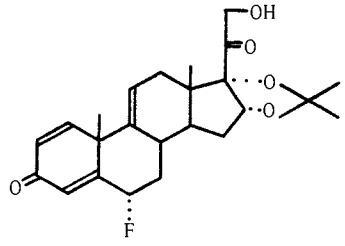
(278) (279) (280) (281) (282) R = $COCH_3$, X = H (283) R = H, X = H (284) R = H, X = Br (285) (286) R = $COCH_3$ (287) R = H (288) (289) R = H (290) R = $COCH_3$ (291) (292)

Sulfur tetrafluoride in hydrogen fluoride has been developed as a selective and general reagent for converting ketones to the corresponding difluoromethylene groups. Application of that reaction to *281* gives the desired 6,6-difluoro derivative *282*. The less-hindered acetate at C-3 is then hydrolyzed selectively (to *283*); bromination in dioxane leads to the 21-bromo derivative *284*. Jones oxidation gives the 3-ketone *(285)*. Reaction of that compound with silver acetate serves to displace the bromine by acetate, to introduce the enone function by elimination of hydrogen fluoride, and to hydrolyze the 17-acetate. There is thus obtained *286*. Saponification of the remaining 21-acetate gives the desired intermediate *287*. Successive microbiological oxidation with *Curvularia lunata* and *Arthrobacter simplex* serves to introduce respectively the 11β-hydroxyl *(288)* and 1-olefin functions *(289)*. Reacetylation *(290)* followed by dehydration gives the required 9,11-olefin *(291)*. This is converted to the 9,11-fluorohydrin by the standard sequence to afford finally *cormethasone acetate (292)*.[83]

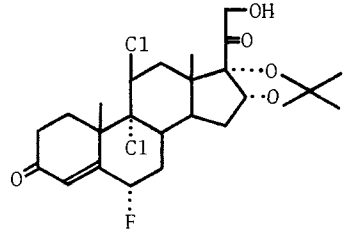
The recurring theme in work on corticoids discussed thus far with the exception of the 17-desoxy compounds consisted in the introduction of additional functions to the basic cortisone molecule. Some further success in producing biologically active molecules has been achieved by substituting unnatural functions for those present in the protoype molecule. Thus the hydroxyl groups at both C-11 and C-21 can be replaced by halogen with retention of activity.



(293)



(294)



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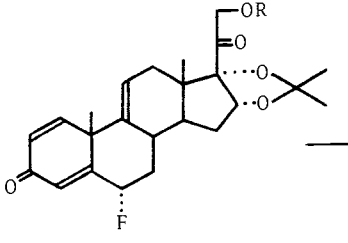
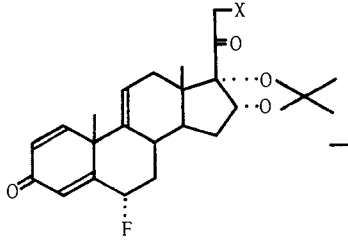


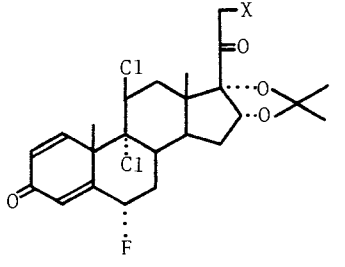
(296) R = SO_2CH_3

(299) R = p-$SO_2C_6H_4CH_3$



(297) X = Cl

(300) X = F

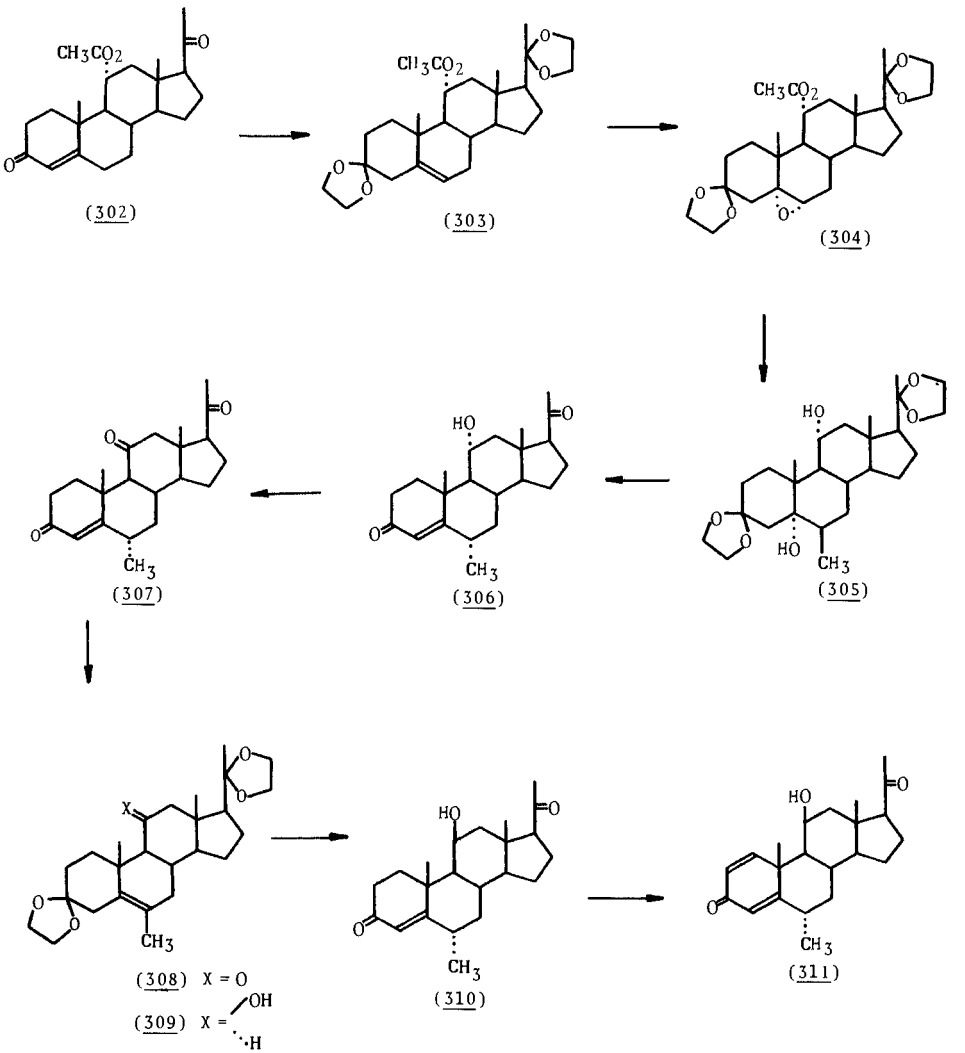


(298) X = Cl

(301) X = F

Reaction of the olefin *(294)*, corresponding to *fludrocortide (293)*,[84] with chlorine affords directly *flucloronide (295)*.[85] The stereochemistry can, as in the case of *277*, be rationalized by invoking the intermediacy of the 9α,11α-chloronium ion. Reaction of *294* with methanesulfonyl chloride affords the corresponding mesylate *(296)*; displacement of the ester by means of lithium chloride affords the 21-chloro intermediate *(297)*. Addition of chlorine to the 9,11-double bond gives *triclonide (298)*.[86] A similar sequence on the tosylate *(299)*, leading through the intermediate fluoride *(300)*, gives the antiinflammatory agent *tralonide (301)*.[87]

Antiinflammatory activity also persists in the absence of oxygen at either C-17 or C-21. In this case, unlike those in which those positions are occupied by halogen, the possibility exists that these are in fact prodrugs. That is, the compounds may have no intrinsic biological activity but need to be hydroxylated to the active entities in vivo. The synthetic sequence starts by formation of the bisketal *303* from 11α-acetoxy progesterone *(302)*. Epoxidation affords predominantly the 5α,6α-oxide *(304)*. Reaction with methylmagnesium bromide both opens the oxiran and cleaves the ester *(305)*. Successive treatment with aqueous acid and base serves to hydrolyze the ketal groups and dehydrate the resulting β-hydroxyketone *(306)*. The α,β-unsaturated function provides a means for epimerization of the 6β-methyl group to 6α. There now remains the task of inverting the configuration at C-11 as well. Oxidation proceeds in


CH3CO2
O
(302)
(303)
(304)
HO
(305)
(306)
CH3
(307)
X
(308) X = O
(309) X = OH, H
(310)
(311)

straightforward manner to give the 11-ketone *(307)*; the highly hindered nature of the 11ketone permits selective ketal formation at C-3 and C-20 *(308)*. Reduction by means of lithium aluminum hydride *(309)*, followed by hydrolysis of the ketal groups affords antiinflammatory steroid *medrysone (310)*.[88] The analogue containing additional unsaturation at C-1, *endrysone (311)*, can presumably be obtained from *310* by any one of the standard dehydrogenation schemes.

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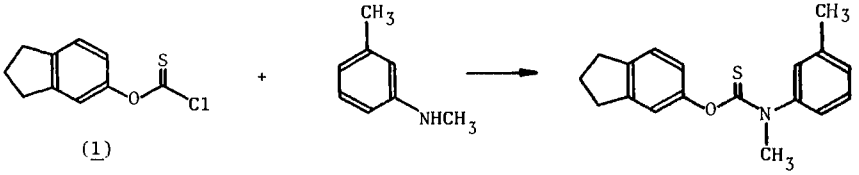
7

Polycyclic Aromatic and Hydroaromatic Compounds

The ring systems covered in this chapter provide the molecular framework upon which the necessary functionality for a diverse range of pharmacologically active agents are assembled. Intrinsic agonist activity is rarely, if ever, attributable to the ring system itself among this class, but often replacement or "simplification" by omission of rings leads to a serious decrease in activity. This is generally considered to be due to a considerable alteration in lipid/water solubility ratio, a deleterious alteration in the spatial arrangement of the functions necessary to fire the receptor, a change in the pK such that altered intracellular concentrations are achieved, or some such factor. This lack of intrinsic pharmacophoric action is demonstrated clearly by the indanes in the first section. Of the six substances covered, each has a different main pharmacological action!

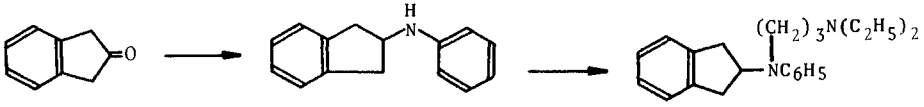
1. INDANES AND INDENES

Of a series of indanylthiocarbamates, *tolindate (2)* had significant antifungal properties. It is prepared simply from 5-indanyl thionochloroformate *(1)* by reaction with N-methyl-m-toluidine.[1] It presumably joins the fairly large family of organic compounds having sulfur divalently bound to carbon which are useful topical agents for dermatophytes.



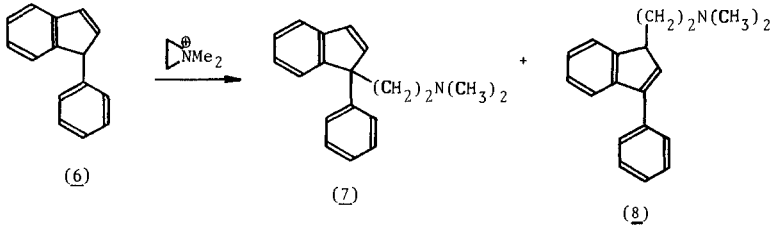
(1) (2)

When indan-2-one *(3)* forms a Schiff's base with aniline and this is reduced with sodium borohydride, the aminoindane *4* is found. The acidic hydrogen is removed with sodium hydride and this is in turn reacted with 3-diethylaminopropyl chloride to complete the synthesis of *aprindine (5)*, an antiarrythmic agent.[2]



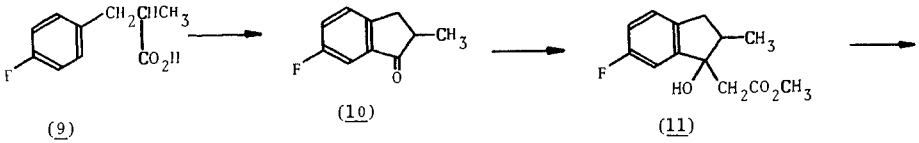
(3) (4) (5)

When 1-phenylindene *(6)* is treated successively with n-butyl lithium and dimethyl β-chloroethylamine, *indriline (7)*, a central stimulant, is formed along with inactive isomer *8*, both presumably arising via reaction with the intermediate aziridinium ion.[3]

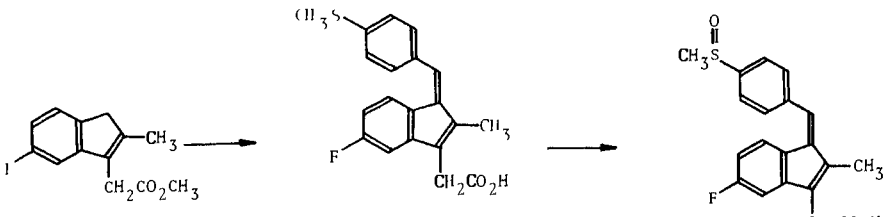


(6) (7) (8)

Reaction of p-fluorobenzyl chloride with the anion of diethylmethylmalonate ester followed by saponification and decarboxylation leads to acid *9*. Polyphosphoric acid cyclization leads to indanone *10*. A Reformatsky reaction with zinc amalgam and bromoacetic ester leads to carbinol *11* which is then



(9) (10) (11)

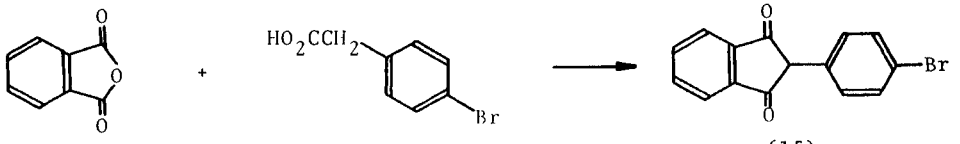


(12) (13) (14)

dehydrated with tosic acid to indene *12*. The active methylene group of *12* is condensed with p-thiomethylbenzaldehyde, using sodium methoxide as catalyst, and then saponified to give Z-isomer *13* which is in turn

oxidized with sodium metaperiodate to sulfoxide *14*, the antiinflammatory agent *sulindac.*[4]

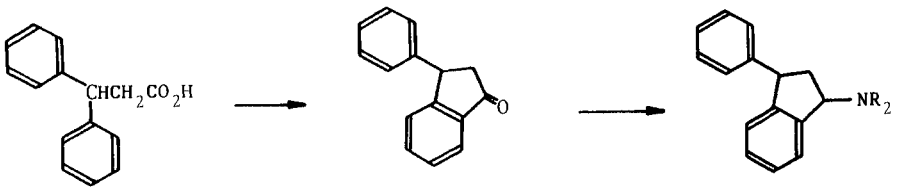
Phenyl indandiones with an acidic hydrogen often interfere with clot formation. When electron withdrawing groups are present in the p-position, acidity is increased and activity goes up. The opposite effect is seen with electron-donating substituents. Synthesized in the usual way, the anticoagulant *bromindione (15)* results from sodium acetate-catalyzed condensation of phthalic anhydride and p-α-bromophenylacetic acid.[5]



(15)

An analgesic compound that does not completely embody the essential structural features of the classical morphine rule is *dimefadane (19)*. Friedel-Crafts alkylation of benzene with cinnamic acid using a Lewis acid catalyst gives β,β-diphenylacetic acid *(16)*, which is cyclized to indanone *17*. Heating with ammonium formate (Leuckart reaction) produces indanylamine 18 in a more efficient manner than does hydrogenation of the oxime. Heating with formaldehydeformic acid (Eschweiler-Clark reaction) then produces *dimefadane (19)*,[6] an analgesic with about the same potency as codeine but without much of the

untoward gastrointestinal side effects of the natural product.

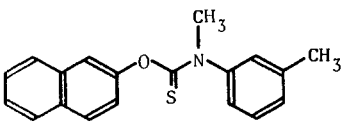


(16) (17) (18) R = H (19) R = CH_3

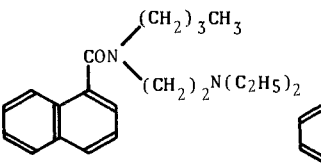
2. NAPHTHALENES

An analogue of *tolindate (2)* which has had greater success as an antifungal drug is *tolnaftate (20)*. The synthesis follows the usual path, condensing β-naphthol with Cl_2CS and then reacting the resulting chlorothioformate with N-methyl-m-toluidine.[7]

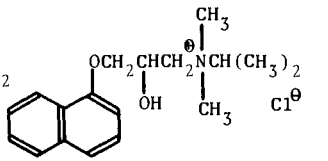
It will be recalled that certain local anesthetic amides, such as *procainamide* and *lidocaine*, are active antiarrythmic agents. Annelation of a second aromatic ring is consistent with bioactivity. *Bunaftine (21)* is such an agent, prepared simply from reaction of the acid chloride of 1-naphthoic acid and β-dimethylaminoethylbutylamine.[7]



(20)



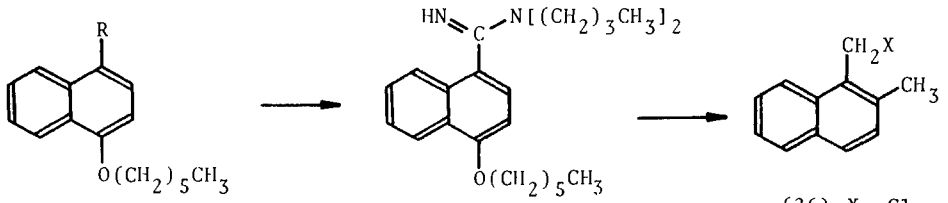
(21)



(22)

Interestingly, when *propranolol* is quaternized with methyl chloride, it loses its β-blocker activity and becomes the antiarrythmic agent *pranolium chloride (22)*.[8]

A number of amidines have anthelmintic activity. *Bunamidine (25)*, indicated for treatment of human pinworm infestations, is prepared from α-naphthylhexyl-ether *(23)* by Friedel-Crafts type reaction with cyanogen bromide and aluminum chloride to give nitrile *(24)*. This, then, is reacted with the magnesium bromide salt of di-n-propylamine leading to the naphthamidine structure *(25)*.[9]



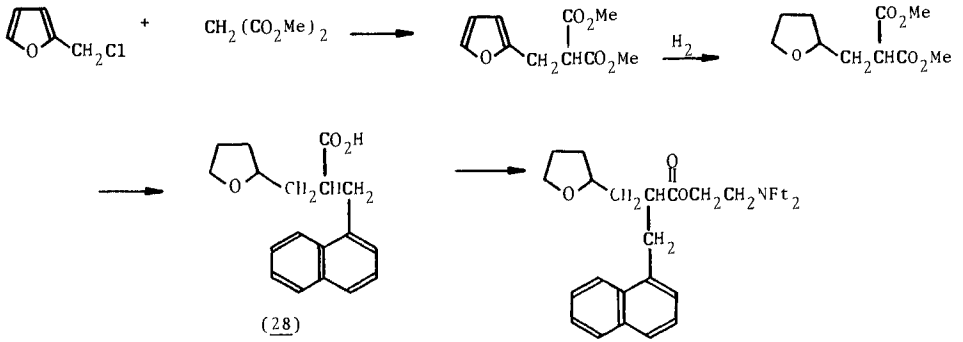
(23) R = H
(24) R = CN

(25)

(26) X = Cl
(27) X = ONH_2

Muscle relaxant activity is found in the aminoxymethylnaphthalene structure of *nafomine (27)*. The synthesis proceeds from 1-chloromethyl-2-methylnaphthalene *(26)*, which is reacted with N-carbethoxyhydroxylamine and base. In this way, the basic nitrogen is protected as the carbamate. Loss of the carbethoxy group either during reaction or on workup affords *nafomine (27)*.[10]

Certain ethanolamine analogues are active as CNS stimulants if they can be transported across the blood-brain barrier. One technique for bringing this about is to esterify them. One agent designed for this purpose, but which is more interesting as a vasodilator, is *nafronyl (29)*.[11] The acid component is synthesized by condensing furfuryl chloride and methyl malonate followed by catalytic reduction, alkylation with 1-chloromethylnaphthalene and saponification/decarboxylation to give 28.[12] Esterification with N,N-diethylethanolamine produces *nafronyl (29)*.

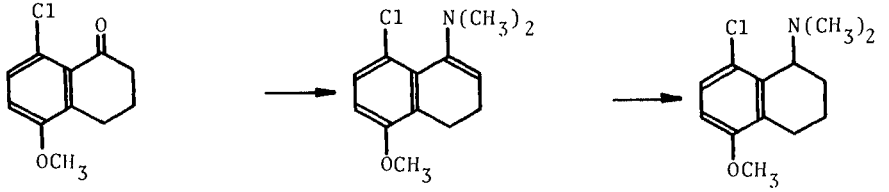


(28)

(29)

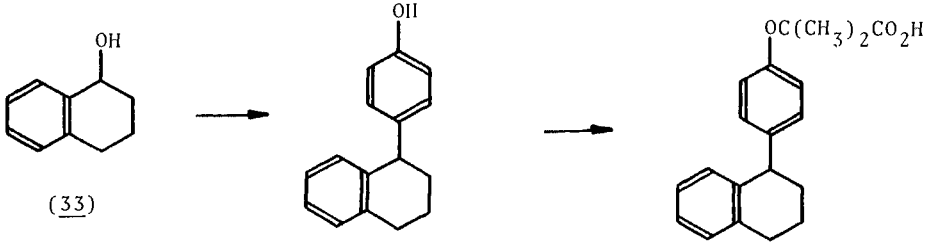
A number of products in which one of the naphthalene rings has been reduced have interesting pharmacological properties. Reaction of tetralone 30 with dimethylamine under $TiCl_4$ catalysis produces the corresponding enamine *(31)*. Reaction with formic acid at room temperature effects reduction of the

eneamine double bond to product the tranquilizer and anti-Parkinsonian agent, *Iometraline (32)*.[13].



(30) (31) (32)

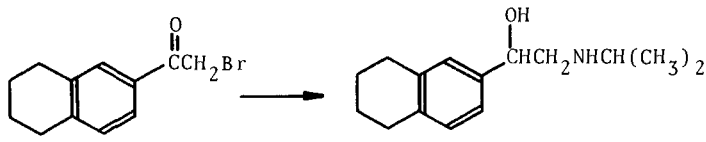
Branched aryloxyacetic acids often have hypochloesterolemic activity. When tetralol *33* is reacted with phenol in a Friedel-Crafts reaction, α-tetralin derivative *34* is formed. This is reacted with ethyl α-bromoisobutyrate and saponified to produce the hypolipidemic agent, *nafenopin (35)*.[14]



(33) (34) (35)

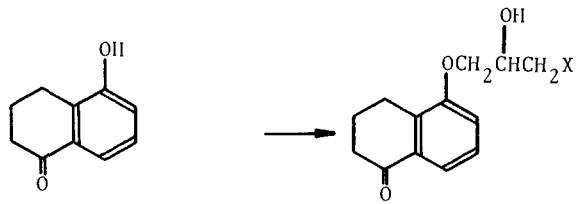
As noted above, phenylethanolamines are usually β-adrenergic agonists, whereas phenylpropanolamines show antagonist activity. A small series of phenylethanolamine blockers is, however, known. When the haloatom of ω-bromo-5,6,7,8-tetrahydro-2-acetonaphthone *(36)* is displaced with isopropylamine and the

carbonyl group is reduced catalytically, the adrenergic blocking agent *bunitridine (37)* is produced.[15]



(36) (37)

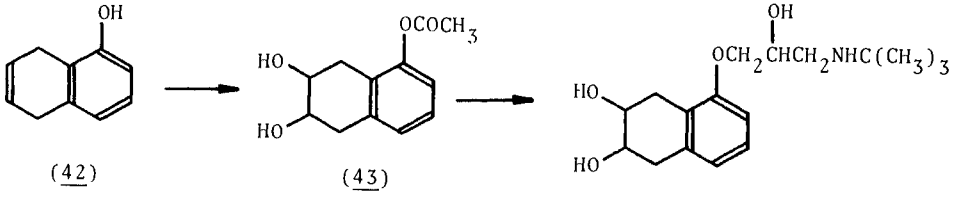
A number of tetralins with the appropriate side chains have β-adrenergic blocking activity. Presumably, the tetralin ring provides greater lipid solubility than the corresponding benzenes. *Bunolol (41)* is synthesized from phenolic tetralone *(38)* by sequential reaction with 2,3-dihydroxypropyl chloride (to *39*), tosyl chloride (to *40*), and t-butylamine to give *bunolol*.[16] Restoration of a considerable amount of the water solubility of this small group of drugs is accomplised by incorporating a glycol moiety in the reduced ring. When 5,8-dihydronaphthol *(42)* is acetylated and then hydroxylated *via* the Woodward



(38)

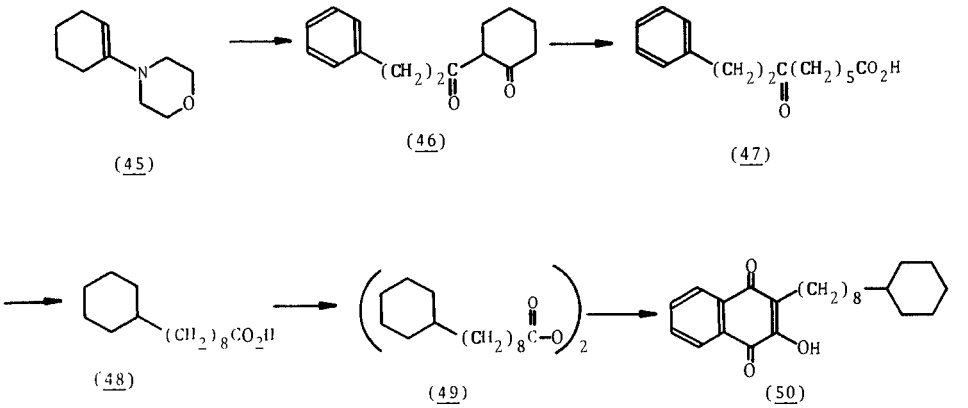
(39) X = OH
(40) X = $OSO_2C_6H_4CH_3$
(41) X = $NHC(CH_3)_3$

modification of the Prevost process (silver acetate and iodine), glycol *43* is formed. The rest of the molecule is constructed in the usual way involving the sequence: saponification to the phenol, alkylation with epichlorohydrin, and displacement with t-butylamine to produce *nadolol (44)*, a β-adrenergic blocking agent.[17]



(42) (43) (44)

Despite the best efforts of the World Health Organization, malaria remains a widespread tropical disease with substantial mortality. Of the many structural types explored in attempts to find prophylactic and chemotherapeutic agents, some have been naphthoquinones. During World War II, a large number of such quinones with aliphatic side chains were investigated. Several were active in ducks but not in man, and the reason for this difference was traced to man's ability to inactivate these materials by hydroxylation. To counter this, some agents with relatively very large hydrocarbon sidechains were made. For example, acylation of cyclohexanone enamine *45* with dihydrocinnamoyl chloride produced *46*, which underwent ring-opening diketone cleavage with base to give acid *47*. Wolff-Kishner reduction and hydrogenation

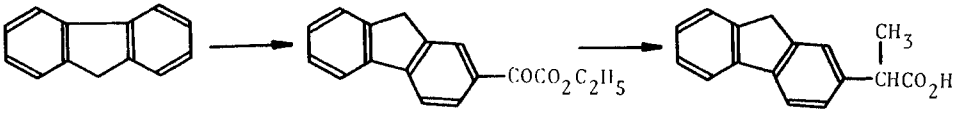


over a platinum catalyst produced saturated acid *48* that was converted to the acid chloride with $SOCl_2$ and then to the acyl peroxide *(49)* with H_2O_2 and pyridine. Heating *49* in acetic acid along with 2-hydroxynaphthoquinone resulted in radical formation and alkylation to produce the antimalarial agent, *menoctone (50)*.[18]

3. FLUORENES

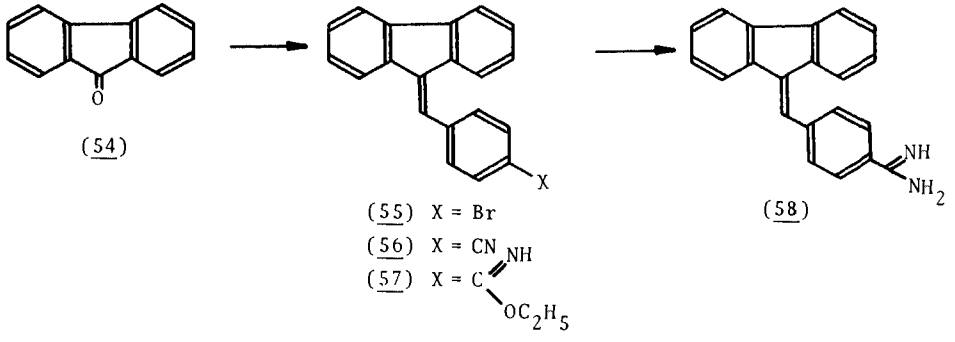
Many nonsteroidal antiinflammatory agents are acids and are believed to act by inhibiting prostaglandin synthesis. The synthesis of one such agent, *cicloprofen (53)*, is illustrative. When fluorene *51* is acylated by ethyl oxalylchloride and $AlCl_3$, ketoester *52* results. Reaction with methyl Grignard reagent, acid dehydration of the tertiary carbinol, and catalytic reduction of the resulting terminal olefinic linkage produces the antiinflammatory agent, *cicloprofen*

(53).[19] Elements of the structure of *ibuprofen* and its congeners are clearly visible in *cicloprofen*.



(51) (52) (53)

A number of amines are also nonsteroidal anti-inflammatory agents. One such agent was uncovered while searching for estrogenic substances. 9-Fluorenone *(54)* undergoes Grignard addition and dehydration with p-bromobenzylmagnesium bromide to give *55*. Displacement of halogen with CuCN gives nitrile *56*, which can be converted to the amidine in the usual way. Reaction with ethanol under acid-catalyzed anhydrous conditions leads to iminoether *57* which undergoes displacement with liquid ammonia to give the antiinflammatory agent, *paranyline (58)*.[20]



(54)

(55) X = Br

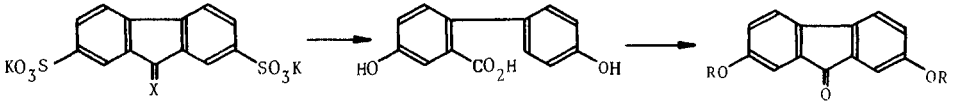
(56) X = CN

(57) X = C(=NH)OC2H5

(58)

One substance intended to be an antiinflammatory agent has achieved much greater prominence because it

is an interferon inducer and is therefore protective against viral infections. This drug is *tilorone (63)*.[21] In its synthesis, fluorene *(51)* is sulfonated and converted to its potassium salt *(59)*. This is oxidized with $KMnO_4$ to the fluorenone *(60)*. Upon KOH fusion, nucleophilic substitution to the *bis*-phenol occurs, accompanied by ring cleavage, to give *61*. Friedel-Crafts cyclization ($ZnCl_2$) restores the fluorenone system *(62)*. Ether formation with β-bromotriethylamine (probably via the aziridinium) produces *tilorone (63)*.



(59) X = H_2
(60) X = O

(61)

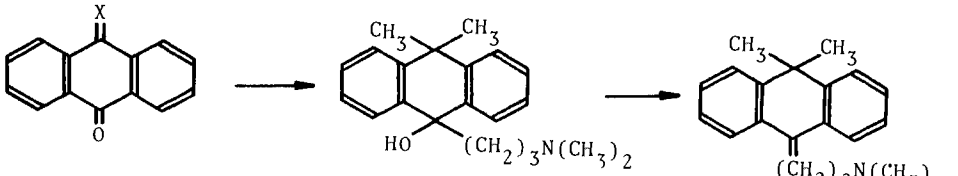
(62) R = H
(63) R = $(CH_2)_2N(C_2H_5)_2$

4. ANTHRACENES

Anthracenes are planar by virtue of the necessity of maintaining aromaticity. When the central ring is reduced, an overall "butterfly" conformation is achieved. For reasons that are not yet understood at the molecular level, this conformation is often associated with central antidepressant activity.

The methylene group of anthrone *64* is acidic by virtue of doubly vinylic activation by the carbonyl group. Thus, treatment with methyl iodide and base leads to the 9,9-dimethyl derivative *65*. Grignard reaction with δ-dimethylaminopropyl magnesium chloride

gives tertiary carbinol *66* and subsequent acid dehydration produces *melitracen (67)*, an antidepressant.[22]



(64) X = H_2
(65) X = $(CH_3)_2$

(66)

(67)

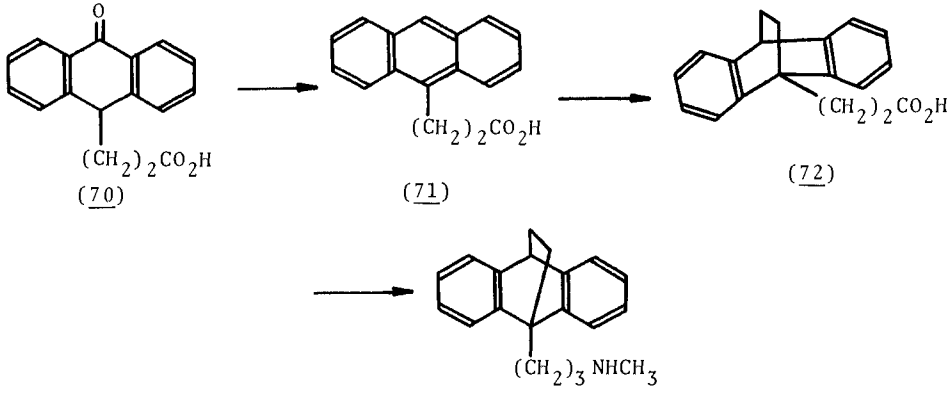
The same nonpolar conformation can be achieved by conversion to bicyclic structures. 1,4-Cycloaddition of ethylene to anthracene-9-carboxylic acid gives acid *68*. Successive conversion to the N-methylamide, via the acid chloride, followed by reduction with lithium aluminum hydride produced *benzoctamine (69)*, a sedative and muscle relaxant.[23]

(68)

(69)

Lengthening the side chain produces the antidepressant *maprotiline (73)*, which has a topological relationship to the clinically useful tricyclic antidepressants. The requisite acid is constructed by conjugate addition of the carbanion of anthrone *(64)* to acrylonitrile, followed by hydrolysis to give *70*. Reduction of the carbonyl group with zinc and ammonia gives anthracene *71* by dehydration of the intermediate

alcohol function. Diels-Alder reaction with ethylene gives *72*, which is converted to *maprotiline (73)*[23] by the same three-step sequence as used for *benzoctamine*.



(70) (71) (72)

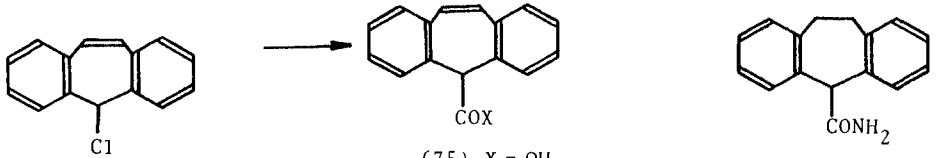
(73)

5. DIBENZOCYCLOHEPTANES AND DIBENZOCYCLOHEPTENES

Drugs in this structural class have effected a revolution in the treatment of severely depressed patients such that deinstitutionalization is a feasible public policy. The compounds often show other CNS activities which depend on the length of the side chain. One-carbon chains generally lead to anticonvulsant activity; amines separated from the nucleus by three carbons usually convey antidepressant activity. Selected examples possess significant anticholinergic activity.

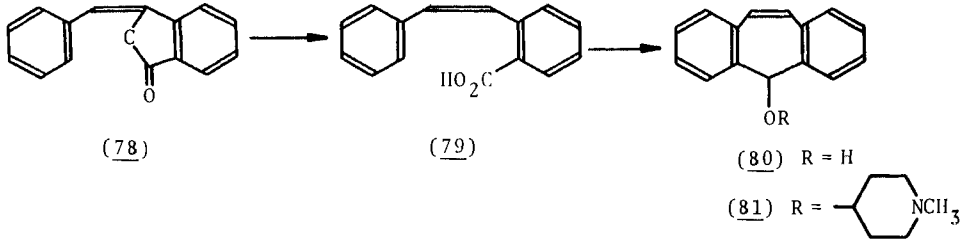
Reaction of chlorodibenzocycloheptatriene *74* with butyl lithium, followed by carbonation produces acid *75*, which is converted by ammonia, via the acid chloride, to *citenamide (76)*, an anticonvulsant.[24] The partially saturated analogue *77* is prepared

essentially the same way from chlorodibenzocycloheptadiene and is *cyheptamide*, also an anticonvulsant.[25] In the dihydro series the two benzene rings are not only out of plane, but also helical with respect to one another.



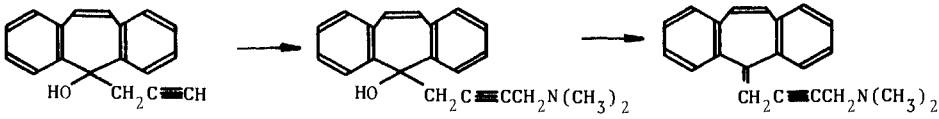
(74) (75) X = OH (76) X = NH_2 (77)

Base-catalyzed condensation between phenylacetic acid and phthalic acid produces enol lactone *78*, which is reduced to benzoate *79* with HI and phosphorous. Friedel-Crafts cyclization by polyphosphoric acid followed by reduction produces alcohol *80*. This alcohol forms ethers exceedingly easily, probably *via* the carbonium ion. Treatment with N-methyl-4--piperidinol in the presence of acid leads to the antidepressant *hepzidine (81)*.[26]



(78) (79) (80) R = H (81) R =

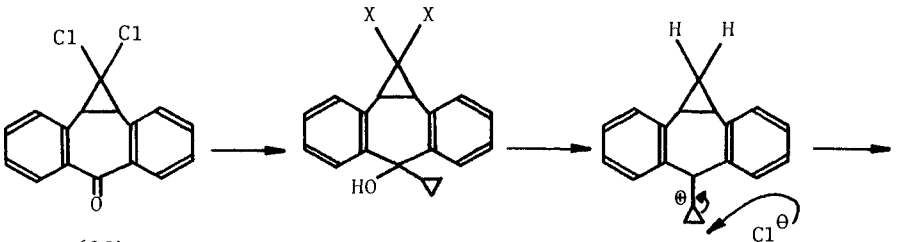
Inclusion of an acetylenic linkage as part of the side chain is apparently consistent with antidepressant activity. Reaction of propargyl magnesium bromide with dibenzocycloheptadieneone leads to carbinol *82*. A Mannich reaction with formaldehyde and dimethylamine leads to *83* which, upon dehydration with $SOCl_2$ and pyridine, was transformed into *intriptyline (84)*, an antidepressant.[27]



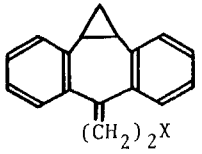
(82) (83) (84)

Rigidity can be achieved with retention of the overall molecular conformation by use of a cyclopropyl ring in place of the olefinic bond bridging the two benzenes. Treatment of dibenzocycloheptatrieneone with dichlorocarbene generated from dichloroacetic ester and sodium ethoxide gives addition product *85*. Reaction with cyclopropyl Grignard reagent gives carbinol *86* from which the *gem*-dihaloatoms are removed by lithium and t-butanol to give *87*. Reaction of the latter with HCl generates chloride *88 via* the intermediate cation *(87a)*. Chloride displacement with methylamine completes the synthesis of antidepressant *octriptyline (89)*.[28]

Incorporation of the side chain amino group into a ring leads to tranquilizers. This is of special interest in that the amino group is now separated



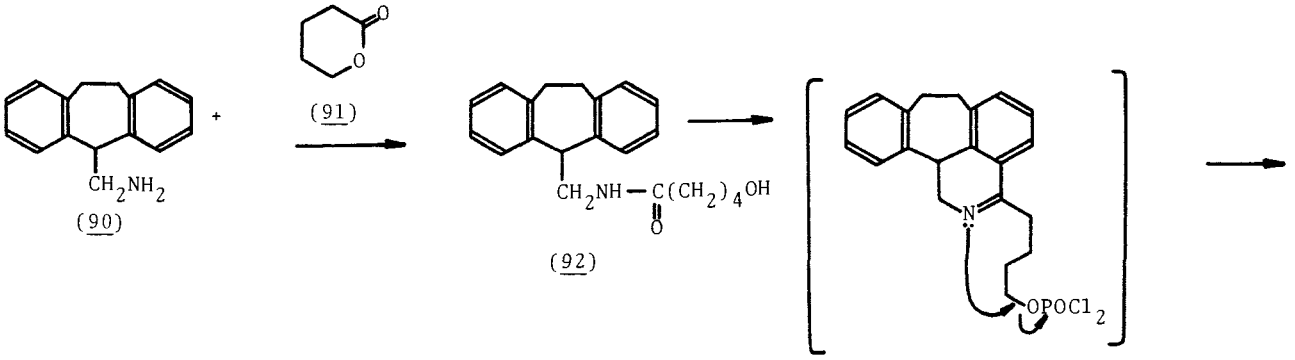
(85) (86) X = Cl_2 (87) X = H_2 (87a)

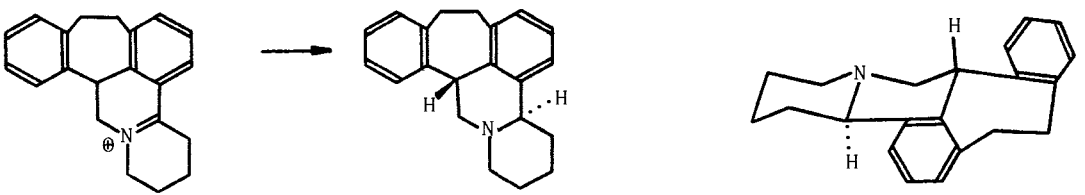


(88) X = Cl
(89) X = $NHCH_3$

from the tricyclic ring system by a smaller distance than is common to the other agents discussed. Reaction of amine *90* with δ-lactone *91* gives hydroxyamide *92*. Cyclodehydration proceeds apparently through the expected Bischler-Napieralski intermediate *93* which cyclizes further to imine *94*. Reduction with sodium borohydride or hydrogenation with platinum catalyst produces the undesired *cis* isomer. On the other hand, zinc and acetic acid reduction leads to the thermodynamically stable *trans* product, the minor tranquilizer *taclamine (95)*.[29] The apparent conformation of *taclamine* is *96*.

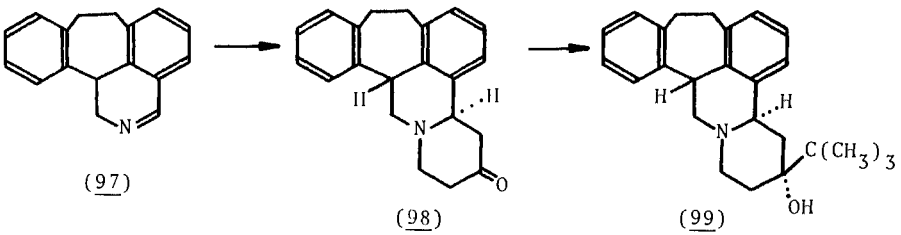
An alternate means of forming *96* arises from reaction of imine *97* with methylvinylketone in a variant of the Robinson annulation reaction. This





(94) (95) (96)

can proceed in two directions, but *98* is the major product. Formation of the dithiolane derivative with $(CH_2SH)_2$ and BF_3 followed by Raney nickel desulfurization also leads to *taclamine*. The availability of ketone *98* makes it possible to prepare more highly functionalized derivatives. Addition, for example, of t-butyl lithium leads to tranquilizer *butaclamol (99)*.[30] The large alkyl group is equatorial.

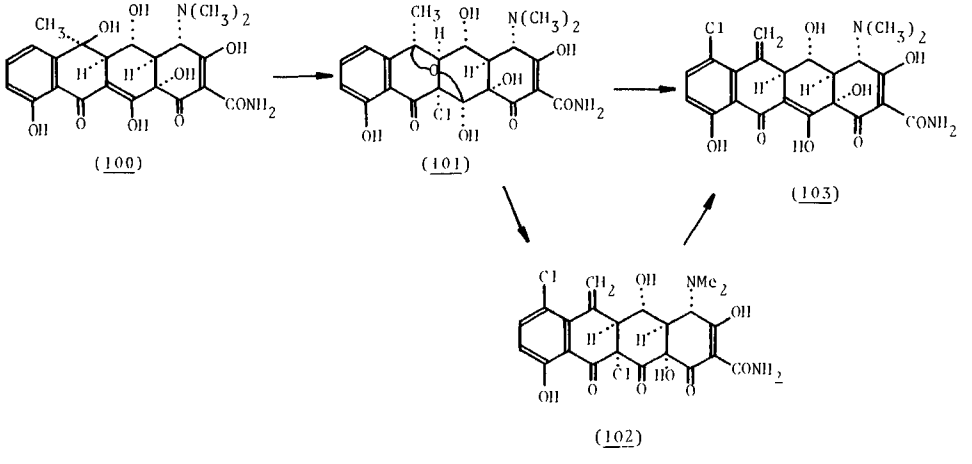


(97) (98) (99)

6. TETRACYCLINES

Still among the most frequently prescribed drugs, the antibiotic tetracyclines have decreased in popularity recently due to development of bacterial resistance in the clinic. The search for improved agents goes on.

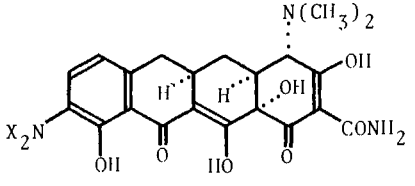
When oxytetracycline *(100)* is reacted with N-chlorosuccinimide in dimethoxyethane, the active methine group at C_{11a} reacts and, apparently, there is formed a hemiketal bond between the C_6-OH and the C_{12}-ketogroup *(101)*. Dehydration with anhydrous HF of the tertiary, benzylic C_6-OH group takes an exocyclic course, partially because aromatization to



(100) (101) (103) (102)

the naphthalene system is forbidden by the presence of the blocking C_{11a}-chlorine atom. The product is sufficiently stable to allow electrophilic aromatic substitution. Reaction with N-chlorosuccinimide in liquid HF results in formation of the 7,11a-dichloro-6-methylene analogue *(102)*. When the latter is subjected to chemical reduction (with sodium bisulfite, for example), the labile C_{11a}-Cl atom is removed and *meclocycline (103)* is formed. This broad spectrum antibiotic is about six times more potent *in vitro* against *Klebsiella pneumoniae* than *methacycline* itself.[31]

Nitro derivative *104* is an undesired side product in the synthesis of *minocycline*.[32] Upon catalytic reduction it is converted to the corresponding aniline, *amicycline (104)*. This substance is slightly less than half as active *in vitro* against *Staphylococcus aureus* than chlortetracycline *(100)*, but is nearly twice as active as its C_7 isomer.[33,34]



(104) X = O
(105) X = H

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8

Five-Membered Heterocycles

Heterocyclic compounds occupy a central position among those molecules that make life possible. In support, one need only mention the molecular basis of continuation of a given species, *i.e.*, the heterocyclic purines and pyrimidines that form the building blocks of DNA and RNA. This realization, along with some early adventitious successes with heterocyclic drugs and the frequency with which the active principles of the important vegetable drugs of antiquity turned out to be heterocycles have led the medicinal chemist to devote a good deal of attention to this class of compounds as a source of potential therapeutic agents. Perhaps as a result of this, somewhat over half the organic drugs to have been assigned generic names are heterocyclic molecules. It does not, however, follow that all biologically active molecules that contain a heterocyclic moiety owe

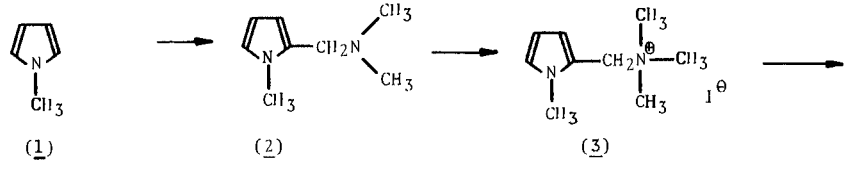
their activity to that fragment. As will be seen below, some classes of heterocycles do share a common biological response; in those cases it is of course a fair assumption that the heterocycle is a significant part of the pharmacophore. Cases are equally frequent, however, where it is apparent that the ring contributes little of a specific nature to the activity. A relatively neutral heterocyclic ring can often be substituted for a benzene ring with little qualitative effect on biological activity. For example, medicinal chemists often substitute a thiophene ring for a benzene ring in a drug. This practice is the venerable device of biological isosterism.

1. DERIVATIVES OF PYRROLE

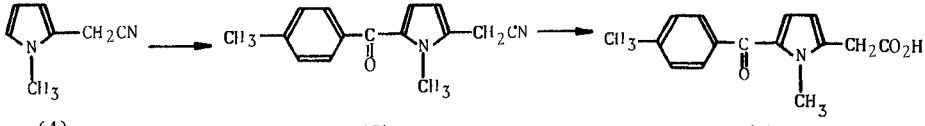
Molecules whose sole heterocyclic moiety consists of a pyrrolidine ring are dealt with elsewhere in this book. There is a wealth of evidence to indicate that N-alkylpyrrolidine is usually a surrogate for a tertiary amine.

The large class of antiinflammatory phenylacetic acids are treated at some length in Chapter 4. A number of these agents consist of acetic or propionic acids substituted by an aroyl group. It is of interest that the central benzene ring of these molecules can be replaced by pyrrole with retention of activity. For example, Mannich reaction of N-methylpyrrole affords the corresponding dimethylaminomethyl derivative *(2)* and treatment with methyl iodide affords the quaternary salt *(3)*. Displacement of the quaternary amine by means of cyanide leads to the substituted

acetonitrile *4*.[1] Friedel-Crafts acylation of that intermediate with the acid chloride from p-toluic acid gives a mixture of the 4-aryl ketone and the desired ketone *5*. Hydrolysis with sodium hydroxide completes the synthesis of the antiinflammatory agent *tolmetin (6)*.[2]

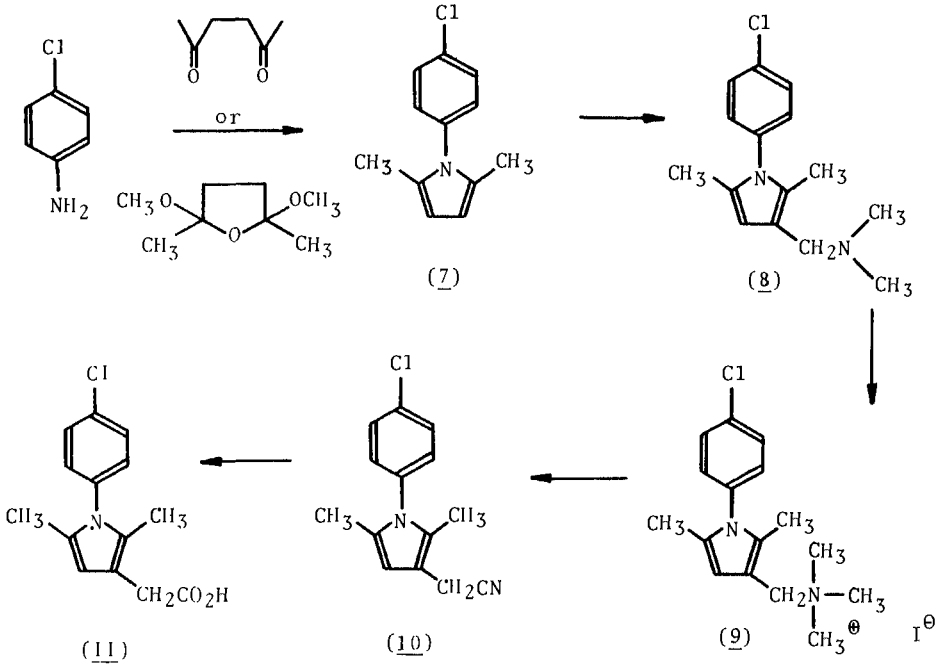


(1) (2) (3)



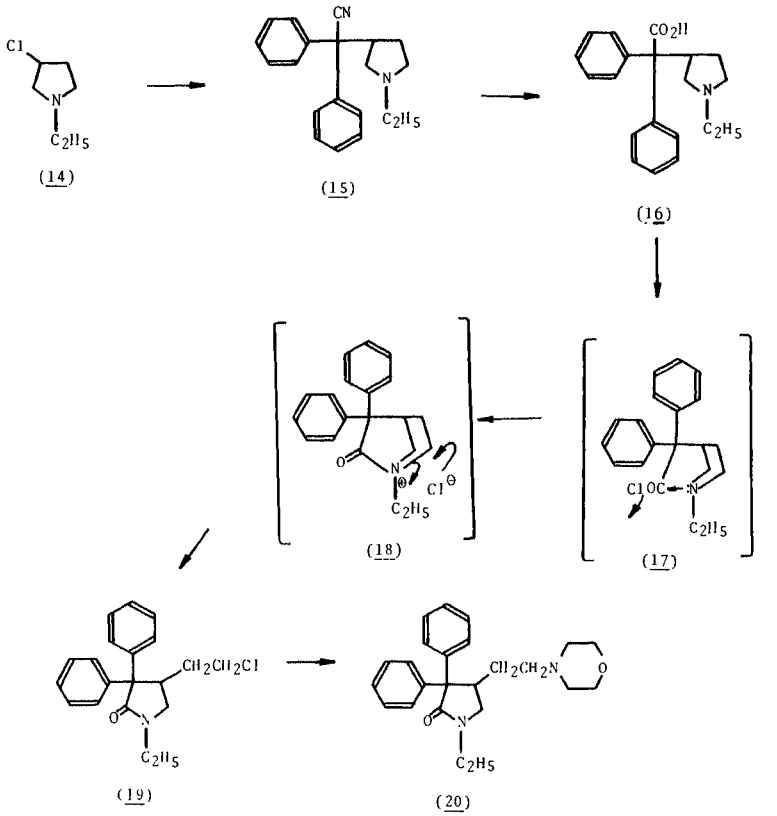
(4) (5) (6)

The wide latitude of structural variation consistent with bioactivity in this series is illustrated by the observation that antiinflammatory activity is maintained even when the second aromatic group is attached directly to the pyrrole nitrogen rather than to the heterocyclic ring via a carbonyl group as in the previous case. Condensation of p-chloroaniline with hexane-2,5-dione (or its dimethoxytetrahydrofuran equivalent) affords pyrrole *7*. The acetic acid side chain is then elaborated as above. Thus, Mannich reaction leads to the dimethylaminomethyl derivative *8*, which is in turn methylated *(9)*; the quaternary nitrogen replaced by cyanide to afford *10*. Hydrolysis of the nitrile then gives *clopirac (11)*.[3]



A change in both the substitution pattern and the oxidation state of the heterocyclic ring leads to a compound that exhibits antidepressant activity. This agent, *cotinine (13)*, is found in nature as a product from the autoxidation of nicotine *(12)* (note the anagram). The compound can also be obtained in decidedly modest yield by oxidation of nicotine with hydrogen peroxide.[4]

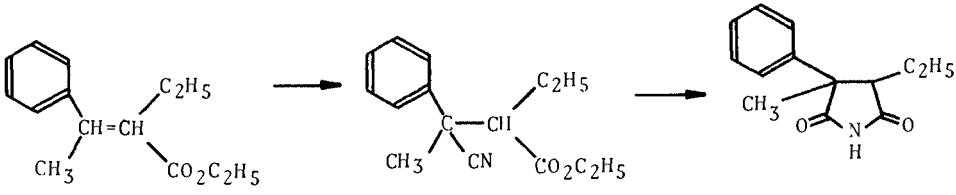
A more highly substituted pyrrolidone, *doxapram*, shows activity as a respiratory stimulant. Preparation of this agent involves an interesting rearrangement, which in effect results in a ring exchange reaction. Alkylation of the anion from diphenylacetonitrile with the chloropyrrolidine *14* affords *15*. Hydrolysis of the nitrile function leads to the



expected acid *16*. Treatment of *16* with thionyl chloride presumably gives first the acid chloride *17*; internal acylation would then lead to the bicyclic

quaternary ammonium salt *18*. Attack on the two-carbon bridge by the gegenion would afford the observed chloroethyl pyrrolidone *19*. (Regioselectivity may be due to the hindered environment about the one carbon bridge.) Displacement of chlorine by morpholine completes the synthesis of *doxapram (20)*.[5]

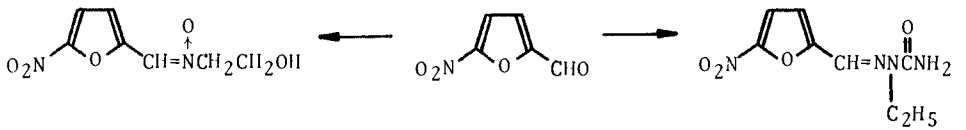
The discovery of the sedative/hynoptic activity of derivatives of barbituric acid has led to very extensive dissections of that molecule. One outcome of this work is the realization that acylurea and acylamide derivatives often exhibit CNS depressant activity. A fair number of such molecules have been prepared that contain a succinimide or glutarimide pharmacophore. For example, Michael addition of cyanide to the stereochemically undefined cinnamate *21* affords intermediate *22*. Acid hydrolysis leads directly to the tranquilizer *fenimide (23)*.[6] Although the stereochemistry of this compound is not specified, the fact that the ethyl group resides on an enolizable center makes it probable that this is in fact the thermodynamically more stable isomer.



(21) (22) (23)

2. DERIVATIVES OF FURAN

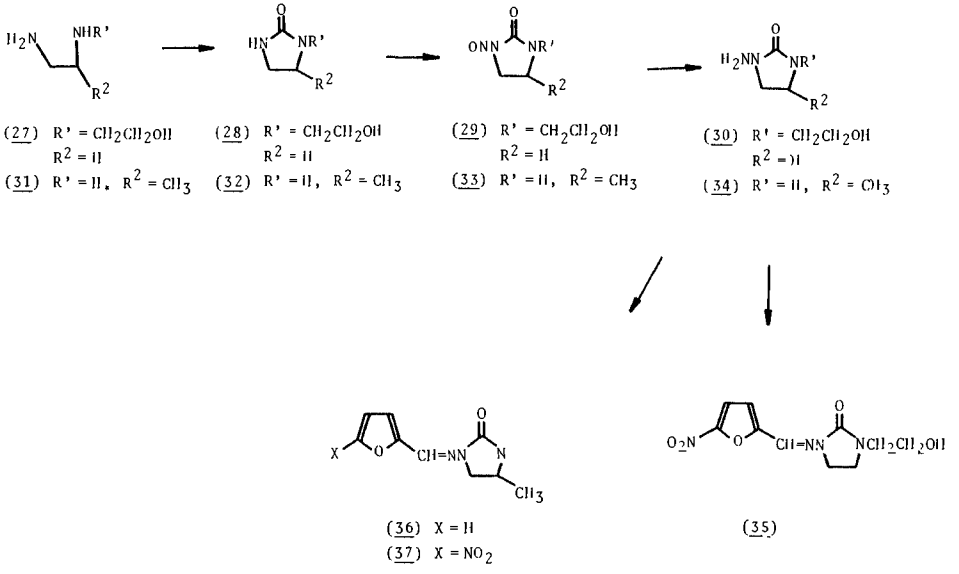
Many carbonyl derivatives of 5-nitrofurfural exhibit bacteriostatic activity. For example, the oxime, *nifuroxime*, has found some clinical use in the treatment of infections of the gastrointestinal and urinary tract. An impressive amount of work has been devoted to such derivatives in attempts to alter both their distribution and pharmacodynamics by modification of the substituents on the imine nitrogen. Much of this was detailed in the earlier volume. By way of additional examples, reaction of 5-nitrofurfural *(24)* with N-(2-hydroxyethyl)hydroxylamine gives the antimicrobial agent *nitrofuratrone (25)*,[7] probably the only nitrone to have been assigned a generic name. In a similar vein condensation with 2-ethylsemicarbazide leads to the semicarbazone *nitfursemizone (26)*,[8] an antiprotozoal agent for use in poultry.



(25) (24) (26)

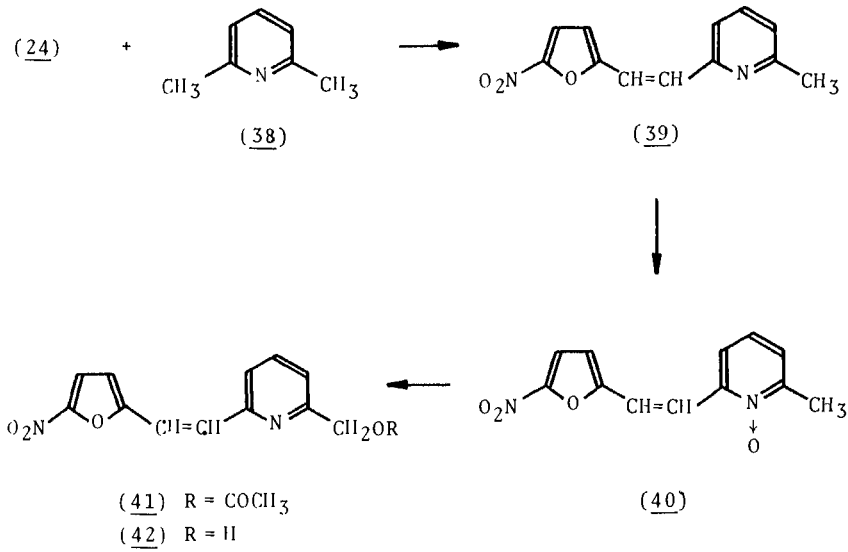
N-Aminoimidazolinones have found extensive use as synthons for such nitrofurans. Reaction of an appropriate 1,2-diamine *(27, 31)* with urea gives the desired heterocycle *(28, 32)*. Nitrosation with

nitrous acid, followed by reduction of the intermediate *(29, 33)* with zinc, gives the desired hydrazine *(30, 34)*. Condensation of *30* with *24* affords *nifurdazil (35)*.[9] In a modification of the usual scheme, condensation of *34* with furfuraldehyde gives the hydrazone *36*. Nitration of that intermediate affords *nifurimide (37)*.[10]



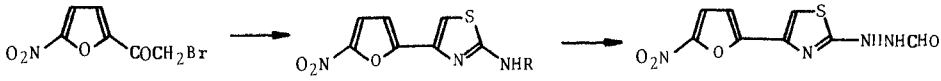
It is of interest that antibacterial activity can be retained even when the imine carbon-nitrogen bond is replaced by a carbon to carbon double bond. Base-catalyzed condensation of 5-nitrofurfuraldehyde *(24)* with 2,6-dimethylpyridine *(38)* affords olefin *39*. Treatment of this compound with hydrogen peroxide gives the corresponding N-oxide *(40)*. Heating of

that intermediate in acetic anhydride leads to acetoxylation of the 2-methyl group by the Polonovski reaction. Hydrolysis of the ester group affords *nifurpirinol (42)*.[11]

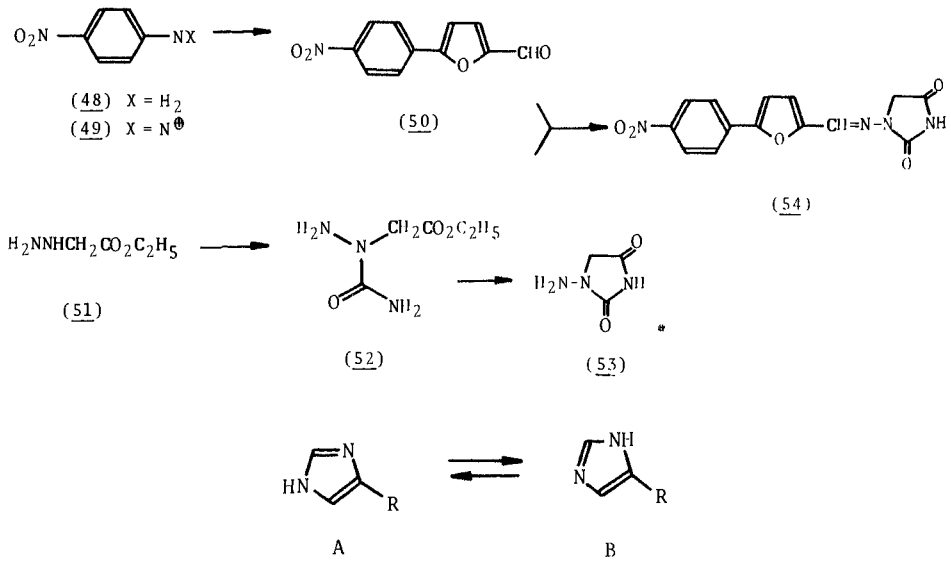


Taking the spacer ethylene moiety out and attaching a heterocyclic ring directly to the nitrofuran ring also results in an active antimicrobial agent. Condensation of bromoketone *43* (obtainable by halogenation of the corresponding acetylnitrofuran) with thiourea gives the aminothiazole *44*. Although the detailed mechanism of this well known method for forming thiazoles is still under discussion, the reaction at least formally represents conversion of the ketone to an imine and displacement of the halogen by sulfur. Next, the primary amine is nitrosated

(45), and this intermediate is reduced to the hydrazine *(46)*. Acylation of the more basic terminal nitrogen with formic acid completes the synthesis of the antimicrobial agent *nifurthiazole (47)*.[12]



Interposition of a phenyl ring between the furan and the nitro group radically changes the biological activity; product from this formal replacement is in fact a centrally acting muscle relaxant. In order to prepare the target lead, reaction of the diazonium salt *(49)* from p-nitroaniline *(48)* with furfural using cupric chloride as catalyst affords the coupling product *50*. In a convergent synthesis, glycine derivative *51* is converted to the urea *52*. Acid-catalyzed cyclization leads to aminohydantoin *53*. Semicarbazone formation from aldehyde *50* with hydrazine derivative *53* affords *dantrolene (54)*.[13]



3. DERIVATIVES OF IMIDAZOLE

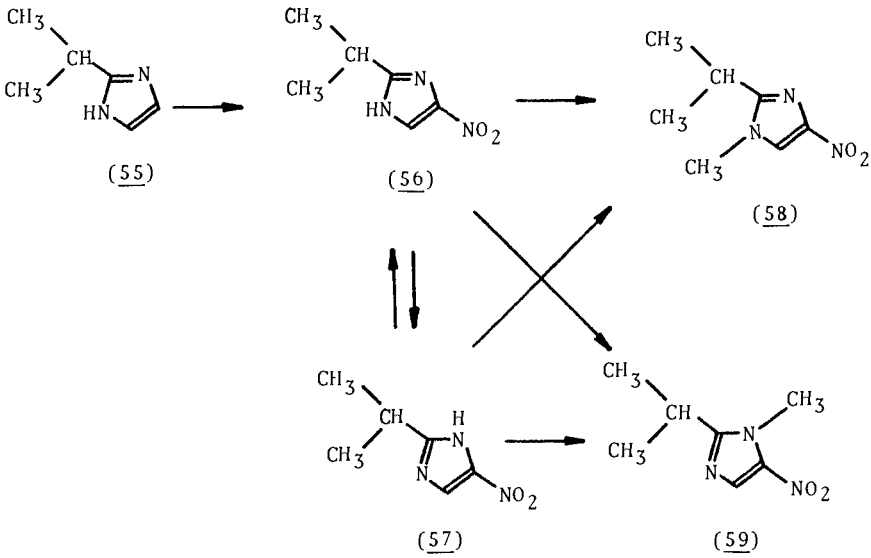
In its various oxidation states, the imidazole nucleus has proven to be an unusually fertile source of medicinal agents. Nitroimidazoles are very often associated with antimicrobial activity, whereas imidazolines are often present in drugs acting as adrenergic agents. These considerations suggest, as a working hypothesis, that these particular imidazole derivatives are integral parts of the respective pharmacophores.

While nitrofurans are often prepared as antibacterial agents, nitroimidazole forms the basis for an extensive class of agents used in the treatment of infections by the protozoans. Unlike bacterial infections, protozoal infections are seldom life-threatening. The physical discomfort occasioned by such infections is, however, of sufficient importance to provide a useful therapeutic place for antiprotozoal agents. A particularly common set of such conditions are parasitic infections of the genitalia caused by *Trichomonas vaginalis*. These disorders are called trichomoniasis.

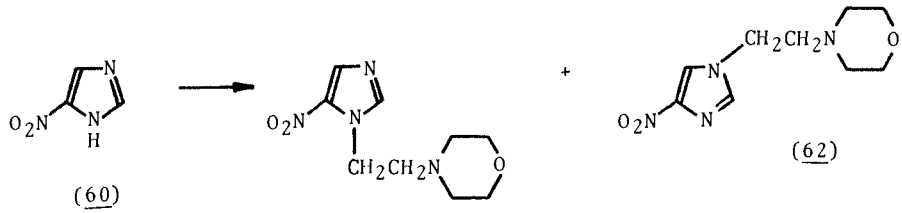
One of the problems complicating the chemistry of the imidazoles needed for preparing these agents is their structural ambiguity. Imidazoles undergo a facile tautomeric equilibrium involving a shift of the proton on nitrogen so that it is sometimes difficult to assign unambiguous structures to unsymmetrically substituted derivatives. Most drugs containing this ring system are alkylated on one of the ring nitrogens, which locks the molecule into a single tautomeric form and removes the source of ambiguity. The ambident character of imidazoles requires care in selecting those conditions that will lead to alkylation on the desired nitrogen atom.

By way of illustration, nitration of 2-isopropylimidazole *(55)* affords the 4- or 5-nitro derivative *(56, 57)*. Alkylation with methyl iodide affords isomer *58*. The same reaction carried out with dimethyl sulfate under neutral or acidic conditions provides the isomer methylated at the alternate

nitrogen atom. There is thus obtained the antiprotozoal agent *ipronidazole (59)*.[14]

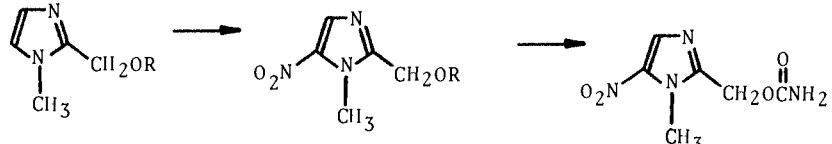


In a similar vein, alkylation of 4-(5)-nitroimidazole with N-(2-chloroethyl)morpholine affords a mixture of N-alkylated imidazoles *(61 and 62)*. The compound containing the adjacent ring substituents *(61)* is the antitrichomonal agent *nimorazole*.[15]



(60) (61) (62)

Acetylation of the hydroxymethyl imidazole *63* affords the corresponding ester *(64)*, nitration *(65)* followed by hydrolysis gives intermediate *66*, and reaction of this alcohol with potassium cyanate in hydrogen fluoride gives the carbamate *ronidazole (67)*.[16]

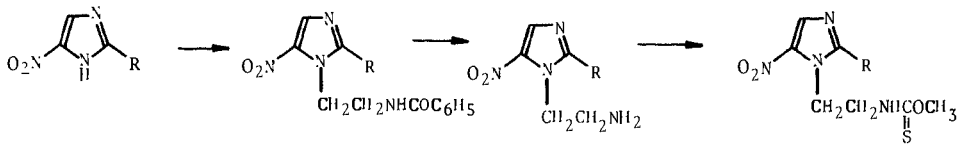


(63) R = H
(64) R = $COCH_3$

(65) R = $COCH_3$
(66) R = H

(67)

Treatment of 2-methyl-4-(5)-nitroimidazole at reduced temperatures with N-benzoylaziridine in the presence of boron trifluoride etherate leads regiospecifically to the N-alkylated derivative *(69)*. Hydrolysis of the amide function affords the primary amine *70*. Acylation of this with methylchlorothioformate affords the antiprotozoal thioncarbamate, *carnidazole (71)*.[17] The same sequence, starting with the C-2 ethyl analogue *(72)* affords *sulnidazole (75)*.[17]



(68) R = CH_3
(72) R = C_2H_5

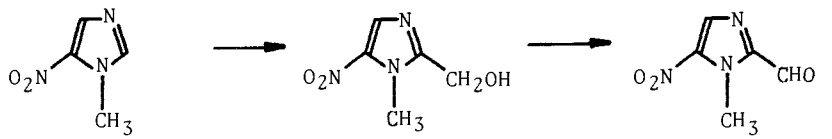
(69) R = CH_3
(73) R = C_2H_5

(70) R = CH_3
(74) R = C_2H_5

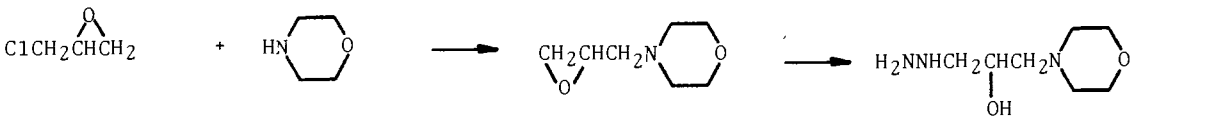
(71) R = CH_3
(75) R = C_2H_5

Hydroxymethylation (formaldehyde) of nitroimidazole *76* affords *77*, which is oxidized to aldehyde *78*. To prepare the other fragment for this convergent synthesis, reaction of epichlorohydrin with morpholine leads to the aminoepoxide *79*, which is reacted with hydrazine to afford *80*. Reaction of this substituted hydrazine with dimethyl carbonate affords oxazolinone *81* by sequential ester interchange reactions. Condensation of *81* with aldehyde *78* affords the antitrichomonal agent *moxnidazole (82)*.[18]

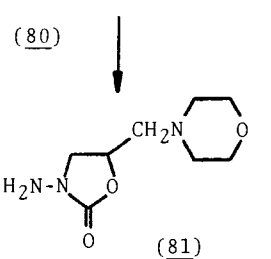
Nitroimidazoles substituted by an aromatic ring at the 2-position are also active as antitrichomonal agents. Reaction of p-fluorobenzonitrile *(83)* with saturated ethanolic hydrogen chloride affords iminoether *84*. Condensation of that intermediate with the dimethyl acetal from 2-aminoacetaldehyde gives the imidazole *85*. Nitration of that heterocycle with nitric acid in acetic anhydride gives *86*. Alkylation with ethylene chlorohydrin, presumably under neutral conditions, completes the synthesis of the antitrichomonal, *flunidazole (87)*.[19]



(76) (77) (78)



(79) (80)



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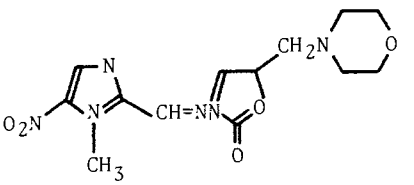
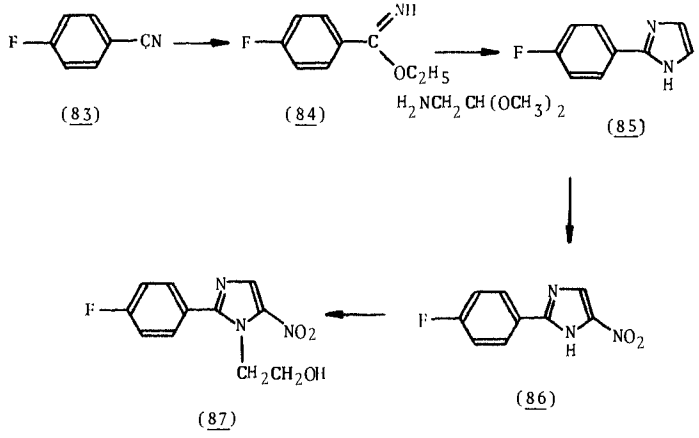
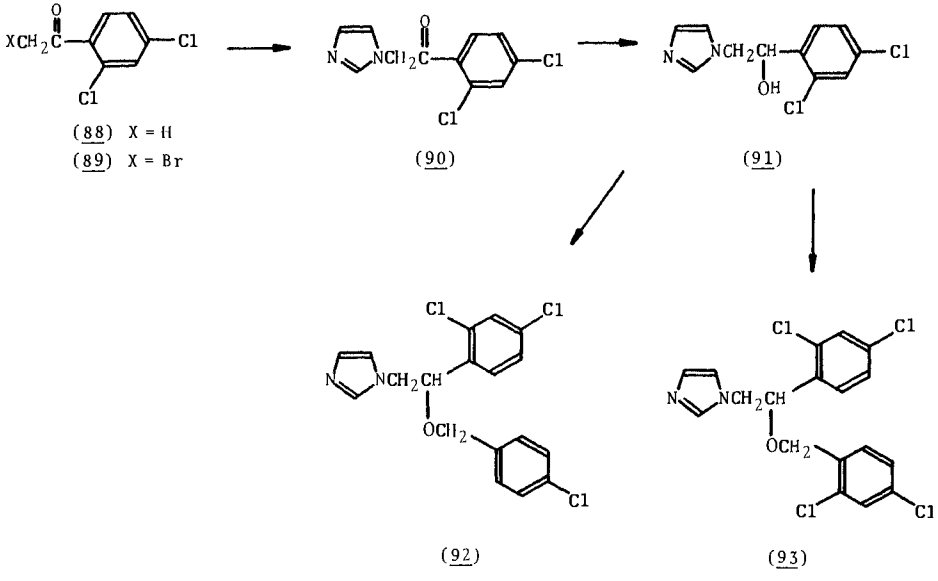


(82)



(83) (84) (85) (86) (87)

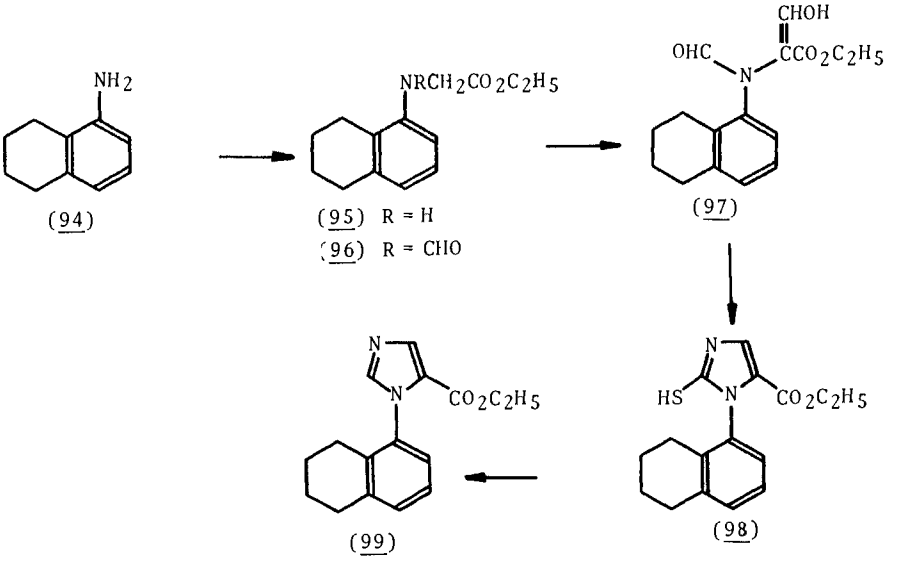
Imidazoles devoid of the nitro group no longer show useful antiprotozoal activity, however, several



(88) X = H
(89) X = Br
(90) (91) (92) (93)

such compounds have proven to be efficacious as antifungal agents. Alkylation of imidazole with bromoketone *89* prepared from 2,4-dichloroacetophenone *(89)* affords the displacement product *90*. Reduction of the carbonyl group with sodium borohydride gives the corresponding alcohol *91*. Alkylation of the alkoxide from that alcohol with 4-chlorobenzyl chloride leads to *econazole (92)*[20]; alkylation with 2,4-dichlorobenzyl chloride gives *miconazole (93)*.[20]

Ethonam (99), an imidazole derivative with a very different substitution pattern, is also reported to possess antifungal activity. To prepare it, alkylation of aminotetralin *94* with methylchloroacetate gives the glycine derivative *95*. Heating with formic acid then affords the amide *96*; this compound is then reacted with ethyl formate to yield hydroxymethylene ester *97*. Reaction with isothiocyanic acid gives the imidazole-2-thiol *98*. (The



(94) (95) R = H (96) R = CHO (97) (98) (99)

sequence may involve first hydrolysis of the formamido group, followed by addition of the amine to isothiocyanic acid; cyclization of the thiourea nitrogen with the formyl function would complete formation of the heterocycle.) Desulfurization by means of Raney nickel finishes the synthesis of *ethonam (99)*.[21]

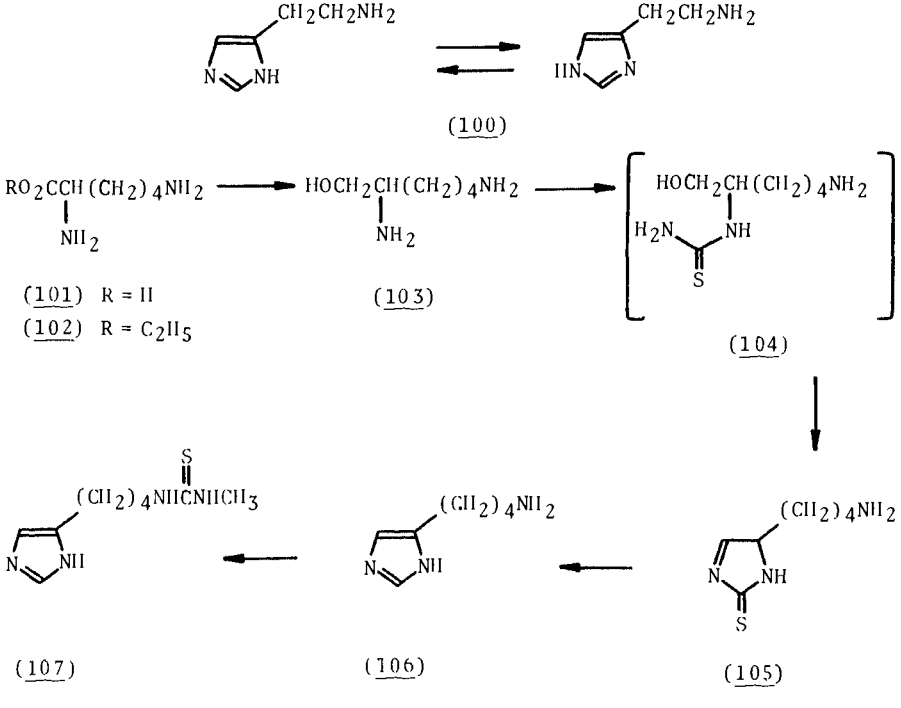
Not a hormone in the true sense of the word, histamine *(100)* does act as a potent mediator, leading to a host of biological responses. Many of the symptoms attributed to allergies owe their manifestations to exaggerated reaction to endogenous histamine released in response to an external stimulus. Secretion of gastric acid is another process under the control of histamine. It was hypothesized quite some time ago that pathological conditions traceable to excess histamine secretion or exaggerated sensitivity to that base could be treated by compounds that antagonized the response to histamine by competition for its receptor sites. The benzhydryl type antihistaminic compounds for the treatment of allergic diseases represent such competitive inhibitors.

It was noted, however, that a subset of responses known to be triggered by histamine failed to be blocked by the classical antihistaminic drugs. This, as well as further sophisticated pharmacological work, led to the classification of histamine receptors as H_1 and H_2. To simplify grossly, the H_1 receptor controls the responses familiar to every hayfever sufferer; these effects can be alleviated readily by classicial antihistamines. The latter interestingly bear little or no structural similarity to histamine

itself. The H_2 receptor on the other hand controls secretion of acid in the stomach; classicial antihistamines have no effect on histamine-induced gastric acid secretion. Excess gastric acid secretion is believed by many to be intimately involved in the etiology of ulcers and exacerbation of preexisting ulcers; thus, compounds that can act as selective antagonists to the H_2 receptor are of considerable potential therapeutic significance.

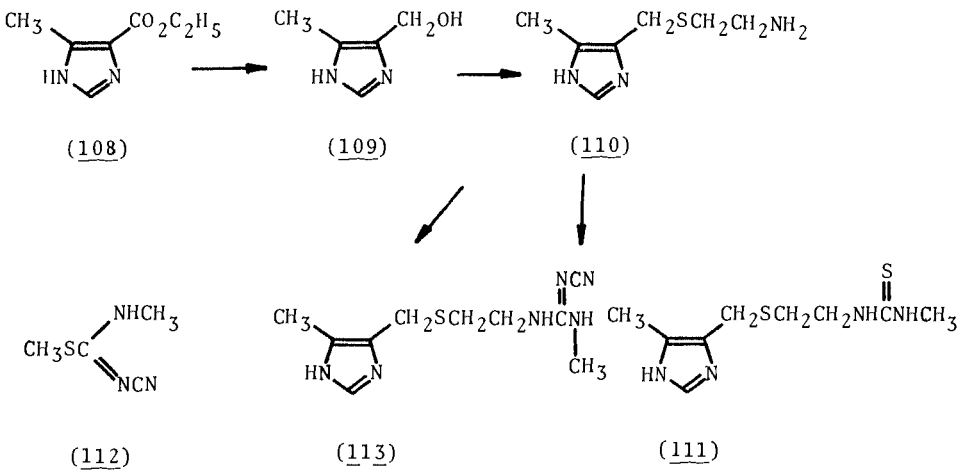
The H_1 antagonists were developed serendipitously in the course of random screening. On the other hand, development of the H_2 antagonists started from the premise that one of the best ways to produce an antagonist is to investigate compounds that bear some structural elements of the native agonists. Precedence for this came from comparison of the structure of β-adrenergic agonists and their blockers. Systematic modification of the histamine molecule achieved its first success toward the preparation of an H_2 antagonist with *burimamide* (*107*).[22] Esterification of diamino acid *101* leads to *102*. Reduction with sodium amalgam serves to convert the ester to a carbinol (*103*), and treatment of that aminoalcohol with ammonium isothiocyanate affords the imidazothione *105*, probably by the intermediacy of thiourea *104*. (Strict accounting of oxidation states seems to demand oxidation of the carbinol to an aldehyde in the course of this reaction.) Reduction of the thione with iron powder in acid probably proceeds via the enol form to afford the desired imidazole (*106*).[23] Condensation

with methyl isothiocyanate completes the synthesis of *burimamide (107).*



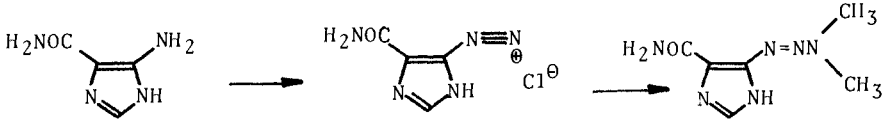
Further exploration of the histamine molecule revealed that addition of a methyl group to the 4-position led to an agonist with appreciably increased selectivity for the H_2 receptor.[24] Application of that principle to the prototype antagonist, as well as bioisosteric replacement of one of the side chain methylene groups by sulfur, affords *metiamide (111).*[25] Reduction of the imidazole carboxylic ester *108* gives the corresponding carbinol *(109).* Reaction of that with 2-mercaptoethylamine, as its hydrochloride, leads to intermediate *110.* In the strongly acid medium, the

amine is completely protonated; this allows the thiol to express its nucleophilicity without competition and the acid also activates the alcoholic function toward displacement. Finally, condensation of the amine with methyl isothiocyanate gives *metiamide (111)*. Side effects observed in some of the clinical trials with this agent were attributed to the presence of the thiourea function in the molecule. A systematic search for a functional group isoelectronic with thioureas revealed that cyanoguanides were biologically equivalent, and this substitution avoided the side effects of the former. In one of the schemes for preparing the desired product, primary amine *110* is reacted with complex nitrile *112*. The resulting



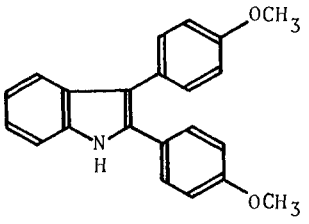
addition-elimination sequence affords the highly successful agent for the treatment of ulcers, *cimetidine (113)*.[25]

Imidazole provides the nucleus for the antineoplastic agent *dacarbazine (116)*. Diazotization of the commercially available aminoamide *114* with nitrous acid gives diazonium salt *115*. Reaction of this salt with dimethylamine under anhydrous conditions leads to *dacarbazine (116)*.[26]



(114) (115) (116)

The diaryl indole, *indoxole (117*, see Chapter 11) represents a unique nonsteroidal antiinflammatory agent in that it lacks the labile acidic proton usually found in this class of drugs. Commercialization of indoxole was precluded by its marked photosensitizing side effect. Subsequent work from another laboratory showed that biological activity was retained when the indole nucleus was replaced by imidazole. Condensation of 4,4'-dimethoxybenzil with ammonium acetate and the ethyl hemiacetal of trifluoroacetaldehyde affords the aniinflammatory agent *flumizole (120)* in a single step.[27] The reaction can be rationalized by assuming either initial formation of a carbinolamine followed by condensation with one of the aryl carbonyls, or, alternately, by formation of an imine with one of the carbonyls followed by attack on the hemiacetal. Repetition of the process and tautomerization will lead to the imidazole ring.



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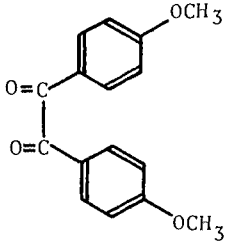

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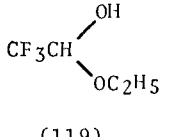

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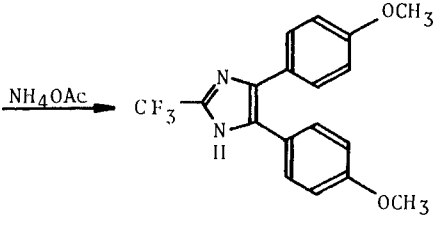


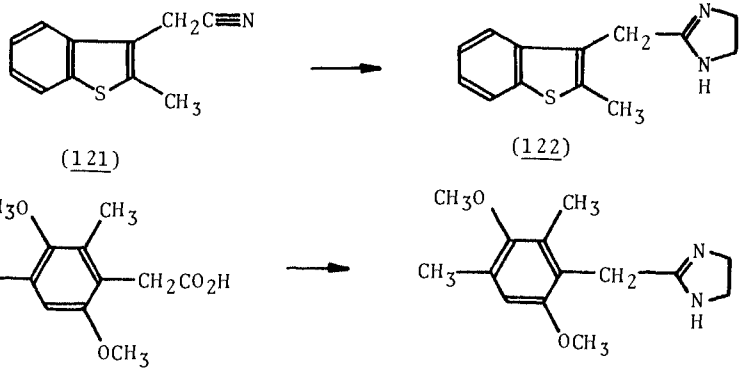
(120)

The pharmacology of both the endogenous amines and drugs that act on the sympathetic nervous system can be best explained by assuming that responses are mediated by two different types of receptors. The existence of α- and β-adrenergic receptors has by now received considerable experimental backing. (It might be added as an aside that there is considerable evidence that these two classes of receptors can be further subdivided into β_1 and β_2 and possibly α_1 and α_2 receptors.) It is an interesting fact that with few exceptions, drugs that act on the β-adrenergic system all possess some chemical elements of the endogenous agonist epinephrine.

In contrast to this, there are no such structural constraints on α-adrenergic agonists or antagonists. Some of the most active α-sympathomimetic agents in fact contain an imidazoline moiety as part of the pharmacophore. The appropriate ring system can be

formed by a variety of methods. One of the more common involves condensation of a compound containing a carbon atom at the acid oxidation level (nitrile, imino ether) with ethylenediamine. Thus, reaction of the benzothiophenoacetonitrile derivative *121* with ethylenediamine gives the adrenergic α-agonist *metizoline (122)*.[28] As expected the α-adrenergic activity of *122* is expressed as vasoconstriction. The compound is used topically as a nasal decongestant, acting on the mucosal vasculature.

In a similar vein, condensation of carboxylic acid *123* with ethylenediamine leads to *domazoline (124)*.[29]

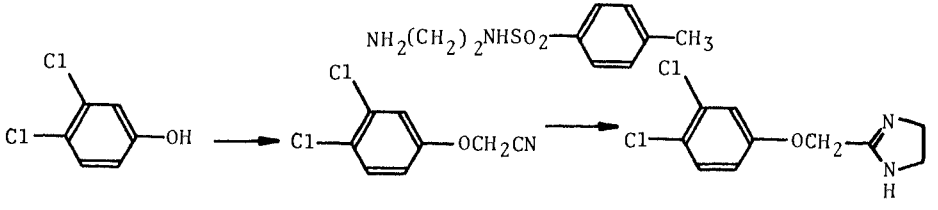


(121) (122)

(123) (124)

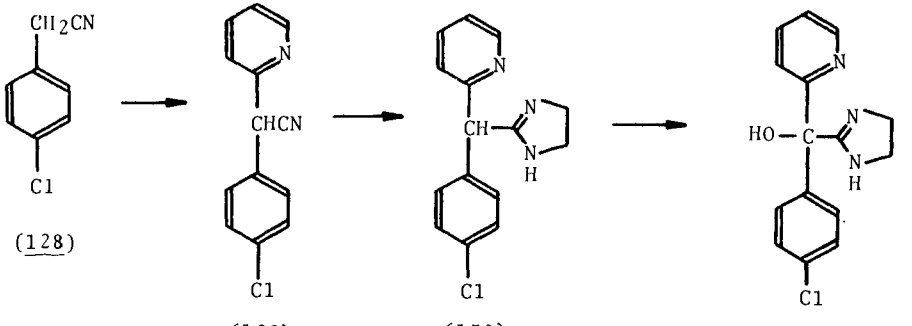
Interposition of an oxygen atom between the aromatic ring and the imidazoline-bearing side chain leads to a compound reported to show antidepressant activity. Its preparation begins with alkylation of phenol *125* with chloroacetonitrile to afford intermediate *126*. Condensation of that nitrile with the

mono-p-toluenesulfonamide from ethylenediamine affords the antidepressant imidazoline, *fenmetozole (127)*.[30]



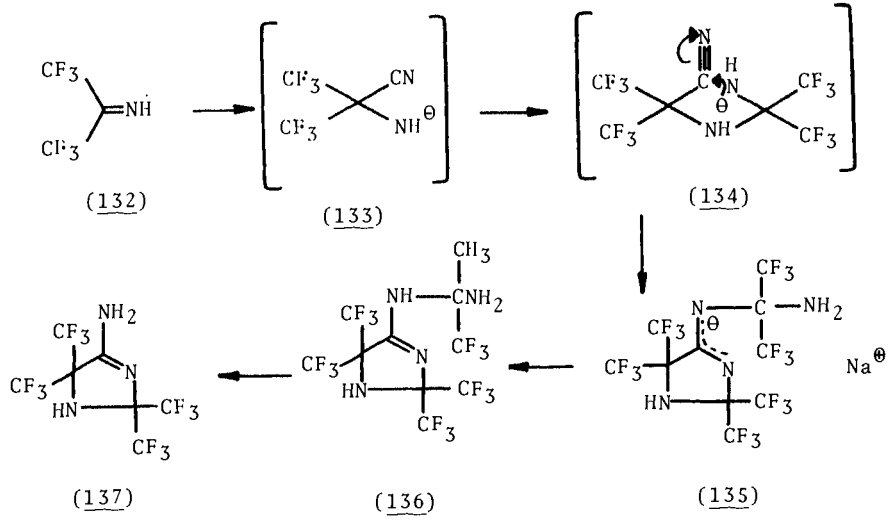
(125) (126) (127)

Preparation of a rather more complex imidazoline drug starts with the alkylation of the carbanion from p-chlorophenylacetonitrile *(128)* with 2-bromopyridine. Reaction of the product *(129)* with ethylenediamine serves to form the imidazoline ring *(130)*. Air oxidation then affords the tertiary carbinol by attack at the highly activated, multiply benzylic carbon. There is thus obtained the antidepressant *dazadrol (131)*.[31]



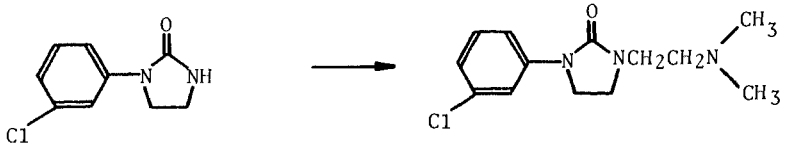
(128) (129) (130) (131)

Replacement of hydrogen by fluorine in biologically active compounds often leads to marked increases in potency. Although much work has gone into incorporation of fluorine in various drug series, compounds in which all the protons are replaced by that halogen atom are rare. One such relatively simple molecule in which only the active hydrogens remain shows sedative activity. Condensation of the imine from hexafluoroacetone *(132)* with sodium cyanide leads to a trimer which incorporates the cyanide *(135)*. The sequence can be rationalized by assuming, as the first step, addition of cyanide to the imine function to form an aminonitrile *(133)*. Reaction of the amine function with a second molecule of imine leads to the aminal *134*. Cyclization, followed by reaction of the newly formed imine function with a third molecule of *133*, gives the observed product as its sodium salt *(135)*. Acidification *(136)*, followed by hydrolytic



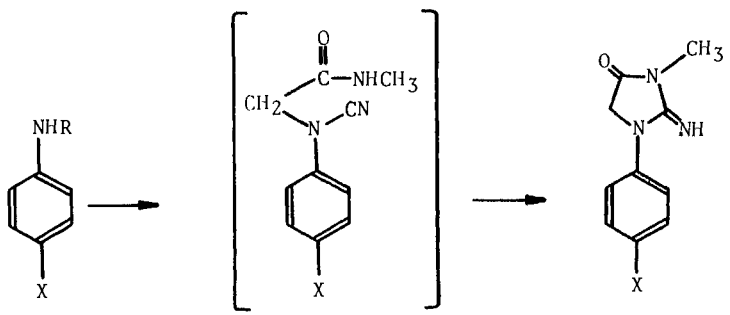
removal of the exocyclic aminal in strong acid, affords the sedative *midaflur (137)*.[32]

CNS activity apparently is retained when the heterocycle is changed to an imidazolidinone. Alkylation of the anion from the imidazolidinone *138* with dimethylaminoethyl chloride affords *imidoline (139)*,[33] a compound with tranquilizer activity.



(138) (139)

The imidazole ring system provides the nucleus for two diuretic agents with structures unusual for that activity. Reaction of the N-cyanoaniline *140* (obtainable from the aniline *(139)* and cyanogen bromide) with N-methylchloroacetamide leads to the heterocycle *142*. The sequence can be rationalized by



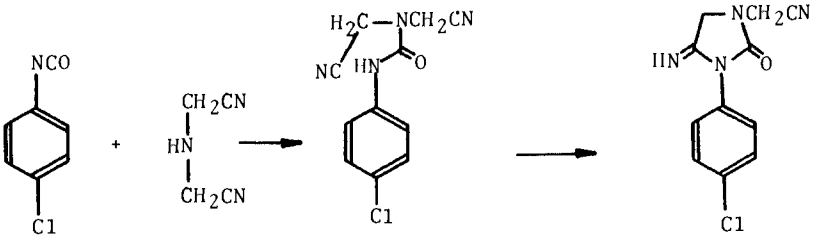
(139) X = R = H
(140) X = H, R = CN
(143) X = Cl, R = H
(144) X = Cl, R = CN

(141) X = H
(145) X = Cl

(142) X = H
(146) X = Cl

assuming N-alkylation of the aniline as the first step *(141)*. Cyclization of that hypothetical intermediate gives *azolimine (142)*.[34] The same sequence starting with p-chloroaniline *(143)* affords *clazolimine (146)*.[34]

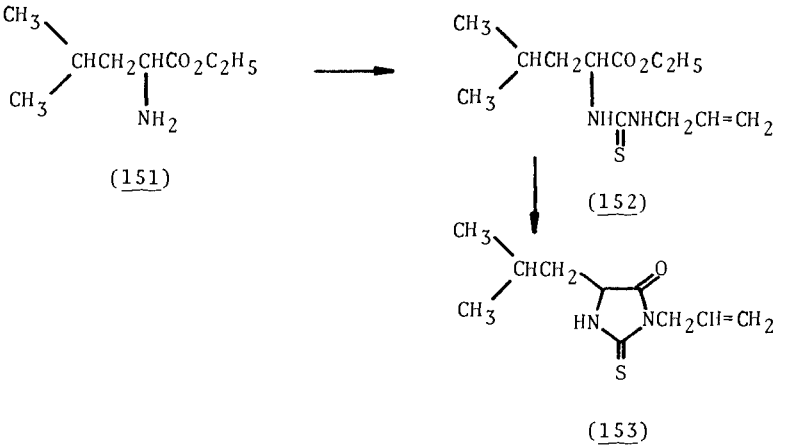
Formal interchange of the carbonyl and imino groups and replacement of the methyl group by acetonitrile interestingly affords a compound with anti-inflammatory and presumably no diuretic activity. Reaction of p-chlorophenylisocyanate *(147*, obtained from *143* and phosgene) with iminodiacetonitrile *(148)* gives the expected urea *149*. Simple heating of that intermediate leads to condensation of the aniline with a nitrile group and formation of *nimazone (150)*.[35,36] It is of interest that this agent is distantly related to the arylacetic acid antiinflammatory agent by a formal hydrolytic step.



(147) (148) (149) (150)

Hydantoins are well-known anticonvulsant agents and as such have found extensive use in the treatment of epilepsy. Replacement of one of the carbonyl groups by thiocarbonyl is consistent with anticonvulsant activity. Thus, condensation of the ethyl ester

of leucine *(151)* with allyl isothiocyanate gives the thiourea *152*. Cyclization of that intermediate affords *albutoin (153)*.[37]



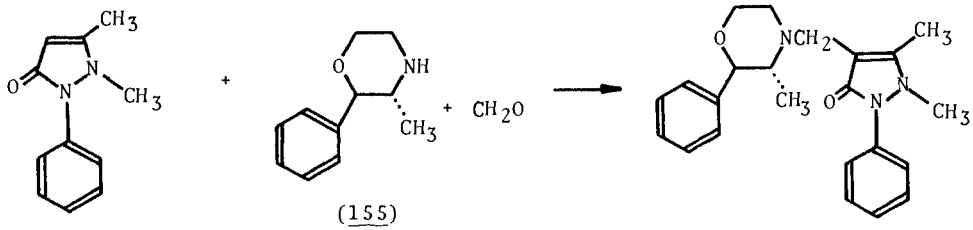
(151) (152) (153)

4. DERIVATIVES OF PYRAZOLE

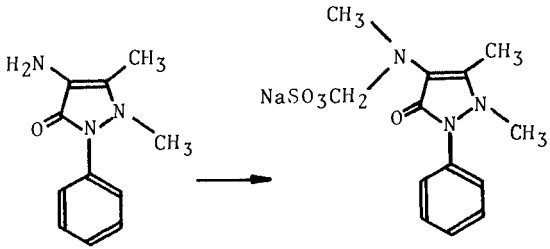
Pyrazolones rank among some of the more venerable nonsteroidal antiinflammatory agents. The activity of *antipyrine (154)* was discovered not too long after that of *aspirin*. The preparation of a plethora of analogues of that compound, all bearing additional substitution at the 4-position, was described in some detail in the earlier volume.

The pyrazolone ring is apparently sufficiently nucleophilic to undergo Mannich reaction. Thus, condensation of *antipyrine* with formaldehyde and the substituted morpholine *155* affords directly the antiinflammatory agent *morazone (156)*.[38] It is of interest that *155* has biological activity in its own right; this amphetamine derivative, *phenmetrazine*,

not surprisingly, shows CNS stimulant and appetite-suppressing activity.[39]



(154) (155) (156)



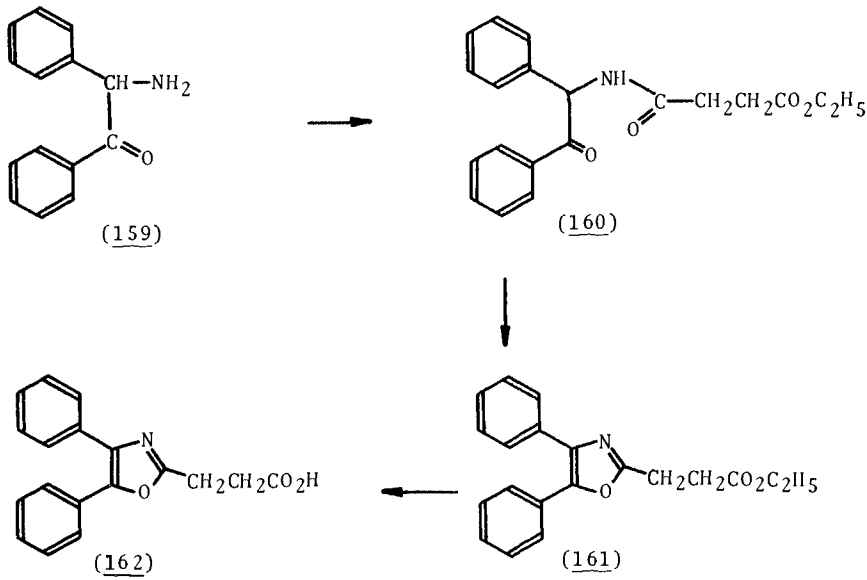
(157) (158)

Many of the modifications of the pyrazolone antiinflammatory agents are intended to increase the limited hydrophilicity of the parent molecules. Reaction of *aminopyrine (157)* with formaldehyde and sodium hydrogen sulfite affords *dipyrone (158)*. The first step can be rationalized as an Eschweiler-Clark type N-methylation reaction, with bisulfite acting as the reducing agent. The resulting mono N-methyl analogue of *157* then apparently forms the sulfite adduct of the carbinolamine of formaldehyde.

5. DERIVATIVES OF OXAZOLE AND ISOXAZOLE

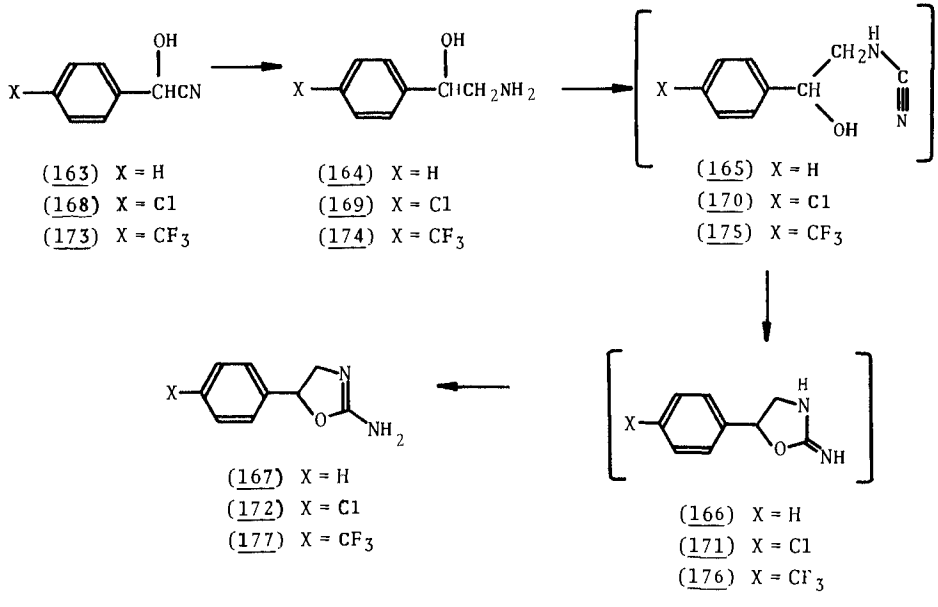
As has been noted previously, the benzene ring of the phenylalkanoic acid antiinflammatory agents can be

replaced by a variety of other aryl groups. However, each of these subclasses does seem to have its own specific SAR. In those cases where the aryl group is phenyl, optimal activity is obtained with a 2-arylated propionic acid; acetic acids are suitable for other classes. In the case at hand a terminally substituted propionic acid was chosen for further development. Acylation of aminoketone *159* with the half acid chloride-ethyl ester of succinic acid affords the amide *160*. Cyclization by means of phosphorous oxychloride serves to form the oxazole ring. Saponification of the ester gives the antiinflammatory agent *oxaprozin (162)*.[40]



Amphetamine and its derivatives have been much used--and abused--as weight-reducing agents. As a consequence of the CNS-stimulating activity shown by

these agents, they are fairly efficient in suppressing symptoms of hunger. Much ingenuity has been exercised towards incorporating the phenylethylamine moiety in various molecules, in attempts to dissociate the anorexic activity of amphetamine from its other effects on the CNS. Never completely successful, this work has led to some molecules that look quite unlike the lead compound. In one study, reduction of the cyanohydrin from benzaldehyde *(163)* with lithium aluminum hydride affords the corresponding amino-alcohol *164*. Reaction of this intermediate with cyanogen bromide in the presence of sodium acetate leads initially to the N-cyano intermediate *165*. Acetate is a sufficiently strong base to catalyze the cyclization of the hydroxyl group onto the nitrile. The initially formed iminooxazolidine then rearranges to the more stable aminooxazoline *(167)* which is



(163) X = H
(168) X = Cl
(173) X = CF_3

(164) X = H
(169) X = Cl
(174) X = CF_3

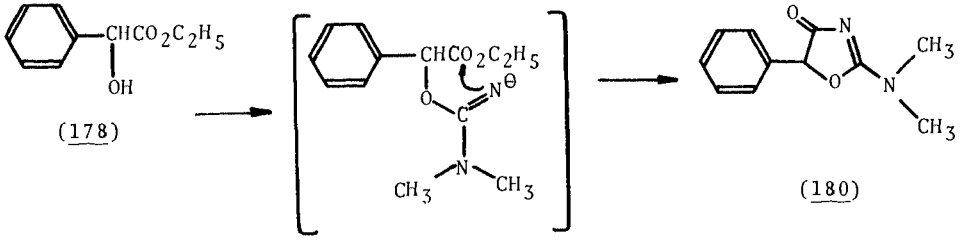
(165) X = H
(170) X = Cl
(175) X = CF_3

(167) X = H
(172) X = Cl
(177) X = CF_3

(166) X = H
(171) X = Cl
(176) X = CF_3

known as *aminorex (167)*.[41] The same sequence starting from the cyanohydrins of p-chlorobenzaldehyde and p-trifluoromethylbenzaldehyde affords, respectively, *clominorex (172)*[41] and *fluminorex (177)*.[41]

Formal oxidation of the methylene group in *aminorex* and dialkylation of the amine affords a compound with antidepressant activity. This activity is also not totally unexpected in a compound related, although very distantly, to amphetamine. Condensation of the alkoxide obtained from treatment of ethyl mandelate *(178)* with N,N-dimethylcyanamide can be envisioned to form initially the adduct *179*. Cyclization of the anion onto the ester group then serves to form the oxazolinone ring. There is thus obtained the antidepressant *thozalinone (180)*.[42]



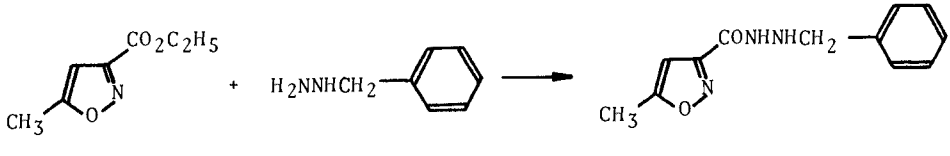
Phenylephrine (181) is a well-known α-sympathomimetic agent. As a consequence of this activity, the drug is used extensively for those conditions requiring a vasoconstricting agent. Modification of the functionality so as to include the aliphatic oxygen and basic nitrogen in an oxazolidine ring is compatible with this biological activity. Condensation of

norphenylephrine *(182)* with cycloheptanone results in formation of the cyclic carbinolamine derivative *ciclafrine (183).*[43]

(181) R = CH_3
(182) R = H

(183)

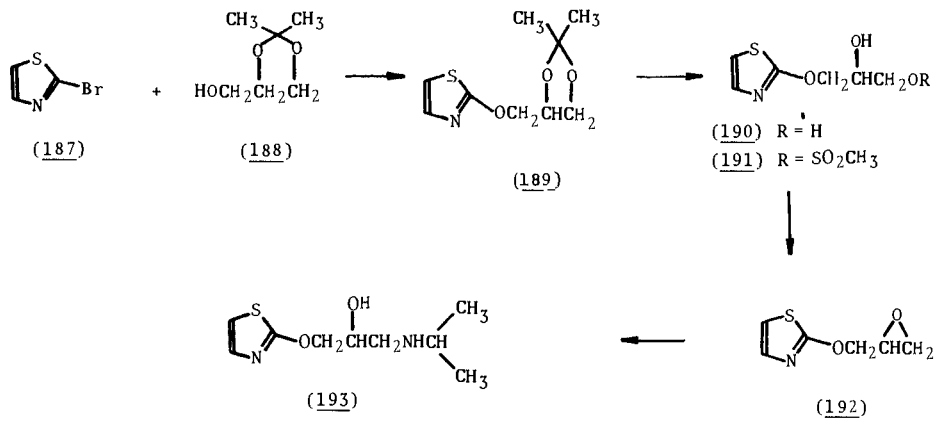
Hydrazides of isonicotinic acid, *isoniazid* for example, were among the first compounds to be used as antidepressant drugs. It is generally accepted that these agents owe their action to increased brain levels of neurotransmitter amines by inhibition of the enzyme monoamine oxidase (MAO). The pyridine ring present in these molecules can, interestingly, be replaced by an isoxazole moiety. Thus, interchange of the isoxazole ester *184* with benzylhydrazine affords directly the MAO-inhibiting antidepressant *isocarboxazid (186).*[44]



(184) (185) (186)

6. DERIVATIVES OF THIAZOLE

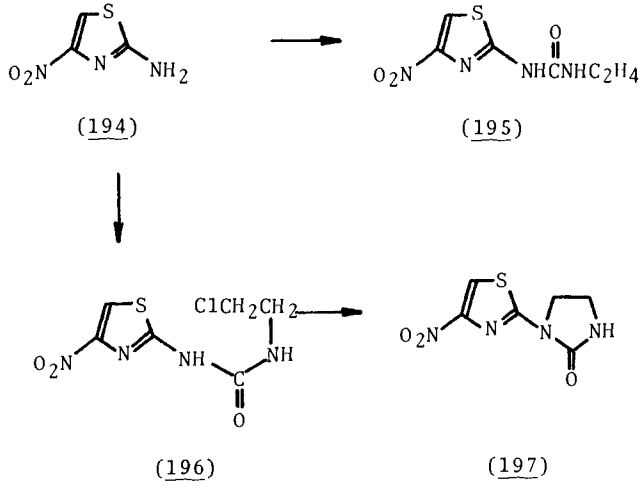
The intensive research on β-adrenergic blocking agents has been discussed in some detail in Chapter 5. As noted there, interposition of an oxymethylene moiety between the aromatic ring and the aminoalcohol side chain of sympathomimetic agents is often compatible with antagonist activity. More recently it has been found that replacement of the aromatic ring in sympathomimetic amines or their antagonists by a heterocycle often gives active compounds (see also *timolol*, below). In the preparation of one example, displacement of halogen on 2-bromothiazole *(187)* by means of the alkoxide from glycerol acetonide (188) affords the ether *189*. Hydrolysis of the acetonide leads to the glycol *190*. Reaction with an equivalent of methanesulfonyl chloride gives the mesylate *(191)*. (Although the terminal mesylate predominates, some secondary ester is probably formed as well; this is



(187) (188) (189) (193) (192)

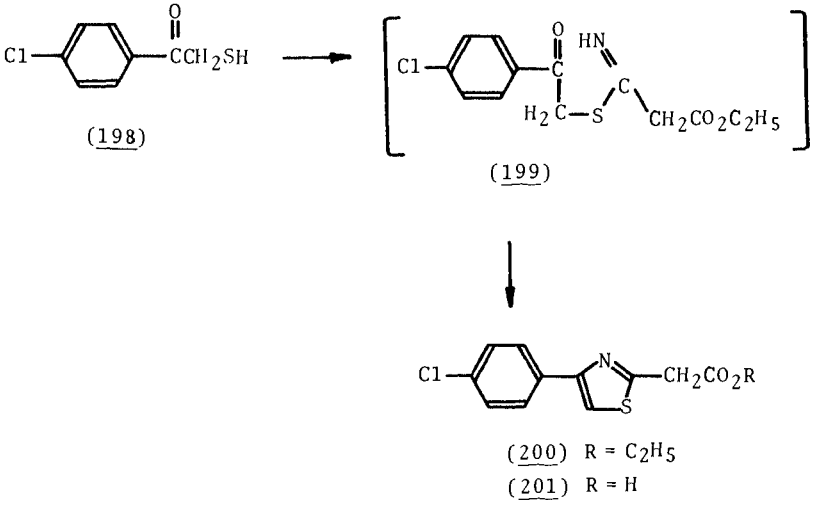
not separated since it serves just as well for the subsequent reaction.) Exposure of the hydroxymesylate to sodium methoxide results in formation of the epoxide by internal displacement *(192)*. Opening of the oxirane by means of isopropylamine affords finally *tazolol (193)*.[45] This compound, unexpectedly, does not show the properties of a classical β-adrenergic blocking agent; *tazolol* retains sufficient intrinsic sympathomimetic activity to be described as a cardiotonic agent.

As noted above, nitrofurans and nitroimidazoles have proven useful moieties for the preparation of antibacterial and antiprotozoal agents. It is thus of note that nitrothiazoles have also been used successfully in the preparation of antiparasitic agents. Condensation of 6-nitro-2-aminothiazole *(194*, available from nitration of aminothiazole) with ethylisocyanate yields the antiprotozoal agent *nithiazole (195)*.[46] In a similar vein, condensation

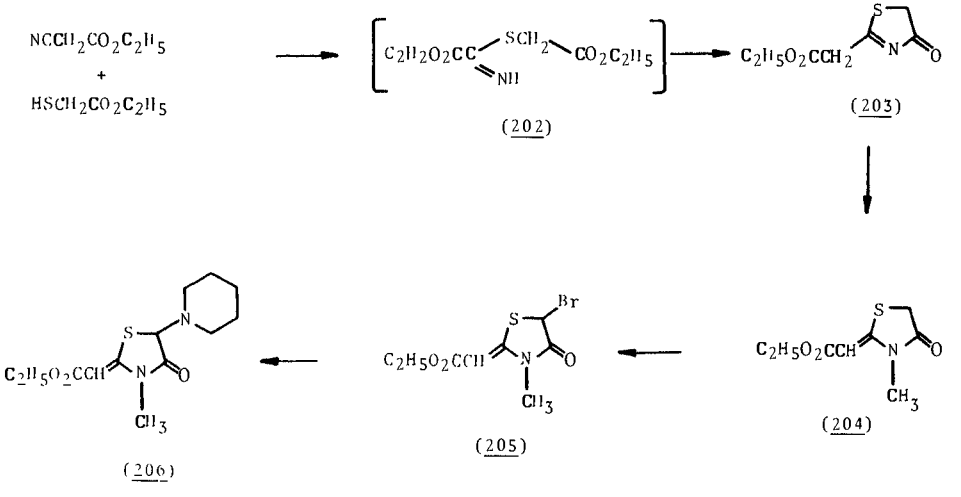


of *194* with 2-chloroethylisocyanate leads to the chloroethylurea *196*. Treatment with base serves to form the pendant imidazolinone ring. There is thus obtained the antischistosomal compound *niridazole (197)*.[47]

The thiazole ring has been found to be an occasional surrogate for a phenyl ring in certain antiinflammatory agents. Note that the side chain is restricted to a simple acetic acid in this series. Reaction of p-chloro-2-mercaptoacetophenone *(198)* with ethyl cyanoacetate in the presence of base affords thiazole *200*. The reaction may involve an adduct such as the iminothioether *199* as an intermediate. Saponification of the ester moiety of *200* then gives the antiinflammatory agent *fenclozic acid (201)*.[48]



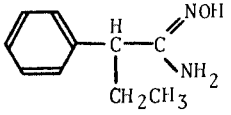
A distantly related acid with a more highly functionalized ring shows choleretic rather than antiinflammatory activity. That is, the compound is useful in those conditions in which the flow of bile is to be increased. Construction of the thiazolone ring is accomplished by a method analogous to that used above to build the thiazole ring. Thus, condensation of ethyl mercaptoacetate with ethyl cyanoacetate leads to the thiazolinone *(203)*; an intermediate such as *202*, involving addition of mercaptide to the nitrile function, can be reasonably invoked. Methylation of *203* with methyl sulfate proceeds on nitrogen with the concomitant shift of the double bond to give *204*. Bromination of the active methylene *(205)* followed by displacement of halogen by piperidine affords the choleretic *piprozolin (206)*.[49]



7. MISCELLANEOUS FIVE-MEMBERED HETEROCYCLES

Acylation with 3-chloropropionyl chloride of the

amidoxime *207* from 2-ethylphenylacetonitrile gives the corresponding N-acylated derivative *208*. This cyclizes to the oxadizole *(209)* on heating. Displacement of chlorine with diethylamine affords the muscle relaxant-analgesic agent *proxazole (210)*.[50]



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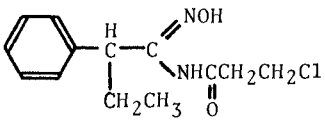

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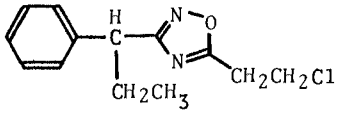

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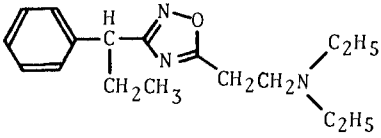
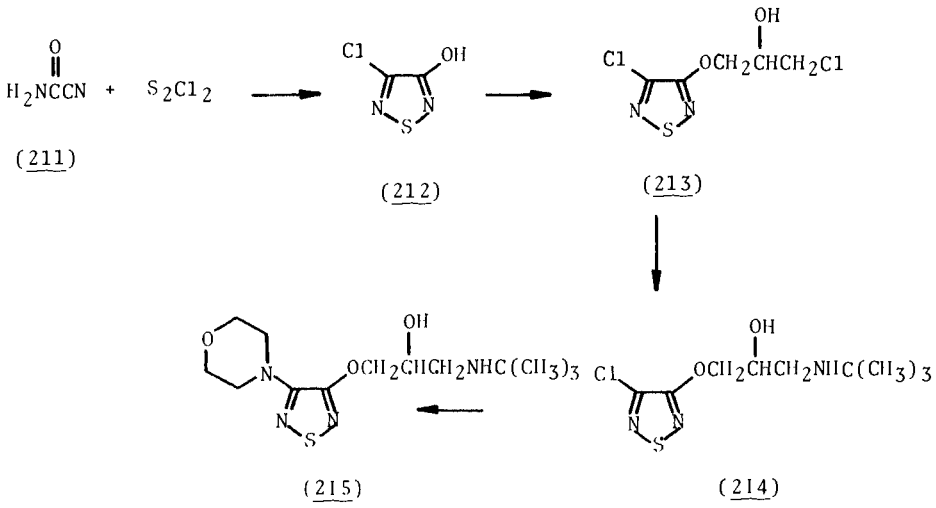


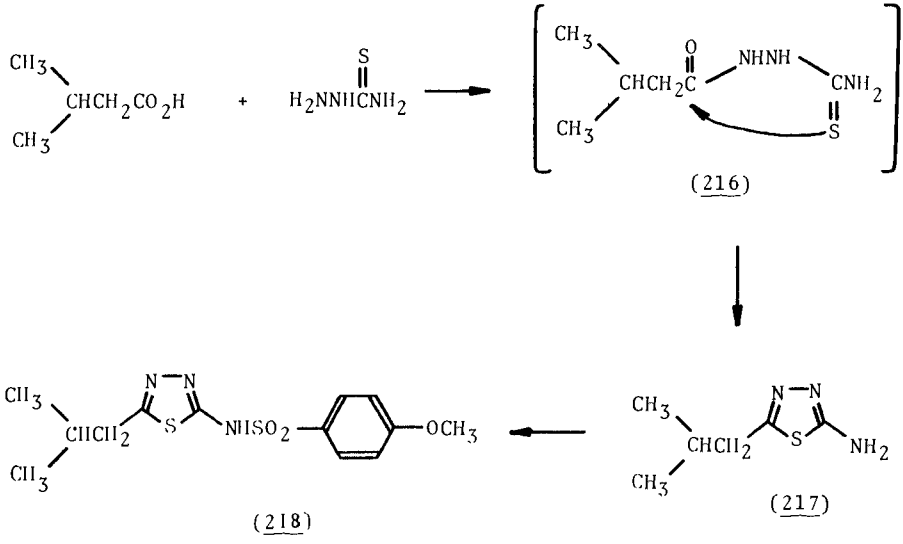
(210)

Thiadiazoles have proven of some utility as aromatic nuclei for medicinal agents. For example, the previous volume detailed the preparation of a series of *"azolamide"* diuretic agents based on this class of heterocycle. It is thus of note that the 1,2,5-thiadiazole ring provides the nucleus for a clinically useful agent for treatment of hypertension which operates by an entirely different mechanism, β-adrenergic blockade. In its preparation, reaction of the amide-nitrile *211* with sulfur monochloride leads directly to the substituted thiadiazole *212*.[51]



Condensation of that intermediate with epichlorohydrin in the presence of a catalytic amount of piperidine affords the chlorohydrin *213*, admixed with some epoxide. Reaction with tertiary butylamine completes construction of the propanolamine side chain. Displacement of the remaining halogen atom of *214* with morpholine under more strenuous conditions affords *timolol (215)*.[52]

A somewhat different scheme is used to gain entry to the alternate symmetrical 1,3,4-thiadiazole ring system. Reaction of thiosemicarbazide with isovaleric acid affords the ring system *(217)* in one step. The reaction may be rationalized by positing acylation to intermediate *216* as the first step. Sulfonylation of the amino group of *217* with p-methoxybenzenesulfonyl chloride affords the oral hypoglycemic agent *isobuzole (218)*.[53] Careful examination of the structure will reveal elements of



the sulfonylurea functionality often associated with that activity.

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9

Six-Membered Ring Heterocycles

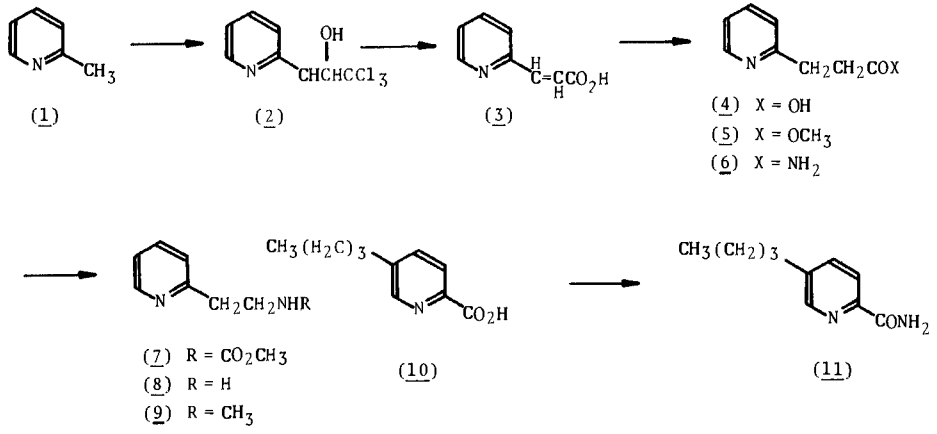
The six-membered ring heterocycles are of exceptional importance in the context of willingly self administered organic substances. One need only mention glucose and nicotine to make this point. The biological acceptability, within reasonable limits, of these materials is paralleled by the availability of a substantial number of drugs.

Substitution of a pyridine ring for a benzene ring often is compatible with retention of biological activity and occasionally this moiety is an essential part of the pharmacophore. Such substitution of =N for CH= is an example of the common medicinal chemical strategy known as bioisosterism.

1. PYRIDINES

The aliphatic hydrogens of α-picoline *(1)* are relatively acidic, so that treatment with phenyl lithium

produces the carbanion which can add to chloral, forming *2*. Acid hydrolysis leads to unsaturated acid *3*, which is sequentially reduced to acid *4*, Fischer-

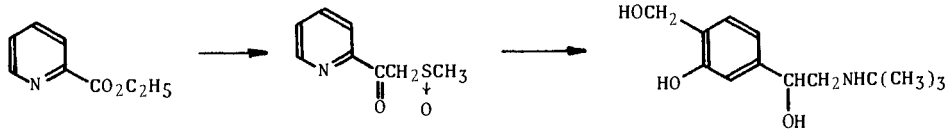


esterified to *5* and transamidated to *6*. Hofmann rearrangement with NaOBr followed by methanol gives carbamate *7*, which is hydrolyzed to *8* and monomethylated. This fairly lengthy process affords the vasodilator, *betahistine (9)*.[1]

As the result of a screening program examining microbial fermentation products for pharmacological activity (other than antibiotic activity), *fusaric acid (10)* was isolated from *Fusarium oxysporum* following the discovery that extracts were potent inhibitors of dopamine β-hydroxylase, and thus interfered with the biosynthesis *in vivo* of the pressor neurohormone, norepinephrine. To refine this lead, amidation of *10 via* the acid chloride was carried out

to give the antihypertensive analogue *bupicomide (11)*.[2]

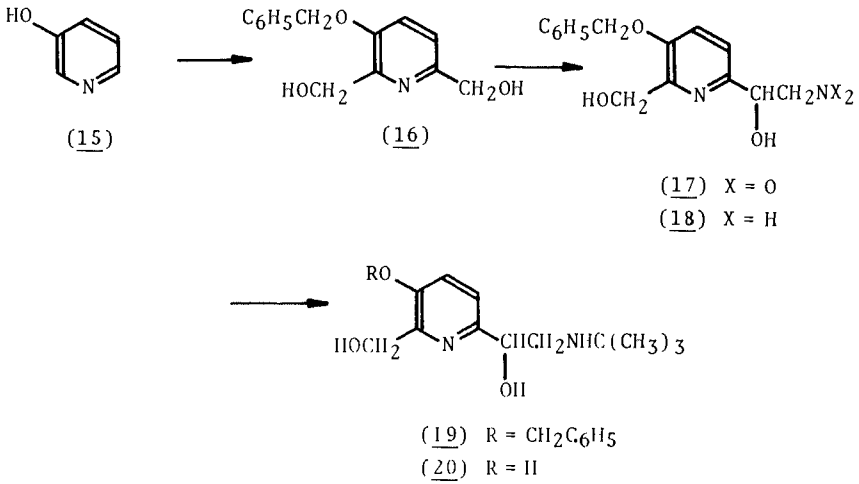
Reaction of ethyl picolinate *(12)* with dimsyl sodium (from dimethylsulfoxide and sodium hydride) produces *oxisuran (13)*, an antineoplastic agent.[3]



(12) (13) (14)

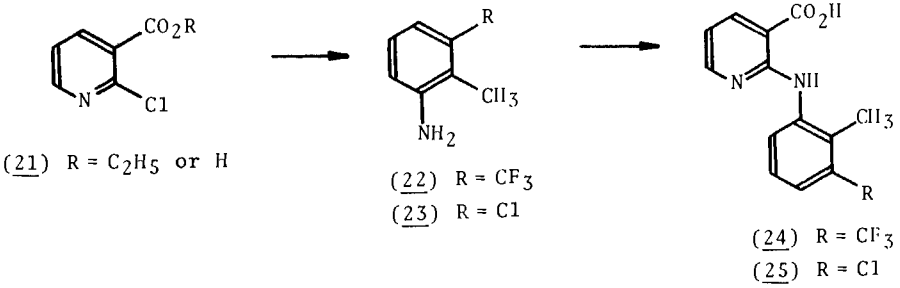
An adrenergic β_2-receptor agonist related conceptually to *salbutamol (14)* can be made by substituting a pyridine ring for the benzene. In this case synthesis starts by hydroxymethylation and formation of the o-benzylether of 3-hydroxypyridine *(15)* to give *16*. Manganese dioxide perferentially oxidizes the sterically more accessible primary alcohol group to the aldehyde, and subsequent aldol condensation with nitromethane produces nitrocarbinol *17*. Catalytic reduction with Raney nickel gives amine *18* which reacts in turn with t-butyl bromide to give amine *19*. Hydrogenolysis of the protecting benzyl moiety finishes the synthesis of the bronchodilator, *pirbuterol (20)*.[4]

Substantial interest in the pharmacological properties of the nonsteroidal antiinflammatory agents related to *mefenamic* and *flufenamic acid* led to examination of a series of aminopyridines instead



(15) (16) (17) X = O (18) X = H (19) R = $CH_2C_6H_5$ (20) R = H

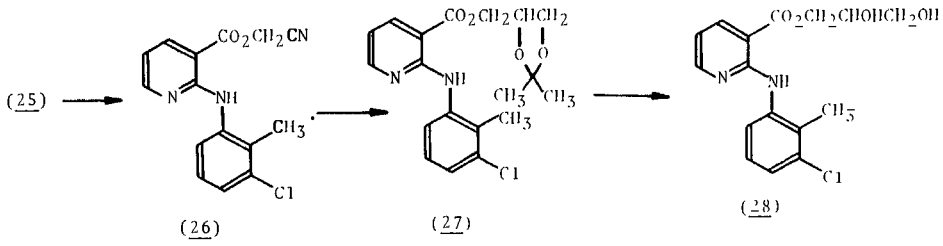
of anthranilates. Thermal displacement of the halogen of 2-chloronicotinate derivatives *(21)* with the requisite anilines *(22 or 23)* led to antiinflammatory agents *flunixin (24)*[5] and *clonixin (25)*,[6] respectively.



(21) R = C_2H_5 or H (22) R = CF_3 (23) R = Cl (24) R = CF_3 (25) R = Cl

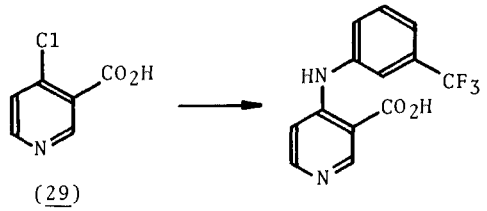
The glyceryl ester of *clonixin, clonixeril (28)*, is also an antiinflammatory agent. It was prepared

via a somewhat roundabout method. *Clonixin (25)* was reacted with chloroacetonitrile and triethylamine to give *26*. Heating *26* with potassium carbonate and glycerol acetonide displaced the activating group to produce ester *27* which was deblocked in acetic acid to produce *clonixeril*.[7]



Interestingly, a substance somewhat closely related to *flunixin*, *triflocin (30)*, is a diuretic rather than an antiinflammatory agent. It can be prepared by nucleophilic aromatic displacement on 4-chloronicotinic acid *(29)* with m-trifluoromethyl-aniline.[8]

The topical antifungal agent *ciclopirox (32)* was formed from 2-pyrone *31* by an azaphilone reaction with hydroxylamine.[9] This may be viewed at least formally as an ester (lactone)-amide exchange to an intermediate oximinoester, which ring-closes *via* an addition-elimination sequence to expel the original lactone ring oxygen in favor of the hydroxylamine nitrogen. Lactones which readily convert to lactams in this manner are known as azaphilones.



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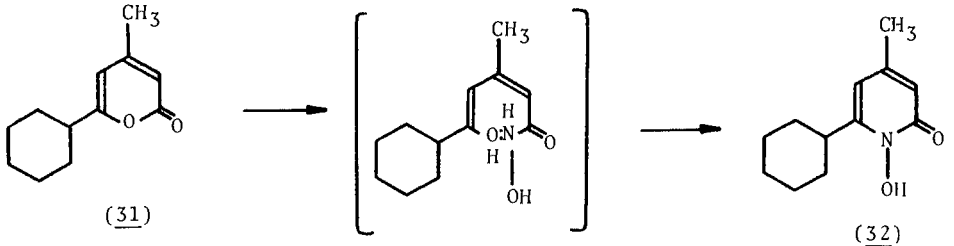
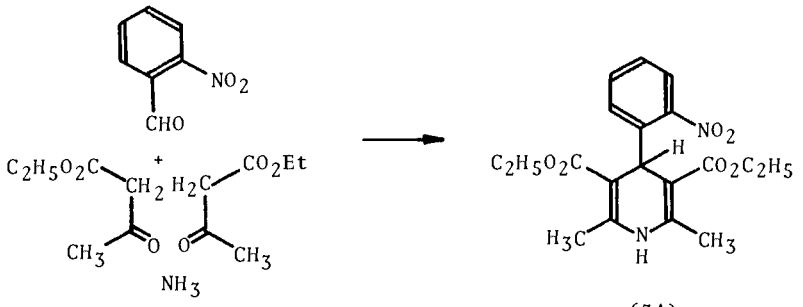


(31) (32)

A 1,4-dihydropyridine having coronary vasodilatory activity and, therefore, intended for relief of the intense chest pains of angina pectoris is *nifedipine (34)*. Using a portion of the classical Hantzsch pyridine synthesis, condensation of two moles of

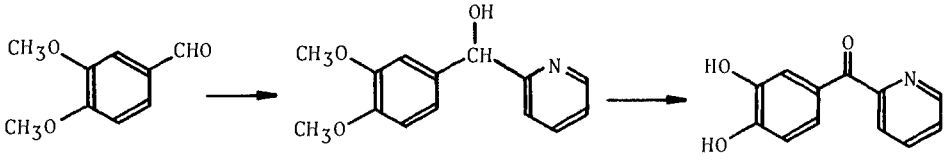


(33) (34)

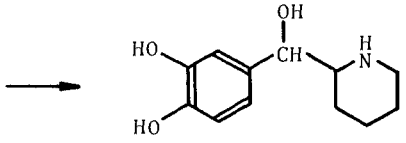
ethyl acetoacetate and one each of ammonia and 2-nitrobenzaldehyde (collectively *33*) leads to *nifedipine*.[10] In the classical Hantzsch process, an oxidative step is needed to produce the pyridine ring system.

2. PIPERIDINES

Perhaps following up the rigid analogue concept, an epinephrine analogue with a cyclized side chain is the $\beta_2$agonist/bronchodilator, *rimiterol (38)*. Reaction of 3,4-dimethoxybenzaldehyde *(35)* with 2-pyridyl lithium gives carbinol *36*. Oxidation with permanganate and ether cleavage with HBr produces catechol *37*. Hydrogenation with a palladium catalyst in acid medium leads to *rimiterol* by reduction of both the pyridine ring and the ketone function.[11]

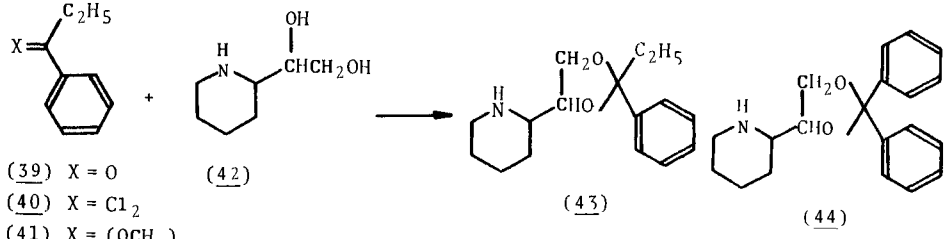


(35) (36) (37)



(38)

Propiophenone *(39)* does not easily form ketals directly. A solution for this difficulty involves conversion to the *gem*-dichloride *(40)* with PCl_5 and solvolysis to the ketal *(41)* using sodium methoxide. Acid-catalyzed ketal exchange with piperidine glycol *42* leads to the parenteral anesthetic, *etoxadrol (43)*.[12] Repetition of the same steps starting with benzophenone led to *dioxadrol (44)*, which is described as an antidepressant agent.[12]



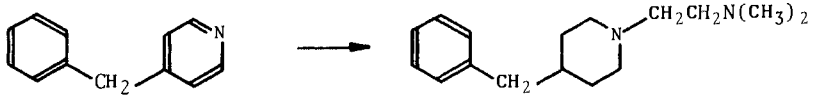
(39) X = O
(40) X = Cl_2
(41) X = $(OCH_3)_2$

(42)

(43)

(44)

In the course of an investigation aimed at refining hypotensive leads, 4-benzylpyridine *(45)* was reduced with a platinum catalyst in acidic medium to the corresponding piperidine, and this was alkylated with dimethylaminoethyl chloride to give *46*. This

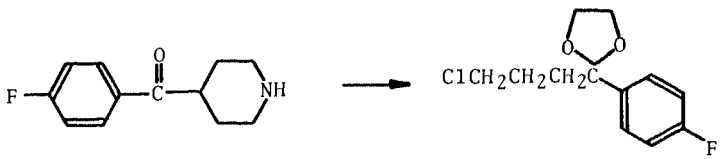


(45)

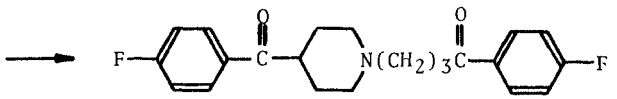
(46)

product, *pimetine*, is primarily of interest as a hypolipidemic agent.[13]

Possibly patterned after the clinically useful p-fluorobutyrophenone *haloperidol*, *lenperone (49)* too is a potentially useful tranquilizer. The synthesis proceeds from ketone *47* by alkylation with halide *48* followed by deketalization.[14]

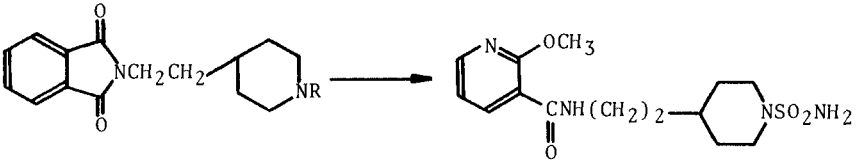


(47) (48)



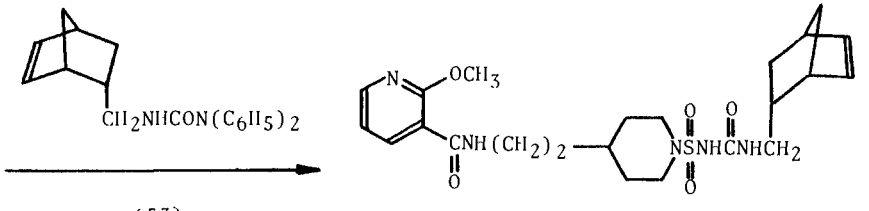
(49)

The reader will recall that many sulfonylurea derivatives are oral hypoglycemic agents and therefore useful oral antidiabetic drugs in adult-onset diabetes. One more complex than most is *gliamilide (54)*. Piperidine derivative *50*, prepared by reduction of the corresponding pyridine, undergoes amide exchange to *51* on heating in pyridine with sulfamide ($H_2NSO_2NH_2$). Reaction with hydrazine and HCl removes the phthaloyl protecting group, and acylation of the liberated amino function with 2-methoxynicotinyl chloride gave sulfonylurea *52*. When this was reacted with the



(50) R = H
(51) R = SO_2NH_2

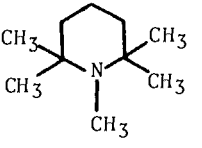
(52)



(53)

(54)

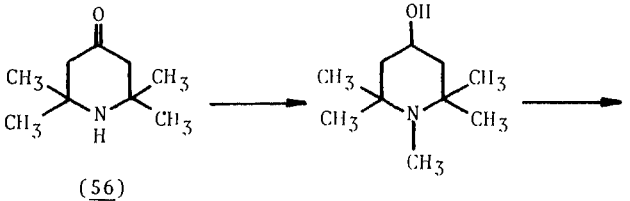
bicyclic *endo*-diphenyl urea *53*, amide exchange took place with expulsion of the better leaving group in this case, diphenylamine. There was thus obtained *gliamilide (54)*.[15]



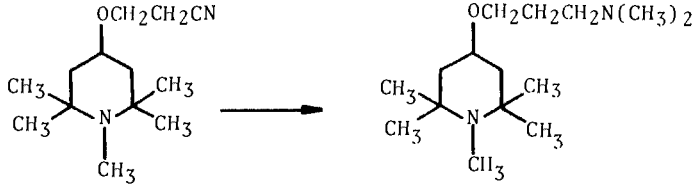
(55)

A number of years ago, pentamethylpiperidine *55* was found to be a rather potent, though not very specific, ganglionic blocking agent. This finding was of particular interest, as it was at that time believed that a quaternary ammonium function was a

minimal structural feature for such drugs. In refining *55* as a lead, triacetone amine (*56*, synthesized from acetone, ammonia and calcium chloride) was reduced with sodium borohydride and N-alkylated to give *57*. Cyanoethylation with acrylonitrile (with the aid of sodium t-butoxide) led to nitrile *58*. Reduction with lithium aluminum hydride produced the primary amine and Eschweiler-Clark methylation (CH_2O and HCO_2H) completed the synthesis of *pemerid (59)*, an antitussive agent.[16] This activity is incidentally unrelated to ganglionic blockade.



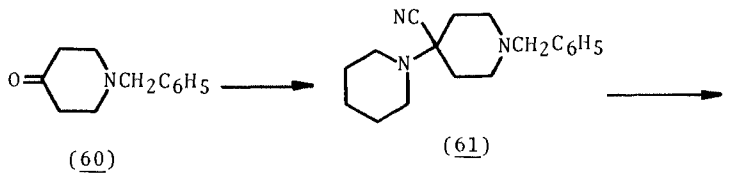
(56) (57)



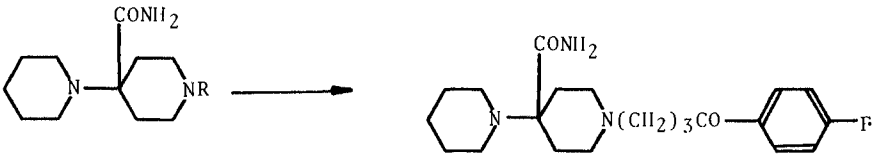
(58) (59)

Yet another (see *lenperone*) butyrophenone related to *haloperidol* is *pipamperone (64)*. N-benzyl-4-piperidone *(60)* has a venerable history as starting material for both central analgesics and CNS drugs. This synthon has been used by the Janssen group as a building block for numerous such drugs. Reaction of

60 with KCN and piperidine HCl, leads to the aminonitrile *(61)*. The reaction probably represents cyanation of the intermediate imine. Hydrolysis with hot 90% sulfuric acid hydrates the nitrile to the carboxamide *(62)* and catalytic reduction deblocks the amine to give *63*. Alkylation with p-fluorophenyl-3-chloropropyl ketone using a catalytic amount of KI completes the synthesis.[17]



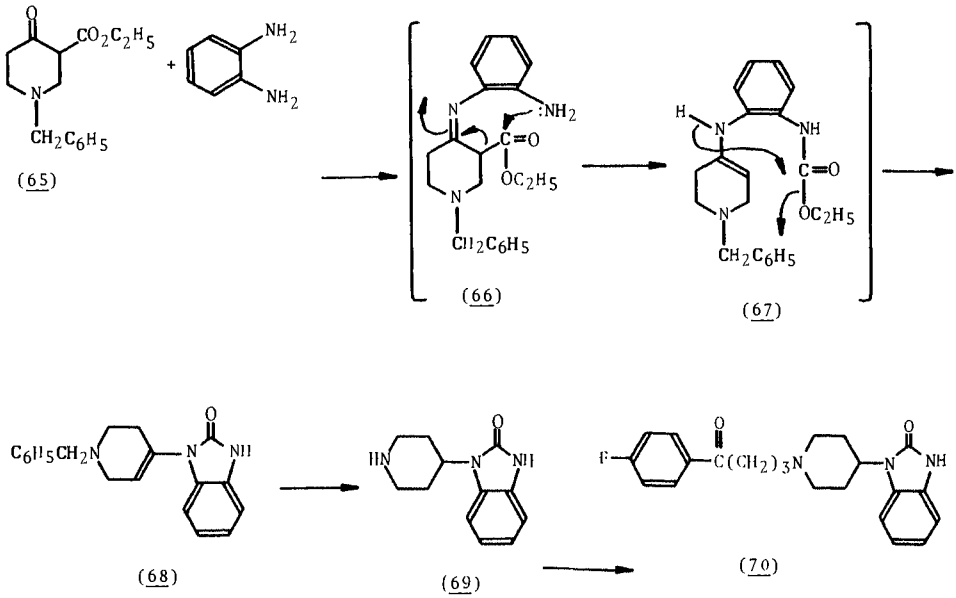
(60) (61)



(62) R = $CH_2C_6H_5$
(63) R = H

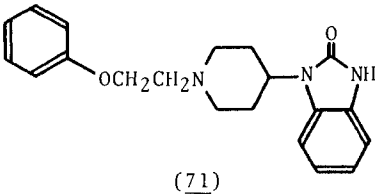
(64)

An interesting reaction ensues when the intermediate synthetic precursor *(65)* to synthon *60* is heated with phenylenediamine. The reaction can be rationalized as involving initial enamine-imine formation *(66)*, followed by intramolecular attack on the ester carbonyl groups resulting in carbamate formation *(67)*, which carbamate undergoes intramolecular transamidation to give urea *68*. Other scenarios can be proposed and defended, but the net result is formation

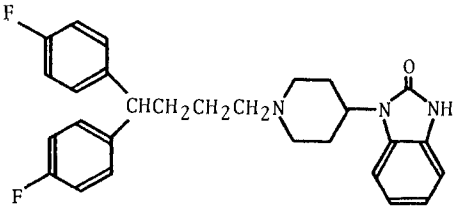


of complex urea derivative *68*, which readily undergoes catalytic reduction to *69*, a versatile intermediate for the preparation of a variety of potential drugs. For example, alkylation with the requisite *haloperidol* fragment led to the tranquilizer, *benperidol (70)*.[18] Minor variants led to the tranquilizers *oxiperomide (71)*,[19] *pimozide (72)*,[20] and *clopimozide (73)*,[21] and the analgesic, *benztriamide (74)*.[22]

Another fruitful investigation was based upon the cyanohydrin of ketone *60*. This substance *(75)* undergoes hydride reduction to the corresponding aminoalcohol, which forms cyclic carbamate *76* on



(71)



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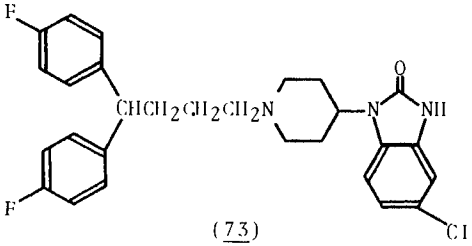
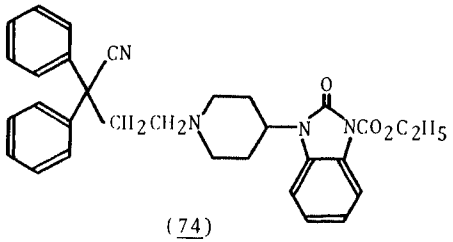
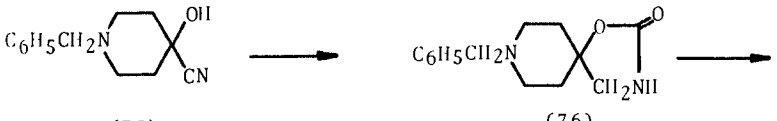


(73)

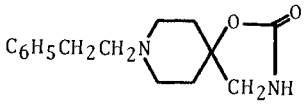


(74)

heating with diethylcarbonate. Hydrogenolysis of the N-benzyl group and alkylation of the liberated amino group with phenethyl chloride gives *fenspiride (77)*, an blocking bronchodilator.[23]



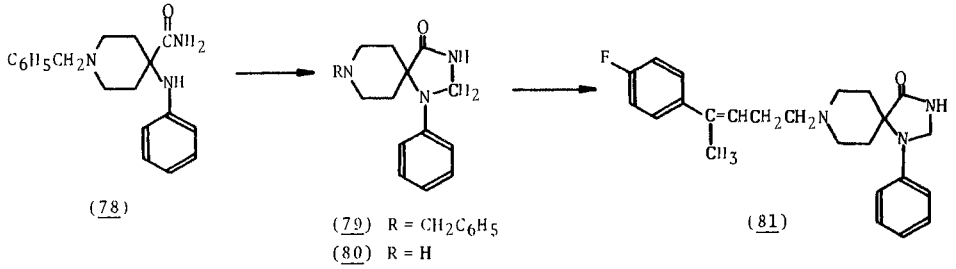
(75) (76)



(77)

Imidazolone analogues are available, for example, starting with piperidone *60* and reacting this with KCN and aniline followed by hydration to amide *78* in

90% sulfuric acid. Heating *78* with formamide results in the desired imidazolone formation (*79*). Catalytic hydrogenolysis (*80*) and suitable alkylation of this

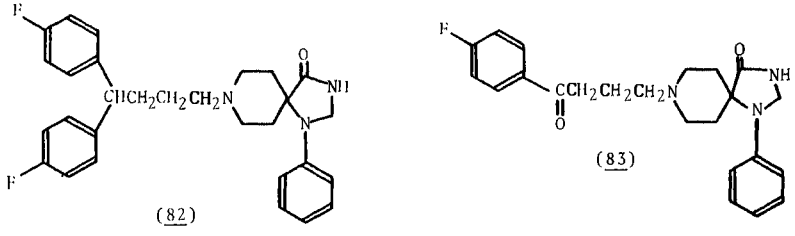


(78)

(79) R = $CH_2C_6H_5$
(80) R = H

(81)

secondary amine gives the tranquilizer, *spiriline (81)*.[24] The closely related tranquilizers *fluspiriline (82)*[25] and *fluspiperone (83)* are made in the same general way.

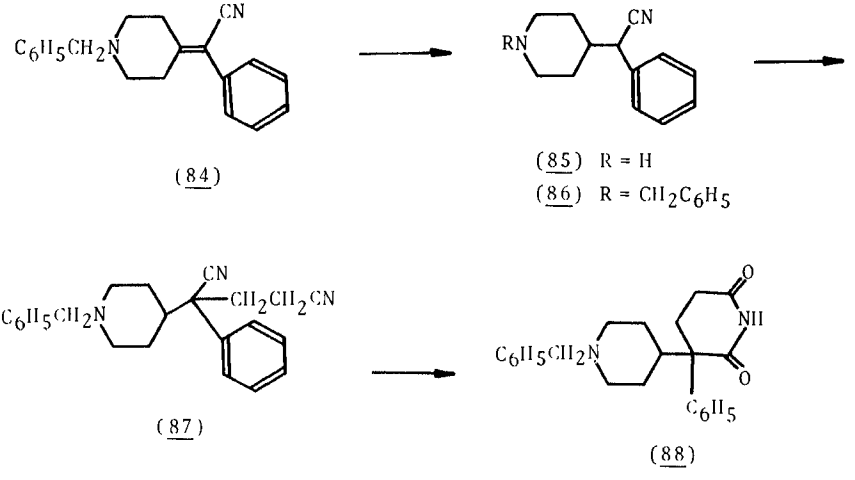


(82)

(83)

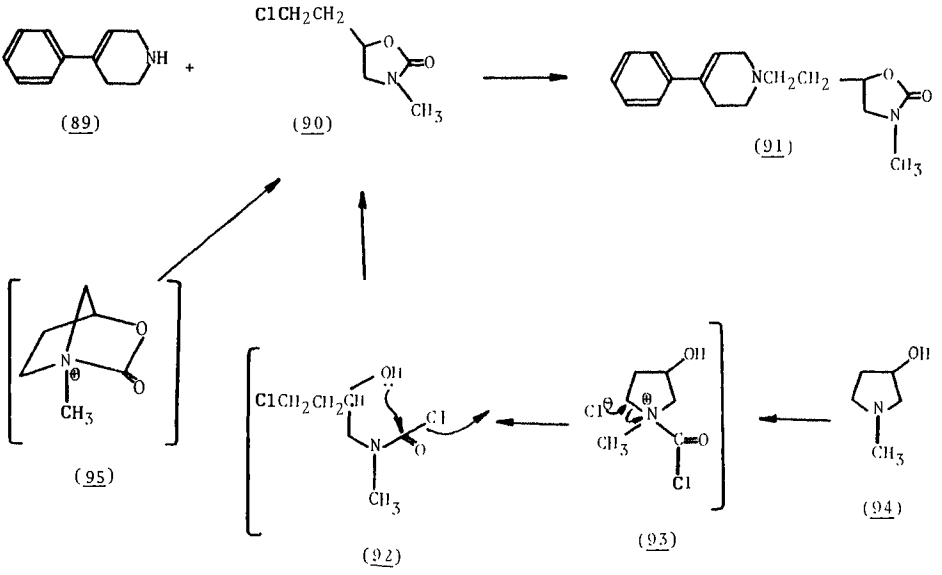
When piperidone *60* is condensed with phenylacetonitrile, using sodium methoxide, *84* results. Catalytic reduction unexpectedly is nonselective, not only reducing the olefinic linkage, but also removing

the benzyl protecting group. The product *(85)* has to be rebenzylated to *86* before cyanoethylation to *87* can be carried out. Hydrolysis of *87* with strong acid stopped at the glutarimide stage with the production of *benzetimide (88)*, an orally active anticholinergic agent.[26]

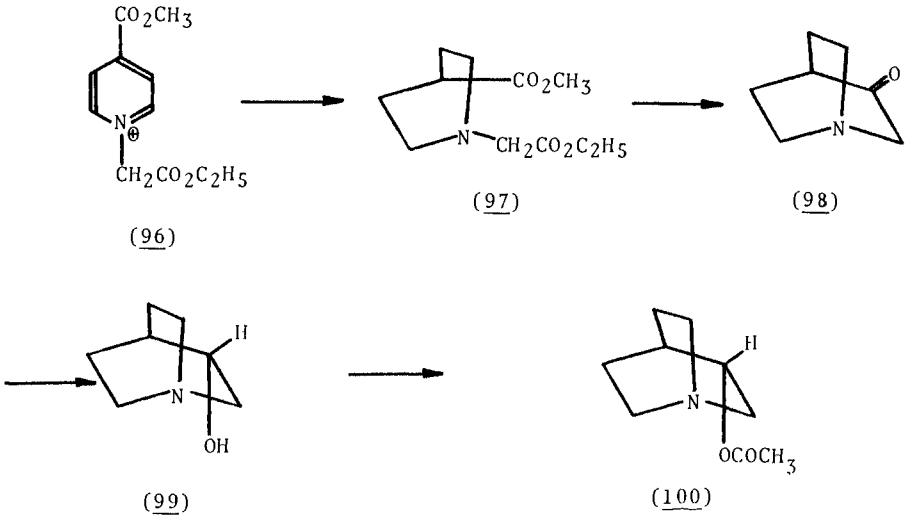


The action of phenyl Grignard reagent on piperidone *60* followed by dehydration and deblocking leads to intermediate *89*. When this is reacted with complex halide *90*, *fenpipalone (91)*, an antiinflammatory agent, results.[27] The requisite halide *(90)* is made by treatment of hydroxy pyrrolidine *94* with phosgene. The reaction may proceed *via* N-acylation to *93* which would undergo ring opening as shown with chloride ion to give *92*, which would then cyclize as indicated to give *90*. Such dealkylation of tertiary amines by acyl halides is a well-established reaction. An

alternate and perhaps equally credible intermediate in this particular case would be bicyclo carbamate *95*, which would be formed whether either O- or N-acylation were the first event.



A number of substituted β-aminoacetates inhibit the enzyme cholinesterase. The main function of this enzyme is to hydrolyze acetyl choline and thereby terminate the action of that substrate as a neurotransmitter. Such inhibition is functionally equivalent to the administration of exogenous acetylcholine. Direct administration of the neurotransmitter substance itself is not a useful therapeutic procedure due to rapid drug destruction and unacceptable side



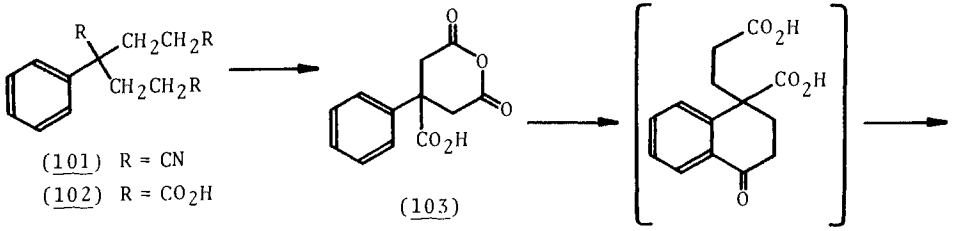
(96) (97) (98)

(99) (100)

effects. *Aceclidine (100)* was synthesized based upon these considerations. When glycine analogue *96* is catalytically reduced, *cis*-diester *97* is produced. Dieckmann condensation and saponification-decarboxylation then leads to bicyclopiperidone *98*.[28] Borohydride reduction gives alcohol *99*.[29] Acetylation completes the synthesis of *aceclidine (100)*, a cholinergic agent.[30]

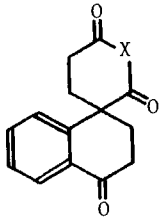
Glutarimides may be regarded as oxidized piperidines, and many drugs containing this moiety are sedatives and anticonvulsants. A spiro derivative, *alonimid (105)* is such a sedative-hypnotic agent. It can be prepared by K t-butoxide catalyzed biscyanoethylation of phenylacetonitrile, leading to *101*. Alkaline hydrolysis produces tricarboxylic acid *102* which is smoothly converted to the glutaric acid anhydride *(103)* with acetic anhydride. Friedel-Crafts

cyclization leads to the 6-membered ring, with concomitant anhydride reorganization to give *104*. The



(101) R = CN
(102) R = CO_2H

(103)

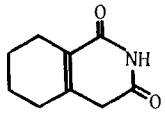


(104) X = O
(105) X = NH

azaphilone character of *104* is taken advantage of as reaction with ammonia produces the desired spiroimide *105*.[31] Interest in compounds of this generic type has cooled considerably in the wake of the *thalidomide* tragedy.

Homophthalimides have an active methylene group, and this property is retained by the octahydroisoquinoline derivative *106*. Base-catalyzed benzylidine condensation with benzaldehyde gives *tesimide (107)*, an antiinflammatory agent.[32] The imine proton may be sufficiently acidic for this drug to be classed among the acidic nonsteroidal antiinflammatory agents.

As a means of introducing both rigidity and asymmetry for receptor discrimination, bicycloimides are potentially interesting pharmacological tools.



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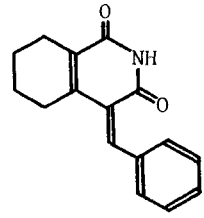
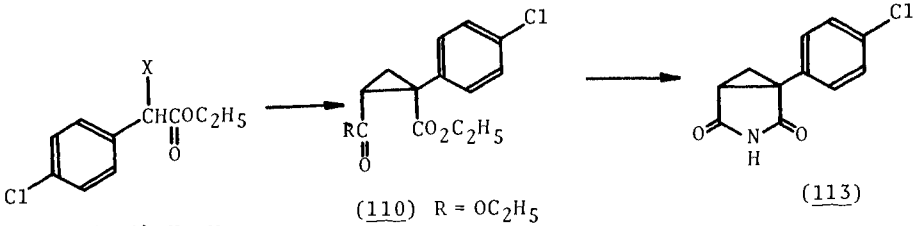


(107)

One such agent is prepared by NBS and peroxide bromination of ethyl 4-chlorophenylacetate *(108)* to give *109*. This is converted by sodium hydride to the benzylic carbene, which is inserted into the double bond of ethyl acrylate to give *cis*-cyclopropane *110*. Partial saponification cleaves the less hindered ester moiety to give *111*. This is next converted to the alkoxyimide *(112)* on reaction with diethyl carbonate and diammonium phosphate. Stronger base (NaOEt) effects displacement to the imide *(113)*, *cyproximide*, which has tranquilizing properties.[33]



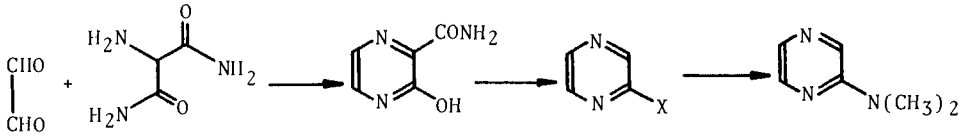
(108) X = H
(109) X = Br

(110) R = OC_2H_5
(111) R = OH
(112) R = $NHCOC_2H_5$

(113)

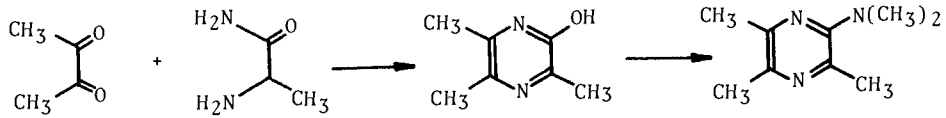
3. PIPERAZINES AND PYRAZINES

The classical synthetic method for constructing 2-aminopyrazines is illustrated by the synthesis of *ampyzine (117)*, a CNS stimulant. Condensation of aminomalonamide and glyoxal leads to pyrazine *114*. Hydrolysis to the acid and decarboxylation gives 2-hydroxypyrazine *(115)*. Reaction with PCl_5 produces chloride *116*, and heating with dimethylamine completes the synthesis of *117*.[34]



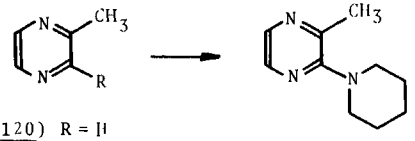
(114) (115) X = OH (116) X = Cl (117)

Methyl groups are introduced into the aromatic rings of pyrazines by varying the starting materials. For example, use of biacetyl and alanylamide produces trimethyl hydroxypyrazine *118*. Chlorination and thermal displacement with dimethylamine gives *triampyzine (119)*, an anticholinergic agent intended to inhibit gastric secretion to control some kinds of peptic ulcer.[35]



(118) (119)

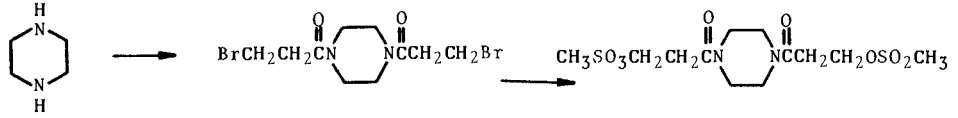
It has been discovered that direct chlorination of pyrazines can be accomplished and this has also been used to make candidate drugs. For example, when 2-methylpyrazine *(120)* is heated with chlorine in carbon tetrachloride, a mixture of the 3-chloro *(121)* and the 6-chloro derivatives result. After separation, *121* is heated with piperidine to give *modaline (122)*, an antidepressant.[36]



(120) R = H
(121) R = Cl

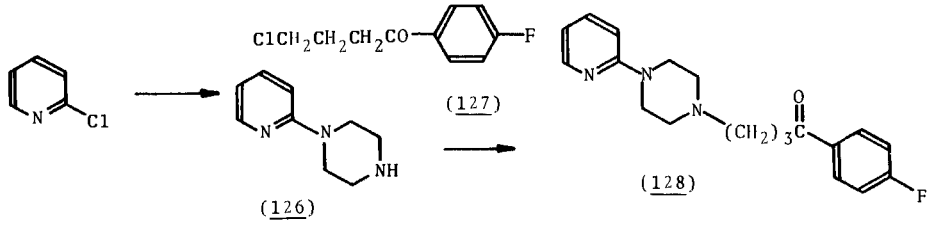
(122)

When piperazine *(123)* is reacted with two molar equivalents of 3-bromoacetyl chloride, the antineoplastic agent *pipobroman (124)* results.[37] This material is probably an alkylating agent. Exchange of the leaving groups by mesylate moieties is compatible with bioactivity. This has been accomplished by reaction of *124* with silver methanesulfonate to give *piposulfan (125)*, also an antineoplastic agent.[38]



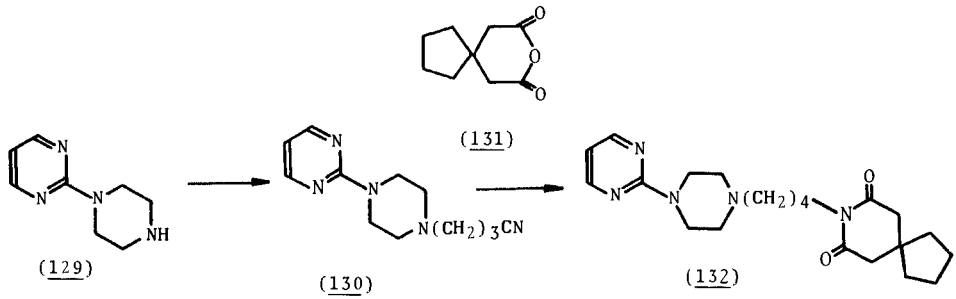
(123) (124) (125)

Azaperone (128) is yet another of the tranquilizers related to *haloperidol*. Nucleophilic aromatic displacement of 2-chloropyridine by piperazine leads to amine *126* which is then alkylated in turn by 4-chloro-p-fluorobuterophenone *(127)* to give *azaperone (128)*, which is said to be active by topical administration.[39]



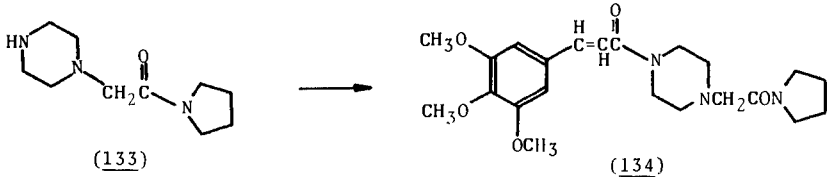
(126) (127) (128)

Alkylation of 1-(2-pyrimidyl)piperazine *(129)* with 3-chloro-1-cyanopropane gives nitrile *130*, which is reduced with LAH and then acylated with spiroglutaric anhydride *131* to synthesize the tranquilizer *buspirone (132)*.[40]



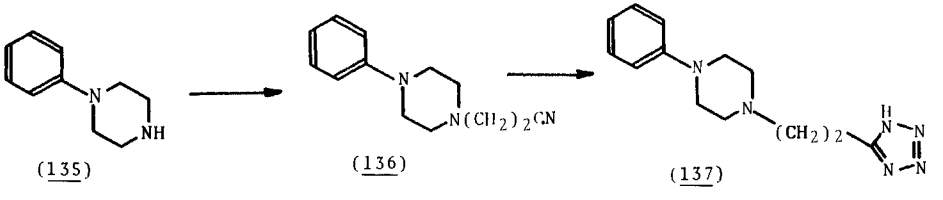
(129) (130) (131) (132)

Alkylation of piperazine with the amide formed by reaction of chloroacetyl chloride with pyrrolidine gives amide *133*. Acylation with 3,4,5-trimethoxycinnamoyl chloride completes the synthesis of the peripheral vasodilator, *cinepazide (134)*.[41]



(133) (134)

To round out this group of drugs in which the piperazine ring appears to serve primarily as a basic spacer unit, or a conformationally restricted ethylenediamine unit, reaction of N-phenylpiperazine *(135)* with acrylonitrile produces nitrile *136*. Conversion



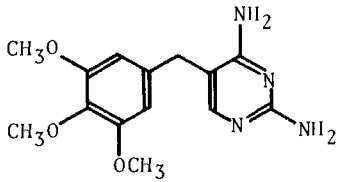
(135) (136) (137)

of the nitrile moiety to a tetrazole ring *via* a 1,3-dipolar addition process by sodium azide under ammonium chloride catalysis produces *zolterine (137)*, an antihypertensive by virtue of its antiadrenergic/vasodilator activity.[42] The tetrazole moiety is an

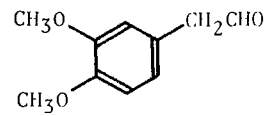
isoelectronic replacement for a carboxylic acid moeity in a number of drugs.

4. PYRIMIDINES

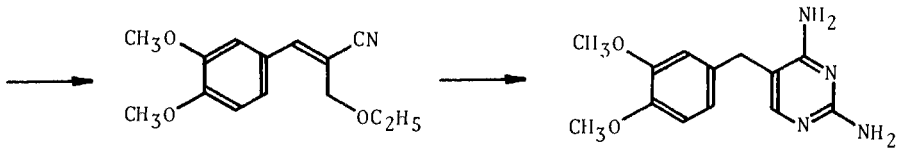
Two antibacterial agents related structurally to *trimethoprim (138)* are *diaveridine (141)* and *ormetoprim (146)*. *Diaveridine* has been synthesized by a minor variant of the trimethoprim route[43] in which veratric aldehyde *(139)* is sequentially condensed with β-ethoxypropionitrile (to *140)* and then guanidine to give *141*.[44] *Ormetoprim* may be made analogously or



(138)



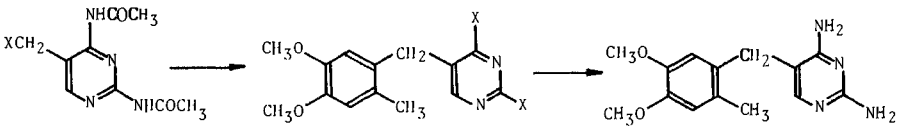
(139)



(140) (141)

by benzylic bromination (NBS and peroxide) of acetylpyrimidine *142* to give *143*, which alkylates 3,4-dimethoxytoluene to give substituted thymine *144* when treated with mercuric chloride in nitrobenzene. The amino groups are restored in the classic fashion by conversion of *144* to chloride *145* with $POCl_3$, and

then displacement with ammonia to yield *146*.[45] *Ormetoprim* (146) is a coccidiostat as well as an antibacterial agent.

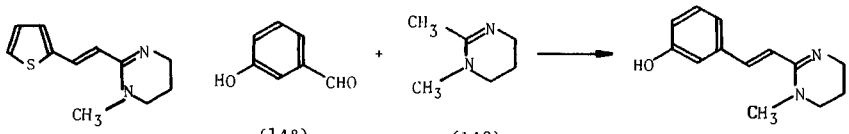


(142) X = H
(143) X = Br

(144) X = OH
(145) X = Cl

(146)

Following the success of *pyrantel (147)* as an anthelmentic[46] a search was undertaken for an analogue that would have activity against adult whipworms as well. This effort was successful with the synthesis of tetrahydropyrimidine *150*, the anthelminitic, o*xantel*.[47] The C-methyl group of *149* is sufficiently activated that heating together with 3-hydroxybenzaldehyde *(148)* in the presence of ethyl formate as a water scavenger produces o*xantel* directly.



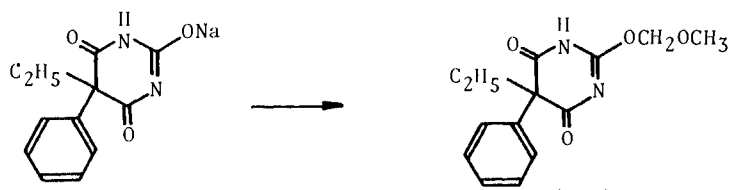
(147)

(148)

(149)

(150)

Convulsive disorders are still a serious therapeutic problem and new agents are being actively sought. Classical therapy was based upon the barbiturates that are no longer in favor because of their many side effects and their suicide potential. Interestingly, a seemingly minor structural variation of phenobarbital (*151*, shown as its sodium salt) leads to an anticonvulsant of increased potency and which has less hypnotic activity. In this case, sodium phenobarbital serves as its own base (so the yield is limited to 50%) and reacts readily with chloromethylmethyl ether to produce *eterobarb (152)*.[48]



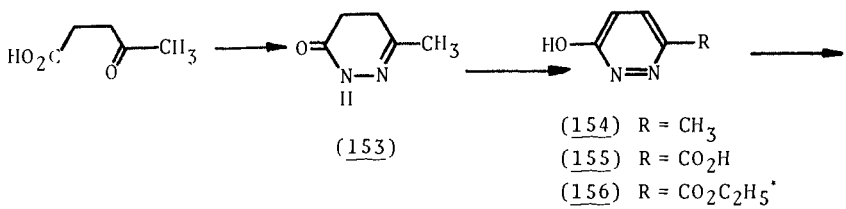
(151) (152)

5. MISCELLANEOUS STRUCTURES

As befits their chemical heterogenecity, the miscellaneous group of drugs in this section belong to a wide range of pharmacological classes as well.

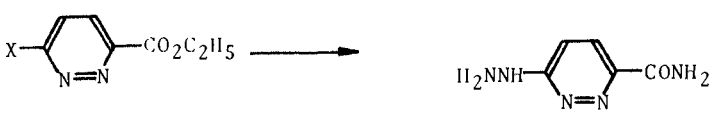
A pyridazine has found use as an antihypertensive agent. When levulinic acid is reacted with hydrazine, *153* results. This is aromatized to pyridazine *154* when reacted with bromine in acetic acid. One presumes a spontaneous dehydrobromination

converts the intermediate to *154*. Oxidation to the acid *(155)* is accomplished with potassium dichromate, and this is esterified to *156* under Fischer conditions. Conversion to chloro derivative *157* (with $POCl_3$) is followed by displacement with hydrazine to give *158*. The synthesis of blood pressure-lowering *hydracarbazine (159)* is then completed by aminolysis with ammonia.[49]



(153)

(154) R = CH_3
(155) R = CO_2H
(156) R = $CO_2C_2H_5$



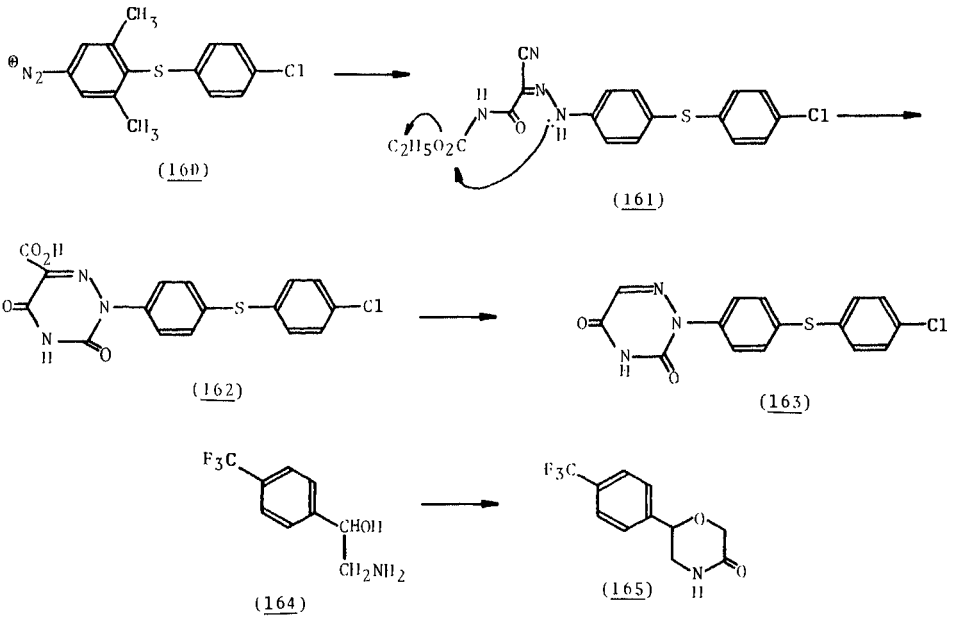
(157) X = Cl
(158) X = $NHNH_2$

(159)

The triazinedione, *triazuril (163)* is active as a poultry coccidiostat. Diazonium salt *160*, prepared from the appropriate aniline, is coupled with the active methylene group of N-carbethoxycyanoacetamide to give *161*. Hydrolysis of the cyano group is accompanied by cyclization, and the resulting acid *(162)* is decarboxylated to *triazuril (163)* on heating.[50]

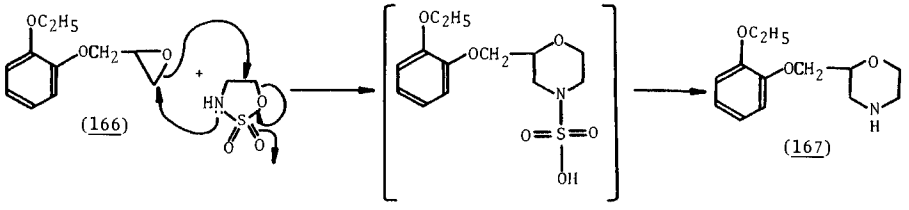
A morpholine derivative is active as a muscle relaxant. To prepare it, reaction of arylphenethanolamine derivative *164* with sodium hydride and ethyl

chloroacetate leads to *flumetramide (165)*.[51]



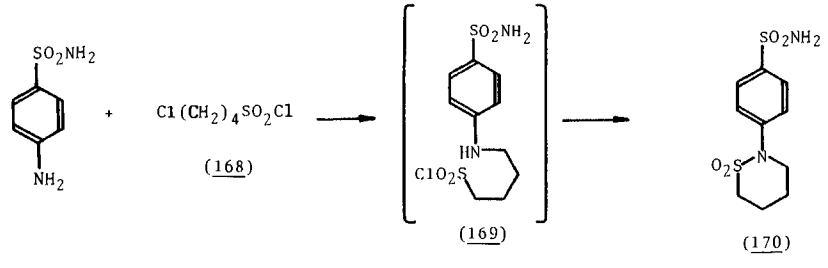
The carbonyl group of compounds related to *165* can be removed with retention of significant pharmacological activity. This can, of course, be done by lithium aluminum hydride reduction[52] or by, in at least one significant case, reaction of aryloxy-epoxide *166* with 2-aminoethylbisulfate to give the antidepressant agent, *viloxazine (167)*.[53]

The sultam, *sulthiame (170)*, shows anticonvulsant activity. p-Aminobenzenesulfonamide can be alkylated by ω-chlorobutylsulfonyl chloride *(168)* in



(166) (167)

base *via* presumed intermediate *169*, which spontaneously cyclizes to give *sulthiame (170)*.[54]

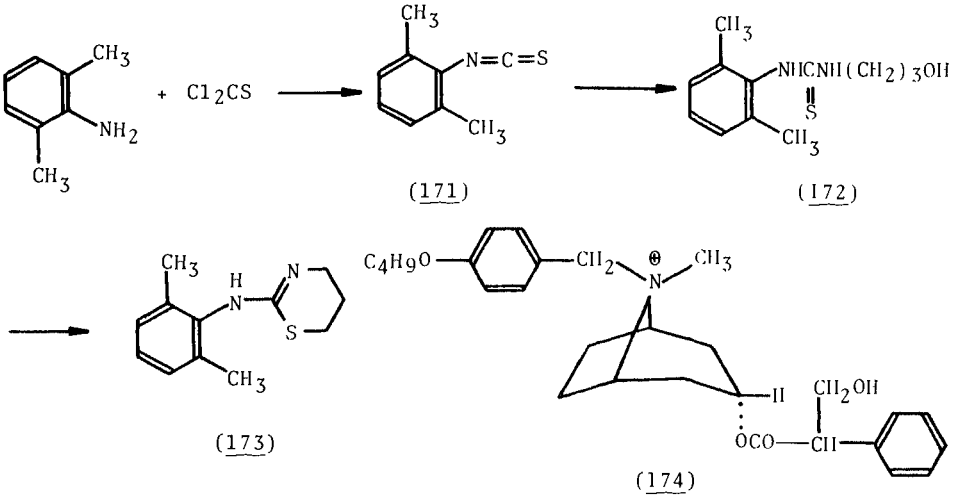


(168) (169) (170)

Reaction of 2,6-dimethylaniline with thiophosgene produces isothiocyanate *171*. When the latter is treated with 3-aminopropanol, thiourea *172* is formed, and this, when treated with hot concentrated hydrochloric acid, cyclizes to *xylazine (173)*, an analgetic and muscle relaxant.[55]

A great many quaternary amines are active anticholinergic agents. One such parasympathetic blocking

agent is made easily by reacting hyoscyamine with 4-butoxybenzylbromide to produce *butropium bromide (174)*.[56]



(171) (172) (173) (174)

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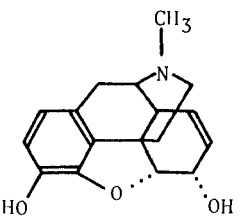
10

Compounds Related to Morphine

The development of the first effective analgesic drug, opium, was almost certainly adventitious, and occurred in prehistoric times. The use of the dried exudate from slitting the immature capsule of the opium poppy, *Papaver somniferum*, as an analgesic, sedative and euphoriant, has a long folkloric history. Isolation of the principal active component *morphine (1)* as a pure crystalline compound represented one of the early landmarks in organic chemistry.



(1)

The history of this class of analgesics might have stopped there were it not for the manifold ancillary activities shown by that molecule. Although still one of the most widely used agents for treatment of severe pain, *morphine* is a drug that must be used with caution. Side effects include respiratory depression, induction of constipation, and sometimes marked sedation. The one property that most severely limits use of this drug is its propensity to induce physical dependence in patients subjected to more than casual exposure.

1. Compounds Derived from Morphine

Attempts to modify the molecule so as to maximize analgesic activity at the expense of side effects date back almost a full century. It is ironic that *heroin* (diacetyl morphine) was in fact prepared in the course of one such program. Although early efforts concentrated on modification of the natural product, the growth of synthetic organic chemistry has led more recently to the preparation of molecules that represent much more deep seated changes in structure. The concept of molecular dissection has been used widely in the design of such lead compounds. Some of the more recent molecules inspired by morphine do in fact show promise of providing analgesia with significantly reduced side effects so that compounds are now available that show a much reduced tendency to induce physical dependence, *i.e.*, addiction liability.

It has long been a puzzle to medicinal chemists

why a natural product that has no evolutionary association with *Homo sapiens* should show such profound biological activity. The puzzle was, if anything, intensified by reports of the occurrence of receptors for morphine and related opioids in mammalian brains. Receptors for various endogenous hormones and other chemical transmitters have been recognized for some time; it was, however, unexpected to find a specific receptor for an exogenous chemical that plays no known role in the normal biochemical functioning of a mammal.

The identification of the morphine receptor spurred an effort in many laboratories to find an endogenous agonist for which that receptor was normally intended.[1] Ultimately, a pair of pentapeptides that bound quite tightly to opiate receptors were isolated from mammalian brains. These peptides, called *enkephalins (2, 3)*, show many of the activities of synthetic opiates in isolated organ systems. They do in fact show analgesic activity when injected directly into the brain. It is thought that lack of activity by other routes of administration is due to their rapid inactivation by peptide cleaving enzymes.

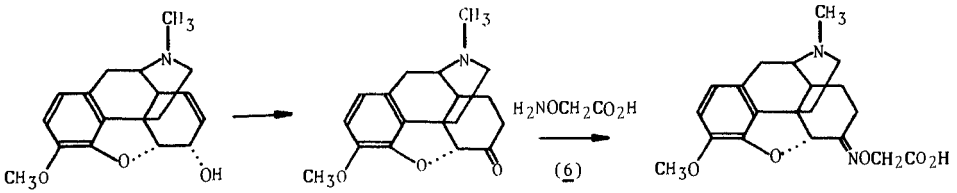
HTyr-Gly-Gly-Phe-MetOH
met-enkephalin
(2)

HTyr-Gly-Gly-Phe-LeuOH
leu-enkephalin
(3)

Fragments of the peptide hormone β-lipotropin have been found to show similar binding to opiate receptors. These molecules, the *endorphins*, show profound CNS activity in experimental animals. It is of interest that one of these, β-endorphin, incorporates in its chain the exact sequence of amino acids that constitutes methionine enkaphalin.

Although these findings are too recent to have had an impact on the design of analgesics, it has already been noted that when properly folded, molecular models of the enkaphalins show a good topographical correspondence with molecules such as morphine. Unless this topographic relationship is fortuitous, this has the most profound future implications for the rational design of analgesic drugs.

Morphine and related opiates are known to suppress the cough reflex; these compounds have thus been used extensively in antitussive preparations. Since this activity is not directly related to the analgesic potency, the ideal agent is one that has much reduced analgesic activity and thus, presumably, lower addiction potential. The weak analgesic *codeine (4)* is



still used in many such preparations, and a variety of analogues have been prepared as substitutes. For example, condensation of *dihydrocodeinone (5)* (available in several steps from 4) with hydroxylamine derivative *6* affords the antitussive agent *codoxime (7)*.[2]

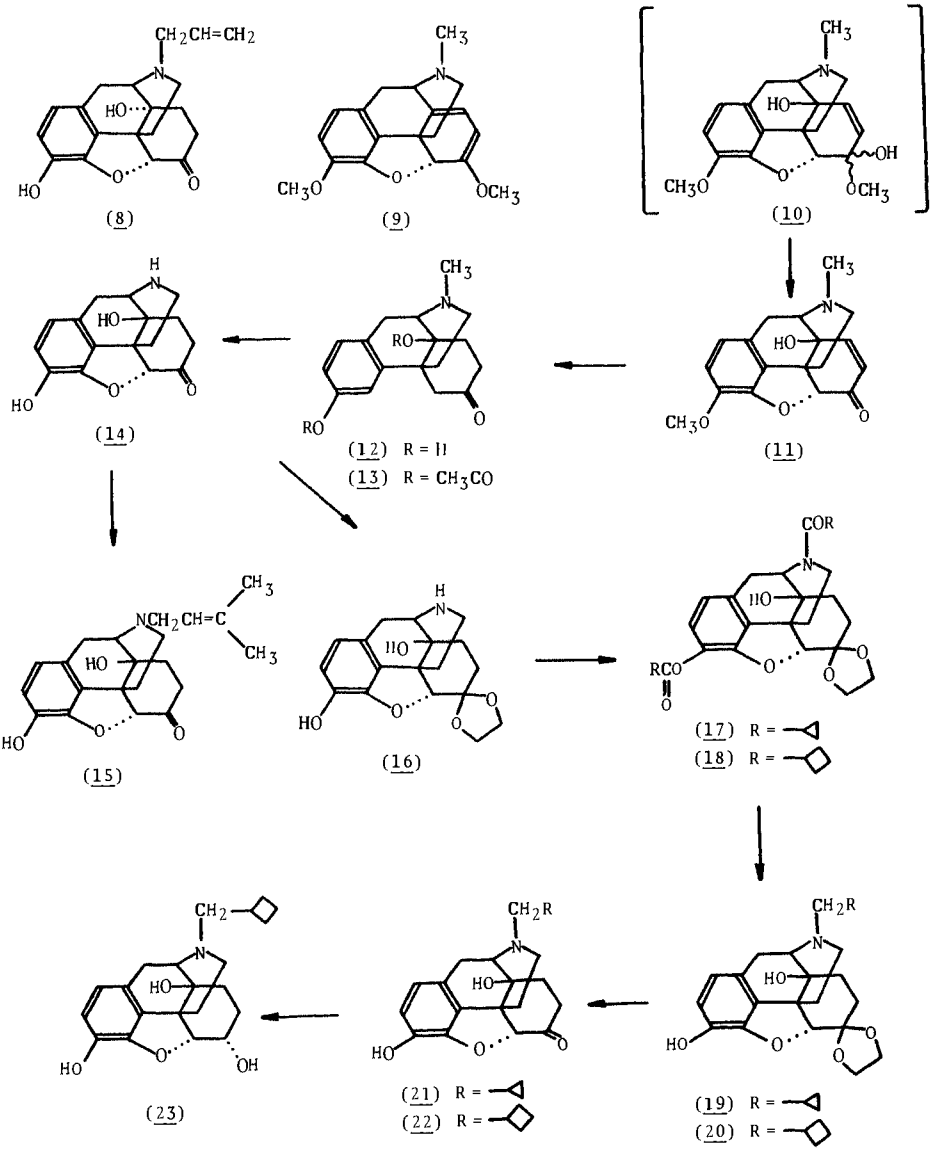
Replacement of the N-methyl group of morphine by an allyl moiety leads to a narcotic antagonist. That is, the resulting drug, *nalorphine*, not only shows little analgesic activity but will in fact block most of the actions of morphine. Presumably, it binds to the opiate receptor but has little intrinsic agonist activity. Incorporation of a new hydroxyl group at the 14-position in morphine has been found empirically to potentiate greatly the activity of morphine. Combination of these two modifications in a single drug gives a very potent narcotic antagonist, *naloxone* (8). It is possible, by suitable modification of various structural features in narcotic analgesic molecules, to devise compounds, which show both agonist and antagonist activities; it has been found both in experimental animals and in man that such mixed agonists-antagonists afford analgesics with much reduced addiction liability. The work that follows apparently was aimed at building agonist activity into the *naloxone* structure.

The starting material for these 14-hydroxy compounds is the opium alkaloid *thebaine (9)*. Although present in only small amounts in the alkaloid fraction from *Papaver somniferum*, it constitutes the major component (as much as 26% of the dried latex) from a

related poppy, *Papaver bracteatum*.[3] Reaction of *9* with hydrogen peroxide leads to intermediate *11*. The oxidation may be visualized as a 1,4-oxidation process of the diene system to afford an intermediate such as *10*. Successive reduction of the double bond *(12)* and demethylation affords *oxymorphone (13)*.[4] This molecule is then protected as the diacetate; N-demethylation followed by saponification affords the key intermediate *14*.[5]

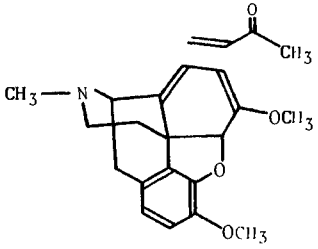
Alkylation of the secondary amine in *14* with 1-bromo-3-methyl-2-butene leads to the mixed analgesic agonist-antagonist *nalmexone (15)*.[6] In a somewhat more elaborate scheme, the carbonyl group in *14* is first protected as its cyclic ethylene ketal (16). Alkylation with cyclopropylcarbonyl chloride affords the O,N-diacylated product *(17)*; treatment with lithium aluminum hydride results in reductive cleavage of the O-acyl group and reduction of the amide carbonyl to a methylene group *(19)*. Hydrolysis of the acetal then affords the mixed analgesic/antagonist *naltrexone (21)*.[7] Acylation of *14* with cyclobutylcarbonyl chloride followed by the same series of transformations as above leads to intermediate *22*. Reduction of the carbonyl group in that molecule with sodium borohydride gives the analgesic agonist/antagonist *nalbuphine (23)*.[7]

An indication that the SAR of the narcotic antagonists was more complex than had been anticipated came from the observation of the tremendous increase in milligram potency obtained by fusing an additional bicyclic ring onto the basic morphine structure. The

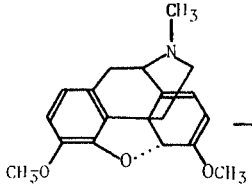

(8)
(9)
(10)
(11)
(12) R = H
(13) R = CH3CO
(14)
(15)
(16)
(17) R =
(18) R =
(19) R =
(20) R =
(21) R =
(22) R =
(23)

resulting molecule, **etorphine** *(26)* shows three orders of magnitude greater potency than morphine; this could be interpreted as a better or tighter fit to the receptor. Synthesis of this molecule also takes advantage of the diene function found in thebaine. Thus, Diels-Alder condensation of *9* with methyl vinyl ketone affords the bicyclic adduct *24*. The new ring is formed by approach of the dienophile from the face containing the nitrogen bridge, since this is in fact the least hindered side of the molecule *(9a)*. Reaction of the side chain ketone with propylmagnesium bromide then leads to intermediate *25*; demethylation of the phenolic ether affords *etorphine (26)*.[8]

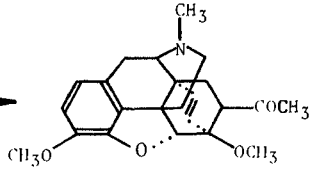
In this series, too, replacement of the N-methyl by a group such as cyclopropylmethyl leads to a compound with reduced abuse potential by virtue of mixed agonist-antagonist action. To accomplish this, reduction of *24* followed by reaction with tertiary butylmagnesium chloride gives the tertiary carbinol *27*. The N-methyl group is then removed by the classic von Braun procedure. Thus, reaction with cyanogen bromide leads to the N-cyano derivative *(28)*; hydrolysis affords the secondary amine *29*. (One of the more efficient demethylation procedures, such as reaction with ethyl chloroformate would presumably be used today.) Acylation with cyclopropylcarbonyl chloride then leads to the amide *30*. Reduction with lithium aluminum hydride *(31)* followed by demethylation of the phenolic ether affords *buprenorphine (32)*.[9]



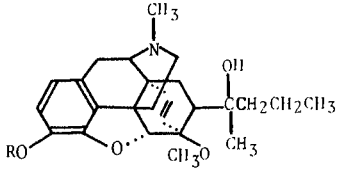
(9a)



(9)

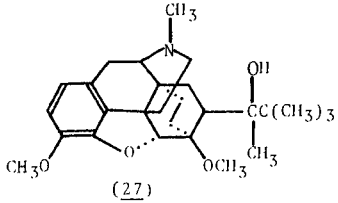


(24)

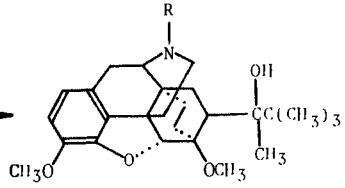


(25) R = CH_3

(26) R = H

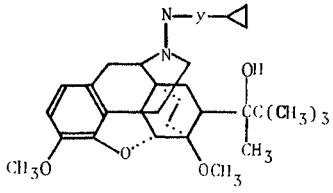


(27)



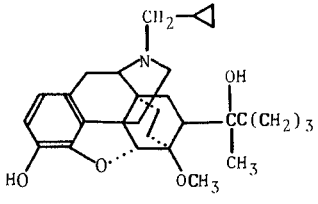
(28) R = CN

(29) R = H



(30) y = CO

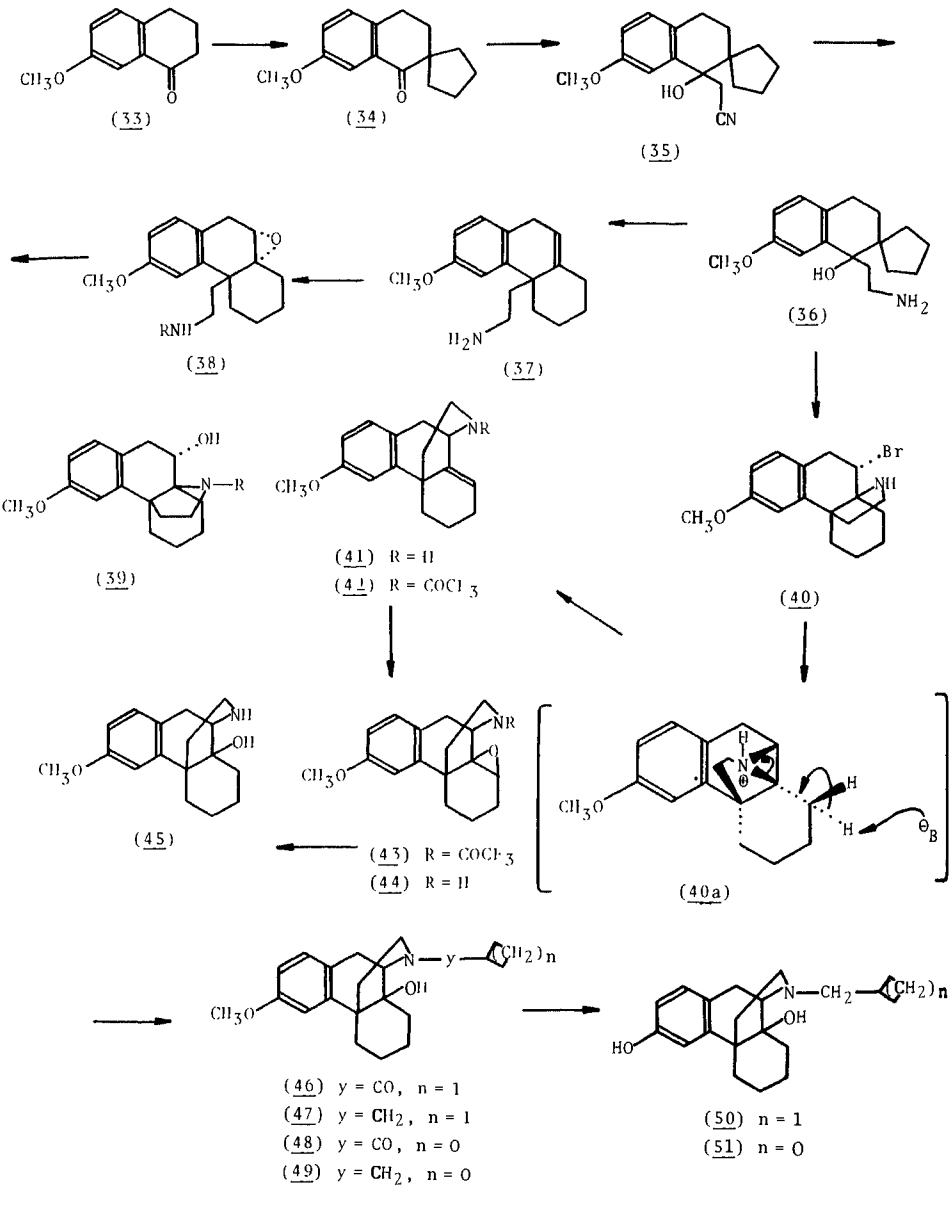
(31) y = CH_2



(32)

2. Morphinans

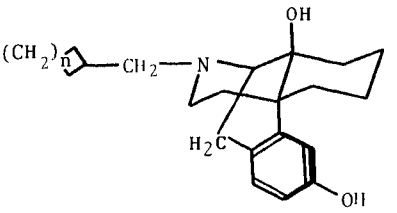
In the course of earlier work it had been ascertained that the furan oxygen of morphine was not essential to analgesic activity.[10] This observation led to the preparation of a considerable number of quite potent deoxy analogues of morphine, since these compounds were relatively easily accessible by totally synthetic routes. Combination of this deoxy nucleus (called *morphinan*) with the tertiary hydroxyl found in molecules such as *naloxone* has led to quite potent analgesics; appropriate modification of the substituent on nitrogen then has led to mixed agonists-antagonists. These compounds, too, show much reduced addiction liability. For example, alkylation of the anion from tetralone *33* with 1,4-dibromobutane gives the spiro ketone *34*. Condensation of the carbonyl group with the anion obtained on treatment of acetonitrile with butyl lithium leads to the carbinol *35*; the cyano group is then reduced to the primary amine *(36)* by means of lithium aluminum hydride. Treatment of *36* with acid leads to the corresponding tertiary benzylic carbonium ion; this undergoes Wagner-Meerwein rearrangement and proton loss to give the phenanthrene derivative *37*, a key intermediate in this series.[11] Several schemes have been developed for proceeding from this point; however, some relatively direct routes suffer from lack of regiospecificity. For example, internal cyclization of epoxide *38* affords both the desired ring system *(45)* and its isomer *(39)*.[12] In one regiospecific route, amine *37* is

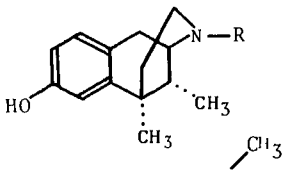

(33)
(34)
(35)
(36)
(37)
(38)
(39)
(40)
(41) R = H
(42) R = COCl 3
(43) R = COCF3
(44) R = H
(45)
(40a)
(46) y = CO, n = 1
(47) y = CH2, n = 1
(48) y = CO, n = 0
(49) y = CH2, n = 0
(50) n = 1
(51) n = 0

treated with bromine to afford the bicyclic bromoamine *40*. The reaction can be rationalized by assuming initial bromonium ion formation on the underside of the molecule; opening of the ring by the amine will lead to the observed product as its hydrobromide salt. Reaction of *40* with sodium bicarbonate results in the rearrangement to the desired skeleton. The inorganic base is not in this case the reagent; rather, it is likely that once *40* is present as the free base, it undergoes the internal displacement *via* the aziridinium ion. Following protection of the amine as the trifluoroacetamide *(42)*, the double bond is oxidized to give mainly the β-epoxide *(43)*. Hydrolysis of the amide linkage *(44)* followed by treatment with lithium aluminum hydride affords the desired aminoalcohol *45*. Both the regio and stereochemistry of this last reaction follow from the diaxial opening of oxiranes. Acylation of this intermediate with cyclobutylcarbonyl chloride gives the corresponding amide *(46)*. Reduction of the amide *(47)* followed by O-demethylation affords *butorphanol (50)*.[13] The same sequence on *45* starting with cyclopropyl carbonyl chloride leads to *oxilorphan (51)*.[14]

3. Benzomorphans

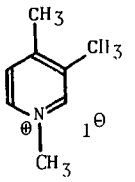
Further dissection of the morphine molecule showed that potent analgesics could be obtained even when one of the carbocyclic rings was omitted. One such compound, *pentazocine (52)*, has found considerable use as an analgesic in the clinic. There is considerable evidence to indicate this drug has much less



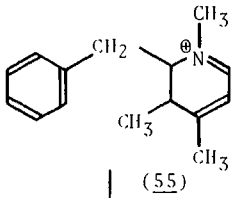


(52) R = $CH_2CH{=}C(CH_3)_2$

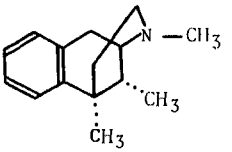
(53) R = CH_2-cyclopropyl



(54)



(55)



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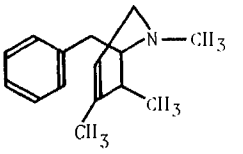

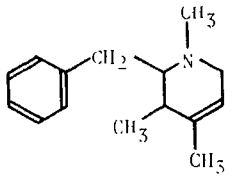

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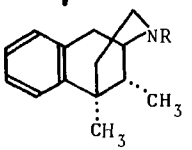
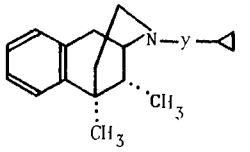


(58) R = CN

(59) R = H



(60) R = CO

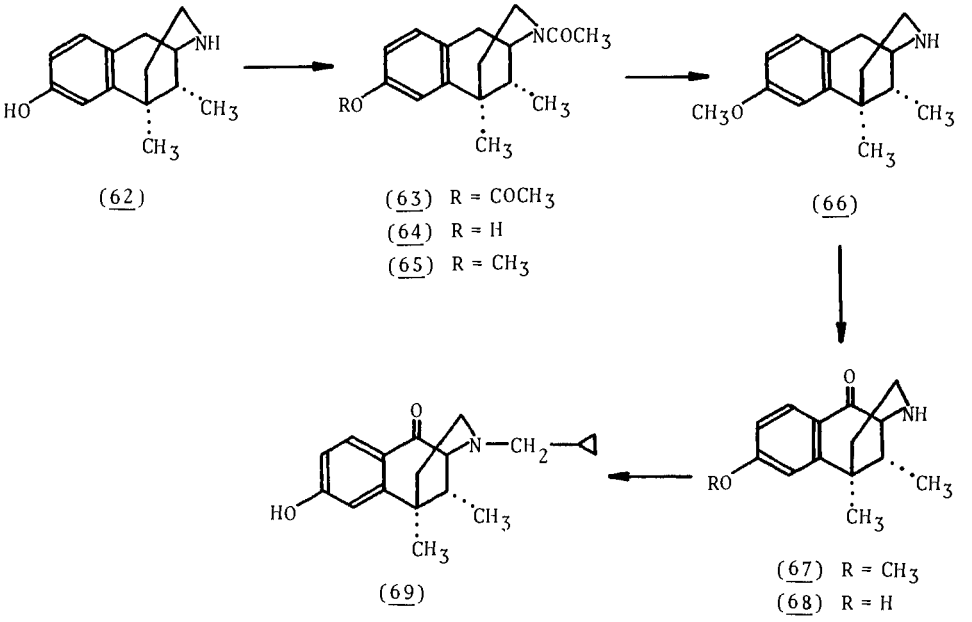
(61) R = CH_2

addiction potential than does morphine. The corresponding cyclopropylmethyl analogue *cyclazocine (53)*, perhaps as a consequence of its greater balance of antagonist activity, has proven to be quite hallucinogenic.

Omission of the phenolic group from *cyclazocine* results in a molecule which retains analgesic activity. In a classical application of the Grewe synthesis,[15] the methylated pyridinium salt *54* is condensed with benzylmagnesium bromide. There is thus obtained the dihydropyridine *55*. Treatment of that intermediate with sodium borohydride results in reduction of the iminium function to afford the tetrahydro derivative *56*. Cyclization of *56* on treatment with acid leads to the desired benzomorphan nucleus. The *cis* compound *(57)* is separated from the mixture of isomers and demethylated by the cyanogen bromide procedure *(58, 59)*. Acylation with cyclopropylcarbonyl chloride (to *60*) followed by reduction of the resulting amide yields *volazocine (61)*.[14]

Oxidation of the benzylic methylene group in *cyclazocine* to a ketone is also consistent with analgesic activity. Acetylation of benzomorphan *62* affords the diacetate *63*. Selective hydrolysis of the phenolic acetate *(64)* followed by methylation of the thus uncovered phenol affords intermediate *65*. The remaining acetate is then hydrolyzed *(66)*. Oxidation of that compound with chromium trioxide in sulfuric acid leads cleanly to the desired ketone *(67)*. Treatment with hydrobromic acid serves to demethylate the phenolic ether function *(68)*. Direct

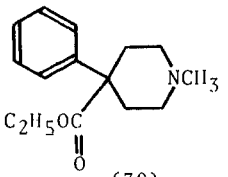
alkylation of the secondary amine with cyclopropylmethyl bromide gives *ketazocine (69)*.[16]



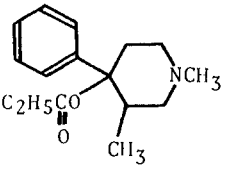
4. Phenylpiperidines

Extensive molecular dissection of the morphine molecule over the past several decades led to a host of molecules which showed narcotic analgesic activity even though they possessed but faint suggestion of the structural features present in morphine itself. Thus, both cyclic molecules such as *meperidine (70)* and *alphaprodine (71)*, and acyclic compounds such as *methadone (72)* were found to be effective analgesics. Common features of these compounds were formalized by the Beckett-Casy rule, which states as minimal required structural features: (a) an aromatic ring attached to

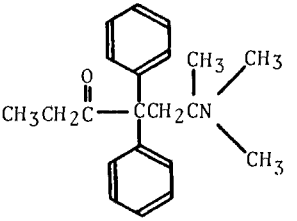
(b) a quaternary center, and finally (c) the presence of nitrogen at a distance equivalent to two carbon atoms from the quaternary center *(73)*. Although sufficient exceptions have recently been found to suggest that this is an oversimplification, it is of historical importance because of its guiding influence on analgesic research over a considerable span of time.



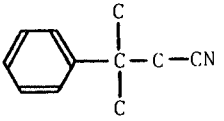
(70)



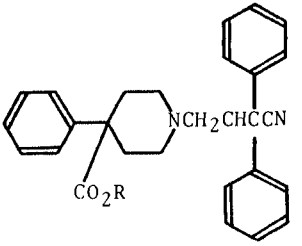
(71)



(72)

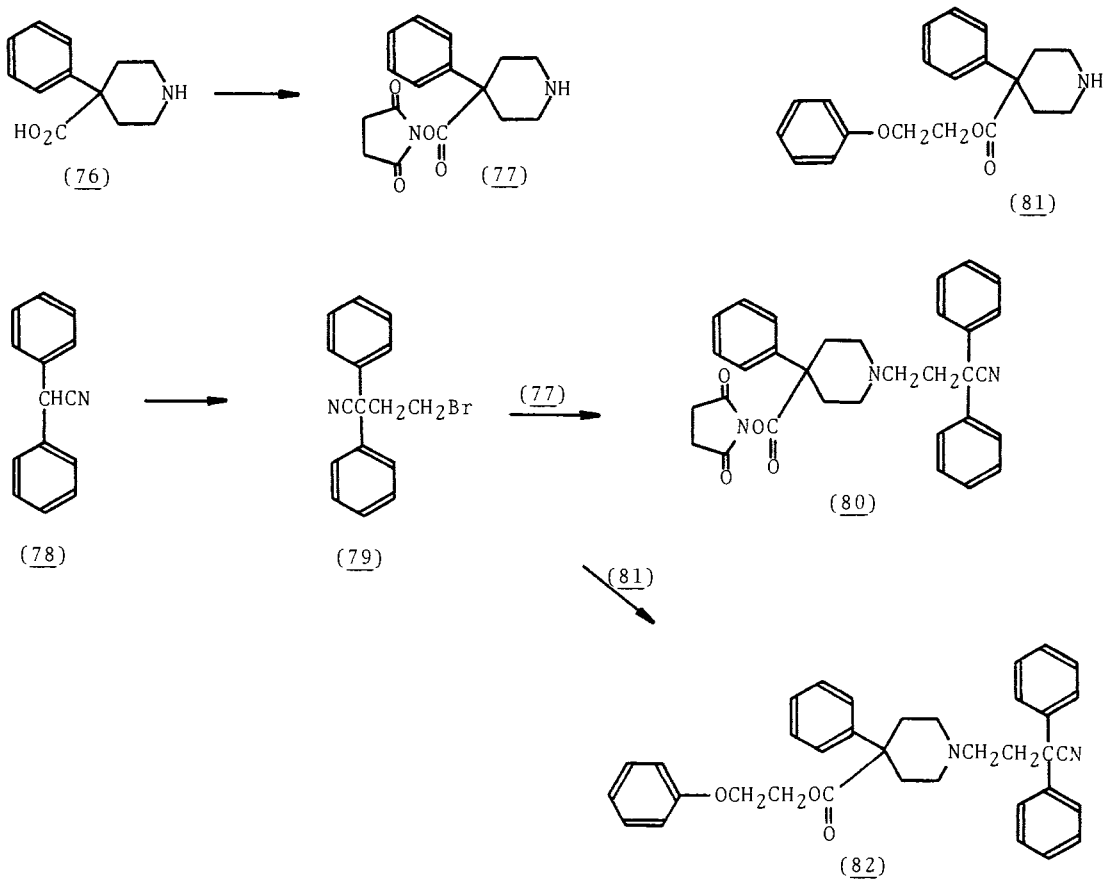


(73)



(74) R = C_2H_5
(75) R = H

It will be recalled that a common side effect of *morphine* is the induction of constipation. This property of the drug has often been exploited in the design of preparations used to control diarrhea.

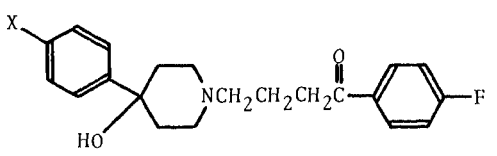

HO2C
NH
(76)
O
NOC
O
O
NH
(77)
OCH2CH2OC
O
NH
(81)
CHCN
(78)
NCCCH2CH2Br
(79)
(77)
NCH2CH2CCN
NOC
(80)
(81)
OCH2CH2OC
O
NCH2CH2CCN
(82)

There has also been some work devoted to the preparation of a compound that would show greater selectivity toward activity on the gut and away from activity over the CNS. *Diphenoxylate (74)*[17] has been used extensively in humans for just this purpose; although the drug shows some selectivity, it is far from free of narcotic effects. (The curious will note the compound follows the Beckett rule both in the piperidine and side chain moieties.) Treatment of *74* with potassium tertiary butoxide in DMSO results in saponification to the free acid *difenoxin (75)*.[18]

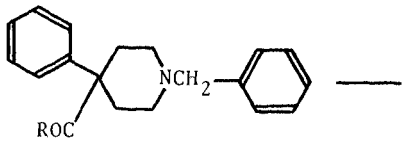
Certain esters have often been employed in attempts to confer organ selectivity to molecules possessing carboxyl functions. Thus, for example, treatment of piperidinecarboxylic acid *76* with N-hydroxysuccinimide and DCC affords the ester *77*. In a convergent synthesis, the anion from diphenylacetonitrile *(78)* is alkylated with dibromoethane to afford the bromide *79*. Alkylation of the piperidine derivative *77* with that halide *79* gives the antidiarrheal agent *difenoximide (80)*. The same sequence starting with the phenoxyethyl ester *81* gives *fetoxylate (82)*.[20]

Derivatives of 4-phenyl-4-hydroxypiperidine, which may be formally regarded as reversed meperidines, have yielded a series of potent antipsychotic drugs such as *haloperidol (83)* and *bromoperidol (84)*. Retention of carbon at the 4-position interestingly leads to a molecule with quite different activity. The starting material for this molecule could be synthesized by first preparing the amide *(86)* from

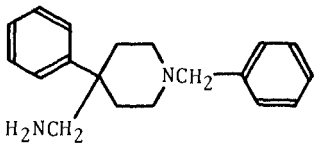
the benzyl *(85)* derivative of meperidine. Reduction of the amide would then afford the primary amine *(87)*. Acetylation *(88)* followed by removal of the benzyl group would afford the key intermediate *(89)*. Alkylation with 4-chloro-p-fluorophenylbutyrophenone affords *aceperone (90)*.[21] This compound exhibits vasodilator and antihypertensive activity.



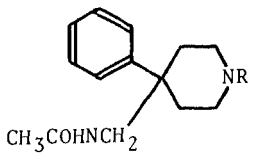
(83) R = F
(84) R = Br



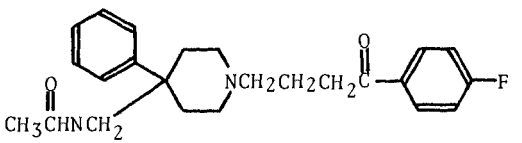
(85) R = OC_2H_5
(86) R = NH_2



(87)

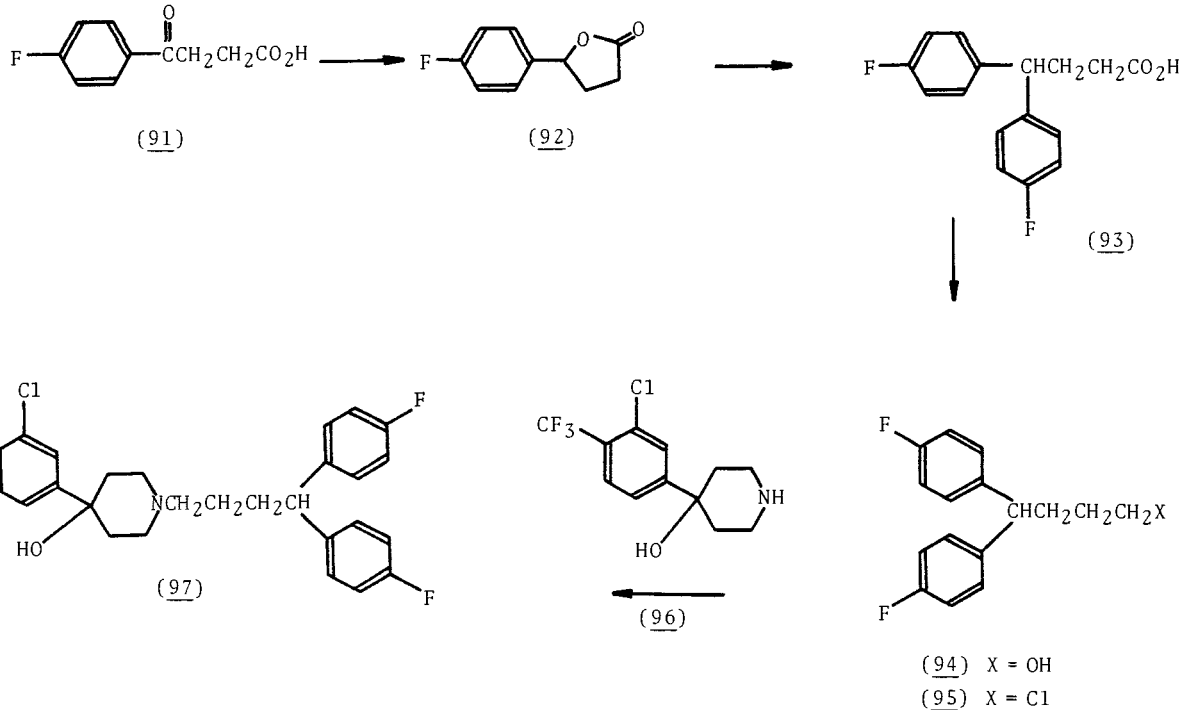


(88) R = $C_6H_5CH_2$
(89) R = H



(90)

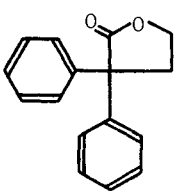
Alkylation of diphenylpiperidinols with bis(p-fluorophenyl)butyl side chains has also led to antipsychotic compounds. For example, reductive cyclization of the acylation product *(91)* from fluorobenzene


F
O
CCH2CH2CO2H
(91)
F
O
O
(92)
F
CHCH2CH2CO2H
F
(93)
F
CHCH2CH2CH2X
F
(94) X = OH
(95) X = Cl
Cl
CF3
NH
HO
(96)
Cl
CF3
NCH2CH2CH2CH
HO
F
F
(97)

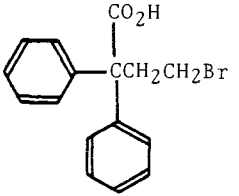
and succinic anhydride gives the corresponding butyrolactone *92*. Treatment with fluorobenzene in the presence of a Friedel-Crafts catalyst leads to the diarylated acid *93*. The carboxyl group is then reduced to the corresponding carbinol *94* by means of lithium aluminum hydride, and this is converted to the chloro compound *95* with thionyl chloride. Alkylation of piperidine *96* with that halide gives the neuroleptic compound *penfluridol (97)*.[22]

The use of phenylpiperidinols rather than the meperidine-related piperidines as the basic component in antidiarrheal compounds results in retention of activity. The fact that the base is not directly related to a narcotic presumably leads to greater selectivity of action on the gut. Ring scission of butyrolactone *98* (obtainable by alkylation of a diphenylacetate ester with ethylene oxide) with hydrogen bromide gives the bromo acid *99*. This is then converted to the dimethylamide by successive treatment with thionyl chloride and dimethylamine. The initial product from this reaction *(100)* is not observed as it undergoes spontaneous internal displacement to the cyclic imino ether salt *101*. Treatment of *101* with amine *102* proceeds at the activated ether carbon to give *fluperamide (103)*;[23] the same reaction with amine *103* affords the antidiarrheal agent *loperamide (105)*.[23]

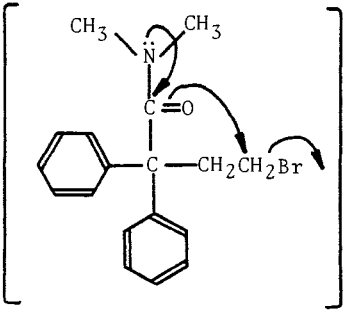
Incorporation of additional basic centers into the phenylpiperidinol nucleus leads to a molecule that shows local anesthetic rather than CNS activity. Condensation of the protected piperidone *106* with



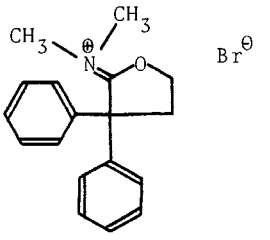
(98)



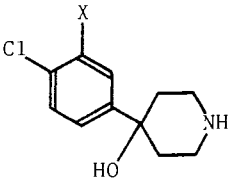
(99)



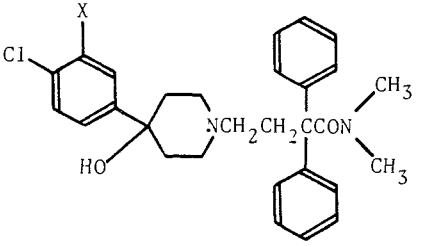
(100)



(101)

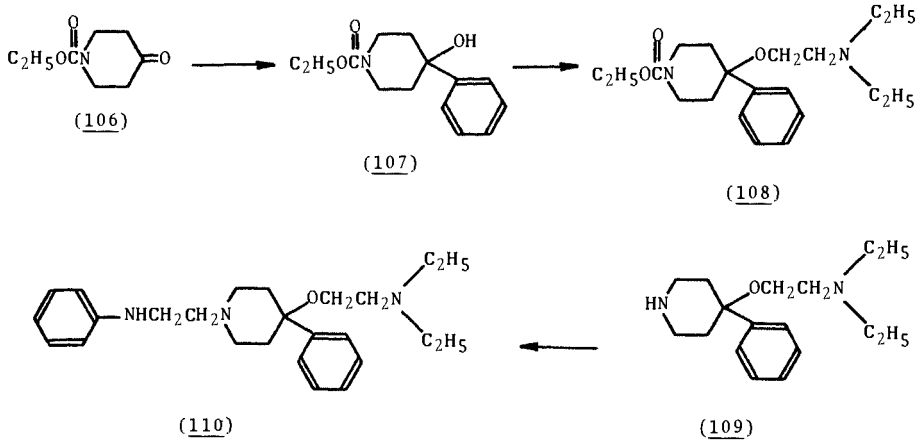


(102) X = CF_3
(103) X = H



(104) X = CF_3
(105) X = H

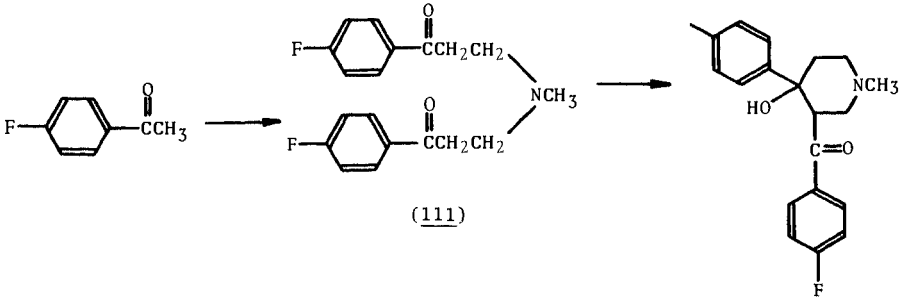
phenylmagnesium bromide affords the desired piperidinol *(107)*. Alkylation of the carbinol by means of 2-chlorotriethylamine gives the corresponding basic ether *(108)*. Hydrolysis of the carbamate protecting group *(109)*, followed by alkylation of the resulting secondary amine with N-(chloroethyl)aniline affords the local anesthetic, *diamocaine (110)*.[24]



(106) (107) (108) (109) (110)

The piperidines discussed thus far contained a single polar substituent on the heterocyclic ring. Except for the last entry, the compounds all showed activity on the CNS or closely related systems. It is thus somewhat surprising to find that simple addition of an aroyl group leads to a compound that shows antiinflammatory activity. The seemingly complex molecule can in fact be obtained in two steps from simple starting materials.[25] Thus, Mannich reaction of p-fluoroacetophenone with paraformaldehyde and methylamine affords condensation product *111*. Treatment with aqueous base leads to cyclization by

internal aldol condensation. There is thus obtained the nonsteroidal antiinflammatory agent *flazalone (112)*.[26]



(111)

(112)

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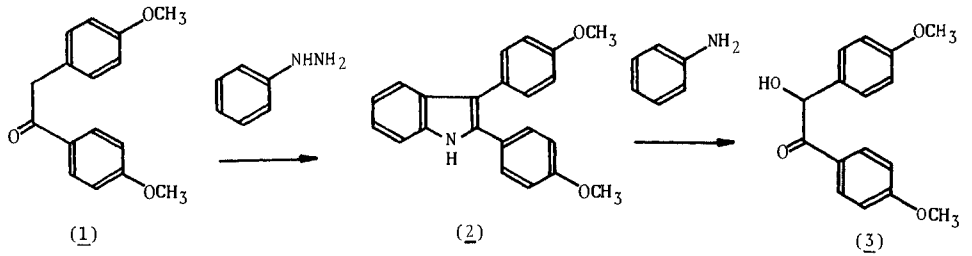
11

Five-Membered Heterocycles Fused to One Benzene Ring

1. INDOLES

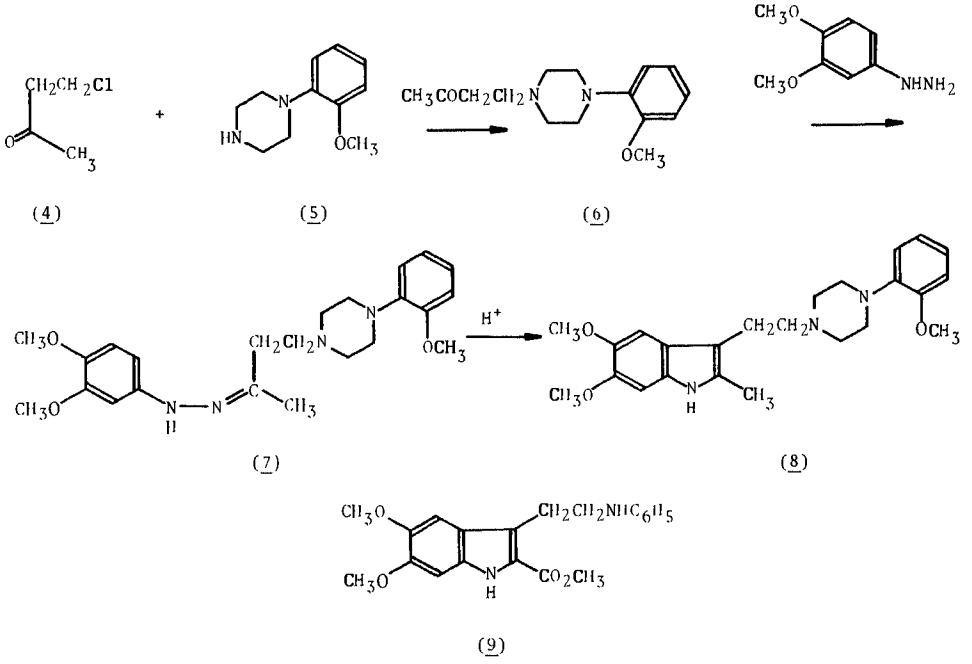
The classic and most convenient synthesis of the indole moiety is that of Emil Fischer. Recent examples of its use for drug synthesis includes one preparation of the nonsteroidal antiinflammatory agent, *indoxole (2)*.[1] Reaction of ketone *1* with phenylhydrazine in acetic acid leads directly to *indoxole (2)*. Alternately, anisoin *(3)* can be reacted



(1) (2) (3)

with aniline by heating in concentrated HCl, proceeding presumably through direct displacement of OH by aniline followed by cyclodehydration to *2*. A credible but more involved mechanism can also be written starting with Schiff's base formation.

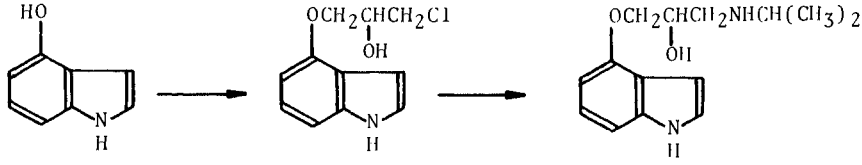
A somewhat more complex example of the Fischer indole synthesis is provided by the tranquilizer, *milipertine (8)*.[2] It can be prepared by reaction of



(4) (5) (6) (7) (8) (9)

1-chlorobutan-3-one *(4)* with 1-(2-methoxyphenyl) piperazine *(5)*, which leads to asymmetrical ketone *6*. Reaction of *6* with 3,4-dimethoxyphenylhydrazine leads to complex hydrazone *7* which, on treatment with strong acid, rearranges to *milipertine (8)*. The course of the last reaction reveals one of the classic

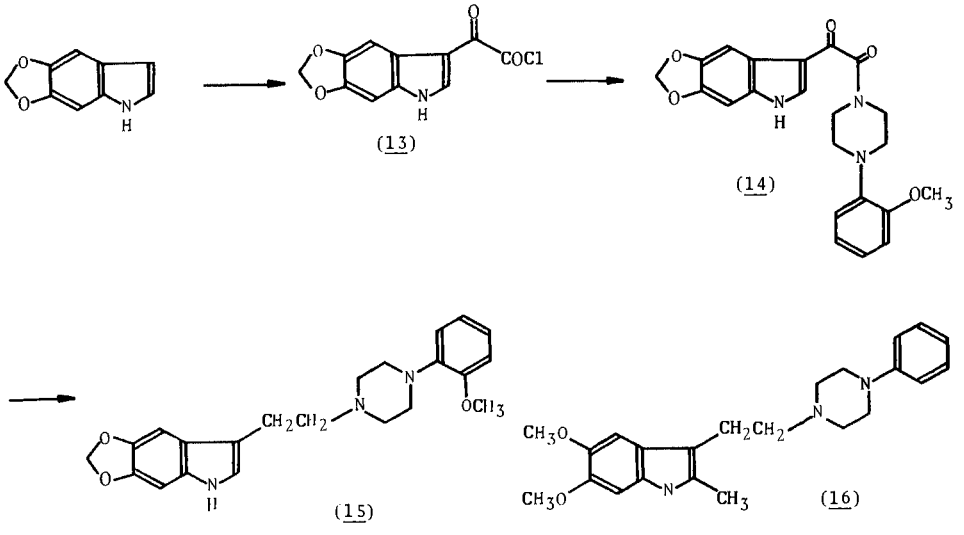
features of the Fischer synthesis-cyclization onto the more substituted side of the ketone. Another tranquilizer, *alpertine (9)*, has a rather similar structure to *8*.



(10) (11) (12)

Interest in the psychotropic features of the mushroom substance, *psilocybine*, led to an exploration of the chemistry of 4-hydroxyindole *(10)*. The availability of this substance provided a suitable starting point for the synthesis of *pindolol (12)*, a β-adrenergic blocking agent.[3] Reaction of *10* with epichlorohydrin and NaOH led to ether *11* whose halo atom was readily displaced by isopropylamine to complete the synthesis of *12*.

One of the more convenient methods of adding a twocarbon side chain to the electron-rich 3-position of indoles is the Speeter-Anthony reaction,[4] illustrated in the synthesis of the antiadrenergic agent, *solypertine (15)*.[5] In this case, the reaction between 5,6-methylenedioxyindole and oxalyl chloride gives ketoacid chloride *13*. The sequence then proceeds by amide formation *(14)* with amine *5*. Reduction with

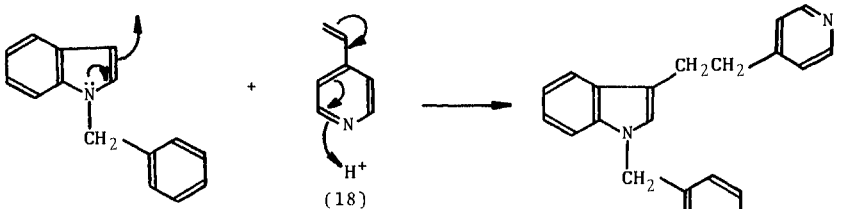


lithium aluminum hydride reduces both carbonyls to give *solypertine (15)* whose structural relationship to *milipertine (8)* is obvious. Another related drug is *oxypertine (16)*, an antidepressant made by essentially the same route as illustrated for *solypertine*.[5]

Combining the nucleophilicity of the indole 3-position just illustrated and the well-known tendency of C-2 and C-4 vinyl pyridines to add nucleophiles, a convenient synthesis of the tranquilizer *benzindopyrine (19)* was devised.[6] Reaction of N-benzylindole *(17)* with 4-vinylpyridine *(18)* in acetic acid produced *19* directly.

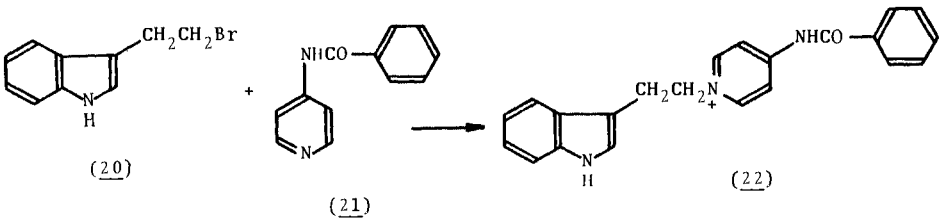
Tryptamine and serotonin are naturally occurring indole ethylamino compounds with pronounced pharmaco-

logical activities. They have served as the inspiration for synthesis of numerous analogues. One such study involved alkylation of 4-benzamidopyridine *(21)*

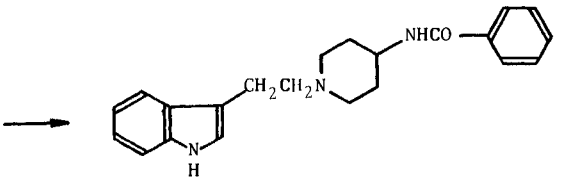


(17) (18) (19)

with 2-(3-indolyl)ethylbromide *(20)* to give quaternary salt *22;* this intermediate was in turn hydrogenated with a Raney nickel catalyst to give *indoramin (23)*, which is antihypertensive, apparently because of its α-adrenergic blocking activity.[7]

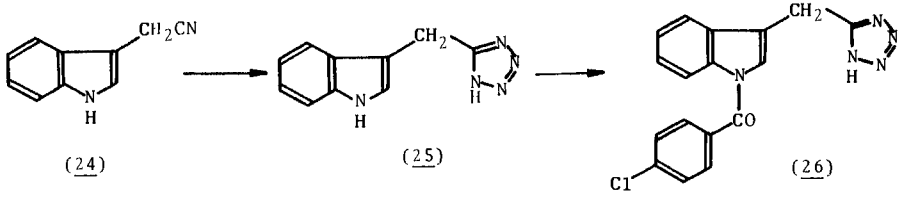


(20) (21) (22)

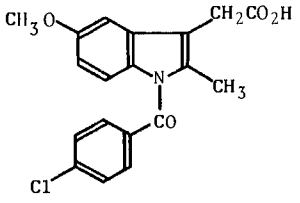


(23)

Because of the resonance stabilization possible in its deprotonated form, the 5-tetrazolyl moiety is actually nearly as acidic (pKa ca. 6) as many carboxylic acids. This has led to its inclusion in many drug series as a carboxyl surrogate. Apparently related in concept to indomethacin *(26a)*, *intrazole (26)* is a nonsteroidal antiinflammatory agent which also inhibits platelet aggregation, and therefore is of potential value in keeping the contents of the



(24) (25) (26)

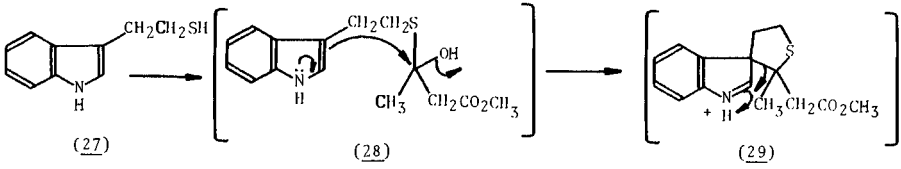


(26a)

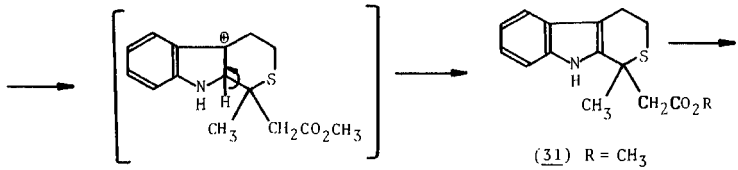
vascular bed free-flowing in certain pathological conditions. The synthesis begins with 2-(3-indolyl)-acetonitrile *(24)* which is transformed to the tetrazoyl derivative *(25)* by 1,3-dipolar reaction with sodium azide. The acidic indole NH hydrogen is abstracted when *25* is treated with two equivalents of sodium

hydride and the salt, when acylated with a single equivalent of 4-chlorobenzoyl chloride, is smoothly transformed to *intrazole*.[8] Note that acylation occurs preferentially at the more nucleophilic (indole) anion.

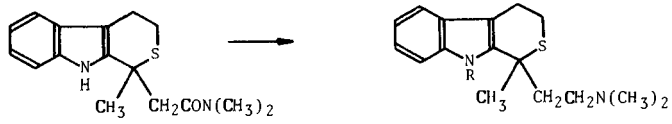
When the indole 3-position is already substituted, electrophilic reagents attack the 2-position instead often through a 3,3-spiro intermediate. For example, when 2-(3-indolyl)ethylmercaptan *(27)* reacts with methyl acetoacetate, the thia-β-carboline analogue *31* results. It seems plausible that the reaction involves initial hemithioketal formation *(28)*, followed by electron release by the indole nitrogen and hydroxide



(27) (28) (29)



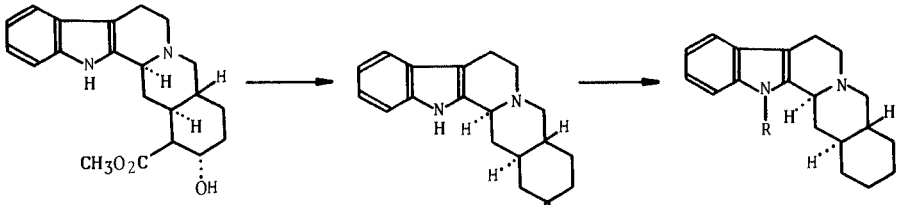
(30) (31) R = CH_3 (32) R = H



(33) (34) R = H (35) R = C_2H_5

displacement to give *29*. Compound *29* has interrupted aromaticity, and a Wagner-Meerwein type rearrangement would led to carbonium ion *30*, which would eject a proton to restore indole resonance *(31)*. In any case, *31* is the product. Saponification to the free acid (*32* is followed by dimethylamide formation *(33)*, mediated by carboxyl activation *via* mixed anhydride reaction with ethyl chlorocarbonate. Lithium aluminum hydride reduction to the tertiary amine *(34)* is followed by base-mediated N-alkylation with ethyl bromide to produce *tandamine (35)*, an antidepressant that inhibits the uptake of norepinephrine into storage granules.[9]

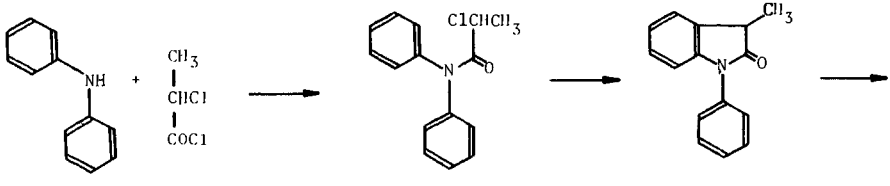
Yohimbine (36) is a well-known and reasonably available alkaloid from *Corynanthe yohimbe, inter alia*. For this reason, and partly because of its intrinsic pharmacological activity (including reputed aphrodisiac activity), chemists have frequently studied its properties. Oppenauer oxidation is usually attended by saponification and decarboxylation in this series, and yohimbone *(37)* is the product. Wolf-Kischner reduction to *yohimbane (38)*, followed by sodium hydride mediated alkylation, leads to the analgesic agent, *mimbane (39)*.[10]



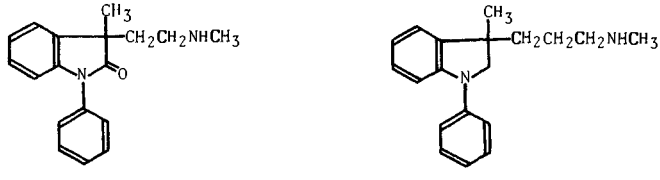
(36) (37) (38) R = H (39) R = CH_3

2. REDUCED INDOLES

Although geneologically related to indoles, the dihydroindoles behave chemically rather like alkyl anilines. When diphenylamine reacts with chloropropionyl chloride, amide *40* results; this in turn readily cyclizes to oxindole *41*. Sodium hydride followed by 2-chloroethyldimethylamine alkylates the 3-position (possibly through an intermediate aziridinium ion); partial demethylation is accomplished by refluxing with ethylchlorocarbonate, followed by hydrolysis of the intermediate carbamate to give indolinone *42*, the antidepressant *amedalin*.[11] Repetition of this sequence on the chloropropyl homologue, followed by reduction of the appropriate indolinone produces dihydroindole *43*, *daledalin*, which also has antidepressant activity.[11]

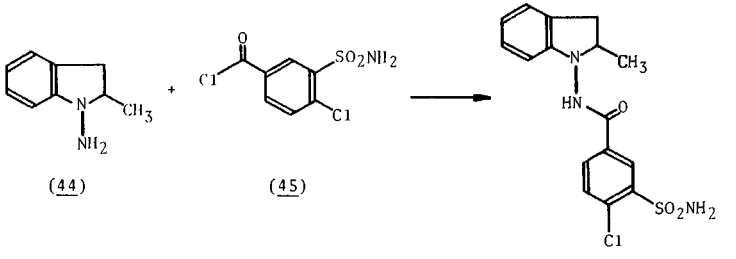


(40) (41)



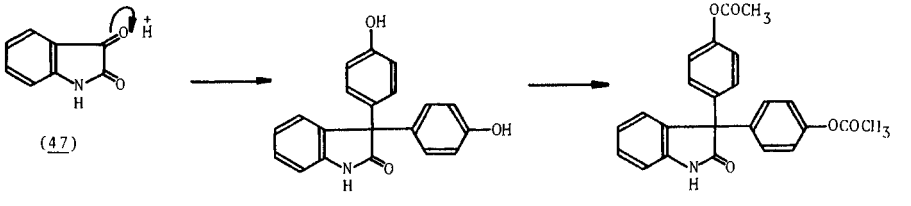
(42) (43)

Hydrazides also containing a metasulfonamide function are known to exhibit diuretic activity. Substitution of an N-aminodihydroindole for the hydrazine is consistent with this activity. Preparation of one such agent is carried out by reaction of 2-methyl-N-aminoindoline *(44)* with 3-sulfamoyl-4-chlorobenzoyl chloride *(45)*, leading to the diuretic *indapamide (46)*.[12]



(44) (45) (46)

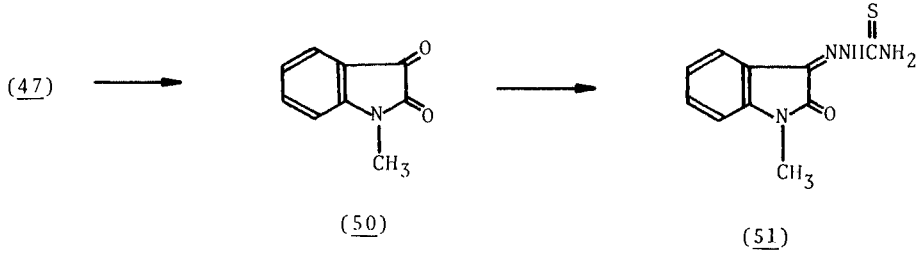
A more highly oxidized indole relative is isatin *(47)*. The ketonic carbonyl group is nonenolizable and has interesting properties. In strong acid it



(47) (48) (49)

becomes protonated, and the oxygen can be replaced by electron-rich moieties. Almost 100 years ago such a condensation with phenol was discovered to lead to *48*. Acetylation led to o*xyphenisatin (49)* which has carthartic properties.[13]

It is also clearly anticipated that the ketonic moiety will form normal carbonyl derivatives. When isatin *(47)* is treated with sodium hydride and methyl iodide, the acidic hydrogen is alkylated to produce *50*. Then, reaction of the ketone carbonyl with thiosemicarbazine leads to *methisazone (51)*.[14] At the time of its discovery, *methisazone* was one of a very few antiviral leads showing activity in whole animal tests, and led to an extensive exploration of the properties of analogues.

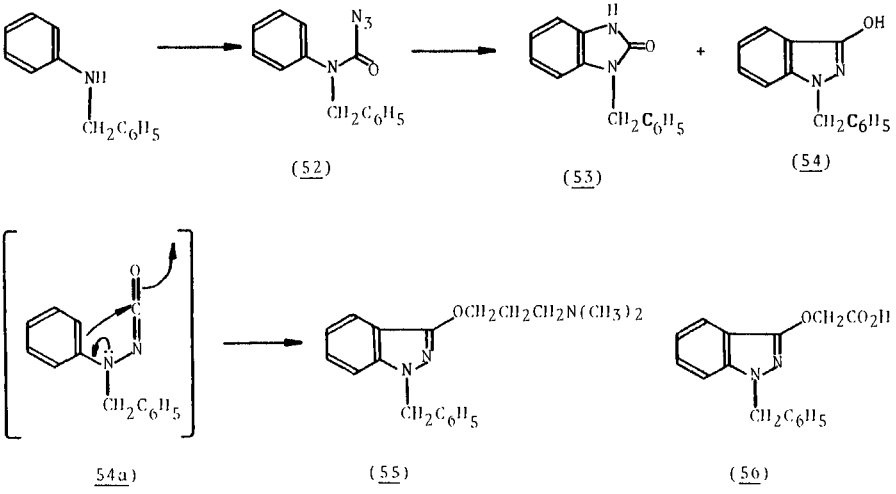


(50) (51)

3. INDAZOLES

The compounds of medicinal interest in this group so far have all been nonsteroidal antiinflammatory agents or analgesics. The prototype is *benzydamine (55)*.[15] An interesting alternate synthesis of this substance starts by sequential reaction of

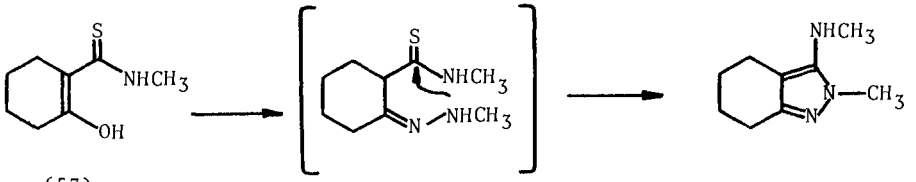
N-benzylaniline with phosgene, and then with sodium azide to produce carbonyl azide *52*. On heating, nitrogen is evolved and a separable mixture of nitrene insertion product *53* and the desired ketoindazole *54* results. The latter reaction appears to be a Curtius-type rearrangement to produce an N-isocyanate *(54a)*, which then cyclizes. Alkylation of the enol of *54*



with sodium methoxide and 3-dimethylaminopropyl chloride gives *benzydamine*.[16] Alternatively, use of chloroacetamide in the alkylation step followed by acid hydrolysis produces *bendazac (56)* instead.[17] *Bendazac*, an acetic acid derivative, more closely resembles the classical nonsteroidal antiinflammatory agents.

Reduction of the benzene ring is also compatible with activity in this group. Reaction of N-methyl-2-thiocarbamoylcyclohexanone *(57)* with methyl hydrazine

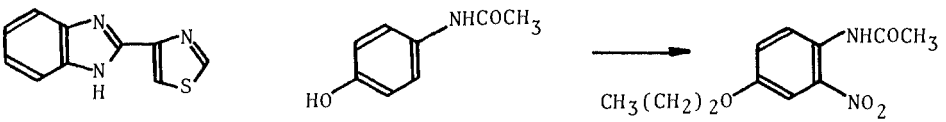
produces the analgesic agent, *tetrydamine (59)*, probably with the intermediacy of alkylhydrazone *58*.[18]



(57) (58) (59)

4. BENZIMIDAZOLES

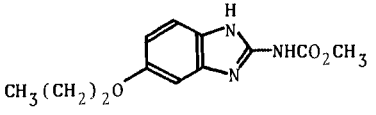
The control of worm infestations of domestic animals (horse, sheep, cattle, pigs) and humans is an important therapeutic objective for which *thiabendazole (60)* serves as the prototype of numerous benzimidazole derivatives.[19] A widely used synthesis of this system is illustrated by the preparation of *oxibendazole (62)*.[20] First, 4-hydroxyacetamide is alkylated by use of KOH and n-propyl bromide, and the product is nitrated to give *61*. The latter compound is



(60) (61)

hydrolyzed, reduced to the phenylenediamine with $SnCl_2$, converted to the 2-aminobenzimidazole system

by S-methylthiourea and subsequently acylated by methylchloroformate to produce *62*. *Lobendazole*



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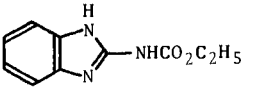

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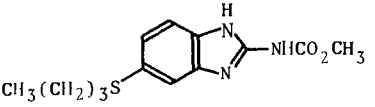
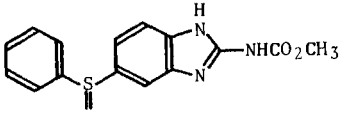


(64)

(63),[21] *albendazole (64)*,[22] *oxfendazole (65)*,[23] *mebendazole (66)*,[24] and *cyclobendazole (67)*[24] are all made by fairly obvious variants on this basic scheme. *Cambendazole (69)*, best of 300 antihelmintic agents in an extensive study, is made by nitration of *thiabendazole (60)* to 68, followed by catalytic reduction and acylation with isopropyl chloroformate.[25]



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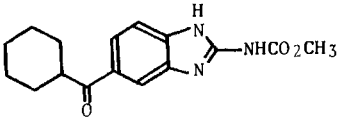

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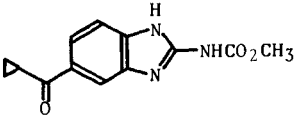

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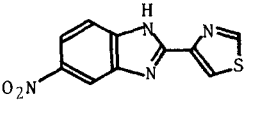

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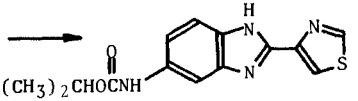
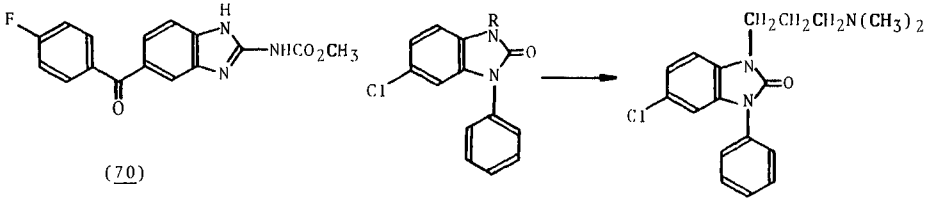


(69)

Flubendazole (70) belongs in this chemical class and is synthesized by similar methods but its bioactivity is expressed as an antiprotozoal agent.

At least in one case, a seemingly minor variation in the overall structure, change to the benzimidazolinone system, considerably alters the nature of



(70)

(71) R = H
(72) R = $(CH_2)_3Br$

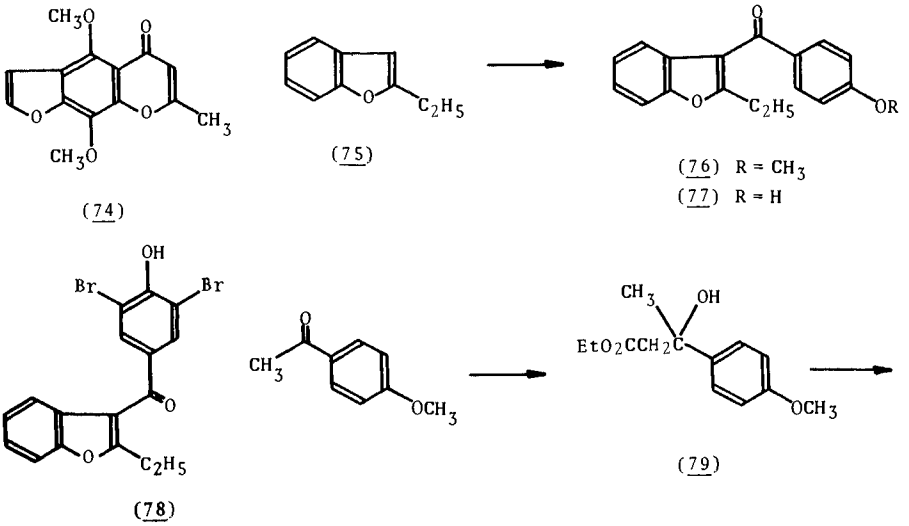
(73)

the bioactivity exhibited. Treatment of 4-chloro-N-phenylbenzimidazolinone *(71)* with t-BuOK and 3-bromopropylchloride leads to halide *72*, which itself undergoes halogen displacement on heating with dimethylamine to produce the antidepressant, *clodazon (73)*.[26]

5. MISCELLANEOUS

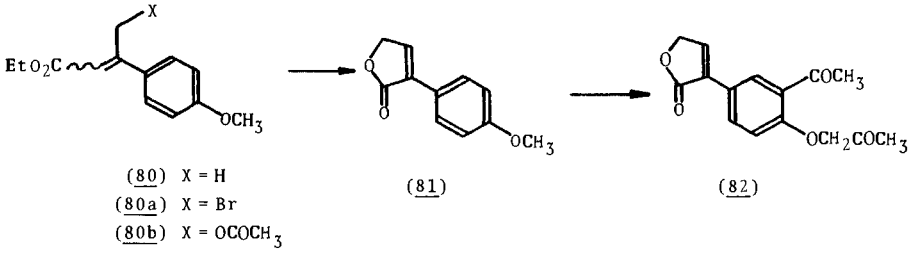
The pharmacological properties of *khellin (74)* have inspired a continuing interest in analogues. Change of the pyrone ring to a benzofuran ring results in a uricosoric agent, *benzbromarone (78)*. In its preparation, Friedel-Crafts acylation of 2-ethylbenzofuran *(75)* with 4-methoxybenzoyl chloride leads to ketone *76*, which undergoes ether cleavage to phenol *77* on

heating with pyridine hydrochloride; subsequent bromination produces *benzbromarone (78)*.[27]



Another khellin-inspired benzofuran is the cardiotonic and vasodilating agent, *benfurodil (84)*.[28] The reported synthesis begins by Reformatsky reaction between zinc, 4-methoxyacetophenone and ethyl bromoacetate to give *79*. The alcoholic function is dehydrated with tosic acid, NBS leads to the allylic bromide *(80a) via* the Wohl-Ziegler procedure, and then SN_2 displacement with NaOAc produces acetoxyketone *80b*. Treatment with HCl then closes the butenolide ring to give *81*. A Fries rearrangement, followed by demethylation, acetylation, and then ether formation with bromoacetone gives *82*, which condenses to form the furan ring on base treatment; then sodium borohydride reduction produces alcohol *83*. The synthesis

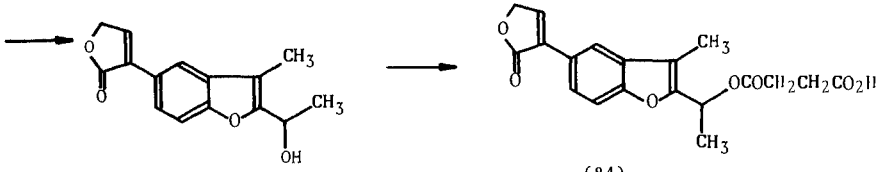
of *benfurodil (84)* is concluded by reaction with succinic anhydride and pyridine.



(80) X = H
(80a) X = Br
(80b) X = $OCOCH_3$

(81)

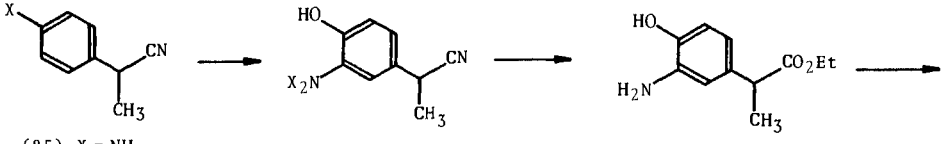
(82)



(83)

(84)

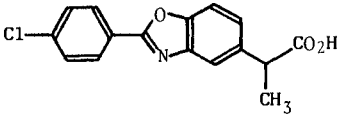
Probably inspired by *ibuprofen* and its analogues, the nonsteroidal antiinflammatory agent *benoxaprofen*



(85) X = NH_2
(86) X = N_2
(87) X = OH

(88) X = O
(89) X = H_2

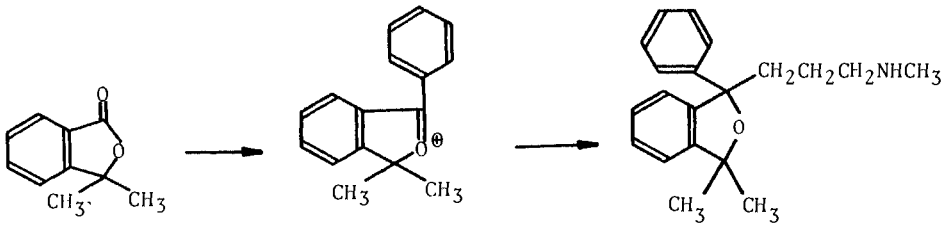
(90)



(91)

(91) is synthesized by starting with substituted aniline *85*.[29] A Sandmeyer-type sequence of diazotization *(86)* and acid hydrolysis leads to phenol *87*, which undergoes nitration *(88)* and reduction to give aminophenol *89*. Hydrolysis of the nitrile and esterification produces ester *90*, which is converted to *benoxaprofen (91)* by acylation with 4-chlorobenzoyl chloride, followed by cyclization and then by saponification of the ethyl ester.

A catecholamine potentiator that apparently operates by inhibition of norepinephrine reuptake and that also inhibits gastric secretion is *talopram (94)*. Its specific synthesis is hard to locate, but a general approach to this class of substance is available in the literature.[30] A suitable sequence would start from *gem*-dimethylphthalide *92* by reaction with phenyl Grignard reagent, followed by perchloric



(92) (93) (94)

acid dehydration of the tertiary carbinol to give oxonium ion *93*. Reaction of *93* with 3-dimethylaminopropyl magnesium chloride would lead to the tertiary

amino analogue of *94*. Demethylation would be accomplished by refluxing with ethyl chlorocarbonate, and the synthesis of *talopram* could be concluded by hydrolysis of the intermediate carbamate.

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12

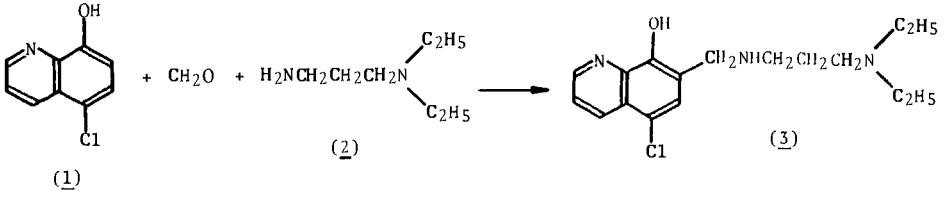
Six-Membered Heterocycles Fused to One Benzene Ring

The prevalence of heterocyclic rings among drugs and biochemical agents of mammalian origin can lead to the erroneous assumption that the presence of such rings in drugs means that this moiety of necessity constitutes part of the pharmacophore. As was noted in the case of the monocyclic heterocycles, these ring systems, in fact, often merely serve the function of a generalized aromatic system. The SAR of such molecules frequently demonstrates that the heterocyclic ring can be replaced by some other moiety with comparable electron distribution and lipophilicity without loss of biological activity. Sometimes, however, a given heterocyclic system does constitute part of the pharmacophore. Replacement of the particular ring system in such cases leads to loss of the desired biological activity. Recognition of pharmacophoric functions is today still largely an empirical

art, although susceptible to experimental inquiry. It is expected that art will more closely approach science with the emergence of a deeper understanding of the mechanisms of action of drugs on the molecular level, and the increasing frequency with which receptors are now being isolated and studied.

1. QUINOLINES

The quinoline antimalarial agents constitute one of the earliest examples of pharmacophoric heterocyclic systems. It was recognized in the 1930's that chloroquinolineamines bearing an additional amino group in the side chain were often endowed with activity against the plasmodia that cause malaria.[1] Further exploration of these molecules led to an agent with antiamebic activity. Mannich condensation of quinolol *1* with paraformaldehyde and N,N-diethylpropylenediamine affords the antiamebic agent, *clamoxyquin (3)*.[2]



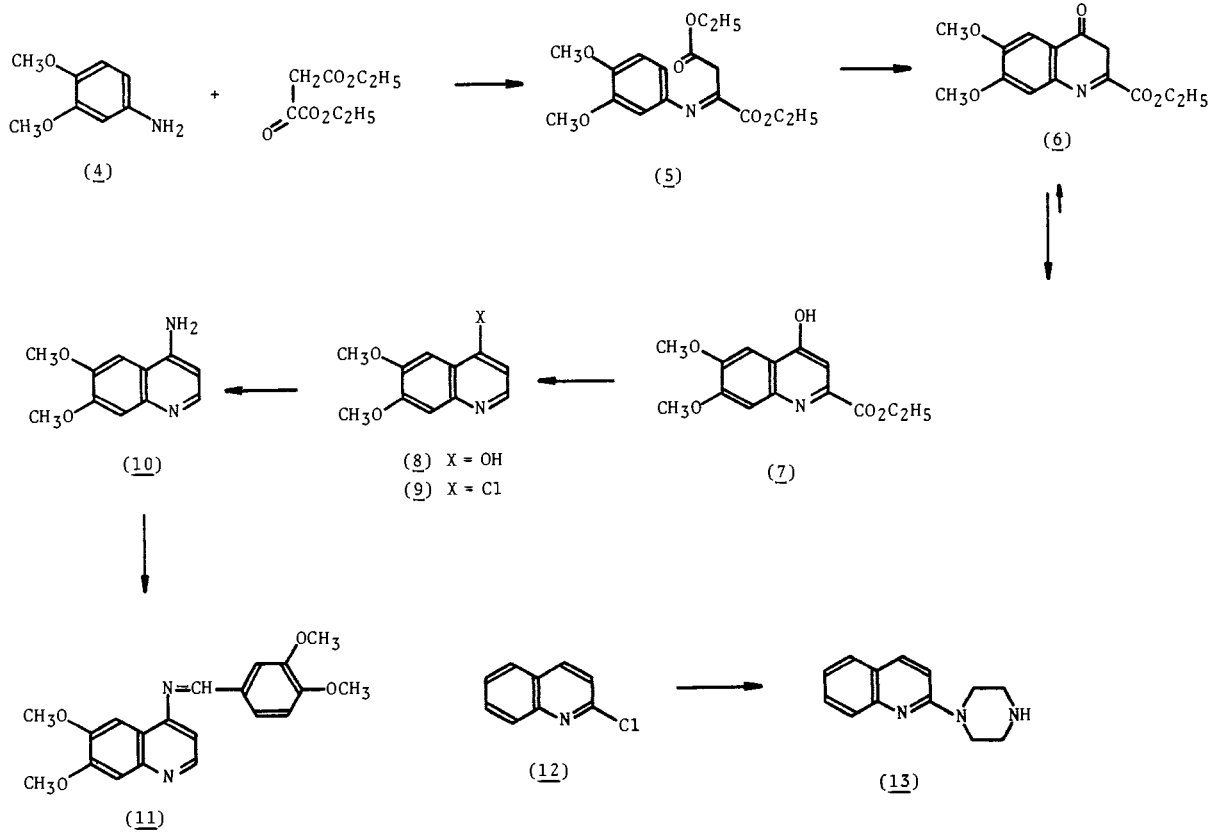
(1) (2) (3)

The structures of drugs that have proven clinically useful for treatment of hypertension tend to fall into discrete classes according to their mode of action. It is thus usually a safe assumption that a drug containing a guanidine function will show the

properties of a peripheral sympathetic blocking agent; also, phenoxypropanolamines and some phenylethanolamines will be effective by virtue of their β-adrenergic blocking activity. Experimental agents on the other hand tend to show much greater structural diversity; by the same token, it is more difficult to relate mode of action to structure in these cases. It is thus of note that a rather simple aminoquinoline shows hypotensive activity.

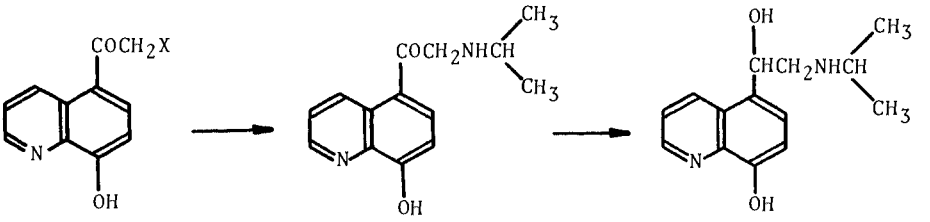
The synthesis of this aminoquinoline starts with one of the standard sequences for preparation of 4-hydroxyquinolines, i.e., with the formation of the Shiff base *(5)* from the appropriately substituted aniline and diethyl oxaloacetate. Thermal cyclization gives the quinolone *(6)*; this then spontaneously tautomerizes to the enol form *(7)*. Saponification followed by decarboxylation gives the desired quinolol *(8)*. Treatment of *8* with phosphorus oxychloride leads to replacement of the hydroxyl group by chlorine *(9)*.[3] Displacement of halogen by ammonia leads to the corresponding amine, probably by an addition-elimination mechanism. There is thus obtained *amquinsin (10)*,[4] a hypotensive agent. Formation of the Shiff base of *amquinsin* with veratraldehyde gives *leniquinsin (11)*,[5] possibly a prodrug.

A related and relatively simple quinoline derivative has been reported to exhibit antidepressant activity. Its preparation merely involves displacement of halogen in *12* with piperazine to afford *quipazine (13)*.[6]


(4)
(5)
(6)
(7)
(8) X = OH
(9) X = Cl
(10)
(11)
(12)
(13)

Derivatives of phenylethanolamine substituted by a phenolic hydroxyl on the para position have been known for some time to exhibit β-adrenergic agonist activity. As a consequence of this property, the compounds have proven useful as bronchodilators for the treatment of asthma (see Chapter 3). Since such sympathomimetic drugs tend to have undesired activity on the cardiovascular system in addition to the desired activity on the bronchii, considerable work has been devoted to the preparation of compounds that would show selectivity for the adrenergic receptors (β_2) that predominate in the lung. Attachment of the side chain to a heterocyclic aromatic phenol has been one avenue that has shown promise for achieving this selectivity.

Halogenation of the acetyl compound *14* affords the corresponding chloroketone *(15)*. (Compound *14* is obtainable by acylation of the quinolol. The pyridine ring is, of course, deactivated in the acidic conditions of the reaction.) Displacement of halogen by means of isopropylamine leads to the aminoketone



(14) X = H
(15) X = Cl

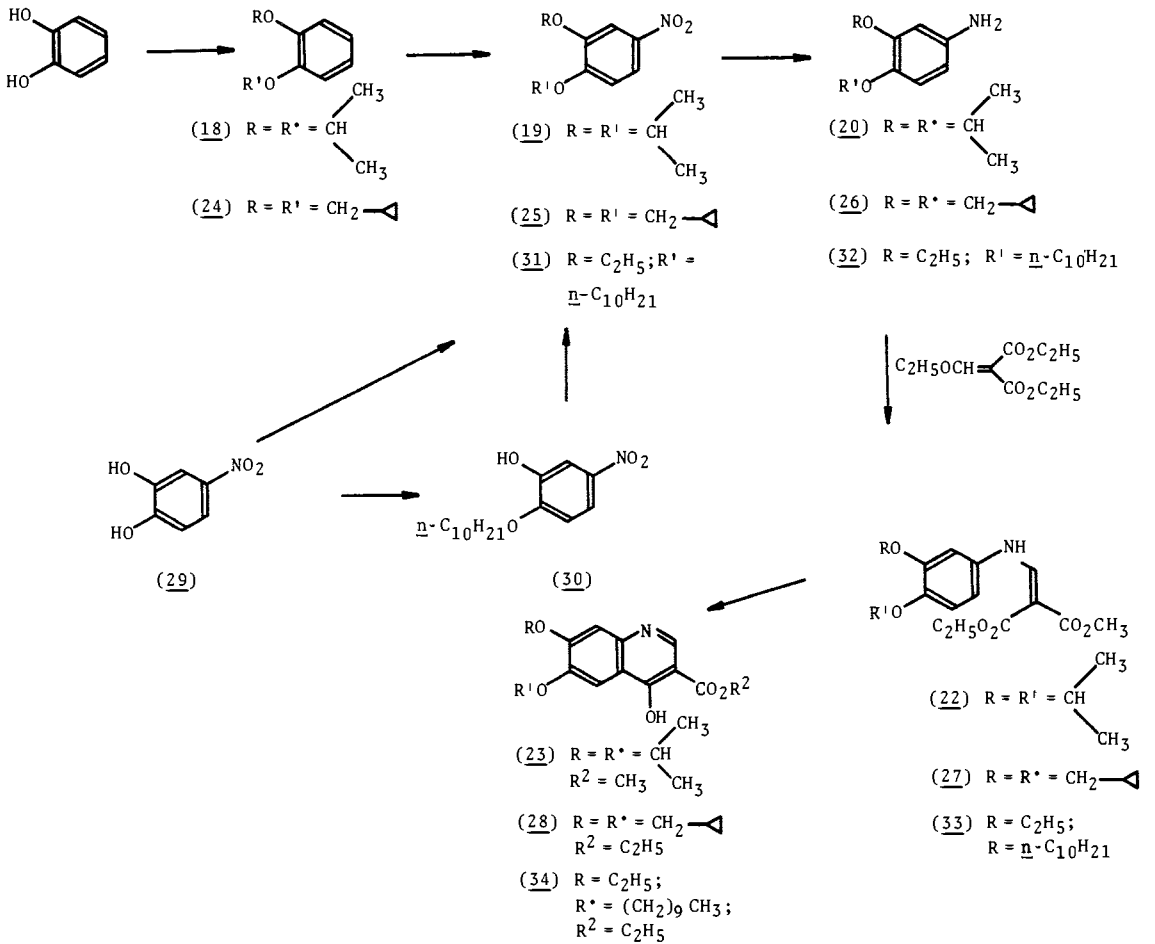
(16)

(17)

(16). Reduction of the carbonyl group by means of sodium borohydride goes in a straightforward manner to give the aminoalcohol, *quinterenol (17)*.[7] It is a reasonable assumption that the heterocyclic system in this case simply serves as a surrogate benzene ring.

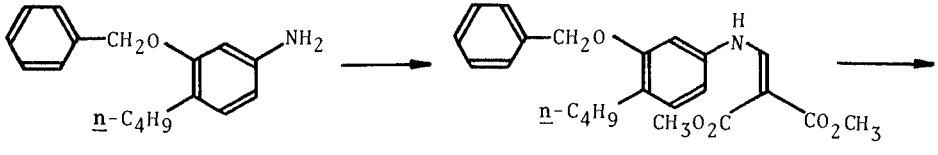
Modern methods for raising poultry tend to concentrate large numbers of birds in a very small space. Although economically very attractive, the resulting dense population is an ideal setting for the extremely fast spread of avian epidemics, particularly those respiratory infections spread by droppings. The single-celled parasitic coccidia pose a particular threat to poultry flocks under these conditions. Considerable work has thus been devoted to the development of poultry coccidiostats. The rapidity with which these parasites develop resistance to chemotherapeutic agents serves as impetus for the development of a constant flow of drugs with new structures.

The "quinates" constitute the prototype for the quinoline poultry coccidiostats; many such agents can be prepared using the following general synthetic schemes. For example, alkylation of catechol with isopropyl bromide affords ether *18*. Nitration perforce affords derivative *19*. Catalytic reduction of the nitro group followed by condensation of the resulting aniline *(20)* with dimethyl ethoxymethylene malonate *(21)* affords the anil *22*. The reaction is most reasonably rationalized by assuming a conjugate addition-elimination sequence. Heating of the last intermediate in Dowtherm affords the coccidiostat

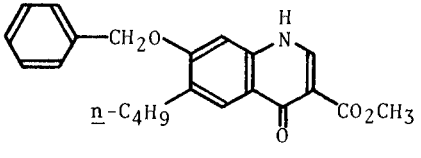

HO
HO
RO
R'O
CH3
CH3
(18) R = R' = CH
(24) R = R' = CH2
NO2
(19) R = R' = CH
(25) R = R' = CH2
(31) R = C2H5; R' = n-C10H21
NH2
(20) R = R' = CH
(26) R = R' = CH2
(32) R = C2H5; R' = n-C10H21
C2H5OCH
CO2C2H5
CO2C2H5
(29)
n-C10H21O
(30)
NH
C2H5O2C
CO2CH3
(22) R = R' = CH
(27) R = R' = CH2
(33) R = C2H5; R = n-C10H21
N
OH
CO2R2
(23) R = R' = CH
R2 = CH3
(28) R = R' = CH2
R2 = C2H5
(34) R = C2H5;
R' = (CH2)9 CH3;
R2 = C2H5

proquinolate (23).[8] The same sequence using cyclopropylmethyl bromide as alkylating agent for catechol and, later, diethylmethoxymethylenemalonate affords *cyproquinate (28).*[9]

The synthesis may be varied by reversing the alkylation and nitration steps. Thus for example, intermediate *25* can be obtained by alkylation of nitrocatechol *29*. The difference in reactivity of the two phenolic groups in *29* (meta and para to an electron withdrawing group, respectively) may be used to prepare derivatives carrying different alkyl groups on each of the catechol oxygens. Alkylation of *29* with decyl bromide gives ether *30;* reaction of the remaining phenolic function with ethyl iodide then gives *31*. This intermediate then is converted to *decoquinate (34)*[10] when subjected to the rest of the synthetic sequence.



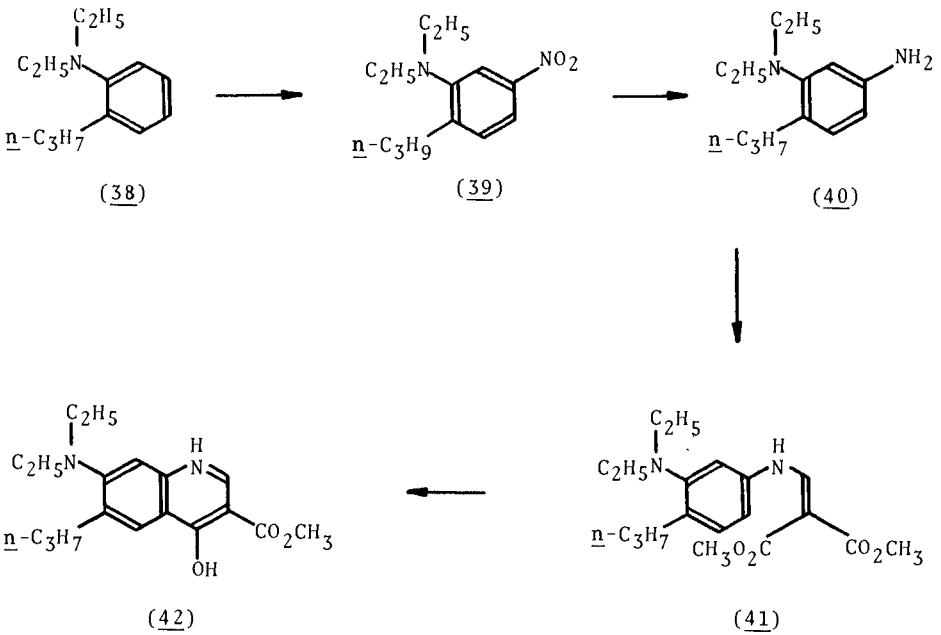
(35) (36)



(37)

Replacement of one of the ethereal oxygen atoms by a methylene group is compatible with anticoccidial activity. For example, condensation of substituted aniline *35* with dimethyl ethoxymethylenemalonate affords aminoacrylate *36*. Thermal cyclization in diphenyl ether gives *nequinate (37)*.[11]

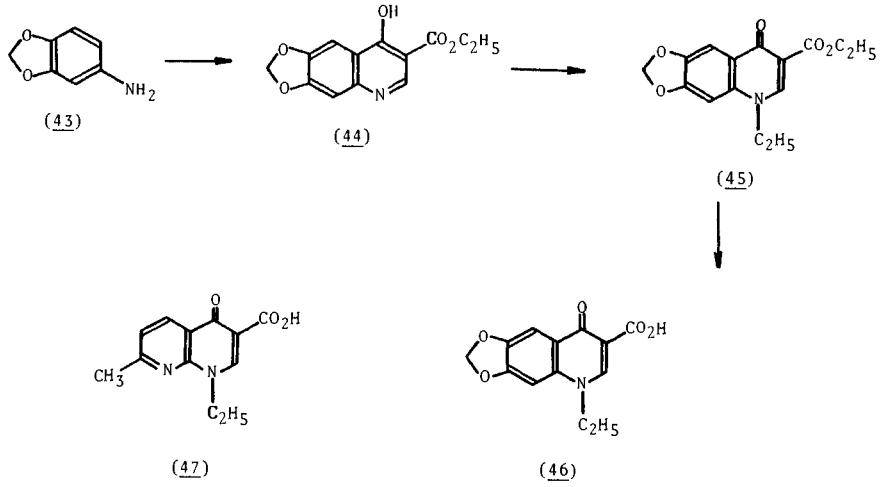
Replacement of the remaining ether oxygen by basic nitrogen leads to a compound that shows antimalarial activity. Nitration of aniline derivative *38* leads to substitution para to the alkyl group. (Protonation of the amine under the reaction conditions leads to deactivation of the position para to that group relative to that para to alkyl. The position meta to the protonated amine is less deactivated.)



(38) (39) (40) (41) (42)

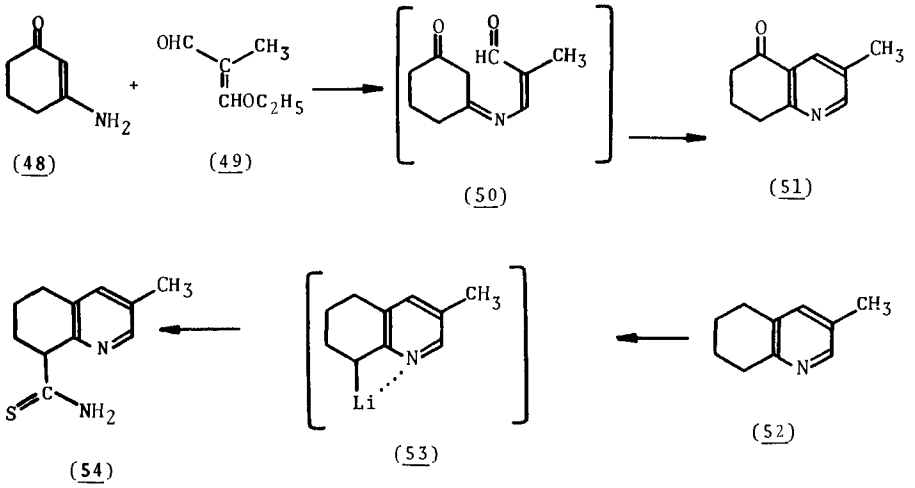
Reduction of the newly introduced nitro moiety affords aniline *40*. This is then subjected to the familiar condensation-cyclization sequence to give antimalarial *amquinate (42)*.[12]

Alkylation on nitrogen in this class leads to compounds with antibacterial activity, apparently due to inhibition of DNA gyrase. Condensation of aniline derivative *43* with diethyl ethoxymethylenemalonate, followed by cyclization of the resulting intermediate affords the quinoline *44*. Alkylation with ethyl iodide by means of sodium hydride in DMF gives the corresponding N-ethyl compound. (Deprotonation of *44* leads to an ambident anion; alkylation at nitrogen may be favored by the greater nucleophilicity and steric accessibility of that atom.) Saponification of the ester affords *oxolinic acid (46)*.[13] This compound interestingly again illustrates the interchangeability of aromatic rings; the prototype antibacterial agent, *nalidixic acid (47)*,[14] contains a



1,8-naphthyridine ring system and can be considered an azaquinolone.

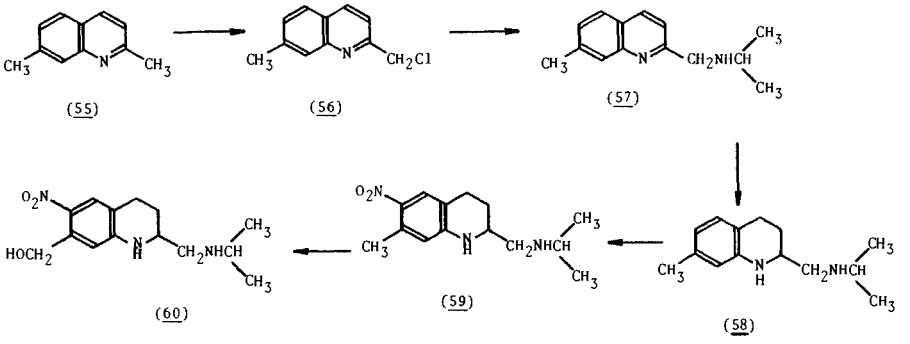
Reduction of either ring of quinolines greatly alters biological activity. Although the agent in which the carbocyclic ring is reduced can be considered a substituted pyridine, it is included here because it is prepared by using chemistry more akin to that of quinolines. Condensation of the cyclohexanedione derivative *48* with the malondialdehyde enol ether *49* leads directly to the tetrahydroquinoline *51*. The sequence can be envisaged as involving first an addition-elimination reaction to afford, after double bond migration, intermediate *50*; aldol cyclization will then afford the observed product.



Reduction of the carbonyl group by Wolff-Kishner reaction gives intermediate *52*.[15] Treatment of that compound with butyl lithium gives the corresponding

metalated derivative *(53)*; reaction of *53* with trimethylsilyl isothiocyanate affords the corresponding thioamide. There is thus obtained the gastric antisecretory agent *tiquinamide (54)*.[16] This synthetic sequence is of special interest in that direct chemical reduction of quinolines usually results in reduction of the heterocyclic ring.

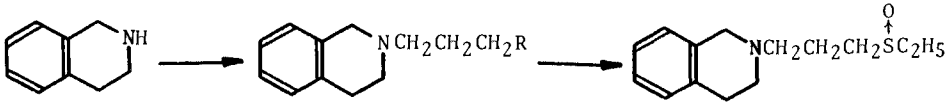
Reduction of the heterocyclic ring and incorporation of a nitro function affords a compound with antischistosomal activity, *oxamniquine (60)*. Its synthesis begins with chlorination of 2,6-dimethylquinoline, which proceeds regiospecifically on the methyl group adjacent to the ring nitrogen *(56)*.



Displacement of halogen by isopropylamine gives intermediate *57*. High pressure catalytic hydrogenation leads to reduction of the heterocyclic ring *(58)*, and nitration proceeds para to the NH group *(59)*. Microbiological oxidation of the methyl group in that last intermediate using *Aspergillus sclerotorium* affords *oxamniquine (60)*.[17]

2. ISOQUINOLINES

As has been noted elsewhere, blockers of α-adrenergic receptors often bear little structural resemblance to the phenylethanolamines which are the endogenous agonists. A relatively simple tetrahydroisoquinoline derivative in fact shows hypotensive activity by virtue of its α-adrenergic blocking properties. Alkylation of tetrahydroisoquinoline itself with bromochloropropane gives intermediate *62*. Displacement of the halogen with sodium ethylmercaptide gives thioether *63*. Oxidation of sulfur by means of peracetic acid is stopped at the sulfoxide stage to afford *esproquin (64)*.[18]

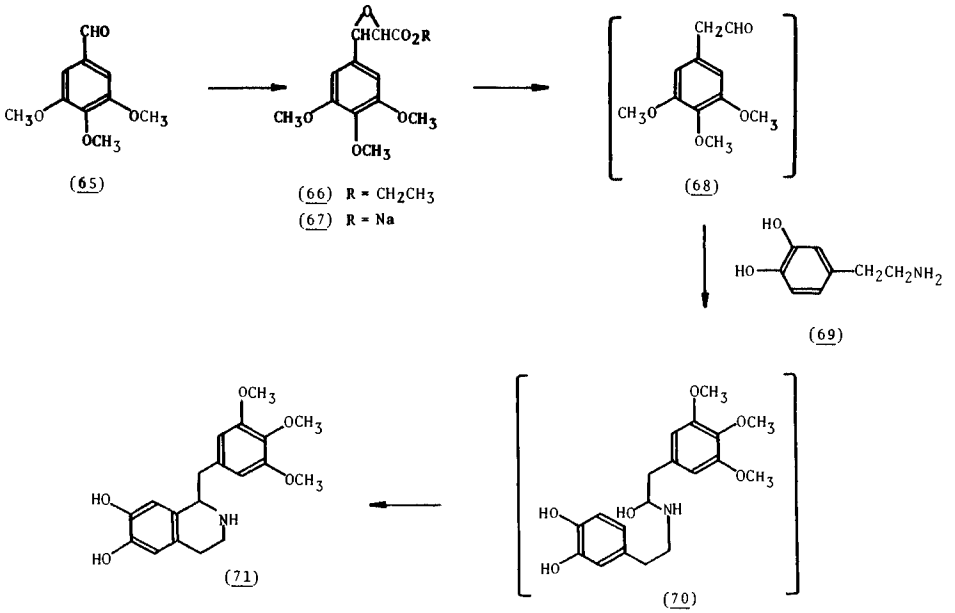


(61) (62) R = Cl (63) R = SC_2H_5 (64)

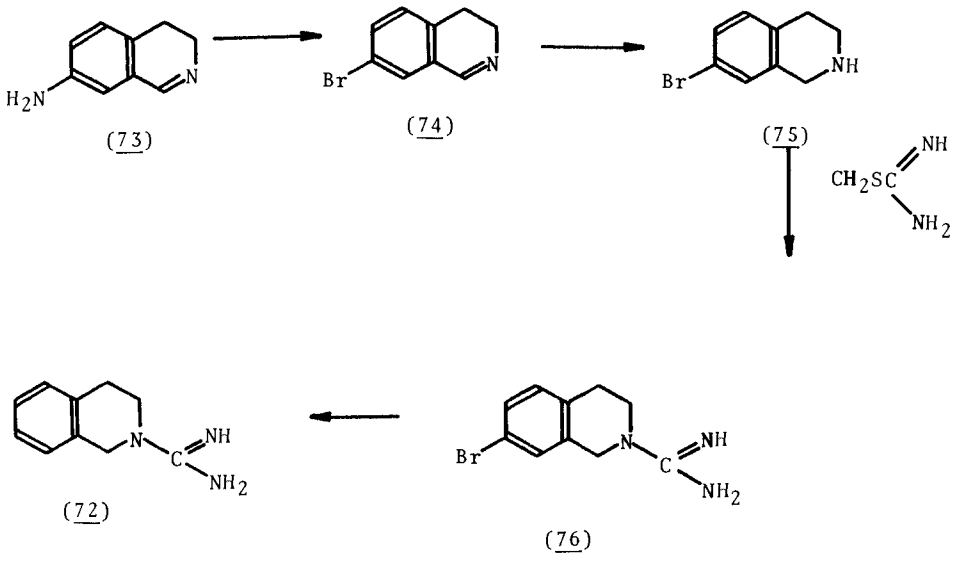
The use of β-adrenergic agonists as bronchodilators is discussed in some detail in Chapter 3.

As mentioned there, requirements for activity include the phenylethanolamine side chain and a phenolic hydroxyl group or its equivalent disposed para to the side chain. It is of note that the side chain hydroxyl can be omitted from molecules that contain the full catechol substitution of epinephrine with retention of good activity. One such compound, *trimethoquinol (71)*, which in addition contains the side chain sterically constrained by cyclization to a tetrahydroisoquinoline has proven to be a clinically useful bronchodilator. Condensation of trimethoxybenzaldehyde with ethyl chloroacetate under Darzens conditions gives the glycidic ester *66;* this is then converted to the sodium salt *(67)*. This salt is then treated with dopamine *(69)* under conditions which will cause decarboxylation and rearrangement of *67* to the corresponding aldehyde *(68)*. The reaction conditions are coincidentally the same as those of the Pictet-Spengler synthesis. Thus, the intermediate aldehyde reacts with the amine to form carbinolamine *70* or the corresponding imine. This then cyclizes to the tetrahydroisoquinoline, *trimethoquinol (71)*.[19] Interestingly, only the l-S isomer is an active bronchodilator.

Guanidines attached to a group of appropriate lipophilicity have proven to be useful antihypertensive agents, active by virtue of their peripheral sympathetic blocking activity. *Debrisoquine (72)* is in fact used clinically for that indication.[20] The 7-bromo analogue *(76)* also shows antihypertensive

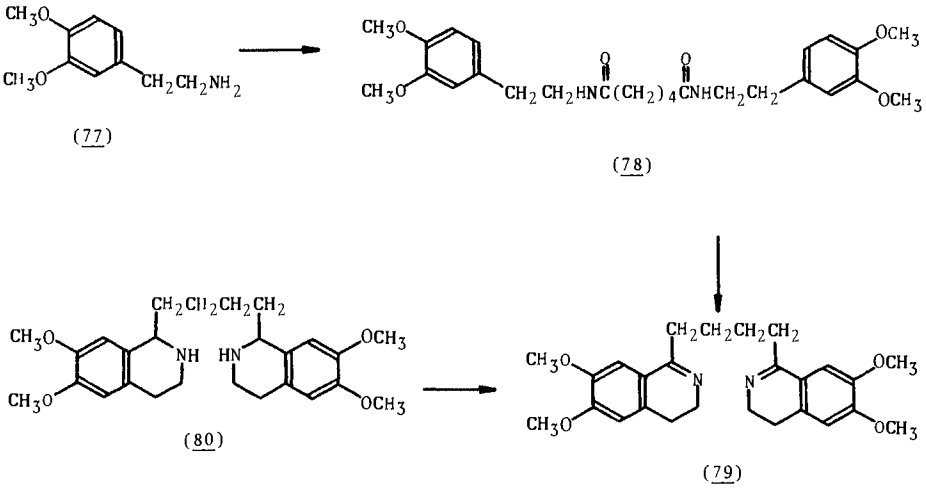


activity, and can be prepared as follows. Diazotization of the aminodihydroisoquinoline *73*, followed by conversion of the diazonium salt to the bromide by heating in the presence of HBr, affords intermediate *74*. Reduction of the imine function with sodium borohydride gives the saturated heterocycle *75*. Condensation of this secondary amine with S-methylthiourea affords *guanisoquin (76)*.[21]



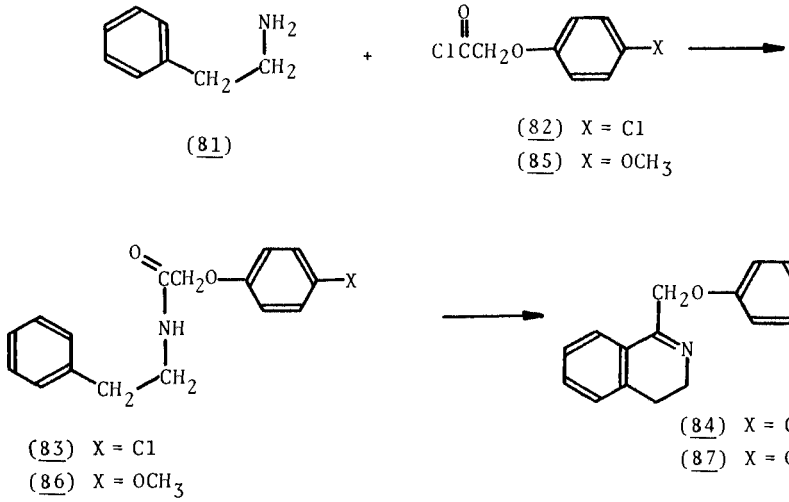
Formation of blood clots is a process necessary for maintenance of the integrity of the circulatory system. Any break in the system results in clotting to seal off the potential leakage. The final step in the process involves stabilization of the clot by a protein called fibrin. A number of pathological conditions result in the formation of clots within the circulatory system in the absence of injury. Such clots--also known as emboli--present a serious hazard by their potential for blocking circulation of blood to vital organs. The considerable research devoted to agents that will lyse the fibrin in clots has led to the development of the clinically useful agent, *urokinase*. This drug is a fibrinolytic proteinaceous enzyme isolated from human urine. The difficulty involved in isolation of significant amounts and the antigenicity of urokinase and a related

microbial product, streptokinase, has led to the search for simple molecules that will accomplish the same end. A tetrahydroisoquinoline derivative *(80)* has shown this activity in animal test systems. Its formation involves classical isoquinoline chemistry, and begins with acylation of two molar equivalents of phenethylamine *77* with adipic acid to afford the diamide *78*. Ring closure of the amide by means of phosphorus oxychloride gives the usual Bischler-Napieralski product *79*--although with an intervening butylene chain. Reduction of the imine by means of sodium borohydride affords the fibrinolytic agent, *bisobrin (80)*.[22]



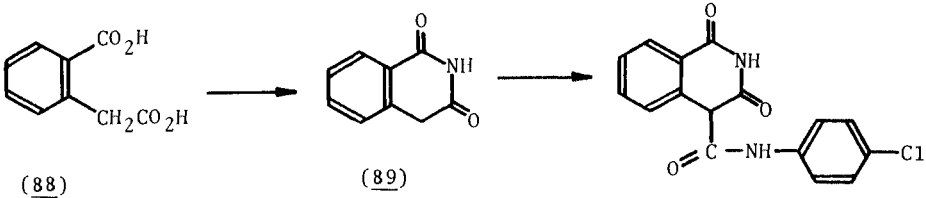
Products of Bischler-Napieralski cyclizations discussed thus far have been reduced in order to afford the desired biologically active compounds. Occasionally, the products obtained directly from the

cyclization have biological activity in their own right. In one example, acylation of 2-phenethylamine with p-chlorophenoxyacetyl chloride affords the amide *83*; then, cyclization by means of phosphorus pentoxide gives the antiviral agent *famotine (84)*.[23] The same sequence starting with the p-methoxy acid chloride *85* gives *memotine (87)*, an antiviral agent.[23]



The majority of nonsteroidal antiinflammatory agents contain an acidic carboxyl group. A series of experimental agents in this class have been prepared in which the acidic proton is supplied by a highly enolizable proton from a function such as a β-dicarbonyl incorporated into a heterocyclic system. As an example, an acylated, highly oxidized isoquinoline moiety can fulfill this function (see also the benzothiazines below). Toward this end, reaction of

homophthalic acid with ammonia affords the imide *89;* triethylamine catalyzed condensation of that intermediate with p-chlorophenylisocyanate affords the corresponding amide. There is thus obtained the antiinflammatory agent *tesicam (90).*[24]



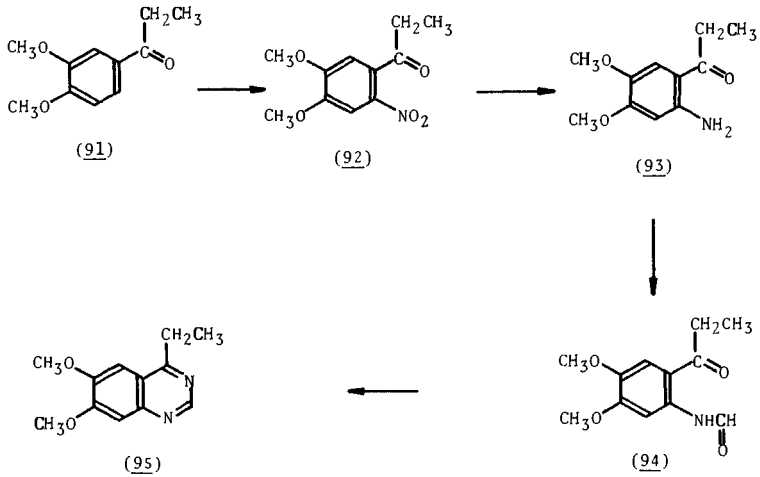
(88) (89) (90)

3. QUINAZOLINES

Quinazolines containing an electron-rich carbocyclic ring have been associated with smooth muscle relaxant activity. The mechanism of action (phosphodiesterase inhibition, α- adrenergic blockade) and organ selectivity (bronchi, vascular smooth muscle) vary greatly with substitution on the heterocyclic ring.

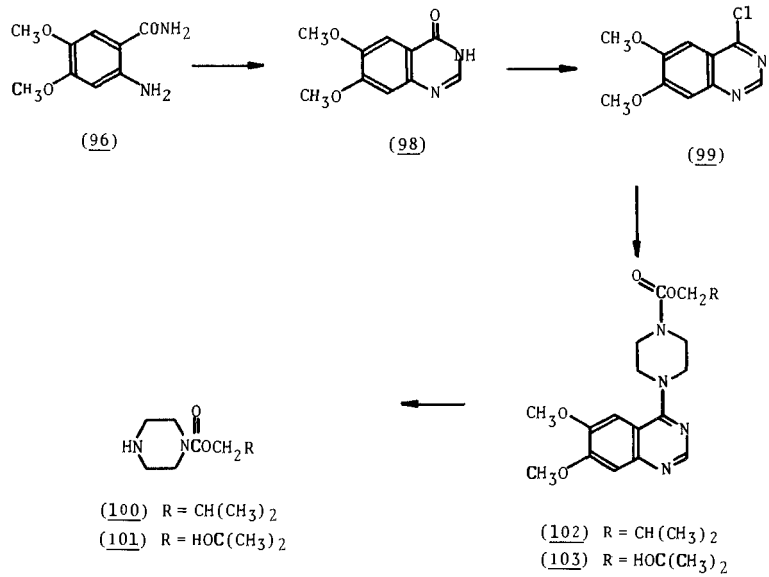
Nitration of 3,4-dimethoxypropiophenone *(91)* affords the nitro derivative *92,* and catalytic reduction leads to the aminoketone *(93).* This is then converted to the corresponding formamide by means of formic-acetic anhydride. Treatment with ammonia completes construction of the quinazoline ring. There is thus obtained the bronchodilator-cardiotonic agent, *quazodine (95).*[25]

In a similar vein, condensation of the substituted anthranilamide *96* with trimethyl orthoformate affords directly the quinazolone *98.* Reaction with phosphorus



(91) (92) (93) (94) (95)

oxychloride converts the carbonyl to the enol chloride *(99)*. Displacement of halogen with monosubstituted



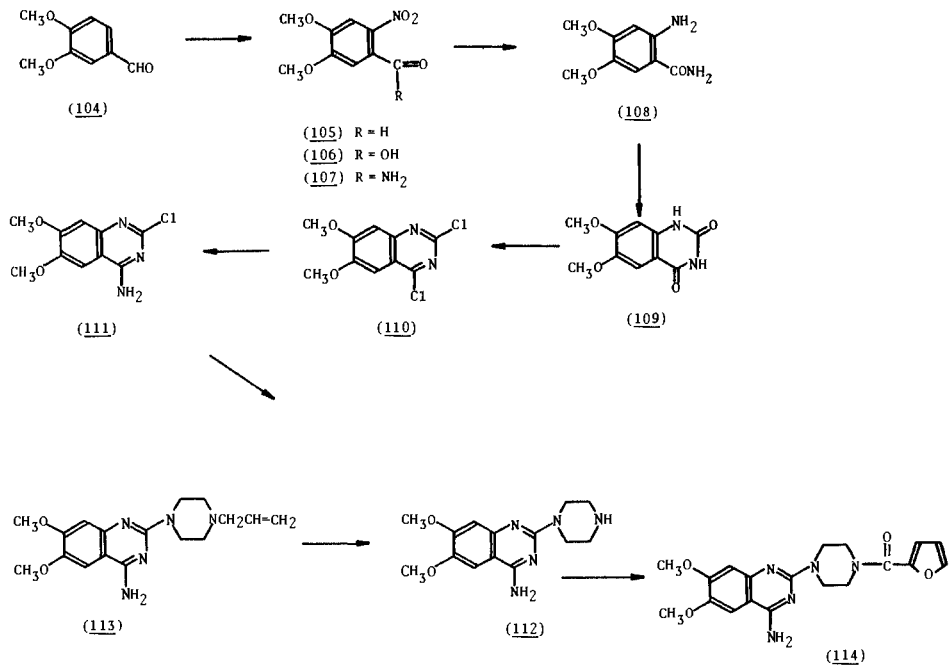
(96) (98) (99)

(100) R = $CH(CH_3)_2$
(101) R = $HOC(CH_3)_2$

(102) R = $CH(CH_3)_2$
(103) R = $HOC(CH_3)_2$

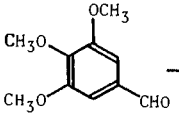
piperazine *100* gives the bronchodilator *piquizil (102)*;[26] the same reaction with piperazine *101* leads to another bronchodilator *hoquizil (103)*.[27]

A similar scheme is used to construct a quinazoline containing halogen at both positions 2 and 4. The differences in reactivity of these halides make available compounds bearing two different amine substituents. Nitration of aldehyde *104*, followed by oxidation affords the acid *106*. The acid is then converted to the primary amide *(107)*, and the nitro group is reduced catalytically to the corresponding

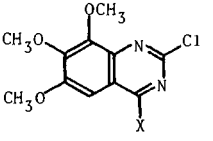


amine *(108)*. Condensation with urea completes construction of the heterocyclic ring *(109)*; this is converted to the desired dichloride by reaction with phosphorus oxychloride *(110)*. Reaction with ammonia in THF at room temperature serves to replace the more reactive chlorine by a primary amine *(111)*. Displacement of the remaining halogen is achieved with piperazine under more strenuous conditions *(112)*. Alkylation of the piperazine nitrogen with allyl bromide affords the antihypertensive agent *quinazocin (113)*.[27] Acylation at the same position gives the recently commercialized antihypertensive agent *prazosin (114)*.[28]

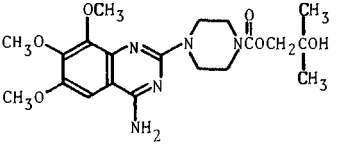
The same scheme starting with 3,4,5-trimethoxybenzaldehyde *(115)* affords initially dichloroquinazoline *116*. Reaction of this intermediate with ammonia leads to replacement of the amine at the 2-position *(117)*. Displacement of the remaining chlorine with piperazine carbamate *101* affords the antihypertensive agent *trimazocin (118)*.[29]



(115)



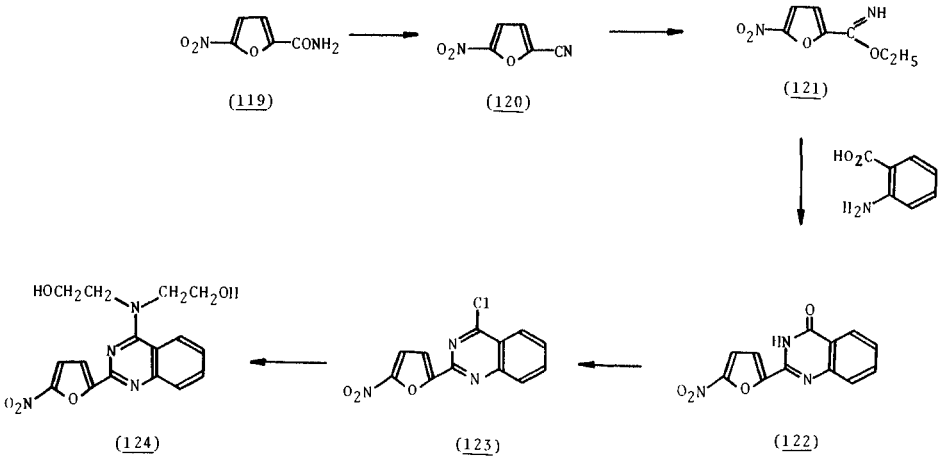
(116) X = Cl
(117) X = NH_2



(118)

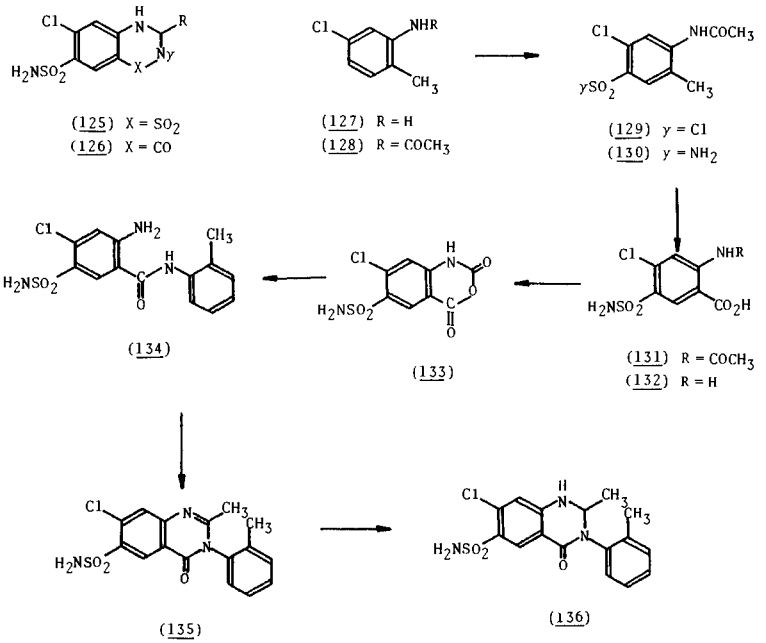
The extensive series of antibacterial agents consisting of derivatives of 5-nitrofurfural has been discussed in Chapter 8. It is of interest that a

derivative of nitrofuran in which the carbonyl is at the acid oxidation stage and incorporated into a quinazoline also shows antibacterial activity; this agent, *nifurquinazol (124)*, is prepared as follows. Treatment of the amide from 5-nitrofuroic acid with phosphorus oxychloride leads to the corresponding nitrile *(120)*. This intermediate is then converted to the iminoether *(121)* with ethanolic hydrogen chloride.[30] Condensation with anthranilic acid in the presence of sodium methoxide gives the quinazolone *122*. The amide function is then converted to the iminochloride with phosphorus oxychloride *(123)*. Replacement of halogen by means of diethanolamine affords *nifurquinazol (124)*.[31]



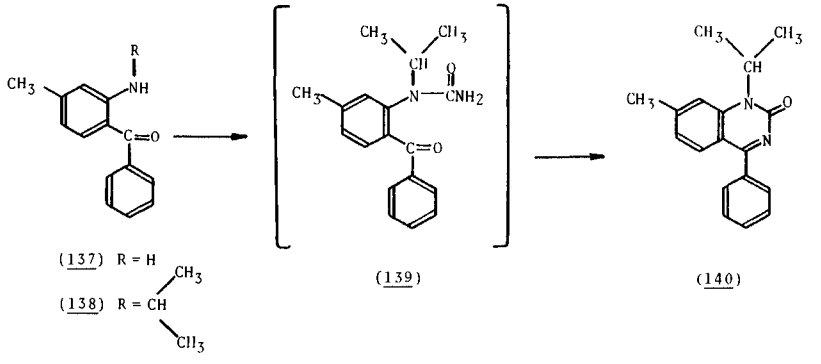
Benzothiadiazines containing halogen and a sulfonamido group on the carbocyclic ring *(125)* form a large class of diuretic agents often referred to as

the thiazides; the ring sulfone group can be replaced by carbonyl with retention of significant biological activity.[32] More recently, it has been found that diuretic activity is retained when one of the ring nitrogen atoms carries an aryl group. Toward this end, the starting aniline *127* is first acetylated *(128)* by means of acetic anhydride to protect the primary amine in subsequent steps. Reaction with chlorosulfonic acid leads to sulfonyl chloride *129;* this is converted to the sulfonamide by reaction with ammonia *(130).* Oxidation of the methyl group by means of permanganate cleanly gives the acid *131;* the acetyl group is then removed by hydrolysis. Treatment of the resulting anthranilic acid *(132)* with phosgene then leads to the isatoic anhydride *133.* Reaction of that anhydride with ortho-toluidine results in acylation of that aniline by the anthranilic acid *(134);* tying up the anthranilic acid up as the anhydride serves to both activate the carbonyl towards amide formation and to protect the amine towards self condensation. The carbamic acid presumably formed as an intermediate decarboxylates. Treatment of the anthranilamide *134* with acetic anhydride affords directly quinazolone *135.* (The sequence may be rationalized by assuming acetylation of the aniline as the first step; formation of an imine between the carbonyl and amide nitrogen gives the observed product.) Reduction of the imine function with sodium borohydride in the presence of aluminum chloride gives the diuretic agent *metolazone (136).*[33]



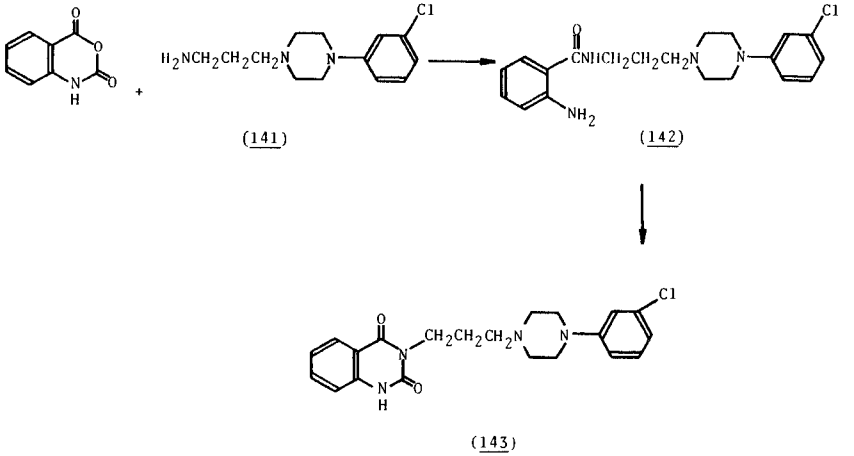
The majority of nonsteroidal antiinflammatory agents contain some function which supplies an acidic proton, be this a carboxyl group or a highly activated enol system. A quinazolone devoid of such potential enolizable protons forms an interesting exception to this generalization. (It is tempting in such cases to speculate that the compound may exert its biological activity by some mechanism distinct from the rest of the class.) Alkylation of aminobenzophenone *137* with isopropyl iodide gives the corresponding N-alkylated amine *(138)*. Treatment of that intermediate with urethane in the presence of zinc chloride serves to form the quinazolone ring. The reaction may be rationalized by assuming acylation of the

amine as the first step to form urea *139*. Intramolecular imine formation then affords the observed antiinflammatory product, *proquazone (140)*.[34]



(137) R = H
(138) R = CH(CH3)2
(139)
(140)

A more highly oxidized derivative of quinazoline forms the heterocyclic moiety of a compound with CNS activity. Condensation of the aminopropylpiperazine *141* with isatoic anhydride gives the anthranilamide *142*. Reaction of that amide with phosgene gives directly the heterocyclic ring. (The reaction may proceed by initial formation of the carbamoyl chloride;

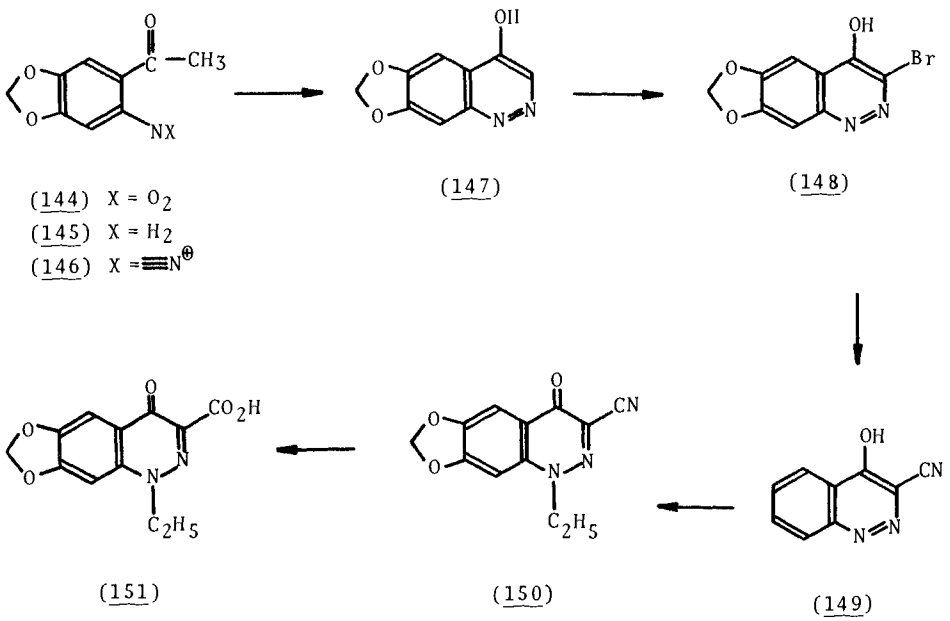


(141)
(142)
(143)

this may then either acylate the amide or alternatively decompose to an isocyanate. This last could then add the amide nitrogen.) The product of this sequence is the sedative: tranquilizer *cloperidone (143)*.[35]

4. CINNOLINES AND QUINOXALINES

Replacement of a methine in *oxolinic acid (46)* by nitrogen is apparently consistent with retention of antibacterial activity. One approach begins with reduction of nitroacetophenone *144* to afford the corresponding aminoketone *(145)*. Treatment of this intermediate with nitrous acid leads to the diazonium salt; the diazonium group condenses with the ketone methylene group (as its enol form) to lead to the cyclized product, cinnoline *147*. Bromination proceeds at the position adjacent the enol grouping *(148)*;



(144) X = O_2
(145) X = H_2
(146) X = $\equiv N^{\oplus}$

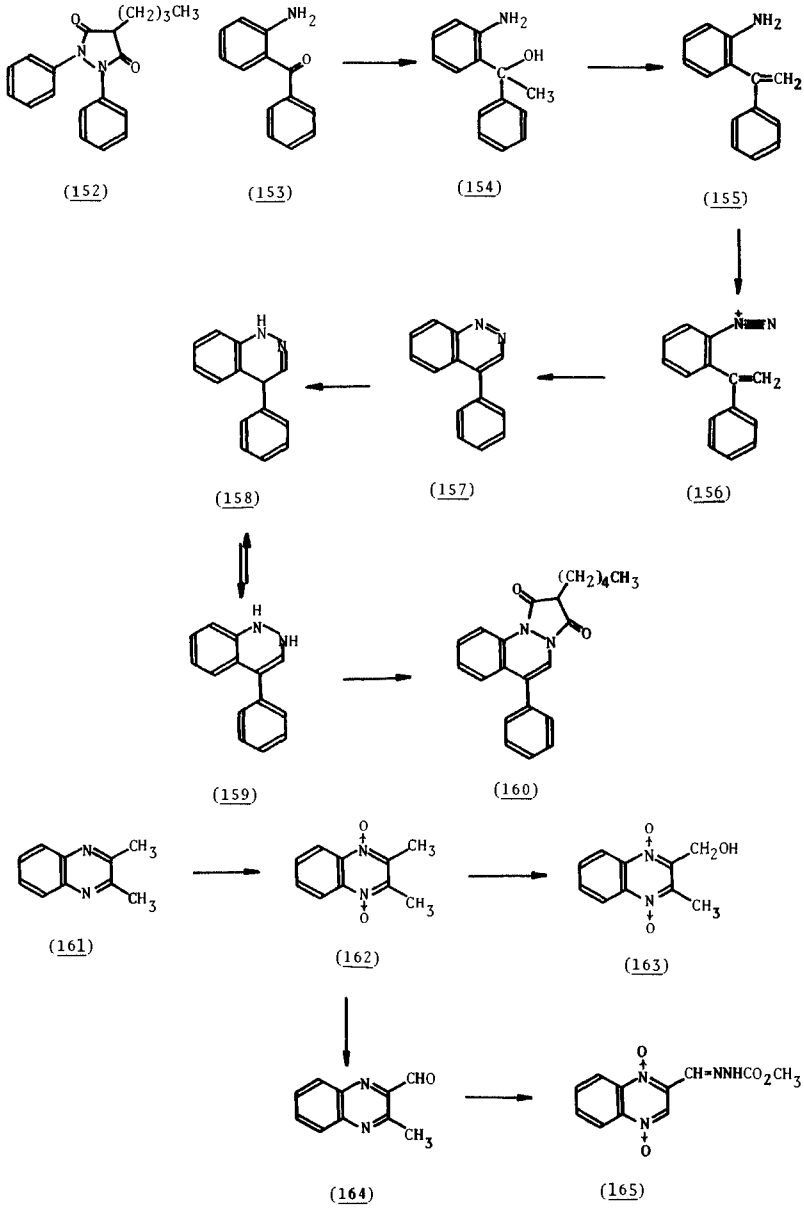
(147) (148)

(149) (150) (151)

then displacement by means of cuprous cyanide *(149)* followed by alkylation on nitrogen affords cyanoketone *150*. Hydrolysis of the nitrile function then gives *cinoxacin (151)*,[36] an antibacterial agent.

The pyrazole derivative *phenylbutazone (152)* has found extensive clinical use as an antiinflammatory agent. (The acidic proton here is generated by a β-dicarbonyl system.) Incorporation of salient portions of the molecule in a condensed heterocycle yields a compound, *cintazone (160)*, which also exhibits antiinflammatory activity. The synthesis of *160* starts with Grignard addition of methylmagnesium bromide to ortho-aminobenzophenone *(153)*, affording carbinol *154*; dehydration gives the corresponding olefin *(155)*. The cinnoline ring is then constructed by a sequence similar to that used above. Thus treatment of the amine with nitrous acid gives the diazonium salt; treatment with mild base (ammonium hydroxide) causes the salt to close to the cinnoline *(157)*. Catalytic reduction in acetic acid affords initially the product *(158)* of 1,4-addition of hydrogen; this product is in tautomeric equilibrium with cyclic hydrazine *159*. Condensation of *159* with diethyl amylmalonate leads to formation of the pyrazolodione ring. There is thus obtained *cintazone (160)*.[37]

Oxidation of 2,3-dimethylquinoxaline (from phenylenediamine and diacetyl) with either peracids or hydrogen peroxide in acetic acid gives the 1,4-dioxide *(162)*.[38] Treatment of this bis-N-oxide with selenium dioxide leads to oxidation of one of the methyl groups to the methyl carbinol and formation of


(152)
(153)
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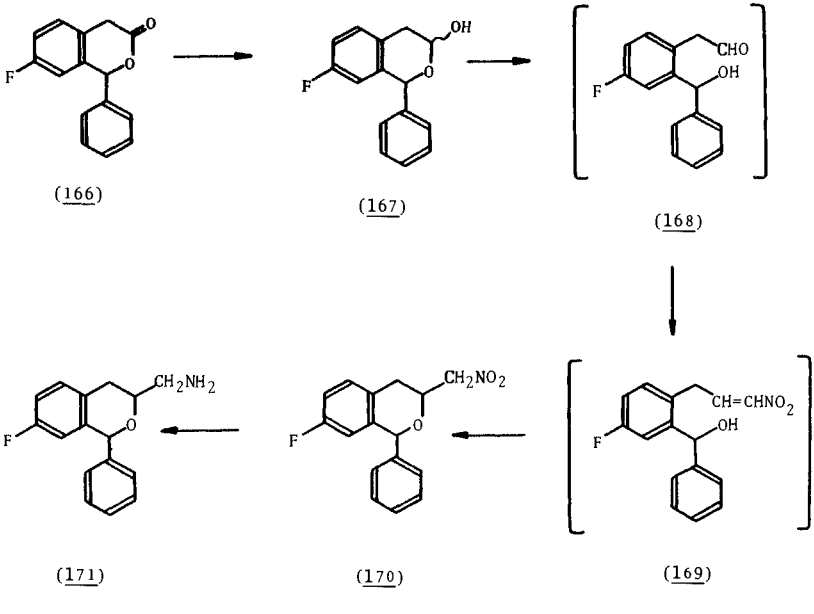
(155)
(156)
(157)
(158)
(159)
(160)
(161)
(162)
(163)
(164)
(165)

mediquox (163),[39] an agent used to treat respiratory infections of poultry. Reaction of *162* with selenium dioxide under more strenuous conditions proceeds to the aldehyde stage *(164)*. Condensation of the carbonyl group with methyl carbazate affords *carbadox (165)*.[40] The biological activity of *carbadox* is similar to that of *mediquox*.

5. MISCELLANEOUS BENZOHETEROCYCLES

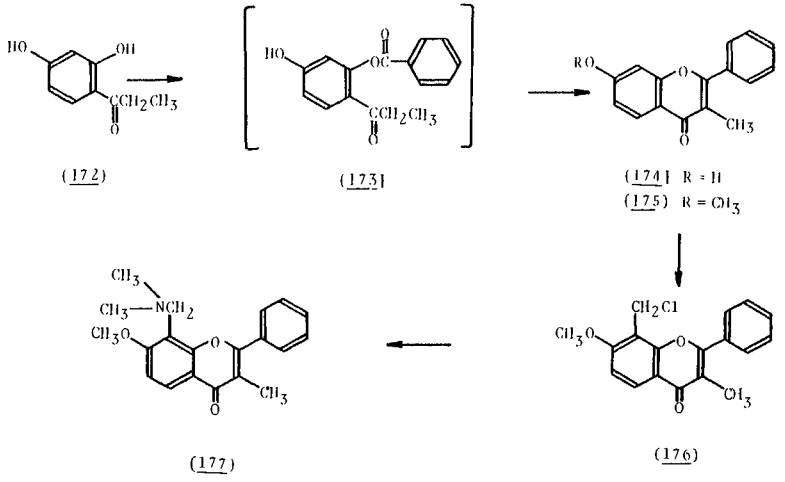
Partial reduction of lactone *166* (using for example diisobutylaluminum hydride in the cold) affords lactol *167*. Condensation with nitromethane leads to the corresponding alkylated tetrahydrobenzopyran *170*. The sequence probably starts by aldol reaction of the hydroxylactone form of the lactol *(168)* with nitromethane to give the vinyl nitro intermediate *169;*



(166) (167) (168) (169) (170) (171)

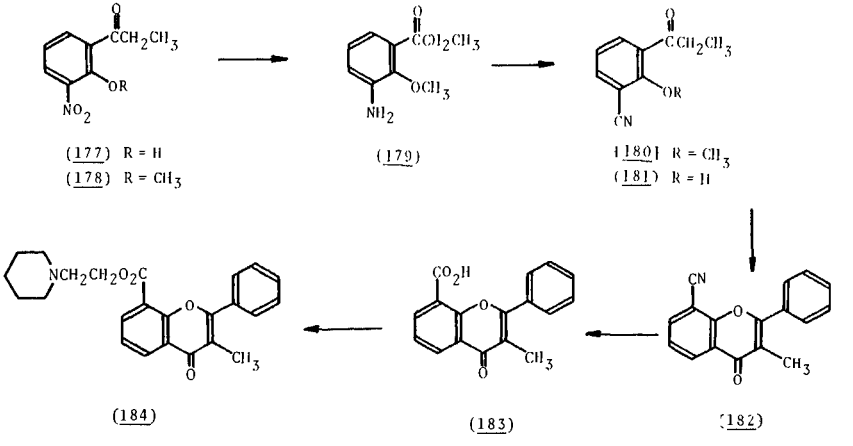
intramolecular conjugate addition of the alcohol will then give the observed product. Since this last step is in principle reversible, the reaction is expected to yield predominantly the thermodynamically favored bisequatorial cis isomer. Catalytic reduction of the nitro group then gives the primary amine anorectic agent *fenisorex (171)*.[41]

Condensation of 2,4-dihydroxypropiophenone *(172)* with benzoyl chloride and sodium benzoate goes to afford chromone *174*, probably via ester *173*. This procedure is known as the Kostanecki-Robinson reaction. Methylation *(175)* of the remaining phenolic function by means of dimethyl sulfate, followed by reaction



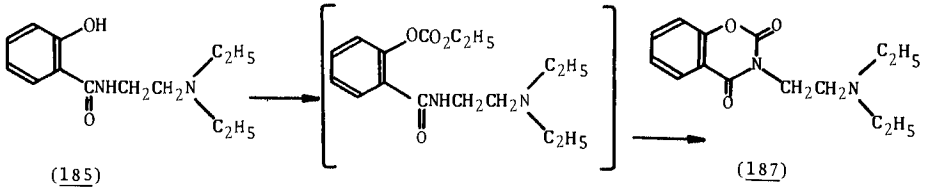
with formaldehyde and hydrogen chloride gives the chloromethyl intermediate *176*. Displacement of chlorine with dimethylamine then affords the respiratory stimulant *dimefline (177)*.[42]

Modification of the substitution pattern on the same chromone gives a compound with smooth muscle relaxant activity, *flavoxate (184)*. The synthesis of this flavone ester is initiated with methylation of the hydroxypropiophenone *177* to *178* followed by reduction of the nitro group to yield aniline *179*. The amine is then used to introduce a nitrile by diazotization followed by treatment of the diazonium salt with cuprous cyanide *(180)*; the methyl ether is then cleaved by means of aluminum chloride. Treatment of the phenolic ketone *181* with benzoyl chloride and sodium benzoate serves to build up the chromone ring *(182)*. The nitrile is next hydrolyzed to the acid with sulfuric acid. Esterification of the carboxyl as--its acid chloride--with N-(2-hydroxyethyl)piperidine affords *flavoxate (184)*.[43]



Reaction of salicylamide *185* (obtainable from a suitable activated derivative of salicylic acid and N,N-diethylethylenediamine) with ethyl chloroformate

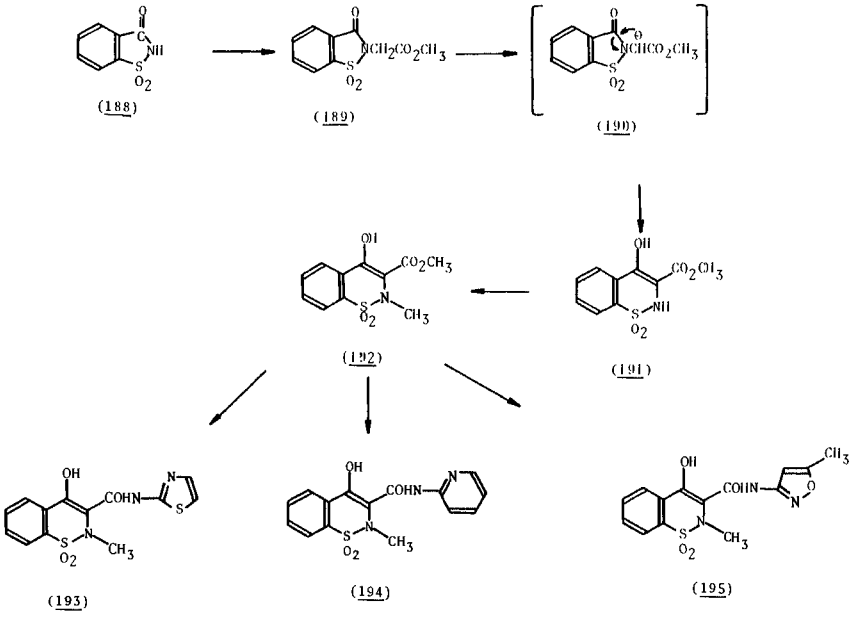
in the cold followed by heating affords the benzoxazinedione *187*.[44] It is likely that the transformation proceeds via carbonate *186*; the product, *letimide (187)*, is reported to show analgesic activity.



(185) (186) (187)

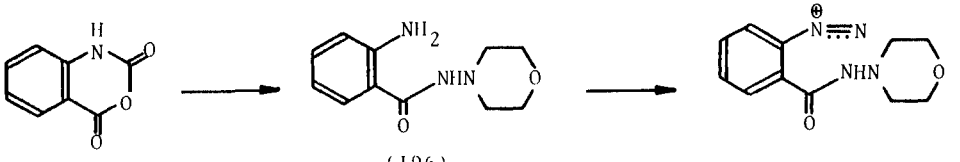
Among the heterocyclic systems that have been used to provide a backbone for acidic, nonsteroidal antiinflammatory agents are benzo-1,2-thiazine dioxides, such as *193-195*. Entry to the ring system is gained by an interesting ringenlarging rearrangement. The necessary intermediate for the expansion reaction is prepared by alkylation of saccharin *(188)* with ethyl bromoacetate to afford the ester *189*. Treatment of that with sodium methoxide results in formation of the anion adjacent to the carbonyl; bond reorganization gives the net result *(190)* of a ring enlargement. The driving force for the reaction may well reside in the fact that the anion of the product is a weaker base than that of starting material. Sodium hydroxide mediated alkylation of the product *(190)* with methyl iodide might occur at any one of three sites (O, N or C) due to the multidentate nature of the anion; interestingly, the reaction proceeds to give only the N-methylated product *(192)*.[45] Amide formation from

192 by interchange with 2-aminothiazole affords the antiinflammatory agent *sudoxicam (193)*;[46] the same reaction using 2-aminopyridine gives *pyroxicam (194)*.[46] Formation of the amide from *192* and 3-amino5-methyl-isoxazole leads to *isoxicam (195)*.[47]



As noted above, a convenient pathway to cinnolines consists of intramolecular condensation of a diazonium group with a ketonic methyl group, or alternately with a double bond. The analogous reaction with an amide nitrogen leads to 1,2,3-benzotriazines, such as *198*. Reaction of isatoic anhydride with N-aminomorpholine affords the hydrazide *196*; then, treatment with nitrous acid yields initially the diazonium salt *(197)*. Under the reaction conditions

this cyclizes to the triazine *198*, the analgesic agent *molinazone*.[48] This must be one of the few--if not the only--compound containing a linear array of four nitrogens ever to be tried in the clinic.



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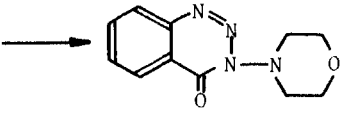
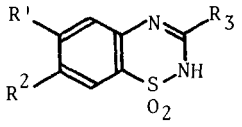
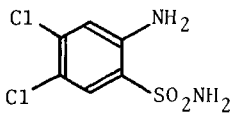


(198)

Changing the substitution pattern on the carbocyclic ring of the benzothiadiazine diuretics is well known to have a marked effect on the qualitative biological activity. Thus, the direct analogue of the diuretic *chlorothiazide (199)* in which chlorine replaces one sulfonamide group, *diazoxide (200)*, shows negligible diuretic activity; instead the compound is a potent antihypertensive vasodilator. The same pattern of activity is maintained in a closely related analogue. Condensation of aminosulfonamide *201* with aldehyde *202* affords the saturated heterocyclic system *(203)*; oxidation with silver nitrate leads to the antihypertensive agent *pazoxide (204)*.[49]



(199) R' = Cl; $R^2 = SO_2NH_2$; $R^3 = H$
(200) R' = H; $R^2 = Cl$; $R^3 = CH_3$



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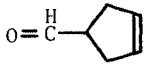

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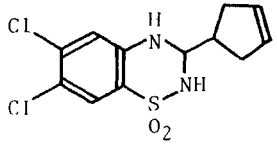

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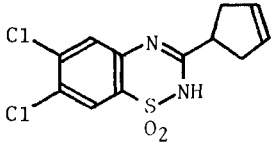

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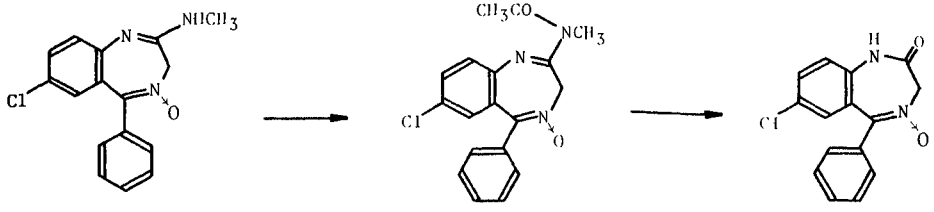
13

Benzodiazepines

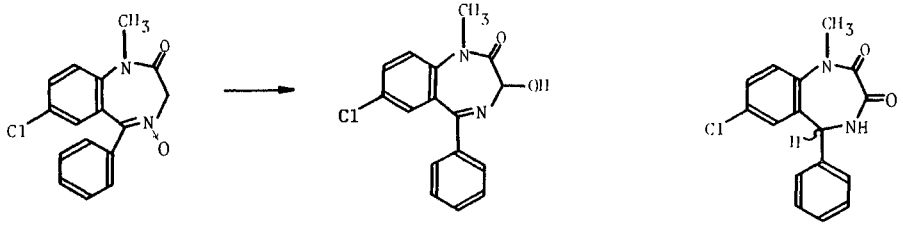
That the benzodiazepines continue to be prominent on the list of the 200 most frequently prescribed drugs in the United States is both a commentary on the nature of our contemporary society and a measure of their acceptance as anxiolytic and tranquilizing substances. Intensively competitive research into new analogues continues and this chapter chronicles some of the more prominent members of this group not detailed in the original volume.

The original entries into this class, such as *chlordiazepoxide (1)*, were N-oxides.[1] Treatment of the N-acetate *(2)* of *chlordiazepoxide* with aqueous acid served to hydrolyze the acylenamine function to liberate the keto analogue *(3)* which has been identified in excreta as an active metabolite of *1;* this minor tranquilizer has been named *demoxepam.*[2]



(1) (2) (3)

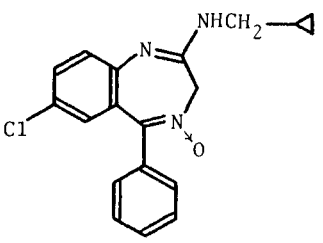
It will perhaps be recalled from the earlier volume that such N-oxides are prone to undergo the Polonovski rearrangement when treated with acetic anhydride, and that this was illustrated by the formation of *oxazepam*.[1] It is not surprising that the N-methyl analogue *(4)* also undergoes this process, and hydrolysis of the resulting acetate gives *temazepam (5)*.[3] Care must be exercised with the conditions, or the inactive rearrangement product *6* results.



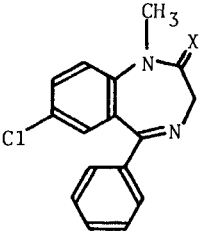
(4) (5) (6)

The lactam moiety in benzodiazepines is active toward nucleophiles and numerous analogues have been made by exploiting this fact. For example, heating *demoxepam (3)* with N-cyclopropylmethylamine leads to amidine formation, the minor tranquilizer *cyprazepam*

(7).[4] On the other hand, treatment of *diazepam (8)*

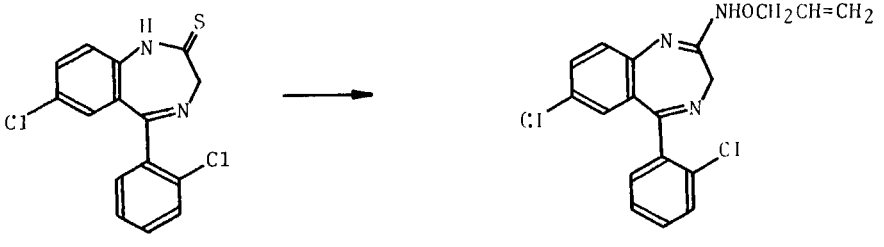


(7)



(8) X = O
(9) X = S

with phosphorus pentasulfide produces the corresponding thionamide, *sulazepam (9)*, also a minor tranquilizer.[5] The thionamide moiety is even more

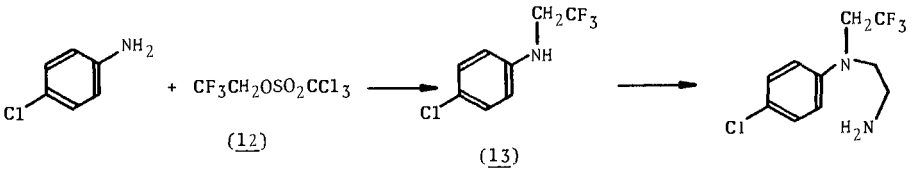


(10) (11)

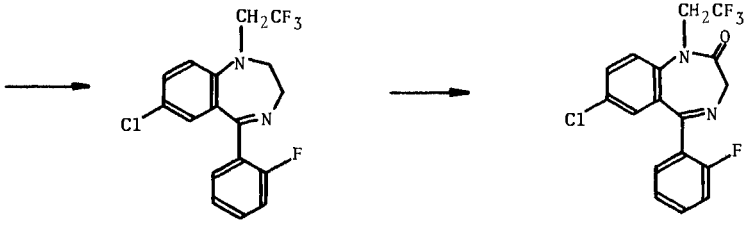
prone to aminolytic amidine formation than the lactam itself. Reaction of thionamide *10* with O-allylhydroxylamine gave the oximinoether *11*, *uldazepam.*[6]

An attempt to reduce metabolic N-dealkylation resulted in the preparation of *fletazepam (16)*, whose activity is expressed as a muscle relaxant.[7] Direct N-alkylation of the amide NH group at a late stage in the synthesis with trifluoroethyl iodide and NaH went

in poor yield, so the desired alkyl group was introduced at an earlier stage. Alkyation of 4-chloroaniline by the trichloromesyl ester of trifluoroethanol *(12)* produced secondary aniline *13*. This underwent alkylation by aziridine to produce diamine *14*. Acylation with 2-fluorobenzoyl chloride produced



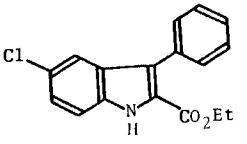
(12) (13) (14)



(15) (16)

the desired secondary amide which underwent Bischler-Napieralski cyclodehydration with $POCl_3$ and P_2O_5 to give *15*. The lactam moiety was introduced by ruthenium tetroxide oxidation to give *fletazepam (16)*. Interestingly, the deoxy analogue minus the fluorine atom, prepared by a similar route,[7] is also a minor tranquilizer.

A rather interesting synthesis of the basic ring system based upon oxidative scission of indole precursors was used to prepare *prazepam (24)*, a muscle relaxant.[8] Starting with indole *17*, N-alkylation to *18* was accomplished with cyclopropylmethyl bromide and NaH. The ester was converted to the amide *(21)* by the usual sequence and then reduced to primary amine *22* using lithium aluminum hydride.



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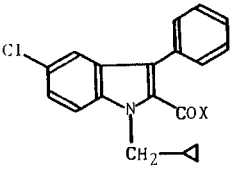
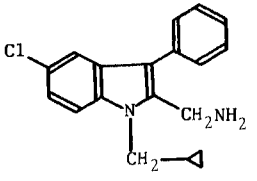


(18) X = OC_2H_5
(19) X = OH
(20) X = Cl
(21) X = NH_2



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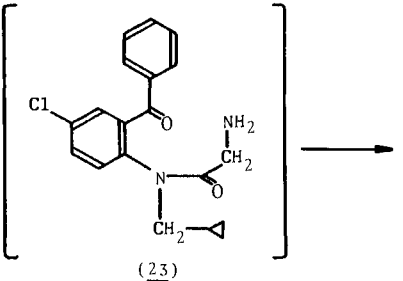
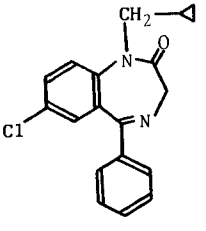
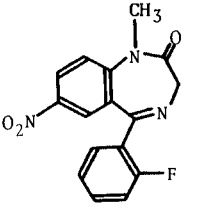


(23)



(24)

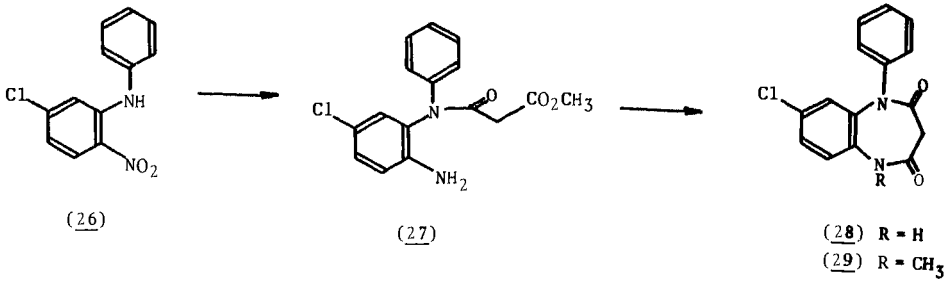


(25)

Oxidation with chromium trioxide in acetic acid cleaved the indole ring to produce intermediate *23* which cyclodehydrated to give *prazepam (24)*.

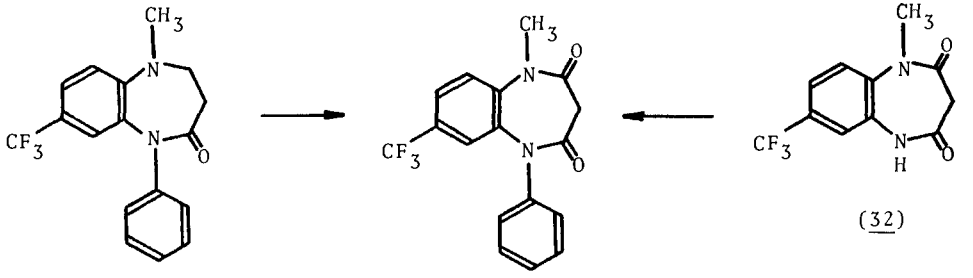
Nitration of benzodiazepines takes place at the electron rich C_7 position, and this was used to prepare *flunitrazepam (25)*, a potent hypnotic agent.[9]

It is interesting to note that some 1,5-benzodiazepines such as *29* also possess CNS depressant activity. Treatment of substituted diphenylamine *26* with methyl malonyl chloride and reduction with Raney nickel led to orthophenylenediamine analogue *27*. Sodium alkoxide treatment led to lactam formation *(28)*, and alkylation in the usual way with NaH and methyl iodide produced *clobazam (29)*.[10]



(26) (27) (28) R = H (29) R = CH_3

On the other hand, MnO_2 oxidation of lactam *30* or arylation of secondary lactam *32* with bromobenzene using Cu powder and potassium acetate both led to anxiolytic *triflubazam (31)*.[11]



(30) (31) (32)

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14

Heterocycles Fused to Two Benzene Rings

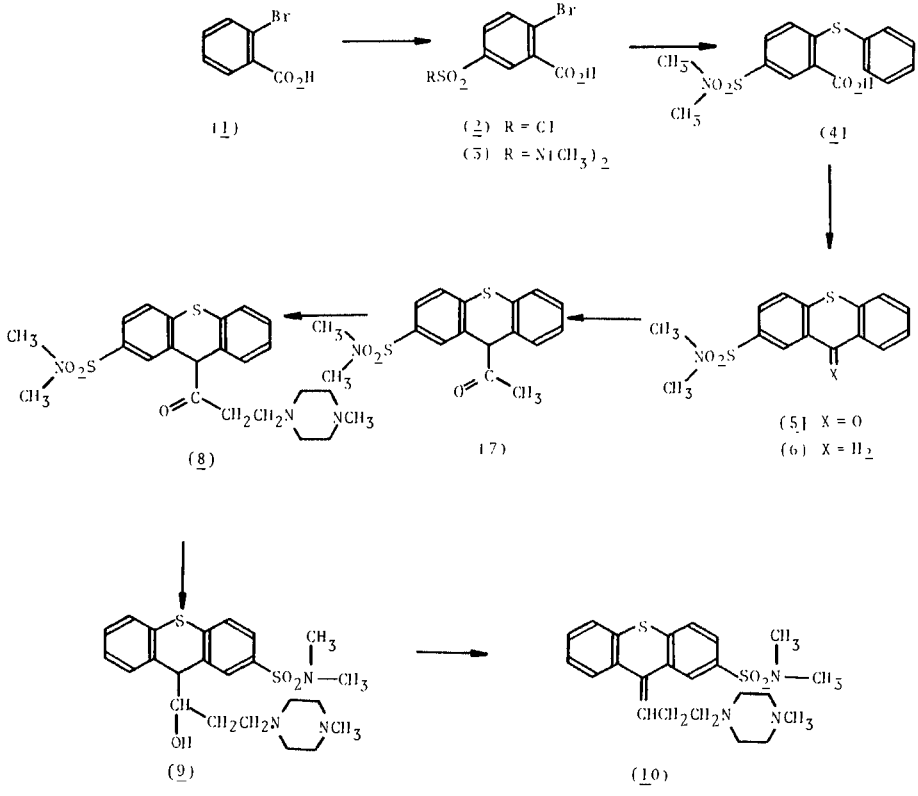
Pharmacological agents based on dibenzo heterocyclic compounds had their inception in the formal cyclization by inclusion of a hetero bridging atom of the two benzene rings characteristic of diphenylamine and benzhydryl antihistamines. As detailed in the earlier volume, this approach led to the development of the first of the antipsychotic agents, *chlorpromazine*. Further modification of the central ring led to compounds that showed antidepressant rather than tranquilizing activity. It might be noted in passing that it was eventually discovered that the central ring in antidepressants need not be heterocyclic at all; some of the more widely used antidepressant drugs are in fact derivatives of dibenzocycloheptadiene. Further modification of the dibenzoheterocycles has not yielded agents with markedly different activities. The compounds discussed below, with few exceptions,

exhibit either antihistaminic or central nervous system activity.

1. CENTRAL RING CONTAINING ONE HETEROATOM

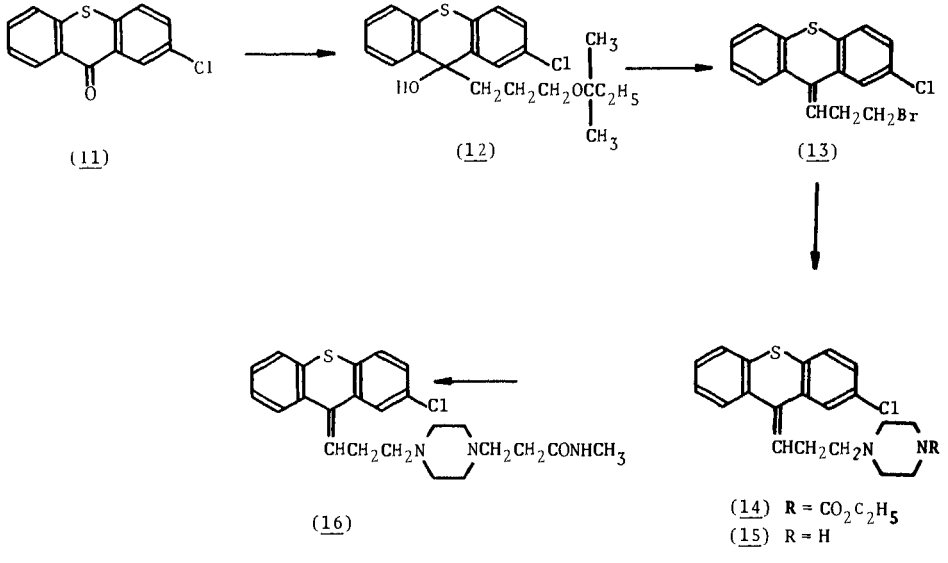
Reaction of 2-bromobenzoic acid *(1)* with chlorosulfonic acid proceeds to afford the sulfonyl chloride *2;* treatment with dimethylamine leads to the corresponding sulfonamide *(3).* Condensation of bromoacid *3* with the anion from thiophenol in the presence of copper powder results in displacement of halogen by sulfur *(4).* Friedel-Crafts cyclization of that sulfide by means of sulfuric acid gives the desired thioxanthone *(5),* which is then reduced to the thioxanthene *(6).* Treatment of that intermediate with butyl lithium serves to form the anion at the methylene group; the corresponding acyl derivative 7 is obtained by condensation of the anion with methyl acetate. Mannich reaction on the ketone with formaldehyde and N-methylpiperazine yields the amino ketone *(8).* The carbonyl group is then reduced with sodium borohydride. Dehydration by means of phosphorus oxychloride in pyridine gives the major tranquilizer *thiothixene (10).*[1] As might be expected, this last reaction gives a mixture of isomers; the more active *Z* isomer is separated from the mixture by fractional crystallization.

The presence of a rather more complex substituent on the remote piperazine nitrogen atom is consistent with tranquilizing activity. The preparation of one such agent, *16,* begins with reaction of thioxanthone *11* (obtained by a sequence analogous to that used to



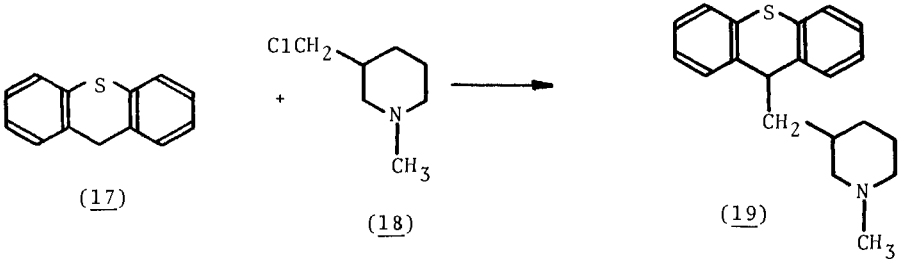
prepare *5)* with the Grignard reagent from 3-(tertiary-amyloxy)propyl bromide to afford alcohol *12.* Treatment with hydrogen bromide serves to dehydrate the carbinol, remove the protecting group from the terminal alcohol,

and finally to convert that alcohol to the corresponding bromide *(13)*. Although this would be expected as a mixture of isomers, the sharp melting point of the product suggests it may be homogenous. This halide is then used to alkylate the monocarbamate from piperazine, yielding *14*. Saponification of the carbamate affords the secondary amine *15*. Michael condensation of that base with N-methylacrylamide gives the neuroleptic agent, *clothixamide (16)*.[2]



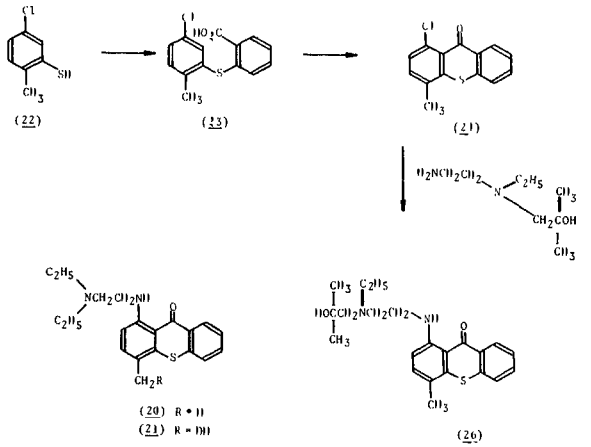
Reduction of the exocylic double bond and inclusion of the side chain nitrogen in a piperidine ring leads to a compound *(19)* which exhibits skeletal muscle relaxant activity. Its one step synthesis begins with reaction of thioxanthene *(17)* with phenyl sodium

to afford the anion at the methylene group of the heterocycle; then, condensation of that anion with piperidine derivative *18* gives directly *methixene (19)*.[3]

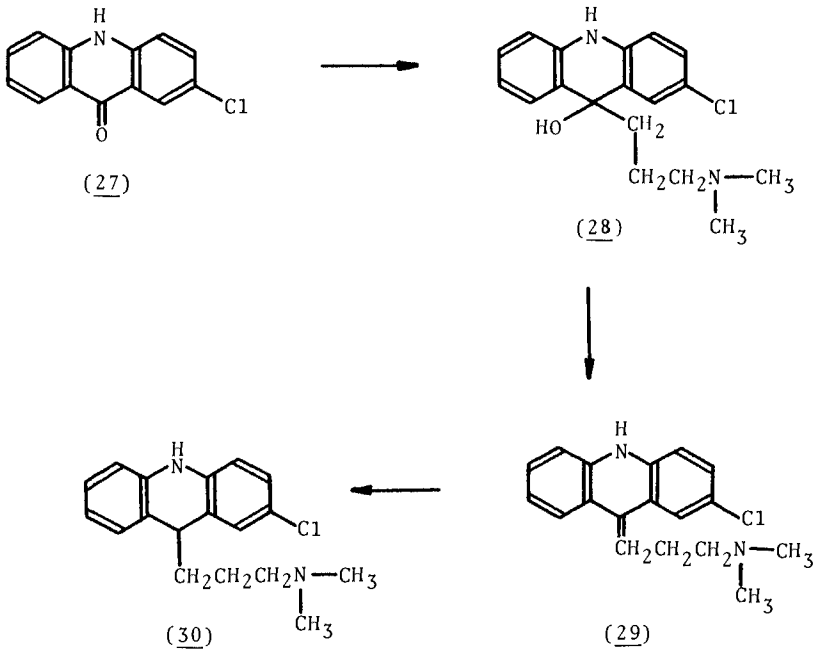


(17) (18) (19)

Lucanthone (20) constitutes one of the first effective antischistosomal agents. Biological investigation of this agent showed that the active species in man is in fact the hydroxylated metabolic product *hycanthone (21)*. The published synthesis for the latter involves microbial oxidation as the last step.[4] Additional hydroxylated derivatives of *lucanthone* have been investigated. One of these, *becanthone (26)*, made as part of an investigation of antitumor agents, shows activity against schistosomes comparable to that of *hycanthone*. Ullmann reaction of the salt of thiophenol *22* with 2-chlorobenzoic acid in the presence of copper gives the sulfide *23*. Ring closure by means of sulfuric acid gives the corresponding thioxanthone *(24)*. Nucleophilic aromatic substitution of the chlorine atom in *24* with aminoalcohol *25* gives *becanthone (26)* directly.[5]

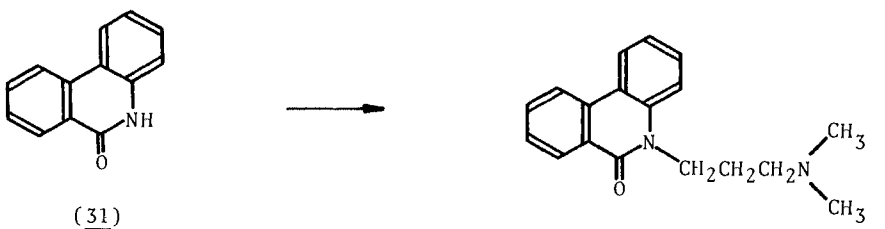


The thioxanthene tranquilizers described above may be regarded as phenothiazine analogues in which a methine group acts as surrogate for nitrogen; that is, the side chain is attached to sp_2 carbon instead of nitrogen. It is thus of some interest that further, rather drastic, modification of the central ring still gives a compound with tranquilizing activity. In the case of *clomacran (30)*, the side chain is again attached to carbon, albeit tetrahedral rather than trigonal carbon. In addition, the sulfur atom present in both phenothiazines and thioxanthenes is replaced by a secondary amine. This might be interpreted to mean that the nature of the bridge between the benzene rings is not crucial for biological activity. The preparation of *30* begins with reaction of acridone *27* with the Grignard reagent from 3-chloro-N,N-dimethylpropylamine to afford tertiary carbinol *28;* dehydration by means of acid or simply heat gives the corresponding olefin *(29)*. Catalytic reduction completes the synthesis of the tranquilizer, *clomacran (30)*.[6]



(27) (28) (29) (30)

Nuclei for tricyclic antidepressants and tranquilizers almost invariably contain the three rings fused in linear array. It is thus interesting to note that an angular arrangement of these rings, such



(31) (32)

as in *fantridone (32)*, is consistent with antidepressant activity. Alkylation of the anion obtained by treatment of phenathridone *(31)* with sodium hydride

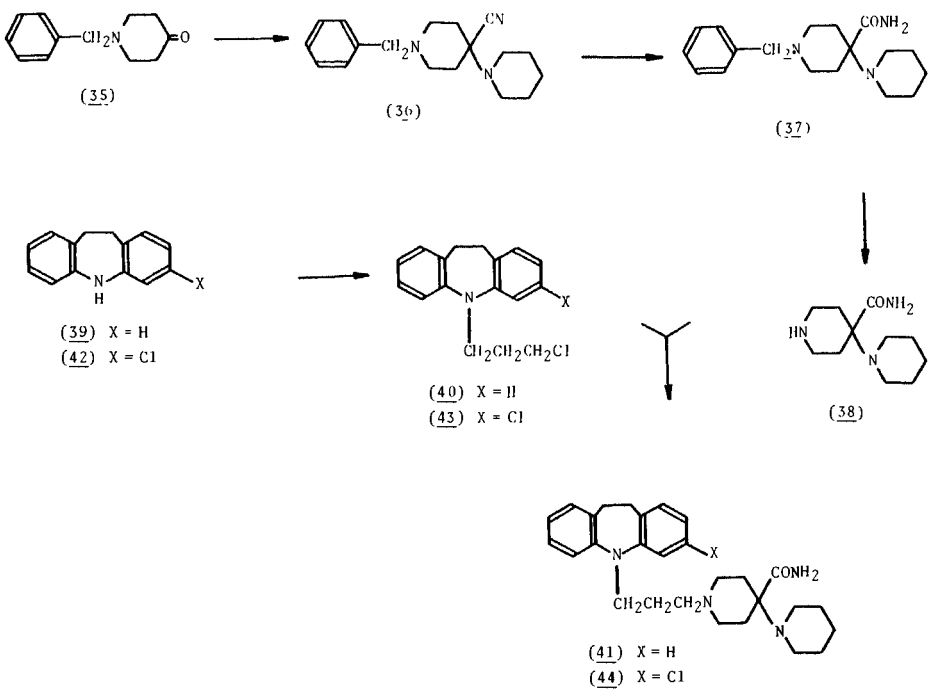
and 3-chloro-N,N-dimethylpropylamine affords *fantridone (32)* directly.[7]

Almost every major structural class discussed to date has featured at least one nonsteroidal anti-inflammatory carboxylic acid. It is thus perhaps not surprising to find a dibenzoheterocycle serving as the nucleus for one of these agents, *furobufen (34)*. Straightforward Friedel-Crafts acylation of dibenzofuran *(33)* with succinic anhydride affords a mixture of 2- and 3-acylated products, with the latter predominating. The mixture is esterified with methanol, and the methyl ester of the 3-isomer is separated by fractional crystallization. Hydrolysis back to the acid affords pure *34*.[8]

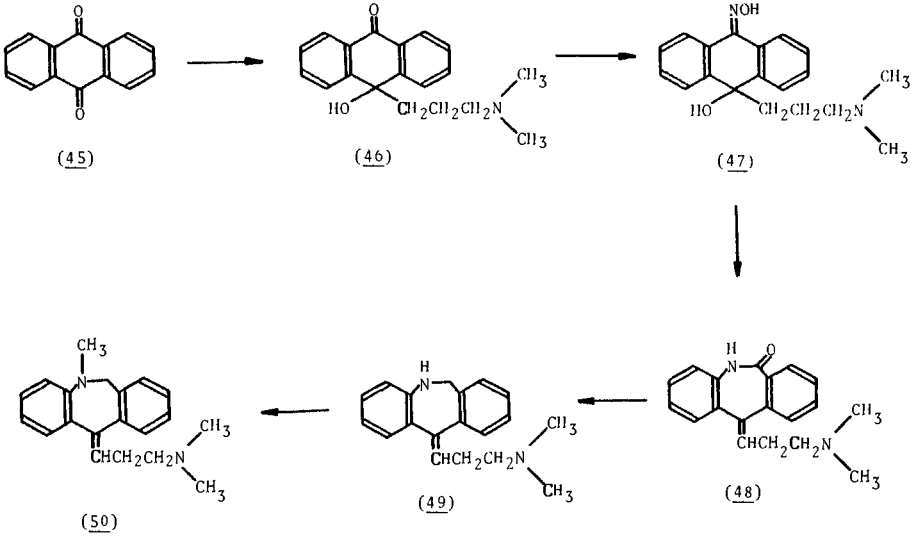
(33) (34)

Replacement of sulfur in the phenothiazines by two methylene groups also results in compounds that retain antipsychotic activity; two examples are *carpipramine (41)* and *clocapramine (44)*. Although one might describe this as yet another example of the bioisosteric equivalence of sulfur and ethylene, the observed broad latitude in the nature of the tricyclic system in tranquilizers suggests caution in drawing such a conclusion. In a convergent synthesis of *41*, reaction of N-benzyl-4-piperidone *(35)* with potassium cyanide and piperidine hydrochloride gives the corresponding α-aminonitrile *(36)*. Hydrolysis of the nitrile by means of 90% sulfuric acid gives the amide

37; hydrogenolysis of the benzyl protecting group then affords the secondary amine *38.*[9] Alkylation of dibenzazepine *39* with 1-bromo-3-chloropropane gives intermediate *40.* Use of that material to alkylate piperidine *38* affords finally *carpipramine (41).*[10] The same sequence starting with halogen substituted dibenzazepine *42* leads to the tranquilizer *clocapramine (44).*[10]

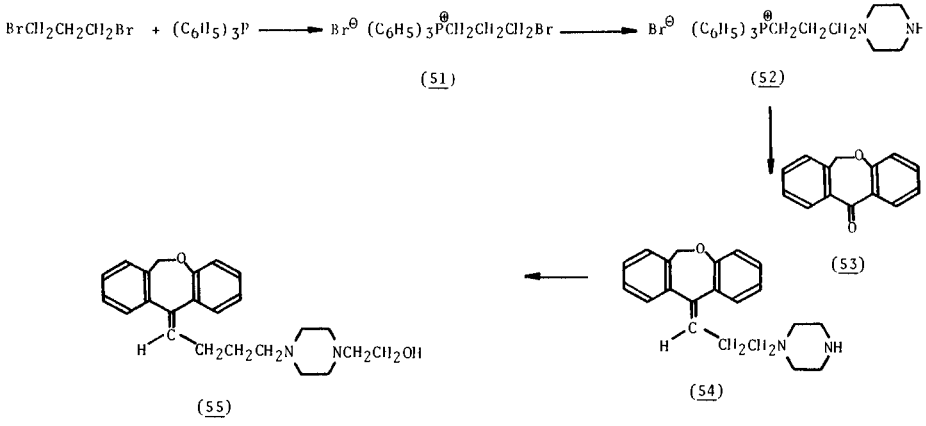


Many tricyclic tranquilizers and antidepressants exhibit some measure of anticholinergic activity. It is of interest to note that attachment of a basic side chain on carbon of an isomeric dibenzazepine affords a compound in which anticholinergic activity predominates, *elantrine (50)*. Reaction of anthraquinone *(45)* with the Grignard reagent from 3-chloro-N,N-dimethylaminopropane in THF in the cold results in addition to but one of the carbonyl groups to yield hydroxyketone *46*. This is then converted to oxime *47* in a straightforward manner. Treatment of that intermediate with a mixture of phosphoric and polyphosphoric acids results in net dehydration of



the tertiary carbinol and Beckmann rearrangement of the oxime to afford the enelactam *48;* the stereochemistry of the product(s) (E,Z) is not specified. The lactam is then reduced to amine *49* with lithium aluminum hydride, and the resulting amine is methylated to obtain e*lantrine (50).*[11]

Replacement of the ring nitrogen in *50* by oxygen yields a molecule that can now again be characterized as a tranquilizer, although one that shows some degree of anticholinergic activity. Synthesis of this agent, *pinoxepin (55),* begins with the reaction of 1,3-dibromopropane with triphenylphosphine to give the bromoalkylphosphonium salt *51.* Displacement of the remaining bromine by piperazine then leads to the



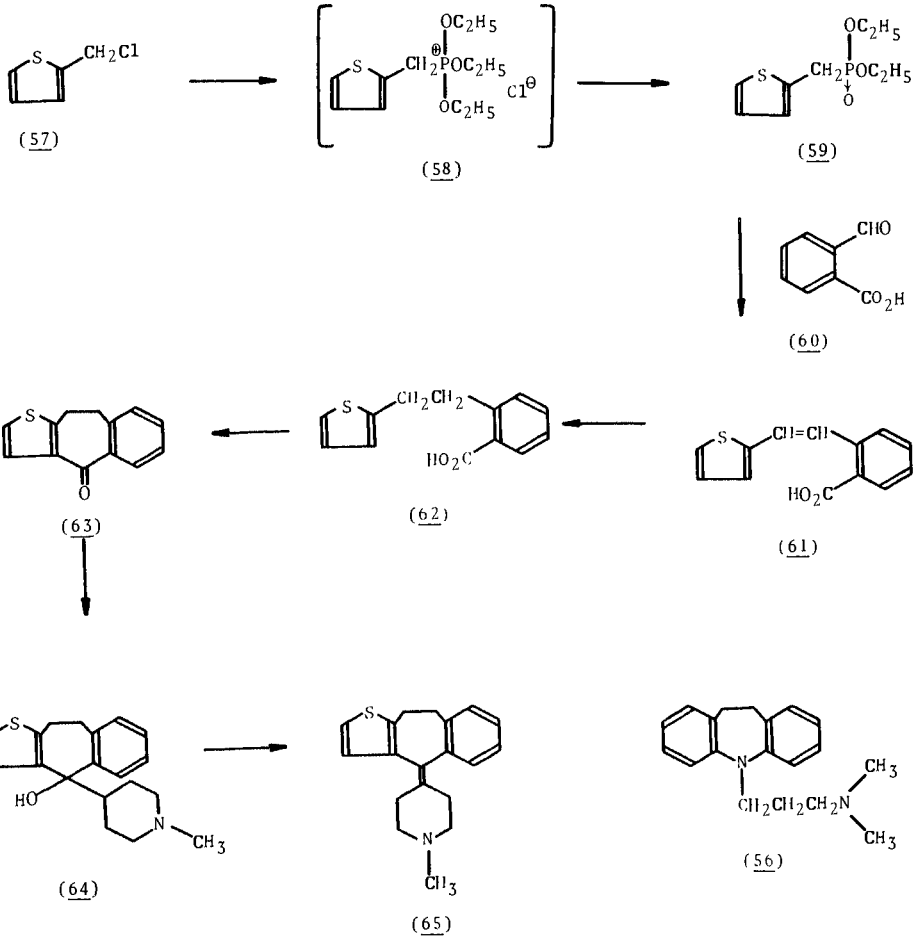
functional phosphonium salt *52.* The latter is then converted to the corresponding ylide by means of

butyl lithium, and the resulting reactive intermediate is condensed with ketone *53*. The product *(54)* in this case consists largely (4:1) of the *Z* isomer. The stereoselectivity may involve complexation of the betaine intermediate with the heterocyclic oxygen. Condensation of the terminal secondary amine with ethylene oxide affords *pinoxepin (55)*.[12]

2. BENZOHETEROCYCLOHEPTADIENES

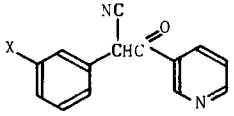
Both this and the previous volume are of course organized on the basis of structural classes. Occasionally, a series of medicinal agents defies attempts at neat classification by such a scheme. The compounds that follow could only be called dibenzoheterocycles by performing the imaginary operation of moving the hetero atom from the flanking to the central ring of the molecule. The chemistry and biological activity of those molecules does seem to argue for their inclusion at this juncture.

The first of these compounds, *pizotyline (65)*, shows activity much akin to related tricyclic depressants such as *imipramine (56)*.[13] One of several schemes for preparation of the key tricyclic intermediate *63* starts by reaction of 2-chloromethylthiophene *57* with triethyl phosphite. The net transformation (Arbuzov reaction) probably starts with formation of phosphonium salt *58*; displacement of one of the ethyoxy groups by chloride at carbon then leads to loss of ethyl chloride and formation of the observed phosphonate *59*. Reaction of the ylide

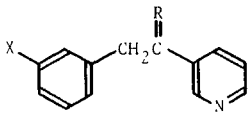


obtained from the last intermediate with hemi phthalaldehyde *(60)* gives the diarylethylene *61*. Reduction of the double bond *(62)*, followed by Friedel-Crafts cyclization by means of polyphosphoric acid affords the requisite ketone *63*. This compound is then condensed with the Grignard reagent from 1-methyl-4-chloropiperidine, and the resulting carbinol *(64)* is dehydrated. There is thus obtained the antidepressant agent *pizotyline (65)*.[14]

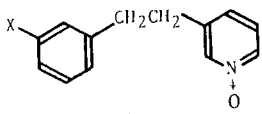
Replacement of the thienyl grouping in *65* by pyridyl affords *azatadin (75)*, a compound in which antihistaminic rather than antidepressant activity predominates. (It is of interest that the equivalent interchange in the acyclic series affords a pair of compounds each of which is an antihistamine.) The synthesis of the tricyclic system in this case starts by acylation of the anion from phenylacetonitrile with ethyl nicotinate to give cyanoketone *66*. Hydrolysis of the nitrile followed by decarboxylation of the resulting keto-acid gives ketone *67*; reduction then leads to the diarylethane *68*. Functionality is then introduced into the pyridine ring by the elegant method introduced by Taylor.[15] Thus, treatment of *68* with peracid gives N-oxide *69*; reaction of that with phosphorus trichloride leads to the corresponding 2-chloropyridine *(70)* with simultaneous loss of the oxide. Displacement of halogen with cyanide followed by hydrolysis of the resulting nitrile *(71)* gives the carboxylic acid *(72)*. Cyclization by means of polyphosphoric acid yields the key tricyclic intermediate *73*. The ketone is then condensed with the Grignard



(66) X = H
(76) X = Cl



(67) X = H; R = O
(68) X = H; R = H_2
(77) X = Cl; R = O



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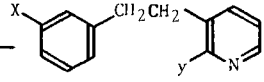
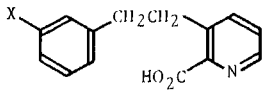
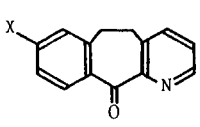


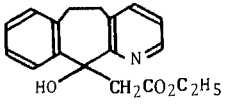
(70) X = H; y = Cl
(71) X = H; y = CN
(80) X = y = Cl
(81) X = Cl; y = CN



(72) X = H
(82) X = Cl



(73) X = H
(83) X = Cl



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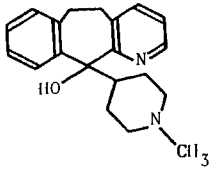

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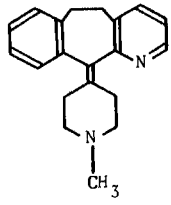

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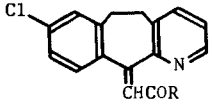
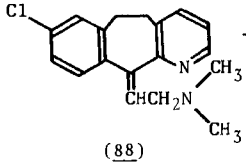


(85) R = OC_2H_5
(86) R = OH
(87) R = $N(CH_3)_2$



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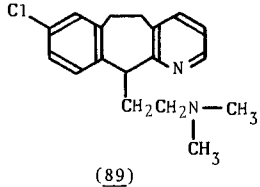


(89)

reagent from N-methyl-4-chloropiperidine to afford the carbinol *74*. Finally, dehydration of this last intermediate affords the antihistamine *azatadine (75)*.[16]

A similar sequence starting with the acylation product *(76)* from metachlorophenylacetonitrile gives the halogenated tricyclic ketone *83*. Condensation of that intermediate with ethyl bromoacetate in the presence of zinc (Reformatsky reaction) gives the hydroxyester *84*. This product is then in turn dehydrated under acid conditions *(85)*, saponified to the corresponding acid *(86)*, and converted to the dimethylamide *(87)* by way of the acid chloride. The amide function is then reduced to the amine *(88)* with lithium aluminum hydride; catalytic hydrogenation of the exocyclic double bond completes the synthesis of *closiramine (89)*.[16] This compound also exhibits antihistaminic activity.

3. DERIVATIVES OF DIBENZOLACTAMS

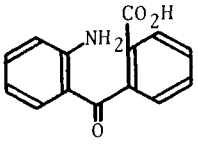
A recurring theme in the present chapter has been the association of CNS activity with dibenzoheterocycles that bear a basic chain pendant from the central ring. As we have seen, considerable latitude exists as to the constitution of the central ring. The earlier volume in this series described the preparation of the antidepressant *dibenzepin (90)*, in which the basic function is attached to a lactam nitrogen.[17] It has been found subsequent to this that attachment of the basic center in the guise of a piperazine ring

as an amidine derivative again affords a series of compounds with activity on the CNS.

Preparation of the simplest of these examples *(95)* starts with hydrogenolysis of o-aminobenzoylbenzoic acid *(91)* with zinc (activated by copper) in ammonia. Thermal cyclization of the resulting diphenylmethane *(92)* gives the desired lactam *(93)*.[18] Treatment of that intermediate with phosphorus oxychloride in the presence of N,N-dimethylaniline leads to iminochloride *94*. Aminolysis with N-methylpiperazine affords the hypnotic agent *perlapine (95)*.[19]

Replacement of the bridge methylene group in 95 by a secondary amine is consistent with CNS activity, although the compound in this case *(99)* is described as a sedative agent. The synthetic approach used in this case relies on cyclization of an intermediate in which the piperazine ring is already in place. Thus, reaction of the acid chloride from *96* (available by Ullmann reaction of anthranilic acid on 2,5-dichloronitrobenzene) with N-methylpiperazine gives the corresponding amide *(97)*. The nitro group is then reduced to yield aniline *98*. Intramolecular dehydration then affords the amidine, *clozapine (99)*.[20]

Replacement of the methylene group in 95 by oxygen results in yet another subtle qualitative change in CNS activity. The products of this replacement, such as *104* and *111*, are characterized as anxiolytic agents. In the synthesis of *104* we find yet a different approach to the amidine function, beginning with reaction of 2-chloronitrobenzene with



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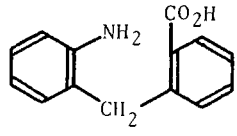

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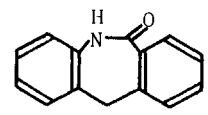

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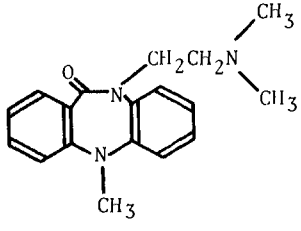

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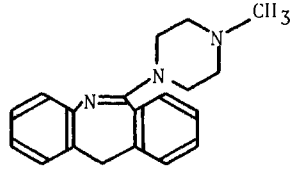

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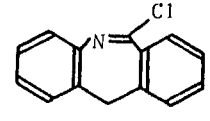

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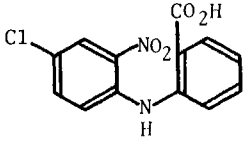

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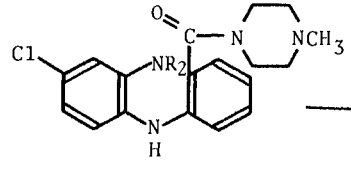
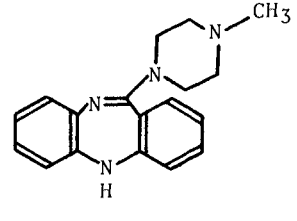
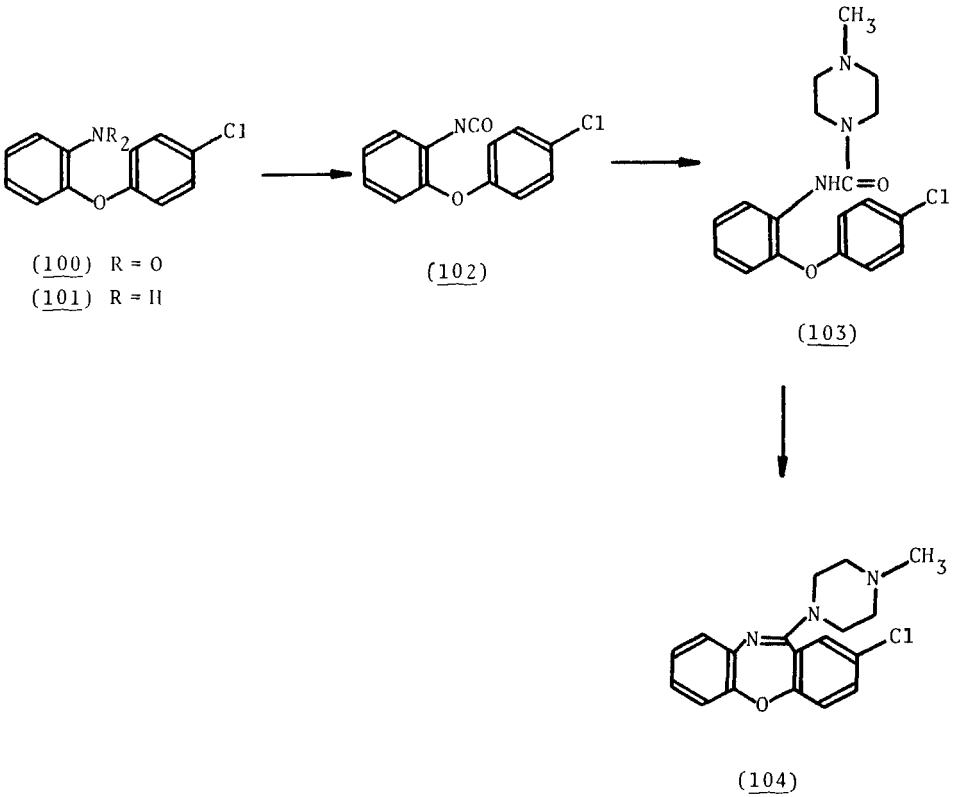


(97) R = O
(98) R = H



(99)

the anion from p-chlorophenol to afford the product of aromatic nucleophilic displacement *(100)*; then, reduction of the nitro group affords the corresponding aniline *(101)*. Treatment of that amine with phosgene in the presence of excess triethylamine converts the aniline to the isocyanate *(102)*. Condensation of that intermediate with N-methylpiperazine affords urea *103*. Bishler-Napieralski type cyclization of the urea into the adjacent ring is accomplished with phosphorus oxychloride. There is thus obtained *loxapine (104)*.[21]



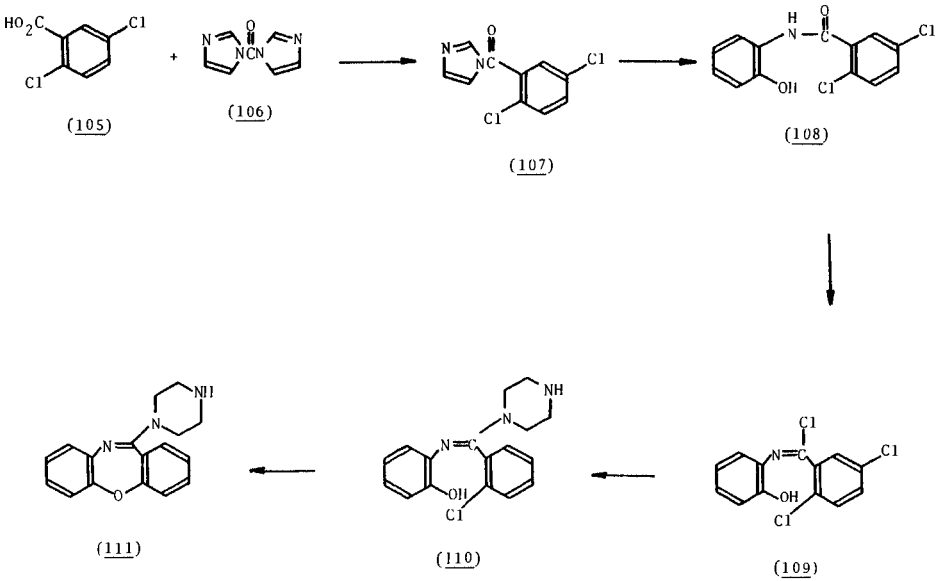
(100) R = O
(101) R = H

(102)

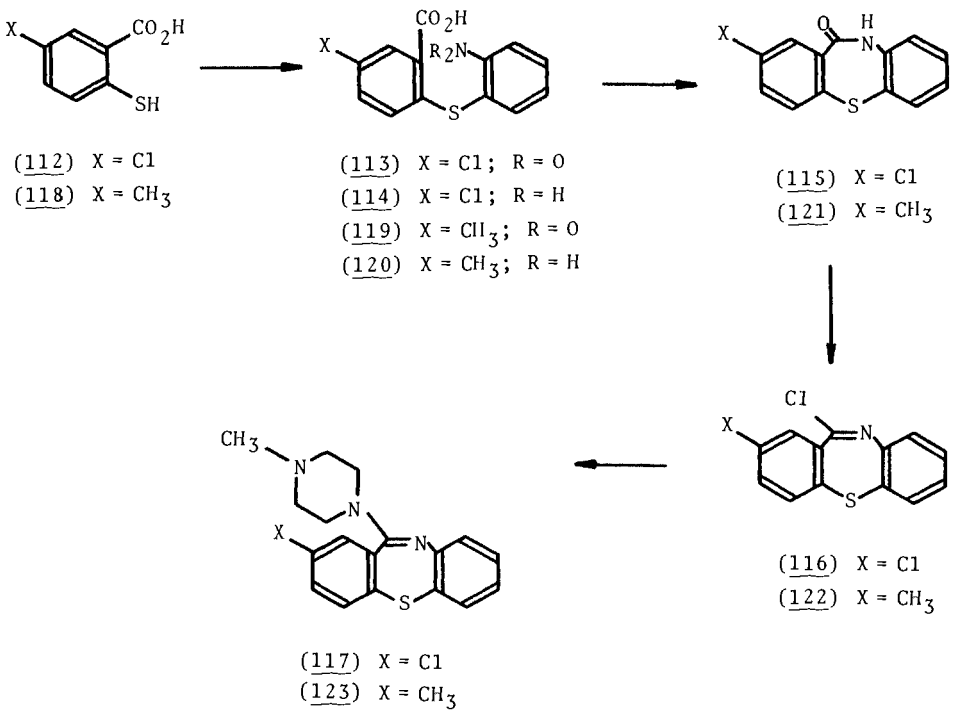
(103)

(104)

Another approach to this ring system leaves the formation of the oxygen bridge to the end. This scheme starts by reaction of the dichlorobenzoic acid *105* with carbonyldiimidazole *(106)* to afford the reactive intermediate *107*. Condensation with o-aminophenol gives the amide *108*, which is then converted to the iminochloride with phosphorus pentachloride. Condensation of *109* with piperazine apparently stops cleanly at monomer *110*. Intramolecular Ullmann condensation in the presence of copper powder leads to formation of the dibenzoxazepin ring, and thus *amoxapine (111)*.[22]



Finally, replacement of the methylene bridge by a sulfur bridge leads to compounds such as *117* and *123* which are major tranquilizers. Thus, Ullmann condensation of thiosalicylic acid *112* with *ortho-chloronitrobenzene* affords thioether *113;* the nitro group is then reduced to the aniline *(114).* Cyclization as above leads to the lactam *115,* which is then converted to the iminochloride derivative *(116).* Condensation with N-methylpiperazine affords *clothiapine (117).*[21] Exactly the same sequence with the methyl substituted thiosalicylic acid derivative *118* leads to *metiapine (123).*[21]

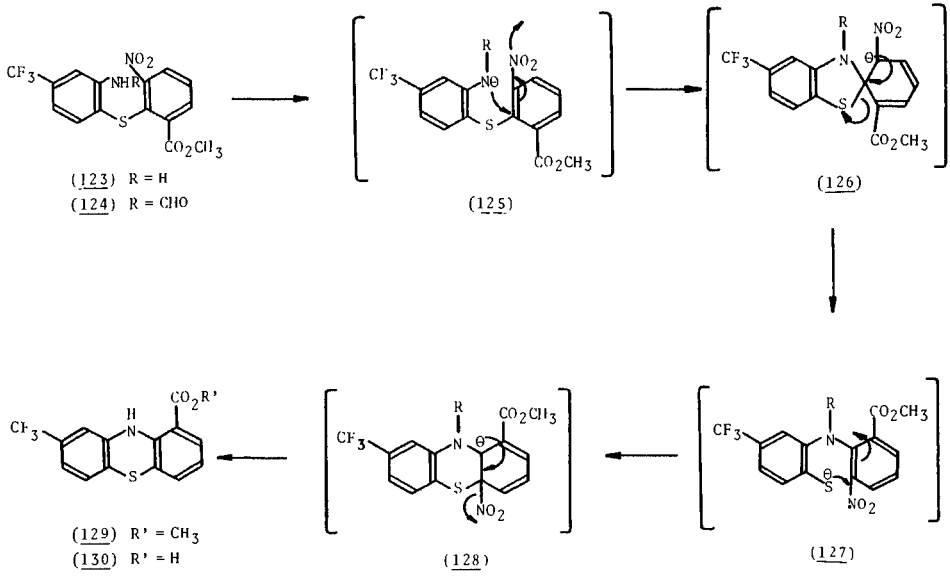


4. OTHER DIBENZOHETEROCYCLES

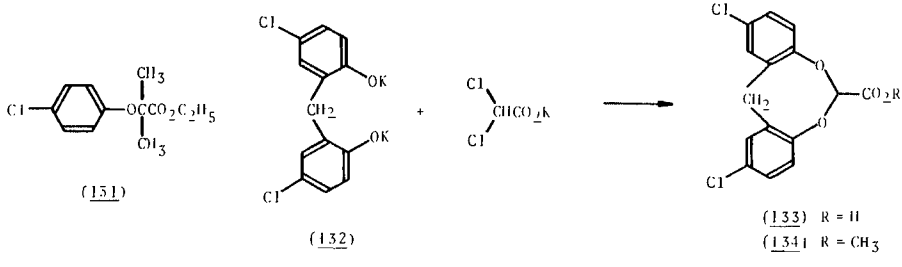
Historically, research in industrial medicinal chemistry has occurred in waves. The discovery of some novel structure with unique biological activity has often occasioned intensive work in numerous laboratories on the preparation and evaluation of analogues. Each such wave recedes when it is realized that further modification of the molecule is reaching the point of diminishing returns. At this juncture, the structure is often represented in the clinic by several commercialized drugs; it is judged unlikely that further work will produce a patentably novel compound that could make significant inroads on the market for drugs already available.

Nowhere, perhaps, is this phenomenon better illustrated than in the phenothiazine class. The earlier volume devoted a full chapter to the discussion of this important structural class, which was represented by both major tranquilizers and antihistamines. The lone phenothiazine below, *flutiazin (130)*, in fact fails to show the activities characteristic of its class. Instead, the ring system is used as the aromatic nucleus for a nonsteroidal antiinflammatory agent. Preparation of *130* starts with formylation of the rather complex aniline *123*. Reaction with alcoholic sodium hydroxide results in net overall transformation to the phenothiazine by the Smiles rearrangement. The sequence begins with formation of the anion on the amide nitrogen; addition to the carbon bearing sulfur affords the corresponding transient spiro intermediate *126*. Rearomatization

affords thiophenoxide *127*; this then attacks the adjacent ring and the resulting negative charge on the ring carbon adjacent to nitrogen is then discharged by expulsion of the nitro group as the nitrite anion. The formyl group on what is essentially a diphenylamine is sufficiently labile so that it too comes off under the reaction conditions. There is thus obtained the phenothiazine carboxylic ester *129*. Saponification of the ester completes the synthesis of the veterinary antiinflammatory agent *flutiazin (130)*.[23]



The association between abnormally high levels of serum lipids and atherosclerosis has been discussed earlier. One of the earliest and still most widely used drugs for normalizing lipid levels and thus presumably treating atherosclerosis is the phenoxyester *clofibrate (131)*. The wealth of analogues in this series has demonstrated that lipid lowering activity is retained when a second chlorophenoxy group is substituted onto the beta carbon of the acid moiety. More recently it was found that the two aromatic rings can be linked to form an eight-membered heterocycle. In one example, treatment of potassium dichloroacetate with the dipotassium salt of bisphenol *132* affords the dibenzoxacin *133* directly, after acidification. Esterification with methanol gives the hypolipidemic agent *treloxinate (134)*.[24]



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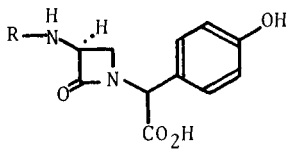
15

β-Lactam Antibiotics

Despite the enormous effort already expended during the past three decades, the β-lactam antibiotic field remains one of the most hotly competitive in the whole field of medicinal chemistry, with new entities constantly being produced to address one or more the clinical deficiencies perceived in existing drugs. Recently, some new basic skeletons have been encountered in fermentation screening programs, and this has given the field yet another burst of activity. *Cefoxitin (31)* is the first fruit of this effort. Whether the nocardicins, clavulanic acid, thienamycins, etc., will reach the marketplace is not yet clear. Meanwhile, intensive work is still being done among the older ring systems.



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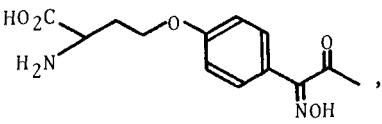

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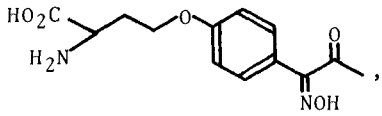

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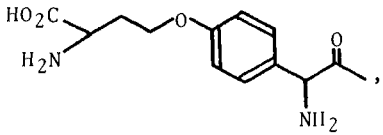

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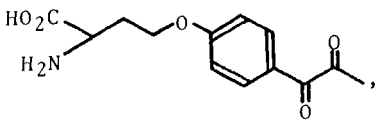

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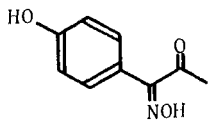
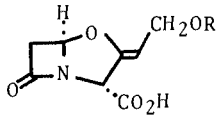
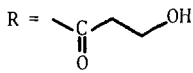


Nocardicins

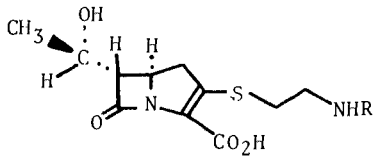


R = H

R =



Clavulanic Acids



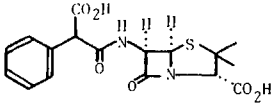
R = H,

R = $COCH_3$

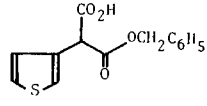
Thienamycins

1. PENICILLINS

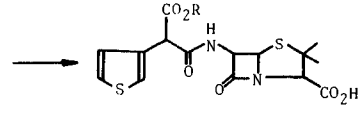
The new entries in this section are the result of manipulation of polar amide side chains to broaden the antimicrobial spectrum of the penicillins. *Carbenicillin (1)* is used in the clinic primarily because of its low toxicity and its utility in treating urinary tract infections due to susceptible *Pseudomonas* species. Its low potency, low oral activity, and susceptibility to bacterial β-lactamases make it vulnerable to replacement by agents without these deficits. One contender in this race is *ticarcillin (4)*. Its origin depended on the well-known fact (to medicinal chemists) that a divalent sulfur is often roughly equivalent to a vinyl group. One synthesis began by making the monobenzyl ester *(2)* of (3-thienyl)malonic acid, converting this to the acid chloride with $SOCl_2$, and condensing it with 6-amino-penicillanic (6APA) acid to give *3*. Hydrogenolysis (Pd/C) completed the synthesis of *ticarcillin (4)*.[1]



(1)



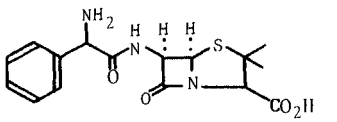
(2)



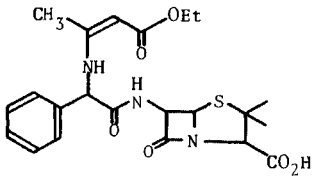
(3) R = $CH_2C_6H_5$
(4) R = H

Ampicillin (5) remains the penicillin of choice for many infections because of its oral activity and good potency against Gram-negative bacteria. A number of prodrugs have been examined in attempts to

improve upon its pharmacodynamic characteristics, and one of these is *talampicillin (8)*.[2] One synthesis involved protecting the primary amino group of *ampicillin (5)* as the enamine with ethyl acetoacetate *(6)*. This was then esterified by reaction with 3-bromophthalide *(7)*, and the enamine was carefully hydrolyzed with dilute HCl in acetonitrile to produce *talampicillin (8)*.



(5)



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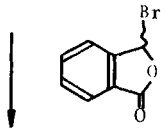

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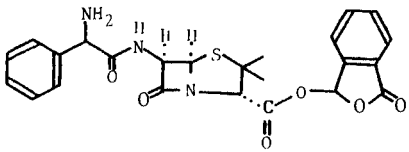

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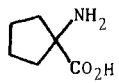
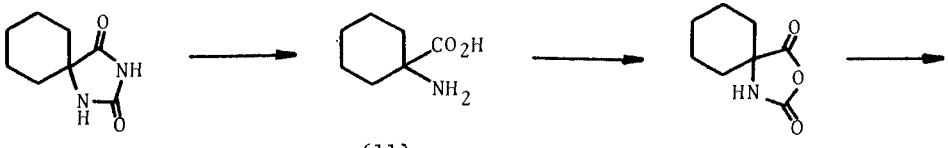


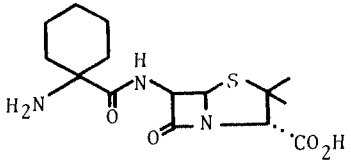
(9)

In an attempt to form orally active penicillins unrelated to ampicillin, use was made of the fact that certain spiro α-aminoacids, such as *9*, are well absorbed orally and transported like normal amino acids. Reaction of cyclohexanone with ammonium carbonate and KCN under the conditions of the Bucherer-Bergs reaction led to hydantoin *10*. On acid hydrolysis, α-amino acid *11* resulted. Treatment with phosgene

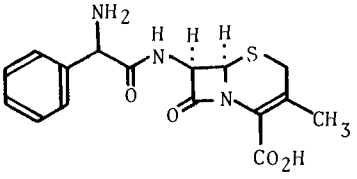
both protected the amino group and activated the carboxyl group toward amide formation (as *12*) and reaction with 6-aminopenicillanic acid gave *cyclacillin (13)*.[3] Interestingly, this artifice



(10) (11) (12)



(13)



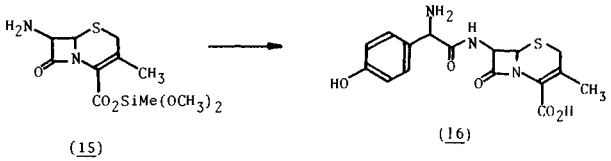
(14)

seems to have worked, since *cyclacillin* is more active in vivo than its in vitro spectrum suggests would be likely.

2. CEPHALOSPORINS

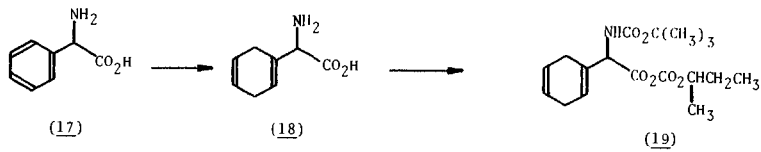
The oral activity and clinical acceptance of *cephalexin (14)* has led to the appearance of a spate of similar molecules. *Cefadroxyl (16)* is an example.[4] The design of this drug would seem to have derived from the success of *amoxycillin*. The synthesis of *cefadroxyl* was accomplished by N-acylation of 7-aminodesacetyl-cephalosporanic acid (7 ADCA) after blocking the carboxy group with $(CH_3O)_2CH_3SiCl$ (to *15*). The

blocking group was removed by solvolysis with butanol to give *cefadroxyl (16)*.

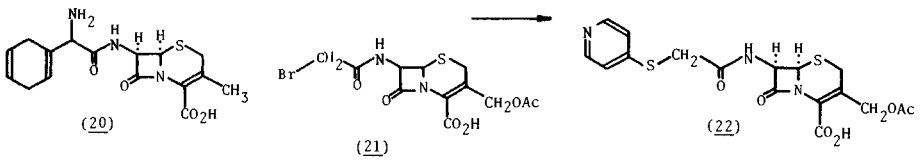


(15) (16)

Noting that 1,4-cyclohexadiene rings are nearly as planar as benzene rings but of greatly different reactivity, a cephalosporin was synthesized with such a moiety. Birch reduction of D-α-phenylglycine *(17)* led to diene *18*. This was N-protected using t-butoxycarbonyl azide and activated for amide formation via the mixed anhydride method using isobutylchloroformate to give *19*. Mixed anhydride *19* reacted readily with 2-aminodesacetoxycephalosporanic acid to give, after deblocking, *cephradine (20)*.[5]



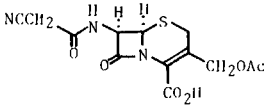
(17) (18) (19)



(20) (21) (22)

A more traditional cephalosporin analogue is *cephapirin (22)*. It was made by reacting 7-aminocephalosporanic acid with bromoacetyl chloride to give amide *21*. The halo group was displaced by 4-thiopyridine to give *22*, *cephapirin*.[6]

One of the few successful analogues in the β-lactam series with an aliphatic side chain is *cephacetrile (23)*. It was made by reacting 7-aminocephalosporanic acid with cyanoacetyl chloride in the presence of tributylamine.[7]



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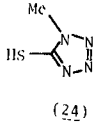

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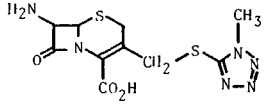
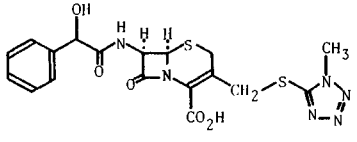
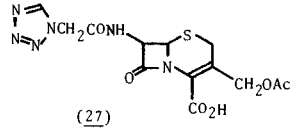


(25)

Modifications of the substituent at C_3 are conveniently accomplished using sulfur nucleophiles to displace the acetoxy moiety which is present in the fermentation products. *Cefamandole (26)* is such an agent. Reaction of 7-aminocephalosporanic acid with thiotetrazole *24* gave displacement product *25*,



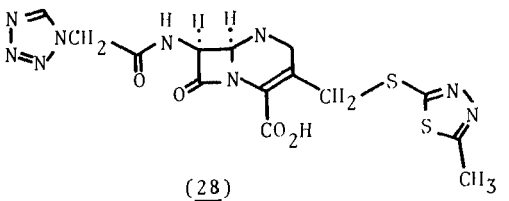
(26)



(27)

which was subsequently reacted with dichloroacetyl mandelate to put on the side chain. Deblocking during workup produced *cefamandole (26)*.[8]

Reaction of sodio 7-aminocephalosporanic acid with 1-(1H)-tetrazoylacetic acid gave intermediate *27*. Reaction of this last with 2-mercapto-5-methyl-1,3,4-thiadiazole led to the widely used parenteral cephalosporin, *cefazolin (28)*.[9]

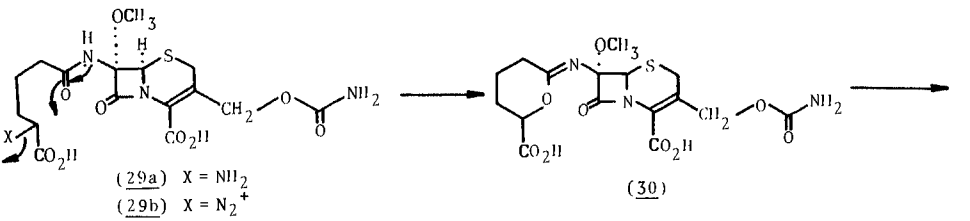


(28)

3. CEPHAMYCINS

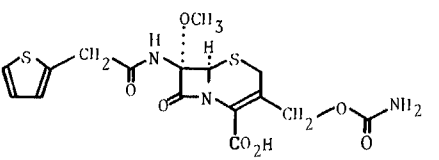
While screening for β-lactam antibiotics stable to β-lactamases, a strain of *Streptomyces lactamdurans* was found to contain several such agents which have a 6-α-methoxy group whose electronic and steric properties protect the antibiotic from enzymatic attack. *Cephamycin C (29a)*, one of these substances, is not of commercial value, but side chain exchange has led to much more potent materials. Of the various ways of effecting this transformation, one of the more direct is to react cephamycin C with nitrous acid so that the aliphatic diazo product *(29b)* decomposes by secondary amide participation giving cyclic iminoether *30*. The imino ether moiety solvolyzes more readily than the β-lactam to produce 7-aminocephamycinic

acid, which was acylated in the usual way to produce *cefoxitin (31)* with broad spectrum activity and excellent resistance to bacterial degradation.[10]



(29a) X = NH_2
(29b) X = N_2^+

(30)



(31)

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16

Miscellaneous Fused Heterocycles

As may be apparent now, compounds in a given structural class are often associated with good biological activity. This means that on the operational level, a good many examples of those structures will be available that have been assigned generic names. In terms of this book, those compounds will merit a chapter or even a section. Thus, for example, although β-lactams represent a relatively narrow structural descriptor, activity in this class is sufficiently promising so that a full chapter is needed to fully cover those compounds. There does, however, exist a sizeable group of compounds that are not so readily categorized, since relatively few examples of each type have been assigned generic names. The medicinal agents discussed below are miscellaneous in that there is no readily apparent unifying thread in terms

of either structure or biological activity by which to group them, other than in a miscellaneous way.

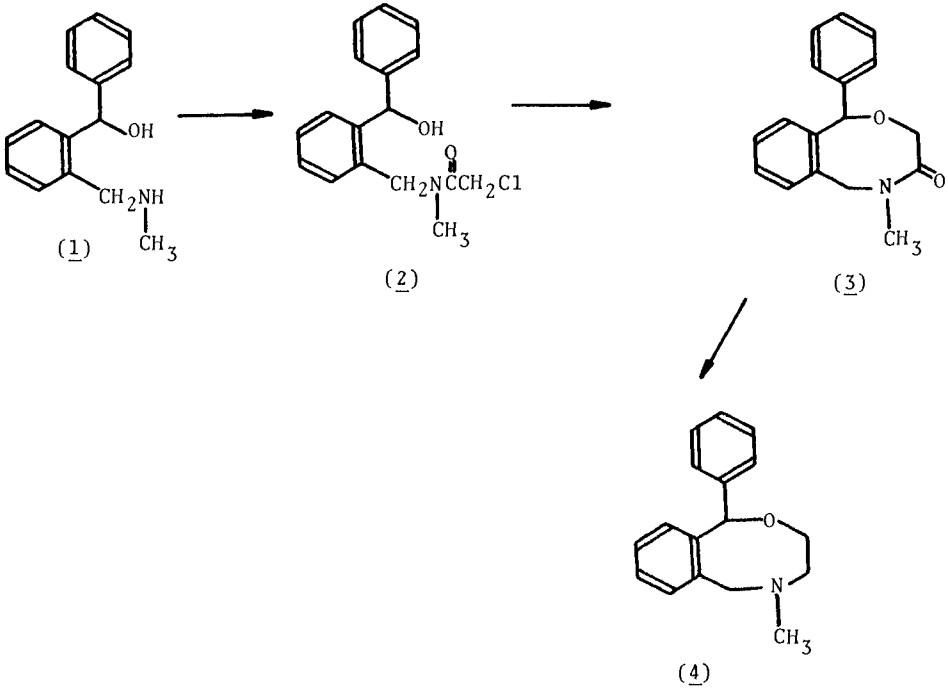
1. Compounds with Two Fused Rings

Discovery in medicinal chemistry is intimately dependent on available animal test systems. Except for certain infectious diseases, it is rare to find a preexisting animal model for the human disease for which drugs are being sought. For example, animals do not develop atherosclerosis spontaneously. As a result, pharmacologists exercise great ingenuity in devising animal test systems intended to be relevant to diseases. Such assays, particularly in the area of agents acting on the CNS, are often quite indirect in that the connection to the human disease may be somewhat circuitous. Those tests are usually validated as far as possible with test results from drugs known to be active in the human. There thus exists the distinct possibility that an animal test will preordain the discovery of compounds that act by a closely similar mechanism, and thus have the same side effects, as those already on the market. This is perhaps best illustrated in the field of the centrally acting analgesics. The animal tests in this area have proven very reliable in detecting compounds that show analgesic activity in man; at the same time, all drugs discovered by these assays have at least some of the side effects of the prototype, *morphine*, to a greater or lesser degree. For this reason, therapeutic breakthroughs are relatively rare and celebrated events.

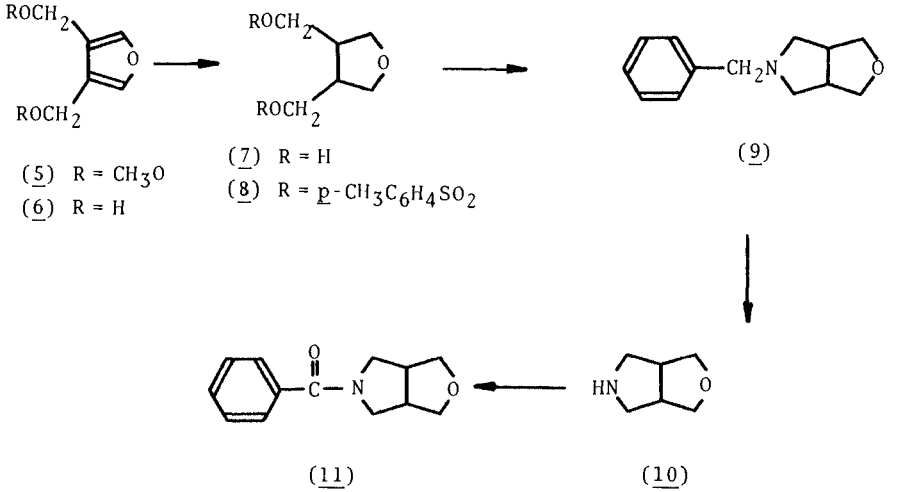
The discovery of an analgesic that acts by a presumably nonopiate pathway, in fact, resulted from a clinical trial of the compound in question, *nefopam (4)*, in man. It might be noted that this trial was designed to study the drug as a muscle relaxant. It should also be noted that *nefopam* fails to show activity in many of the tests used to detect compounds with central analgesic activity. At the present time, there does not seem to exist any solution to that conundrum, short of the clearly unacceptable alternative of using man as the test animal. The huge expense and the bureaucratic requirements needed before embarking on a clinical trial in the late 1970's serve to make this kind of discovery less common and inclines the field more and more to modest advances in modulating potency or side effects. Does the old saw, "drugs are discovered in the clinic," still have relevance? Time will tell.

Preparation of *nefopam* starts with the acylation of aminobenzhydrol *1* (obtainable by reduction of the corresponding benzoylbenzamide) with chloroacetyl chloride; treatment of the chloroamide *(2)* with potassium tertiary butoxide results in internal alkylation to give the eight-membered ring *(3)*. Reduction of the lactam function with lithium aluminum hydride gives the amine and, thus, *nefopam (4)*.[1]

Although most nonsteroidal antiinflammatory agents depend on the presence of an acidic proton for activity, examples of nonacidic drugs are scattered among the various structural classes. A furanopyrrole,



octazamide (11), represents yet another structure that has been found to act as a peripheral analgesic/antiinflammatory agent. Hydrolysis of substituted furan *5* gives the corresponding diol *(6)*, which is then reduced catalytically to afford the tetrahydrofuran *7*. Both the method of reduction and the subsequent cyclization suggest that the product has the *cis* configuration. Reaction of *7* with tosyl chloride leads to ditosylate *8;* use of that intermediate to bisalkylate benzylamine affords the bicyclic heterocyclic system *(9)*. Debenzylation *(10)* followed by acylation of the resulting secondary amine with benzoyl chloride affords finally *octazamide (11)*.[2]



(5) R = CH_3O
(6) R = H

(7) R = H
(8) R = p-$CH_3C_6H_4SO_2$

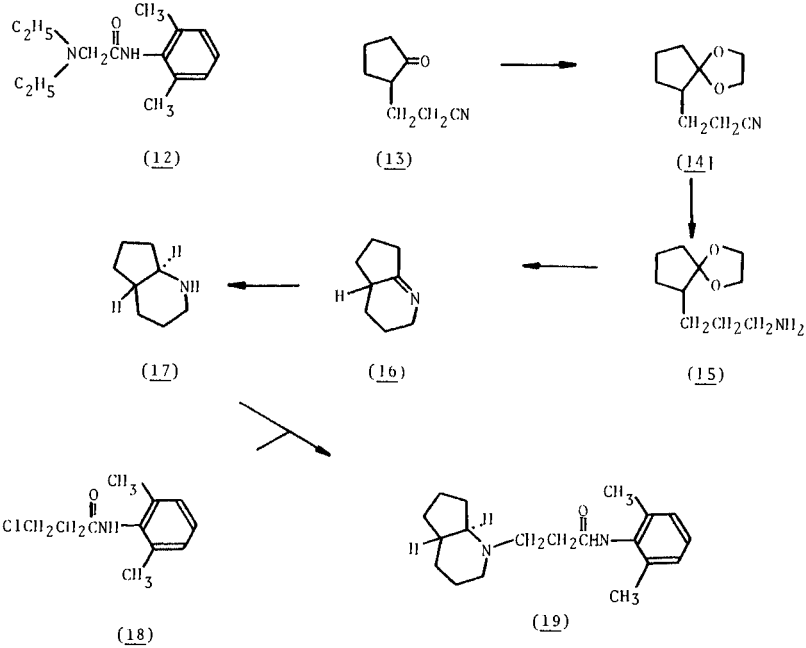
(9)

(11)

(10)

One of the first pharmacological classes to be studied by medicinal chemists was local anesthetics. Many of the guiding principles which are used to this day, for example, molecular dissection, side chain substitution and inversion, and the like, were first developed in the course of those early researches. The most tangible fruit of that work was the development of a host of local anesthetic drugs; since there is a limited demand for such agents, the field lay quiescent for a good many years. The adventitious discovery that the local anesthetic agent *lidocaine* *(12)* showed antiarrhythmic activity in man has lent impetus to renewed interest in local anesthetics for new application. In particular, compounds are being sought which escape the main shortcoming of *lidocaine*; that drug is active for clinical purposes by intravenous administration only.

Preparation of one of these newer local anesthetic/antiarrhythmic agents, *rodocaine (19)*, starts with the synthesis of an octahydropyrindene. Conjugate addition of the enolate from cyclopentanone to acrylonitrile gives the cyanoketone *13*. The carbonyl group is then protected as its ethylene ketal *(14)*, and the nitrile is reduced to the corresponding primary amine *(15)*. Deketalization in dilute acid affords a transient aminoketone, which spontaneously cyclizes to the imine *16*. Dissolving metal reduction (sodium in ethanol) affords the *trans*-fused bicyclo *17*.[3] (Catalytic reduction of *16* affords the *cis* isomer.



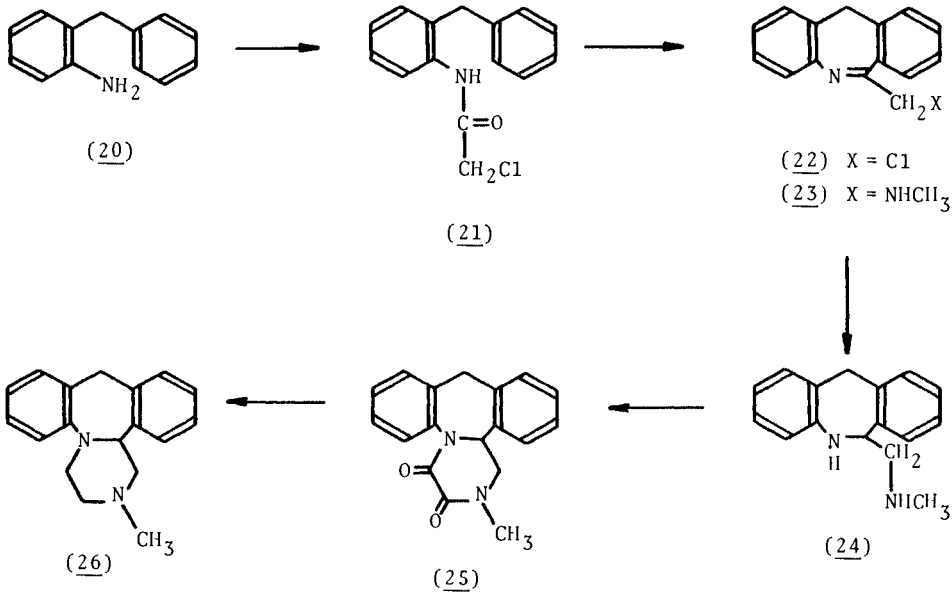
It is unexpected that the presumably thermodynamically controlled metal in alcohol reduction gives the

trans compounds; the *cis* isomer is usually the more stable in the analogous all-carbon hydrindane system.) The amide portion of the molecule *(18)* is assembled by acylation of 2,6-dimethylaniline with 3-chloropropionyl chloride. Alkylation of *17* with chloroamide *18* affords *rodocaine (19).*[4]

2. Compounds with Three or More Fused Rings

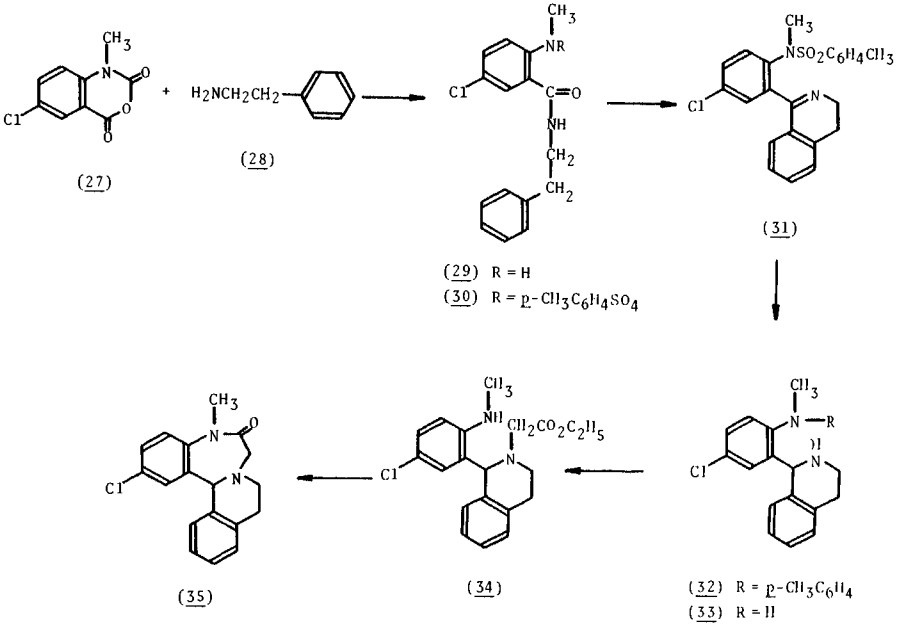
Preparation of rigid analogues of medicinal agents sometimes leads to compounds with greatly increased activity. Briefly, the success of a rigid analogue depends on locking a previously freely rotating side chain or flexible molecule into a conformation that will give a better fit with some putative receptor. Application of this principle to the tricyclic antidepressants does indeed afford a compound, *mianserin (26),* which retains the activity of the parent molecule. Preparation of *26* begins with acylation of the benzylaniline *20* (available from the benzophenone) with chloroacetyl chloride to give amide *21.* Treatment with a mixture of phosphorus oxychloride and polyphosphoric acid leads to cyclodehydration of the amide to the corresponding tricyclic intermediate *22.* Displacement of the now allylic chloride by means of methylamine gives the amine *23;* this is then reduced to the diamine *24* with sodium borohydride. Construction of the last ring is accomplished by formation of the cyclic diamide *(25)* from *24* by ester interchange with diethyl oxalate. Reduction of this α-diamide with diborane proceeds with no apparent difficulty to

the diamine, the antidepressant compound *mianserin (26)*.[5]

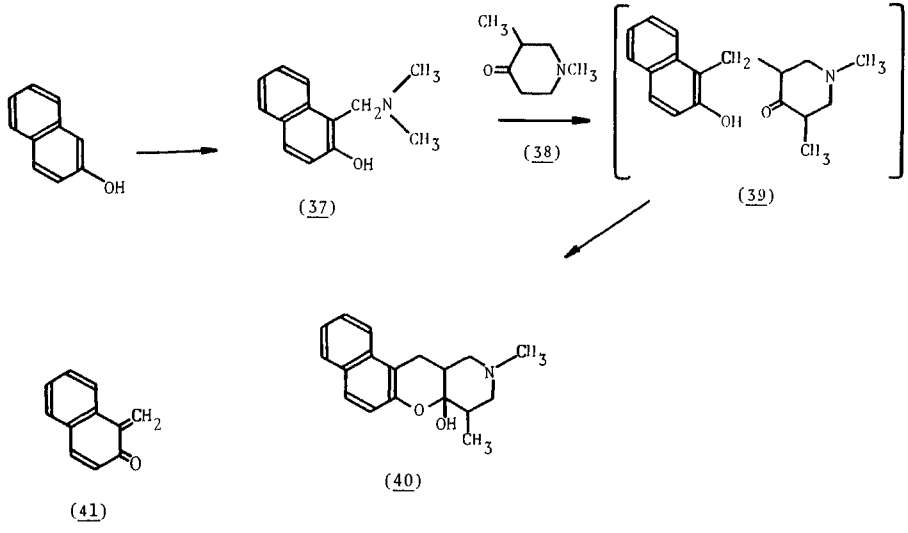


Application of the same type of reasoning to an anxiolytic benzodiazepine results in a rigid analogue, *clazolam (35)*, which also retains the activity of the parent molecule, *diazepam*. It should be noted that in this case it is a benzene ring rather than a side chain that is conformationally restricted. Condensation of isatoic anhydride *27* with 2-phenethylamine *(28)* results in net acylation of the aliphatic amine. The anhydride is in essence both an activated carboxyl derivative and a means of protecting the aniline nitrogen against self-condensation reactions. The secondary amine in *29* is then converted to the tosylamide to protect it during subsequent steps. Treatment of the amide *30* with phosphorus pentoxide results in

a Bischler-Napieralski cyclization to the dihydroisoquinoline *31*. The protecting group is then removed by hydrolysis in strong acid *(32)*, and the double bond is reduced catalytically. Alkylation of the diamine *33* with ethyl bromoacetate proceeds as expected at the more basic aliphatic amine to give the glycinate *34*. Base-catalyzed ring closure of the aminoester serves to close the diazepine ring; there is thus obtained the anxiolytic agent *clazolam (35)*.[6]



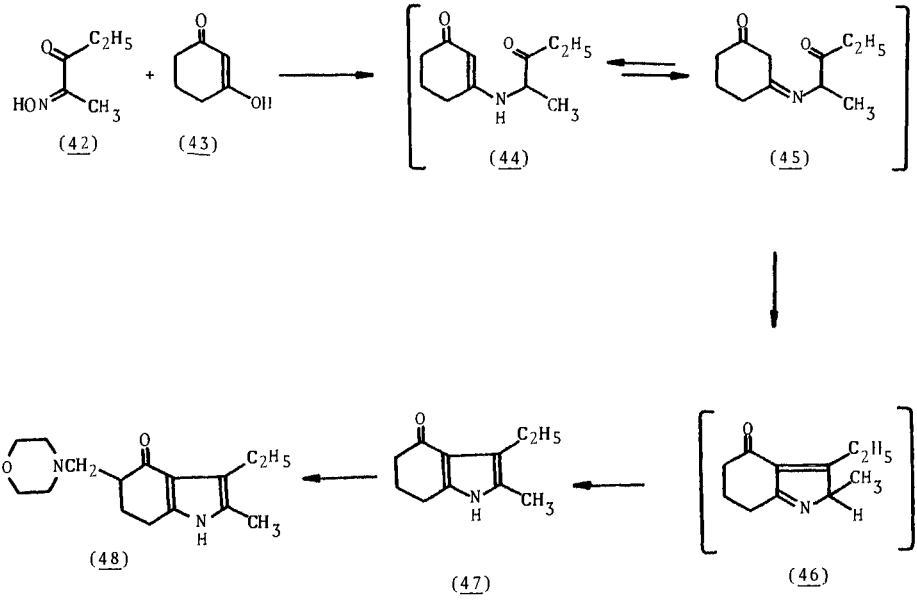
When the pharmacophoric group in a rigid compound is fused in some position remote from that in the nonrigid compounds, it is likely that the agent is active by some different biological mechanism. Thus, although *naranol (40)* is formally related to the tricyclic compounds, the basic center is in a quite different position from that in the majority of tricyclic CNS agents. Synthesis of *40* is begun by Mannich reaction of 2-naphthol with formaldehyde and dimethylamine to afford the adduct *37*. Reaction of this aminophenol with the substituted piperidone *38* affords the tetracyclic product *40* in a single step.



This seemingly complex transformation can be rationalized by assuming, as the first step, formation of an enolate of ketone *38*. Displacement of dimethylamine on *37* by the enolate will give the phenolketone *39*. Although both regioisomers of the enolate may in fact be formed, the observed product is from reaction of the less hindered enol. (An alternate sequence involves loss of dimethylamine from *37* to give quinonemethide *41;* conjugate addition of the same enolate will give *39.*) Simple internal hemiketal formation gives the product *40, naranol,*[7] of unspecified stereochemistry.

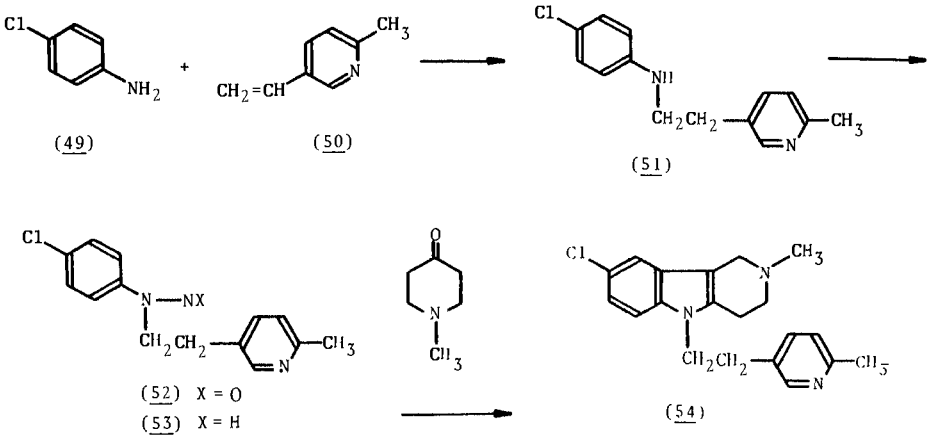
Although most available CNS agents are quite effective, they are not without side effects. There is, thus, some impetus for a search for novel structures in the hope that these will be better than available drugs. During this search a derivative of a partly reduced indole, *molindone (48),* has been reported to have sedative and tranquilizing activity. Condensation of oximinoketone *42* (from nitrosation of 3-pentanone), with cyclohexane-1,3-dione in the presence of zinc and acetic acid leads directly to the indole derivative *47*. The transformation may be rationalized by assuming as the first step, reduction of *42* to the corresponding α-aminoketone. Conjugate addition of the amine to *43* followed by elimination of hydroxide (as water) would give ene-aminoketone *44*. This may be assumed to be in tautomeric equilibrium with intermediate *45*. Aldol condensation of the side chain carbonyl group with the doubly activated ring methylene would then result in cyclization to

pyrrole *46;* simple tautomeric transformation would then give the observed product. Mannich reaction of *47* with formaldehyde and morpholine gives the tranquilizer *molindone (48).*[8]

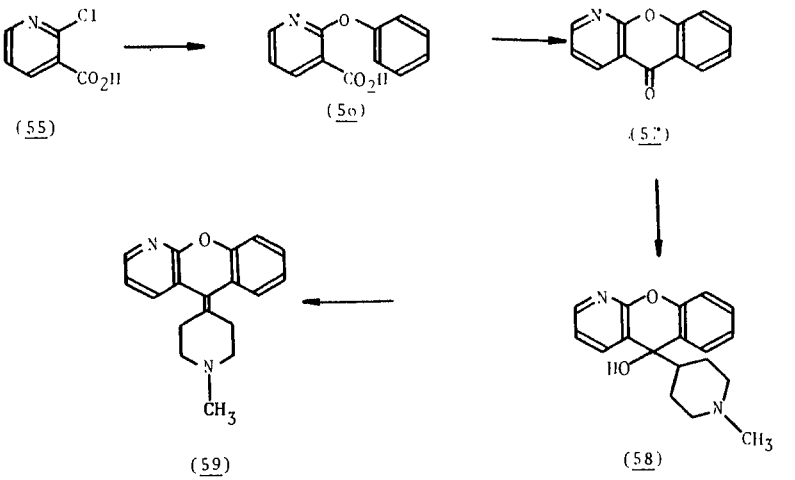


Tricyclic antihistamines as a rule carry aliphatic nitrogen as a substituent on a side chain attached to the central ring; the side chain nitrogen may be part of a heteroaromatic ring. Conjugate addition of p-chloroaniline *(49)* to the substituted vinylpyridine *50* gives the alkylated aniline *51.* Treatment of that intermediate with nitrous acid leads to N-nitroso intermediate *52* which is then reduced to the hydrazine *(53).* Reaction of *53* with N-methyl-4-piperidone

under the conditions of the Fischer indole synthesis affords *dorastine (54)*,[9] an antihistamine.

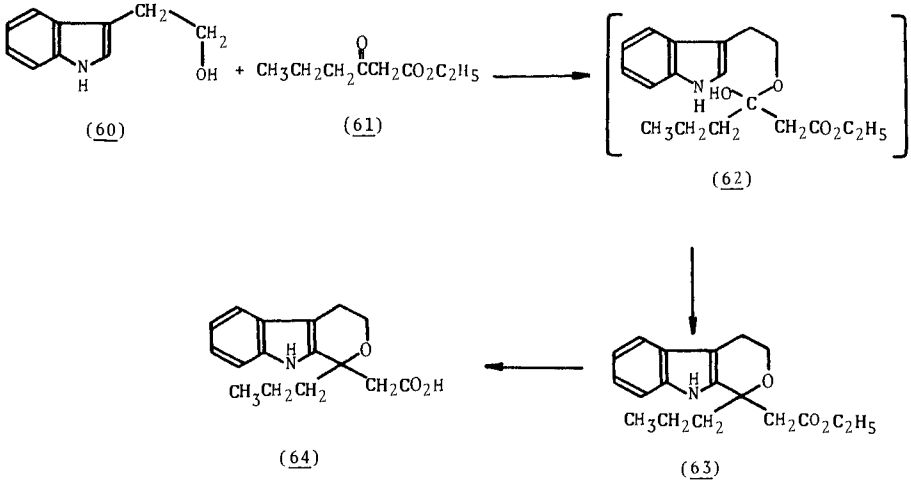


Azanator (59) represents a more classical antihistaminic structure, since the more basic nitrogen in this case occurs in the side chain. Preparation



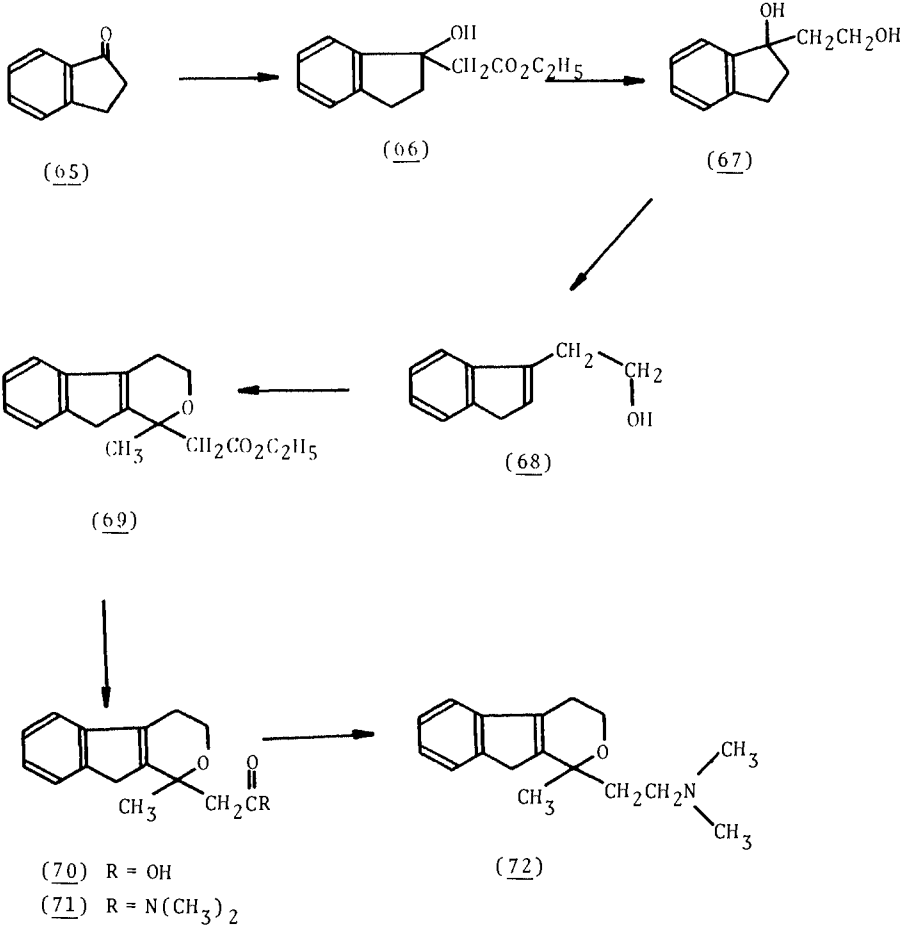
of this compound starts with aromatic nucleophilic displacement on pyridine *55* (see Chapter 14) with phenoxide anion. Friedel-Crafts ring closure of the product *(56)* by means of polyphosphoric acid leads to the azaxanthone *57*. This is then converted to the final product by condensation with the Grignard reagent from N-methyl-4-chloropiperidine *(58)*, followed by dehydration to yield *59*.[10]

As noted previously, a wide variety of aromatic systems serve as nuclei for arylacetic acid anti-inflammatory agents. It is thus to be expected that fused heterocycles can also serve the same function. Synthesis of one such agent *(64)* begins with condensation of indole-3-ethanol *(60)* with ethyl 3-oxocaproate *(61)* in the presence of tosic acid, leading directly to the pyranoindole *63*. The reaction may be rationalized by assuming formation of hemiketal *62*, as the first step. Cyclization of the carbonium ion



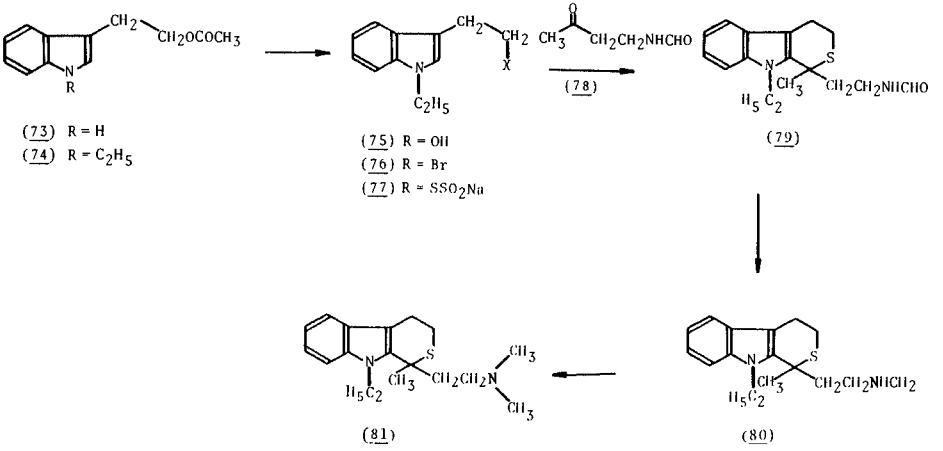
(from loss of hydroxyl) into the nucleophilic indole 2-position will give the observed product *(63)*. Saponification of the ester gives the antiinflammatory agent *prodolic acid (64)*.[11]

A closely related compound, *pirandamine (72)*, bearing a basic rather than an acidic side chain and having a methylene in place of the indole nitrogen,



interestingly exhibits antidepressant activity. Basically, the same synthetic scheme is used for the preparation of this analogue as for compound *64* above. Condensation of 1-indanone *(65)* with ethyl bromoacetate and zinc affords Reformatski product *66;* then, reduction with lithium aluminum hydride gives diol *67.* Dehydration with sulfuric acid gives the indene ethanol *68.* Acid catalyzed condensation of *68* with ethyl acetoacetate then gives the fused tetrahydropyran derivative *69,* no doubt by a scheme quite analogous to that above. The ester is then saponified to the corresponding acid *(70),* which is then converted to the dimethylamide *(71).* Reduction with lithium aluminum hydride completes the synthesis of the antidepressant agent *pirandamine (72).*[12]

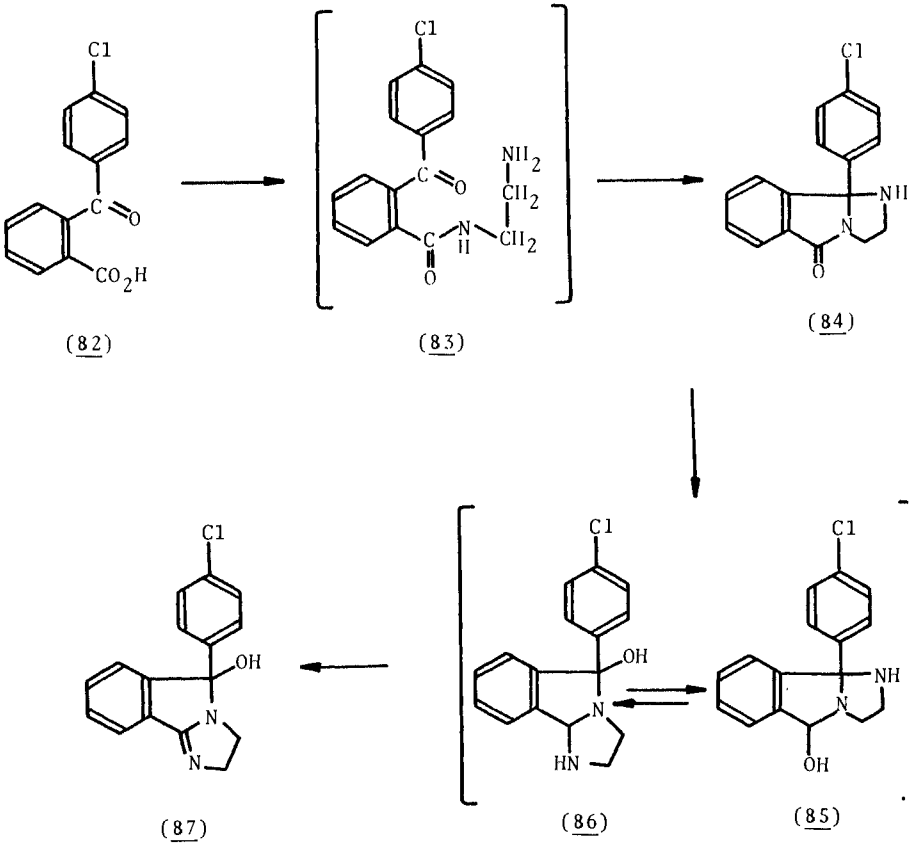
Antidepressant activity is retained in *tandamine (80),* an analogue in which the indole ring is restored, the basic side chain is retained, and the oxygen heterocycle is replaced by the corresponding sulfur-containing ring. Acetylation of indole ethanol *60* affords the corresponding acetate *73;* the indole nitrogen is then alkylated by means of ethyl iodide and sodium hydride *(74).* Conversion of the side chain oxygen to sulfur is accomplished by first treating the alcohol (from hydrolysis of the acetate *(75)* with phosphorus tribromide to give *76;* displacement of halogen with thiosulfate anion then affords the covalent thiosulfate *(77).* In a departure from the synthetic scheme used above, the basic side chain is introduced directly. Thus, reaction of thiosulfate *77* with amidoketone *78* in the presence of



boron trifluoride leads directly to the fused heterocycle *(79)*. Reduction of the formamide by means of lithium aluminum hydride then affords monomethyl derivative *80;* N-methylation of that intermediate completes the synthesis of the antidepressant agent *tandamine (81)*.[13,14]

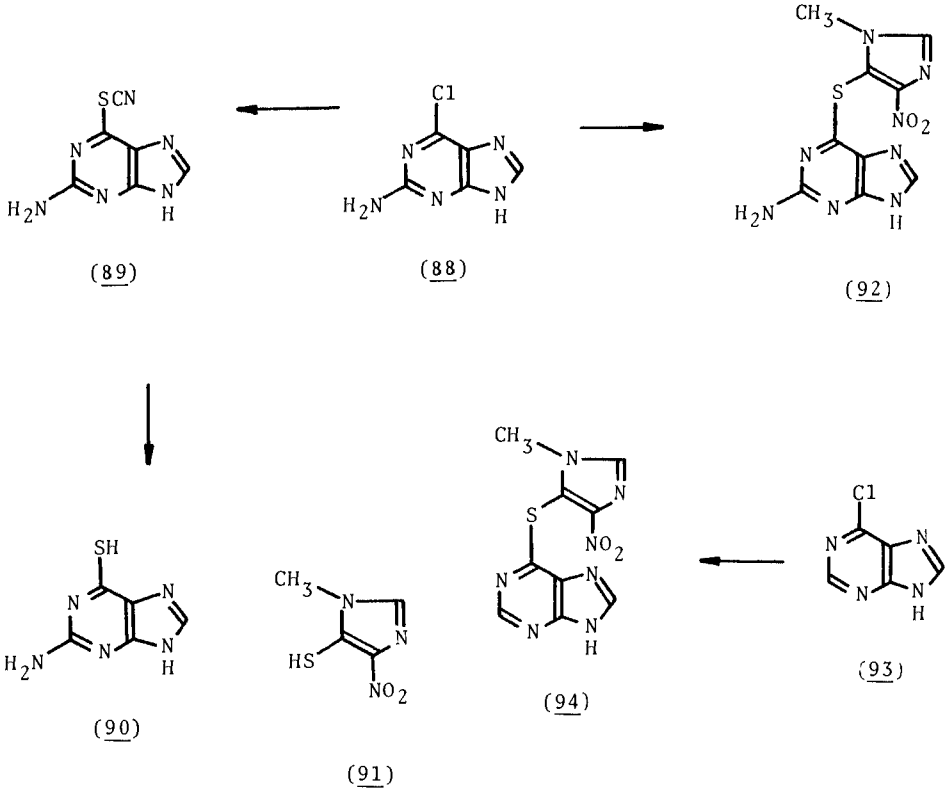
A rather complex fused isoindoline *(87)* has been found to show good anorectic activity. This substance differs from other anorectic agents by not being a β-phenethylamine analogue. Preparation of this compound starts by reaction of a substituted benzoylbenzoic acid *(82)* with ethylene diamine. The product *(84)* can be rationalized as being the aminal from the initially obtained monoamide *83*. This is then subjected to reduction with lithium aluminum hydride

and--without isolation--air oxidation. Reduction probably proceeds to the mixed aminal/carbinolamine *85*; such a product would be expected to be in equilibrium with the alternate aminal *86*. The latter would be expected to predominate due to the greater stability of aldehyde aminals over the corresponding ketone derivatives. Air oxidation of the tetrahydroimidazole to the imidazoline will then remove *86* from the equilibrium. There is thus obtained the anorectic agent *mazindol (87)*.[15]



3. Purines and Related Heterocycles

Considerable research has been devoted to preparation of modified purines in the expectation that such compounds could act as antagonists to, or possibly false substrates for, those involved in normal metabolic processes. It is surprising to note the relatively small number of such compounds that have found clinical use.



(89) (88) (92)

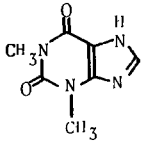
(90) (91) (94) (93)

Thioguanine is one of the most familiar of the medicinal purine analogues. This compound acts as a false guanine and has found a role as an antineoplastic agent by reason of its resulting activity as a metabolic inhibitor. The compound is obtained most simply by displacement of halogen from 6-chloroguanine *(88)* with thiocyanate anion. Hydrolysis of the product *(89)* yields *thioguanine (90).*[16]

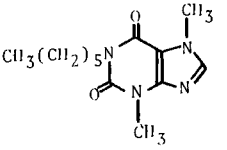
In much the same vein, displacement of chlorine from *88* with the sodium salt of imididazolethiol 91 affords the antineoplastic agent *thiampirine (92).*[17] The same reaction starting with purine 93 gives the immunosupressant agent *azathioprine (94).*[18]

Contraction and relaxation of smooth muscle is known to be mediated by way of the cyclic nucleotides. In brief, increase in intracellular levels of cyclic adenosine monophosphate (cAMP) leads to relaxation of smooth muscle. In the normal course of events, cAMP is hydrolyzed to its inactive form by the enzyme phosphodiesterase (PDE). Drugs that inhibit the action of that enzyme--PDE inhibitors--will tend to promote smooth muscle relaxation. One such drug, *theophylline (95)* has found extensive use in treatment of asthma based on its ability to relax bronchial smooth muscle. A search for more lipophilic analogues of theophylline led to a compound, the hexyl analogue *96* of theobromine, which seemed to have greater selectivity for vascular smooth muscle. Further biological investigation revealed that the active agent was in fact the metabolite *101* resulting from ω-1-oxidation of the aliphatic side chain.

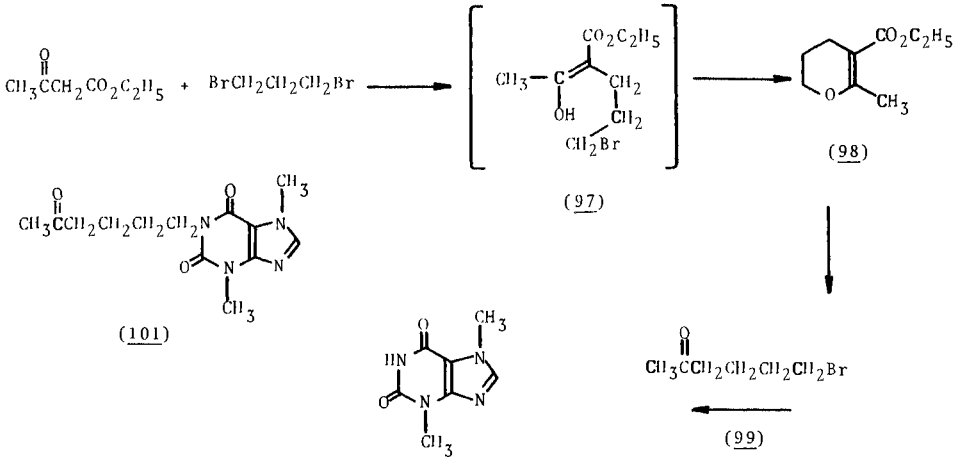
Preparation of the requisite side chain starts by alkylation of ethyl acetoacetate with 1,3-dibromopentane; the initially formed bromoketone (shown as the enol *97*) undergoes O-alkylation under the reaction conditions to give the dihydropyran *98*. Reaction of that masked hydroxy ketone derivative with hydrogen



(95)



(96)



(97)

(98)

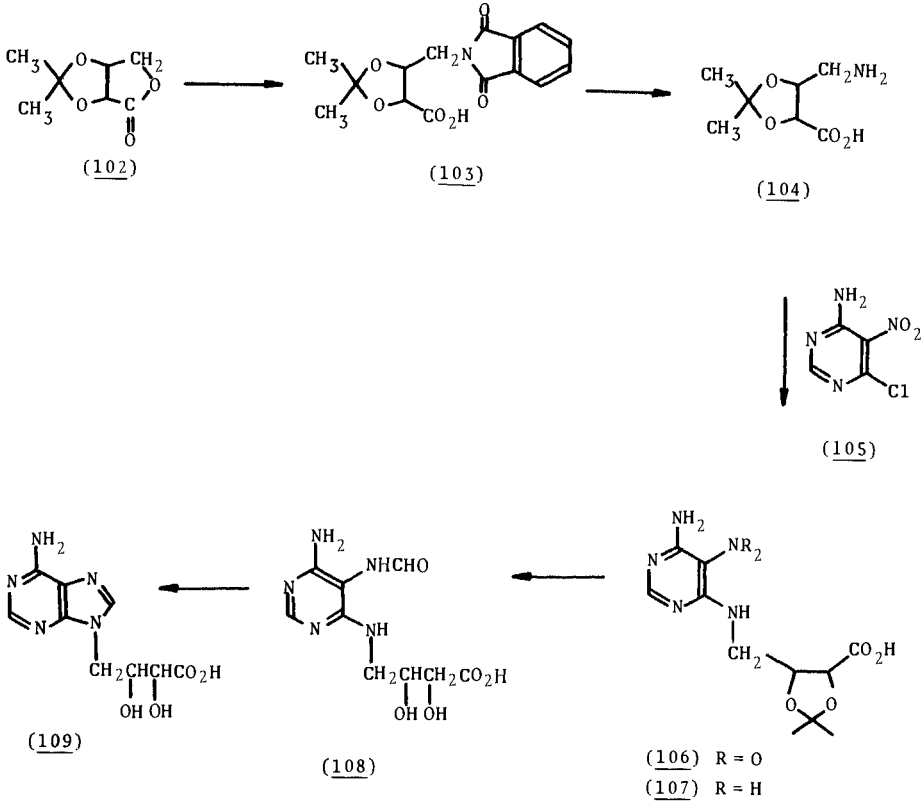
(99)

(100)

(101)

bromide affords the requisite bromoketone *(99)*; reaction conditions are apparently sufficient to

insure decarbethoxylation of the ketoester intermediate. Alkylation of theobromine *(100)* with *99* affords the vasodilator, *pentoxifylline (101)*.[18]

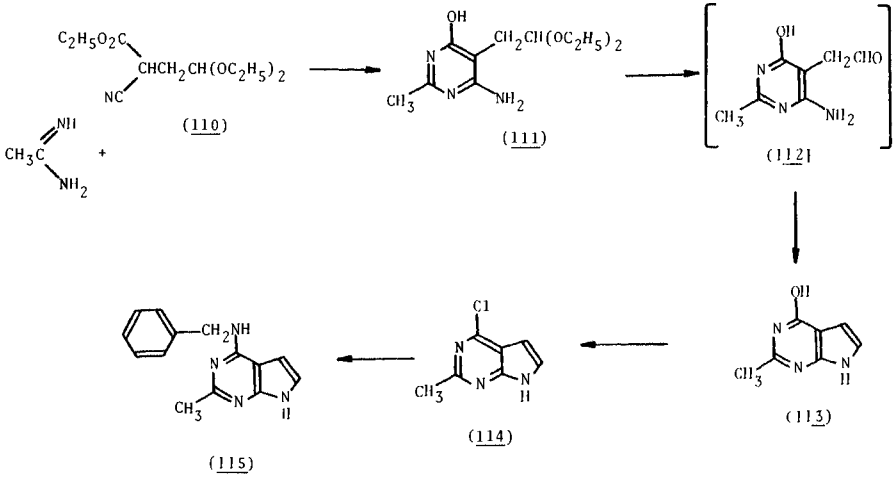


Pharmacognosy, the study of plant products with medicinal properties, has contributed many structural leads to drug development. Although findings have in recent years been less frequent this discipline

continues to uncover unusual structure-activity combinations. In one example, methanol extracts of the Japanese mushroom *Lentinus edodes* Sing. were found to have hypolipidemic activity. The active compound *eritadenine (109)* proved to be a purine alkylated with an oxidized sugar fragment; its synthesis can be accomplished as follows. Ring opening of the protected lactone *(102)*, derived from erythrose, with sodium phthalimide gives the acid *103;* hydrazinolysis then leads to the amino acid *104*. Displacement of chlorine in pyrimidine *105* by the amine function on *104* serves to attach the future imidazole nitrogen and the sugar-derived side chain *106*. The nitro group is then reduced by catalytic hydrogenation *(107)*, the resulting primary amine is the most basic, and is selectively formylated with formic acid. These strongly acidic conditions serve to remove the acetonide protecting group as well *(108)*. Treatment with sodium hydroxide then serves to close the imidazole ring, forming *eritadenine (109)*.[19]

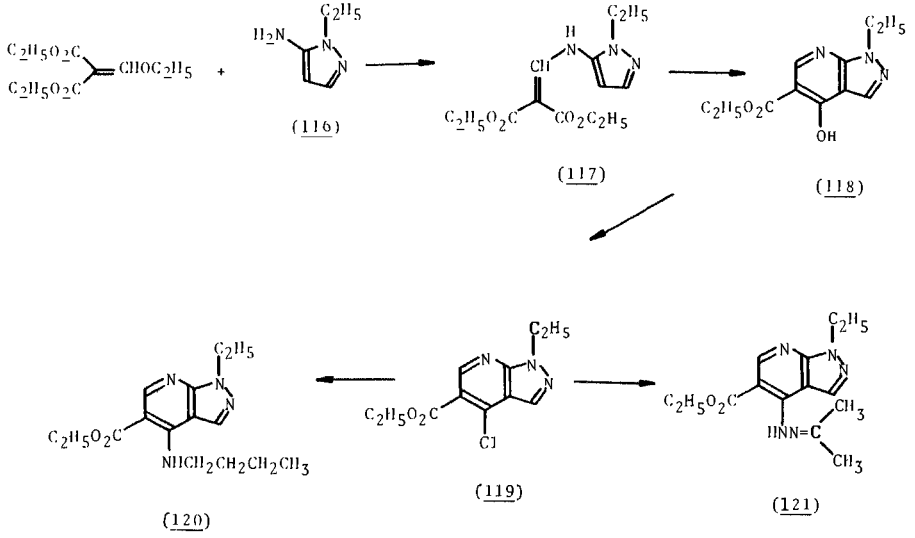
The several compounds below *(115, 120, 121)* are related to purines only in that they contain some three nitrogen atoms formally distributed among an indene nucleus. Despite the varied structures, all three analogues share activity mediated through the CNS. In one of the classical methods for construction of a pyrimidine ring, synthesis of *115* begins with condensation of the substituted cyanoacetate *110* with acetamidine to give the corresponding pyrimidone *(111)*, shown as the enol. Treatment with acid probably results initially in hydrolysis of the acetal function

to give the transient aminoaldehyde *112*. This then cyclizes to the corresponding imine under the reaction conditions, and this interemdiate tautomerizes to the observed pyrrolopyrimidine *113*. Reaction with phosphorus oxychloride serves to replace the hydroxyl group by chlorine *(114)*. Displacement of halogen with benzylamine gives the muscle relaxant *rolodine (115)*.[20]



Condensation of aminopyrazole *116* with ethoxymethylene malonic ester gives the product of addition-elimination *(117)*, which is then cyclized to the piperidone by heating in diphenyl ether. The product tautomerizes spontaneously to the hydroxypyridine *118*. The hydroxyl group is then converted to the chloro derivative by means of phosphorus oxychloride *(119)*. Displacement of halogen by n-butylamine gives

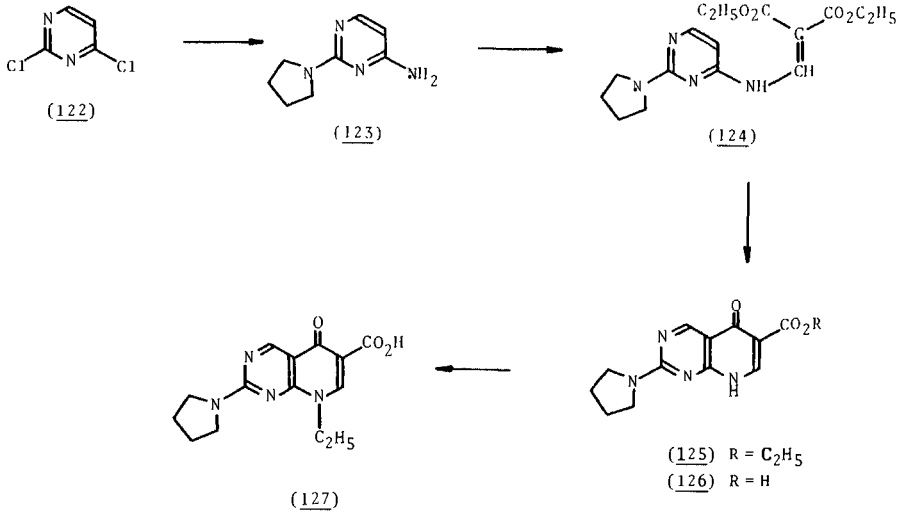
the antidepressant compound *cartazolate (120)*.[21] Replacement of halogen by the basic nitrogen of acetone hydrazone affords the antidepressant *etazolate (121)*.[21]



4. Polyaza Fused Heterocycles

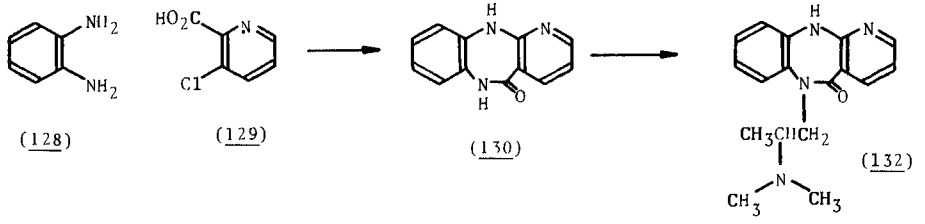
As noted earlier (see Chapter 12), considerable latitude exists in the *nalidixic acid* type antibacterial agents as to the exact nature of the two heterocyclic rings. The minimum requirement for activity seems to reside in a fused enaminoketone carboxylate function. (Even so, an additional nitrogen atom may be interposed in that function, viz. *cinoxacin*.) Consistent with this, it is interesting that inclusion of an additional nitrogen atom in the pyridino ring also gives a molecule *(127)* that shows

antibacterial activity. Synthesis of this agent begins with successive displacement reactions on 2,6-dichloropyrimidine *(122)* with pyrrolidine and then ammonia, leading to the diaminopyrimidine *123*. The rest of the synthesis follows the usual pattern. Condensation of *123* with ethoxymethylenemalonate gives the substituted malonate *124*. Thermal cyclization serves to form the fused pyridone ring *(125)*; saponification of the ester with base then gives the corresponding acid *(126)*. Alkylation of the pyridone nitrogen with diethyl sulfate completes the synthesis of *piromidic acid (127)*.[22]

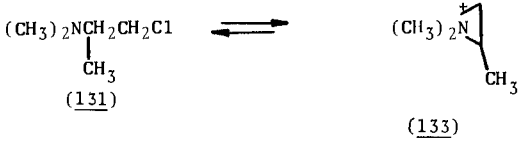


Replacement of methine by nitrogen, i.e., replacement of a phenyl moiety by pyridine, is consistent with biological activity in quite a few structural-

biological classes (see Chapter 9). This retention of activity in the face of an interchange of aromatic rings is well illustrated in the case of the acyclic and tricyclic antihistamines. It is of note that the same interchange in at least one tricyclic antidepressant drug (*dibenzepin*, see Chapter 14), affords



(128) (129) (130) (132)



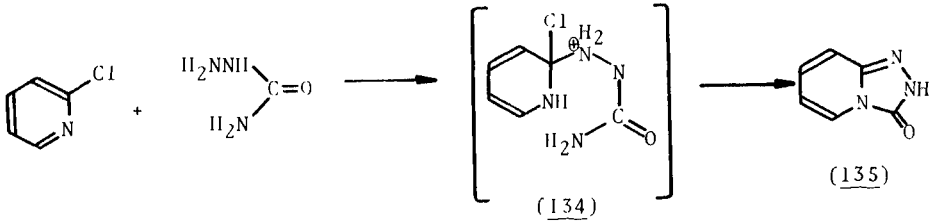
(131) (133)

an analogue that retains the CNS profile of the parent compound. Another centrally acting tricyclic agent bearing a pyridino moiety *(132)* is prepared as follows. Condensation of phenylenediamine *(128)* with 2-chloronicotinic acid *(129)* leads directly to the tricyclic lactam *130*. Although the reaction obviously includes amide formation and nucleophilic aromatic displacement of chlorine, the order of these steps is

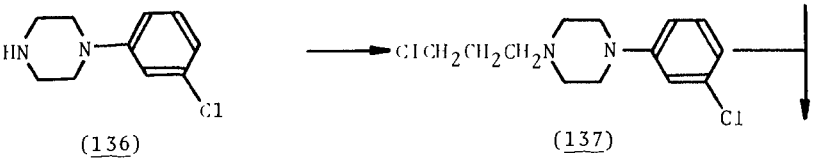
not known. Alkylation of the anion obtained from treatment of *130* with the chloroethylamine *131* affords the antidepressant compound *propizepine (132).*[23] The last step in this sequence is less straightforward than it might seem. There is considerable evidence that such alkylations often proceed by way of the aziridinium ion *(133).* It will be appreciated that attack of the anion at the secondary or tertiary carbon of the aziridinium ring will lead to different products. Extensive investigation of this problem[24] has established that the product from attack at secondary carbon usually predominates. This is, of course, the same compound that would be formed by direct displacement of halogen without involvement of the aziridnium intermediate *133.*

Two rather broad structural classes account for the large majority of drugs that have proven useful in the clinic for treating depression. Each of these has associated with it some clearly recognized side effects: the monoamine oxidase inhibitors, most commonly derivatives of hydrazine, tend to have undesirable effects on blood pressure; the tricyclic compounds on the other hand may cause undesirable changes in the heart. Considerable effort has thus been expended toward the development of antidepressants that fall outside those structural classes. An unstated assumption in this work is the belief that very different structures will be associated with a novel mechanism of action and a different set of ancillary activities. One such compound, *trazodone*

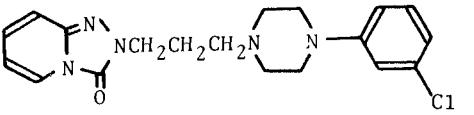
(138), has in fact shown clinically useful antidepressant activity without the typical side effects of the classical drugs. In a convergent synthesis, reaction of 2-chloropyridine with semicarbazide in the presence of a catalytic amount of acid affords the fused triazole *135*. The reaction may be rationalized by assuming addition of semicarbazide to the protonated atom of chloropyridine to give intermediate *134*. (Although semicarbazide is a stronger base, protonation of that compound does not lead to any reaction.) Elimination of hydrogen chloride



(134) (135)



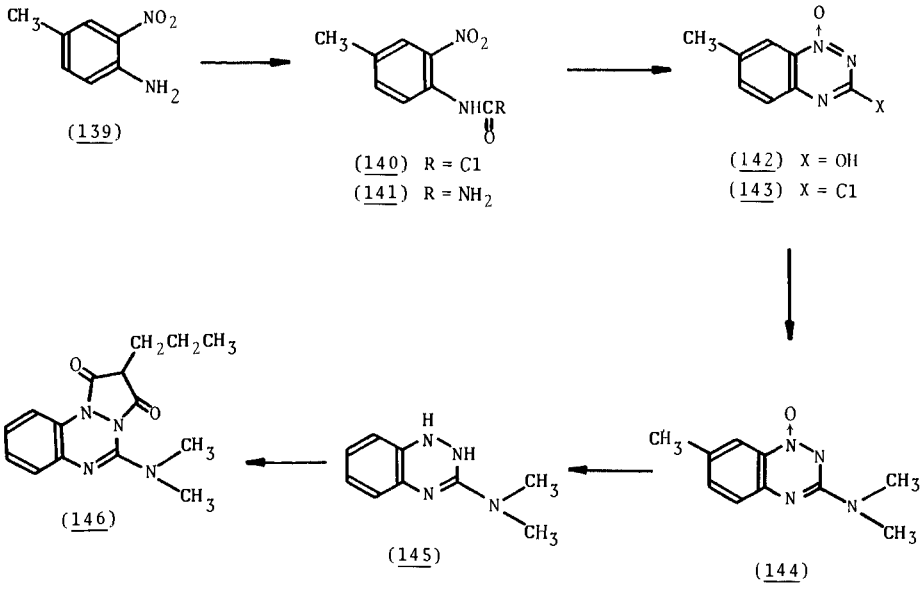
(136) (137)



(138)

restores aromaticity, and leads to attack by the pyridine nitrogen on the semicarbazide carbonyl. This or the reverse order will give the observed product *(135)*. Alkylation of piperazine *136* with 1-bromo-3-chloropropane gives the piperazine derivative *137*; use of that intermediate to alkylate heterocycle *135* affords the antidepressant agent *trazodone (138)*.[25]

A fused heterocyclic compound *(146)* distantly related to the antiinflammatory agent *cintazone* (Chapter 12), which itself can be viewed as a cyclized derivative of *phenylbutazone*, retains the activity of the prototype. In the synthesis of *146*, reaction of the nitroaniline *139* with phosgene gives intermediate *140*, which is then reacted with ammonia to afford the substituted urea *(141)*. Cyclization of the ortho nitrourea function by means of sodium hydroxide leads to the N-oxide *(142)*; this last reaction represents



one of a series of transformations in which nitro and nitroso groups reveal electrophilic character akin to carbonyl groups. Reaction of *142* with phosphorous oxychloride serves to convert the hydroxyl group to chloride *(143)*, which is then displaced with dimethylamine to give the key intermediate *144*.[27] Catalytic reduction then converts the azoxide function to the corresponding cyclic hydrazine derivative *(145)*. Finally, condensation with diethyl n-propylmalonate affords the antiinflammatory agent, *apazone (146)*.[28]

5. Ergolines

Ergotism, popularly known at the time as "St. Anthony's Fire," was one of the dread epidemic diseases of the Middle Ages. Its victims suffered gangrenous degeneration, madness, and death. Scientific investigation eventually revealed that this disease was due to ingestion of foods prepared from rye which was infected with a fungus, *Claviceps purpurea*. These infected foods were more likely to be ingested in times of famine, so prevention of ergotism in modern times is a simple matter. Chemical investigation of *Claviceps purpurea* revealed mycotoxins that were amides of *lysergic acid (147)*, involving a series of unusual internally cyclized tripeptides.

Some of these natural products--and drugs made from them--are known collectively as the ergot alkaloids, and have found use in medicine. *Ergonovine*, for example, is a selective stimulant for contraction of uterine muscle and is used in conjunction with labor and delivery. A mixture of hydrogenated ergot alkaloids--reduced at the 9,10-position--has found

use as a cerebral vasodilator by reason of its α-adrenergic blocking activity.

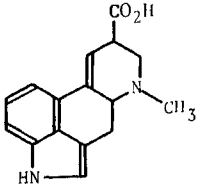
Lysergic acid itself has been used as starting material for a small series of drugs. This natural product was until quite recently difficultly accessible because *Claviceps* molds could only be cultivated on growing grains and grasses. Once harvested, the mixture of ergot alkaloids needed to be subjected to alkaline hydrolysis to yield the free acid. The search for a more efficient method of production led to the finding of a related mold, *Claviceps paspali*, which can be grown in submerged culture in fermentation tanks; this method of culture is additionally advantageous, as it affords the acid directly, thus bypassing the hydrolysis step.[28]

The discovery of the potent hallucinogen LSD-25 *(148)*, (or in street parlance, "acid"), represents one of the classics in serendipity. In the course of an analogue program on lysergic acid derivatives in the Sandoz laboratories in Switzerland, Hoffman had occasion to prepare the simple diethylamide derivative. On his way home from work that day, he saw the city of Basle in an entirely new light. The fantastic potency of the compound had led him to ingest sufficient drug as dust to experience the hallucinogenic effect. Recognizing the probable cause of his "trip," he verified the effect by deliberately taking a second dose. This is one of those interesting cases where animal pharmacology and toxicology came after the human trial.

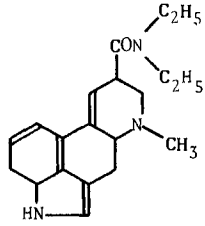
A number of hallucinogens, including LSD-25, enjoyed considerable vogue in the counterculture of the late nineteen sixties. Since there exists no legitimate source for the drug (it has no recognized clinical use), underground laboratories no doubt broadened their repertoire from acetylation of morphine (to produce heroin) to include amide formation from lysergic acid. (The reaction goes particularly well in dimethylformamide; for some years a major manufacturer of this solvent showed this reaction in its advertisements to illustrate the versatility of their products!) Lysergic acid has been prepared by total synthesis by a group at Lilly[29]; rumor has it that some of the illicit LSD was racemic, and thus a product of underground total synthesis. If so, this reflects a considerable and unexpected degree of expertise!

Migraine is a particularly virulent form of headache of which that suffered by the majority of mankind is but a pale reflection; the common remedies, such as aspirin, are all but useless against these attacks. Although the exact etiology of migraine is not known, an attack does involve at one stage dilation of the cerebral vasculature. The skull is a bony case that cannot accommodate volume expansion of any magnitude. *Methysergide (152)*, a lysergic acid derivative, which acts as a cerebral vasoconstrictor, has proven of use in treatment of migraine. Alkylation of methyl lysergate *(149)* with methyl iodide, by means of the anion formed with potassium amide, gives the N-methylated product *(150)*. This is then

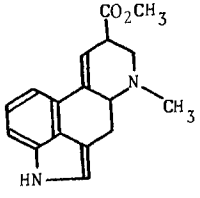
saponified (to *151*) and converted to the amide with 2-amino-1-butanol. There is thus obtained *methysergide (152)*.[30]



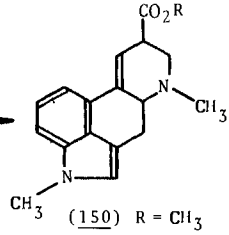
(147)



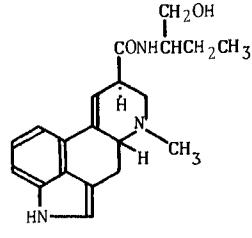
(148)



(149)

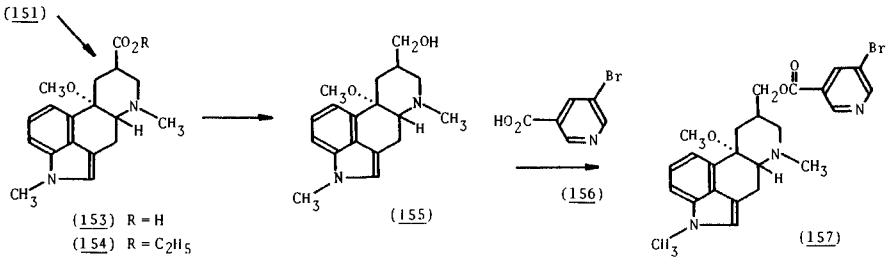


(150) R = CH_3
(151) R = H

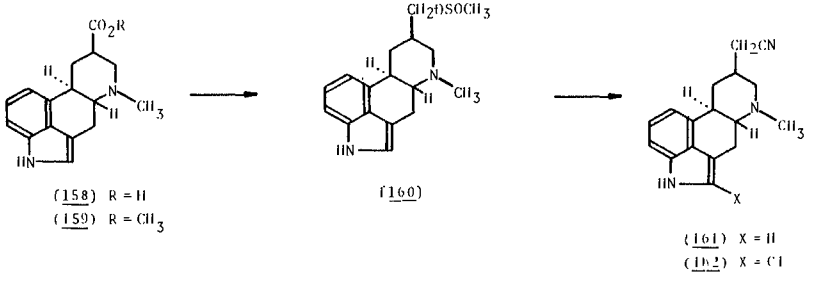


(152)

A different substitution pattern leads to *157*, a molecule that exhibits peripheral α-adrenergic blocking activity. This is manifested as vasodilating activity. Photochemical addition of methanol to the 9,10-double bond of acid *151* affords the methyl ether with the trans ring fusion *(153)*.[31] Reduction of the corresponding ethyl ester *(154)* with lithium aluminum hydride then gives the carbinol *155*. Esterification of that alcohol with substituted nicotinic acid *156*, gives the vasodilator *nicergoline (157)*.[32]



Yet different elaboration of the same molecule affords a compound *(162)* that acts as an inhibitor to the pituitary peptide hormone *prolactin*, the factor responsible for supporting lactation. As such the drug has found use in suppressing lactation and in the treatment of prolactin-dependent breast tumors. In the synthesis of *162*, catalytic hydrogenation of lysergic acid proceeds from the less hindered side of the molecule to afford the derivative with the trans ring junction *(158)*.[30] As above, reduction of the methyl ester *(159)* gives the corresponding carbinol. This is then converted to the methane sulfonate *(160)*, and that function is displaced with cyanide ion to afford the acetonitrile derivative *161*.



Chlorination with N-chlorosuccinimide at the activated indole 2-position gives the corresponding chloro derivative, the prolactin inhibitor *legotrile (162).*[33]

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Diclofenac
Diflumidone
Diflunisal
Etoclofene
Fenamole
Fenbufen
Fenclorac
Fenclozic Acid
Fenoprofen
Fenoterol
Fenpipalone
Flazolone
Flufenamic Acid
Flumizole
Flunisolide
Flunixin
Flutiazin
Furobufen
Indoxole
Intrazole
Isoxicam
Ketoprofen
Meclofenamic Acid
Nimazone
Oxaprozin
Paranyline
Pirprofen
Prodolic Acid
Proquazone
Proxazole
Pyroxicam
Salsalate
Sudoxicam
Sulindac
Suprofen
Tesicam
Tesimide
Tetrydamine
Tolmetin
Triflumidate

Oral Hypoglycemics

Gliamilide
Glibornuride
Glipizide
Glydanile
Glymidine
Glyoctamide
Glyparamide
Metformin
Tolpyrramide

Pituitary Suppressant

Danazol

Progestins

Algestone Acetonide
Algestone Acetophenide
Angesterone Acetate
Cingestol
Clogestone
Clomegestone Acetate
Delmadinone Acetate
Dexnorgestrel Acetime
Ethynerone
Flurogestone Acetate
Gestaclone
Gestonorone

Progestins (cont.)

Haloprogesterone
Medrogestone
Methynodiol Diacetate
Norgestomet
Tigestol

Prolactin Inhibitor

Lergotrile

Respiratory Stimulants

Dimefline
Doxapram

Sedatives

Benzoctamine
Clozapine
Midaflur
Alonimid
Flunitrazepam
Nisobamate
Nisobamate
Tricetamide
Trimetozine
Perlapine
Roletamide

Sedatives - Tranquilizers

Acepromazine
Alpertine
Azaperone
Benperidol
Benzindopyrine
Bromperidol
Buspirone
Butaclamol
Butaperazine
Carpipramine
Cinperene
Cintriamide
Clazolam
Clobazam
Clocapramine
Clomacran
Cloperidone
Clopimozide
Clothiapine
Clothixamide
Cyclophenazine
Cyprazepam
Cyproximide
Demoxepam
Etazolate
Fenimide
Fletazepam
Fluspiperone
Fluspiriline
Halazepam
Hydroxyphenamate
Imidoline
Lenperone
Lometraline
Loxapine
Metiapine
Milipertine
Molindone
Naranol
Nisobamate
Oxiperomide
Penfluridol

Sedatives - Tranquilizers (cont.)

Pimozide
Pinoxepin
Pipamperone
Pipotiazine
Prazepam
Spirilene
Sulazepam
Taclamine
Temazepam
Thiothixene
Triflubazam
Tybamate
Uldazepam

Serotonin Inhibitors

Chlorophenylalanine
Cinanserin
Fenclonine
Fonazine
Mianserin
Xylamidine

Thyromimetic

Thyromedan

Uricosurics

Benzobromarone
Halofenate

Vasoconstrictors

Ciclafrine
Methysergide

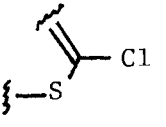
Vasodilators

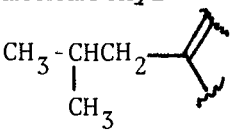
Aceperone
Bamethan
Benfurodil
Betahistine
Cinepazide
Flunarizine
Hexobendine
Ifenprodil
Isoxsuprine
Mesuprine
Nafronyl
Nicergoline
Oxprenolol
Pentoxifylline
Pindolol
Zolterine

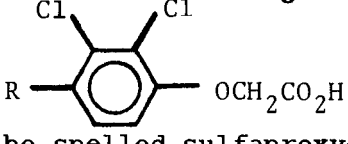
Index

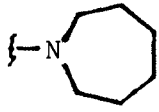
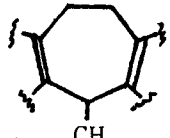
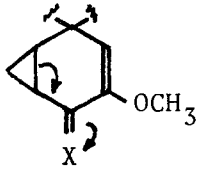
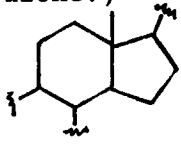
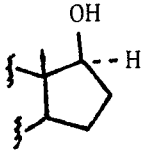
Errata for Volume One

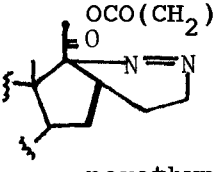
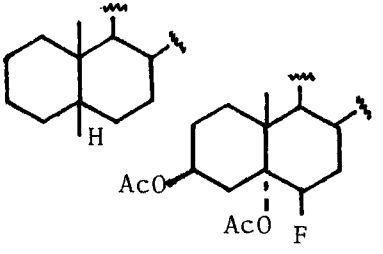
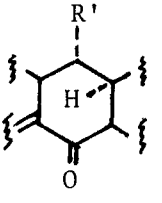
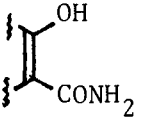
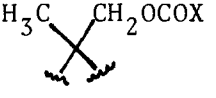
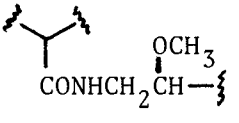
In a work of this magnitude it is an unfortunate fact of life that errors will creep in. We are grateful to our friends and students who have enabled us to compare their lists with ours. Fortunately, the majority are typos and other grammatical mistakes that are embarassing but do not obscure the meaning nor the veracity of what we were conveying. These have been corrected in subsequent printings of the work and are not reproduced here. Those mistakes that are less obvious and/or which we feel might mislead those not familiar with the particular subject matter involved are listed here. The interested reader can annotate volume 1 accordingly. Every effort has been made to ensure that the number of mistakes that creep into volume 2 have been held to a minimum. It is hoped that the authors have the reader's understanding if not forebearance for those which remain.

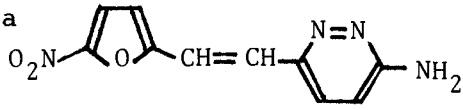
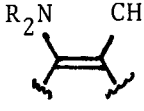
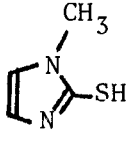
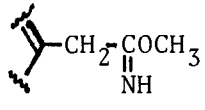
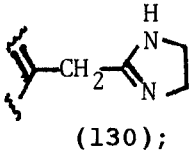
Page	Line	Old Entry	New Entry
6	19	tropane.	tropane.[13]
8	9	Hydrogenation	Cyanohydrin reaction
8	11	ester, 19.	ester, 20.
11	Tab.	(X and Y for ambucaine are reversed.)	
16	3	(64)	(64a)
16	4	(65)	(65a)
16		Formula 64	64a
16		Formula 65	65a
17		Formula 74	$(CH_2)_2$
17	6	butylamine	propylamine
18	21	(85) via	(88) via
32	6	,36,	,39,
33	1	43,	42,
33	5	43,	42,
33	29	41	47
34	2	(7).	(7).[14]
36	8	(8).	(8).[14]
36	7	dicyclonime	dicyclomine
36	13	dihexyrevine	dihexyverine
38	last	clocental (25)	clocental (75)
42	14	-1-methylpyrro-diline	-1-methylpyrrolidine
47	2	azacyclonol	pipradol
47	4	pipradol	azacyclonol
54		Formula 76	

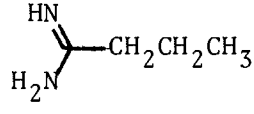
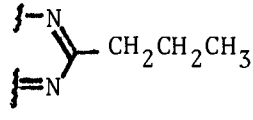
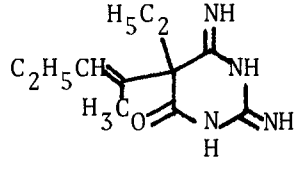
66	2	pronethanol	pronethalol
66	4	soltalol	sotalol
67		Formula 6	(remove "6")
68		Formulas 37 and 38	(numbers are reversed)
70		Formula 51	(remove "51")
70	15	(54).[12]	(54).[13]
70	23	(58)	(59)
70	26	phenylbutanone-2	phenylpentanone-2
72	17	oxoethazine	oxoethazaine
74	7	fencamfine	fencamfamine
78	3	p-chloroaceto-phenone	p-methylacetophenone
78		Formulae 109, 110, 111	(p-CH_3)
86	2	isopropylbenzene	isobutylbenzene
86	15	alkylation of	alkylation with ethyl iodide of
86	16	base with ethyl iodide affords	base affords
86	23	monoethyl	monomethyl
86		Formulas 1-5	
90	5	dimethylamine	diethylamine
90	6	carbetapentane (39)	(38)
90		Formula 38	38, X=N(C_2H_5)$_2$
91		Formula 44	

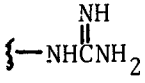
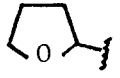
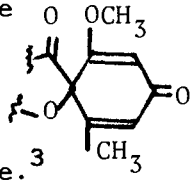
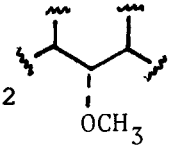
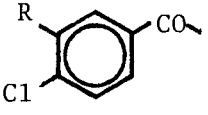
92	6	cyclopyrazolate	cyclopyrazate
93	11	benactizine	benactyzine
96	10	phenol, 77.	phenol, 77a.
96	13	of 77	of 78a
96	15	ether (79).	ether (79a).
96	19	of 79	of 79a
97	4	(80) to afford	to afford
97		Formula 77	77a
97		Formula 78	78a
97		Formula 79	79a
97		(Unnumbered formula	should be 80)
100	15	,2,[2]	,2,[1]
102		(Formula 7 is superfluous and should be removed.)	
111		Formula 16	X=Z=CH_3; Y=H
111	17	of 21	of 20
111	18	hydrazone (24)	hydrazone (23)
115	5	(42).[9,10]	(43).[9,10]
116	2	moxysylyte	moxisylyte
117	last	(66).[19]	(66).[18]
119		Formulas 76 and 75	(convert Cl to CH_3)
120		Formula 81	
123		(Compound 94 should be spelled sulfaproxy-line.)	
136	4	1930s	1920s
137	3	piperidine	azepine
137	7	tolazemide	tolazamide

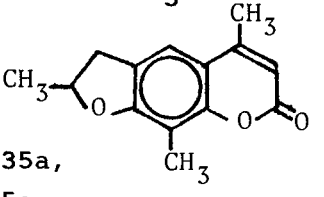
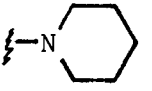
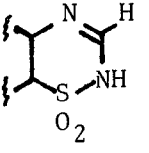
137		Formulas 190, 191, 193	
138	3	carbutemide	carbutamide
138	5	1-butyl-3-metanyl-urea	1-butyl-3-meta-nilylurea
141	9	thiazosulfone	thiazolsulfone
150		Formula 29	
151	17	amytriptylene	amitriptyline
151	23	methylpipyridine	methylpiperidine
152	6	tylene	tyline
153		Formulas 45/46	
172		Formula 78b	(Replace angular Me group by H but leave formulae 78a and 78c alone.)
173		Formula 80	
174	7	eneone (91)	eneone (95)
175		Formula 92	(Also remove arrow from 91.)
			

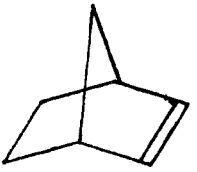
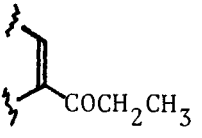
176	39	(109),	(107),
180		Formula 124	$OCO(CH_2)_4CH_3$
183		Formula 145	
186	Tab.	norethinodrel	norethynodrel
193		Formulas 174 and 175	(Renumber to 174a and 175c)
196	21	N-bromosuccinide	N-bromosuccinimide
196-7		Formulae 192-198	
198		Formulae 205-207	
199		Formulae 211-212	
200		Formula 219	
203		Formula 240	OH instead of OAc
213		Formulae 1-3	
213		Formulas 9 and 10	
219		Formulas 3 and 4	
225		Formula 47	

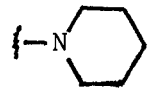
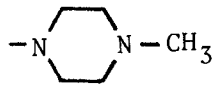
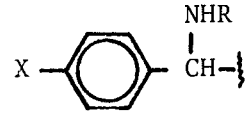
224		(Unnumbered formula is 41.)	
231	last	gives nifurprazine (46).[13]	gives the thiadiazole analogue (46) of nifurprazine (46a).[13]
232		Add formula 46a	
233	8	isocarboxazine	isocarboxazid
233		Formula 50	(Reverse the methyl and allyl groups.)
234	18	reduction affords	reduction and methylation affords
234	19	(61),	(61a).
235		Formula 68	$CH_3(CH_2)_3CH(CO_2C_2H_5)_2$
235		Formula 61	 61, R=H 61a, R=CH_3
241		Formula 95	
242		Formula 101	
242		Formula 102	
246	4	(132);	(130);
246	2	acetophenone	propiophenone
246	last	tetratoin	tetrantoin

246		Formulae 130-133	C_2H_5-C
247	10	aminitrazole	aminitrozole
249	27	ambient	ambident
257	9	glutethemide	glutethimide
257	12	aminogluthemide	aminoglutethimide
260	6	guancycline	guanacline
263	6	(71).	(71a).
263	8	(72).	(72a).
263	(Renumber formulas 71 and 72 to 71a and 72a.)		
263	(An arrow should connect formulas 73 and 74.)		
264		Formula	
264		Formulas 75-79	
265	8	uracyl	uracil
265	12	uracycls	uracils
266	15	(92).[28] (94),[29]	(94).[28] (95),[29]
266	1	amisotetradine	amisometradine
265	last	aminotetradine	aminometridine
269	1	105	105a
269		entry 110	$CH_3CHCH_2CH_2CH_3$
270	6	allilic	allylic
262	2	phenylacetonitrile	p-chlorophenylaceto-nitrile
262		Formulas 63-65	(add a p-chloro group)
272		Formula 124	

278	19	171.	171a.
279		Formula 171	171a.
281		Formula 182	
287	last	(4).	(4).[2]
295		Formula 30	40 (also remove +)
301	1	furfuryl	tetrahydrofurfuryl
301		Formulae 82-85	$-CO_2C_2H_5$
301		Formulae 85-87	
305	7	prolidine	prodilidine
308	20	pirintramide	piritramide
315		Formula 14	
316	15	predominate	predominate.[3]
318	last	scision	scision.[7]
319	5	Rawaulfia	Rauwolfia
320	13	fused to	fused α to
320	17	potassium per-chlorate	potassium chlorate
320		Formulas 30-32	
321	7	synthesis.	synthesis.[12]
322		Formulas 47-49	

325	13	clonitazine	clonitazene
325	14	etonitazine	etonitazene
327	3	ethoxysolamide	ethoxazolamide
333	last	salicylaldehyde	acetophenone
334		Formulae 21-30 should have a CH_3 group instead of H as 30 is	
335	13	,35,	,35a,
336		Formula 35	35a
336	8	the bronchodilator	the antiasthmatic
336	9	its extremely insoluble disodium	its disodium
337		Formulas 46 and 47	-CHOH-
338	23	cincona	cinchona
340	10	59.	59.[13]
343		Formula 76	76a
346	15	,101.	,103.
346	19	(103) affords	(101) affords
348	13	same	name
352	8	diethylamine	piperidine
352		Formula 138	
355	29	anthralic	anthranilic
355	30	anthranillic	acetic anhydride
356		Formula 163	

358		Formula 182	
358		Compound 179	ethiazide
359	1	trichlomethiazide	trichlormethiazide
359	7	cyclopentadiene.[49]	cyclopentadiene.[44]
359	2	althizide	althiazide
359	16	altizide	althiazide
365	13	the oxime	the N-methyl analogue of the oxime
365		Formula 14	$N\text{-}CH_3$
366	7	of diazepam	of desmethyldiazepam
368	22	amide (37).	amide (36).
368	25	The N-methylated analog of intermediate, 15, contains	Intermediate 15 contains
370	1	cloxazepam	cloxazolam
373	28	of 3,	of 1,
376		Formula 22	
379	1	(30)	(31)
380		Formulas should all have $CH_2CH(CH_3)N(CH_3)_2$ as the side chain.	
386	6	piperactizine	piperacetazine
389	8	of the methylthio-substituted	of substituted
389	8	phenothiazine with	phenothiazine 113 with
389	10	(115).[19]	(114).[19]

389	14	(114)	(115)
389		Formulae 112, 113 and 115	$-SCH_3$
390	5	pyrrolidyl	piperazinyl
390	9	at the expense of	in favor of
390		Formulas 118 and 120	
390		Formulas 117 and 119	$-N(CH_3)_2$
394	5	propanthe-	pronanthe-
394	34	catalyst.	catalyst.[3]
400	7	thiothixine	thiothixene
401		Formula 42	
404	10	amytriptyline	amitriptyline
405		(The unnumbered formula should be 76)	
405	10	dibenzepine	dibenzepin
410	32	4, a	4,[1] a
410	36	phenbencillin	phenbenicillin
414	21	carbencillin	carbenicillin
414	17	amoxycillin (35)	amoxycillin (28a)
414		Formula 27, $R=CO_2CH_2C_6H_5$, X=H	
414		Formula 28, R=X=H	
414		Formula 28a, R=H, X=OH	
417	11	43.	43.[24]
426	10	oncolyltic	oncolytic

426	12	oxidate	oxidase
429	9	(39).	(39).[8]
430	2	(47);[10]	(47);[11]

Changes To Be Made In The Index:

Althiazide
Aminitrozole
Aminoglutethimide
Aminometradine
Amisometradine
Amitriptyline, 151, 404
Benactyzine
Benzphetamine
Betamethasone
Biperiden
Butallonal
1-Butyl-3-metanilyl urea
Caramiphen
Carbenicillin
Carbetidine
Carbutamide
Carisoprodol
Chlorimpiphenine
Chloropyramine
Chlorotrianisene
Cromoglycic acid
Clonitazene
Cloxazolam
Ethoxzolamide
Etonitazene
Fencamfamine
Flumethiazide
Glutethimide
Guanacline
Gaunochlor
Guanoxan
Hydroflumethiazide
Iodothiouracil
Isocarboxazid
Isoproterenol
Levarterinol
Levalorphanol
Mebhydroline
Mephenoxalone
Metaproterenol
Metaxalone
Methaphenilene
Methdilazine
Methyclothiazide, 360
Methylthiouracil
Methyridine, 256

Cyclopyrazate
Debrisoquine
Desipramine
Dexamethasone
Dicyclomine
Dihexyverine
Dimetacrine
Dipiproverine
Dithiazanine
Etriptamine
Ethacrynic acid
Ethiazide
Prolintane
Pronethalol
Propylthiouracil
Prontosil
Protriptyline
PTU, see propylthiouracil
Rescinnamine
Sotalol
(delete Sulfadiazene, 128)
Sulfaproxyline
Tetrantoin
Thiomestrone
Thiazolsulfone
Trichlormethiazide
Trifluperidol
Trihexyphenidyl
Tripelennamine
Uracils
Moxisylyte
Nikethamide
Norethynodrel
Nortriptyline
Oxoethazaine
Paraethoxycaine
Pargyline
Phenbenicillin
Pholcodine
Piperacetazine
Piritramide
Prodilidine