THE ORGANIC CHEMISTRY OF DRUG SYNTHESIS

VOLUME 4

DANIEL LEDNICER

National Cancer Institute
Bethesda, Maryland

LESTER A. MITSCHER

Department of Medicinal Chemistry
The University of Kansas
Lawrence, Kansas

with

GUNDA I. GEORG

Department of Medicinal Chemistry
The University of Kansas
Lawrence, Kansas

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We dedicate this book to Beryle and Betty who continue to support us in every imaginable way and to the memory of Katrina Mitscher-Chapman (1958-1987) who was looking forward with her customary enthusiasm to helping us prepare the manuscript.

I cannot tell how the truth may be;

I say the tale as 'twas said to me.

Sir Walter Scott, "The Lay of the Last Minstrel"

Preface

Over a decade and a half have flown by since we started on the preparation of the first volume in this series. We did not at that time envisage a series at all but simply a book which filled what we then perceived as a vacuum. There were not in print in the midnineteen seventies any contemporary monographs in the English language dedicated to the synthesis of medicinal agents. The result was the original *Organic Chemistry of Drug Synthesis*. The reception accorded that volume confirmed that there was indeed a place for a book devoted to that subject matter. Having laid the groundwork, it seemed worthwhile to rectify a number of omissions present in the book and at the same time to bring the coverage for compounds included in the compilation to a common date. The result was of course Volume 2 and the birth of a series. The next volume, 3, was produced at the time we again felt the need to update our narrative; a semidecenial period was settled upon since it seemed to represent the best compromise between currency and a sufficient body of material to merit treatment in a monograph. The volume at hand continues the series; it covers the chemistry of those compounds which have been granted a United States Adopted Name (USAN) in the five years between 1983 and 1987. The bulk of the references thus fall in the 1980s; the reader will note occasional much older references. We suppose that those represent compounds which were synthesized many years ago and set on the shelf at that time; they were then revived for clinical development for one reason or another and a USAN applied for.

It is well known that regulatory approval of new chemical entities has slowed markedly over the past decade. Some would even argue that the very rate of decrease is accelerating. This phenomenon has been attributed to a wide variety of causes, none of which are particularly germane to this volume. It is thus surprising, and pleasing, to note that the decreased probability of bringing a given new chemical entity to market has not led to a diminution in the rate of acquisition of new generic names as noted in *USAN and USP Dictionary of Drug Names*. The 300 odd compounds discussed in this volume are within a few entities of the number covered in the preceding volume. The acquisition of 60 new generic names each year has been so uniform over the past decade that this should perhaps be recognized as a new physical constant!

This relatively steady rate of addition of new generic names has resulted in books which are quite uniform in size, at least after accounting for the text which was used to bring the subject up to date . The individual chapter titles do not show a corresponding uniformity; the composition of

the more recent volumes in some ways represents a socio economic history of research in medicinal chemistry. The first volume in this series, for example, contained a sizable chapter devoted to compounds based on the phenothiazine nucleus. This had disappeared by the second volume due to a dearth of new material. This in all probability simply represents a shift away from the research which took place on these compounds in the midnineteen fifties. Occasional chapters have lasted through all four volumes. One of these, to the authors' surprise is that devoted to " Steroids." That particular chapter is, however, by now a mere shadow of those which appeared in the first two volumes. Some chapters have persisted but changed significantly in content. "Alicyclic Compounds" has evolved from a collection of miscellany to a virtual compendium of prostaglandin syntheses.

The diligent reader will note that succeeding volumes increasingly show agents which are the result of rational drug design of the synthesis targets. The older rationale for preparing specific compounds—to produce a hopefully superior and clearly patentable modification of a successful new drug—still however persists. Note that the present volume lists seven quinolone antibacterial agents, the same number of dihydropyridine calcium channel blockers, and no fewer than an even dozen angiotensin-converting enzyme inhibitors. Once the initial lead is discovered, a very significant expenditure of effort takes place; this persists until it becomes clear that no further improvements are taking place and that new entries are unlikely to gain a share of the market.

This book is addressed primarily to practitioners in the field who seek a quick overview of the synthetic routes which have been used to access specific classes of therapeutic agents. Publications of syntheses of such compounds in the open literature remains a sometimes thing. One can, however, be certain that any compound which has commercial potential will be covered by a patent application. Many of the references are thus to the patent literature. Graduate students in medicinal and organic chemistry may find this book useful as an adjunct to the more traditional texts in that it provides many examples of actual applications of the chemistry which is the subject of their study. This volume, like those which came before, presumes a good working knowledge of chemical synthesis and at least nodding acquaintance with biology and pharmacology.

Finally, the authors express their gratitude to Ms. Vicki Welch who patiently and skillfully prepared the many versions of this book including the final camera ready copy.

Rockville, Maryland DANIEL LEDNICER
Lawrence, Kansas LESTER A. MITSCHER
Lawrence, Kansas GUNDA I. GEORG
January, 1990

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THE ORGANIC CHEMISTRY OF DRUG SYNTHESIS

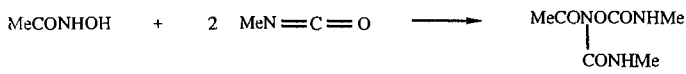
VOLUME 4

1 Aliphatic and Alicyclic Compounds

I. ACYCLIC COMPOUNDS

There are relatively few important drugs which are alicyclic. Other than inhalation anesthetics, which are a special case, the compounds in the acyclic aliphatic class owe their activity to the functionality present and its specific spacing on the aliphatic framework. Thus, in most instances, the framework itself is not of comparable importance to the functionality attached to it.

Caracemide (3) is an antitumor agent. This simple molecule is constructed by reacting acetohydroxamic acid (**1**) with methylisocyanate (2) promoted by triethylamine. The resulting O,N-biscarbamate (3), **caracemide**, is metabolized readily either by deacetylation or by decarbamoylation and its antitumor properties are believed to result from the reactivity of the resulting metabolites with DNA [1].



(1) (2) (3)

Viral infections continue to be significant causes of morbidity and mortality and at the same time continue to be resistant to treatment by small molecules. **Avridine** (6) is an antiviral compound which has shown some activity in a variety of animal tests apparently based upon its ability to stimulate a number of cells to produce the high molecular weight endogenous antiviral substance **interferon**. Thus, the compound is believed to operate indirectly by stimulating the **body**'s own natural defenses against viral penetration into host cells. **Avridine** is synthesized by

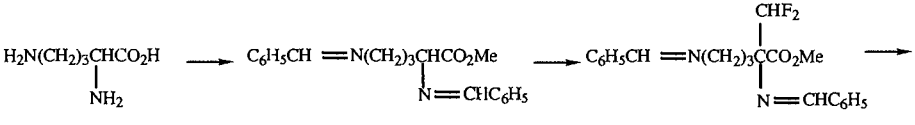
alkylating N-(3-aminopropyl)diethanolamine (**5**) with octadecyl bromide (**4**) using potassium carbonate in the usual fashion [2].

(4) (5) (6)

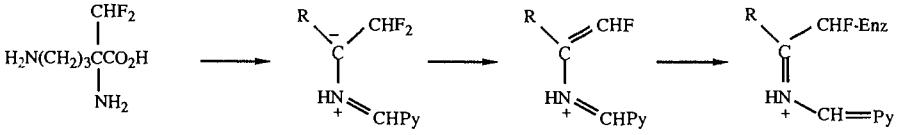
Much attention has been focused upon the exciting promise of enzyme activated enzyme inhibitors for potential use in therapy. In contrast to the ordinary alkylating agents which are aggressive chemicals in the ground state and, thus, lack specificity in the body and produce many side effects and unwanted toxic actions, the so-called K-cat inhibitors or suicide substrates turn the enzyme's catalytic action against itself. The enzyme first accepts the suicide substrate as though it were the normal substrate and begins to process it at its active site. At this point, it receives a nasty surprise. This intermediate now is not a normal substrate which peacefully undergoes catalytic processing and makes way for another molecule of substrate, but rather is an aggressive compound which attacks the active site itself and inactivates the enzyme. As the suicide substrate is only highly reactive when processed by the enzyme, it achieves specificity through use of the selective recognition features of the enzyme itself and it works out its aggression at the point of generation sparing more distant nucleophiles. Thus, much greater specificity is expected from such agents than from electrophiles which are highly reactive in the ground state.

Eflornithine (**10**) represents such a suicide substrate. Cellular polyamines are widely held to be involved in cellular growth regulation and, in particular, their concentration is needed for accelerated growth of neoplastic cells. The enzyme ornithine decarboxylase catalyzes a rate determining step in cellular polyamine biosynthesis and a good inhibitor ought to have antitumor activity. The synthesis of **eflornithine** starts with esterification of the amino acid ornithine (**7**) followed by acid-catalyzed protection of the two primary amino groups as their benzylidine derivatives (**8**). The acidic proton is abstracted with lithium diisopropylamide and then alkylated with chlorodifluoromethane to give **9**. This last is deprotected by acid hydrolysis to give **eflornithine** (**10**) [3].

Ornithine decarboxylase is a pyridoxal dependent enzyme. In its catalytic cycle, it normally converts ornithine (7) to putrisine by decarboxylation. If it starts the process with **eflornithine** instead, the key imine anion (**11**) produced by decarboxylation can either alkylate the enzyme directly by displacement of either fluorine atom or it can eject a fluorine atom to produce vinylogue **12** which can alkylate the enzyme by conjugate addition. In either case, **13** results in which the active site of the enzyme is alkylated and unable to continue processing substrate. The net result is a downturn in the synthesis of cellular polyamine production and a decrease in growth rate. **Eflornithine** is described as being useful in the treatment of benign prostatic hyperplasia, as an antiprotozoal or an antineoplastic substance [3,4].



(7) (8) (9)

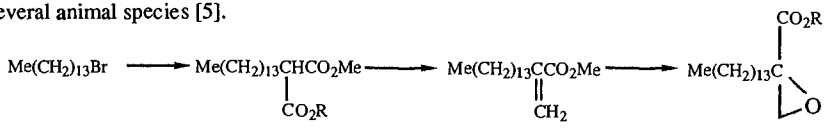


(10) (11) (12) (13)

Py = pyridoxal phosphate

One interesting metabolic theory is that glucose and lipid levels in the blood affect each other's metabolism. Glucose metabolism is disturbed in sugar diabetes and some of the toxic effects of the resulting metabolic imbalance is believed to be due to enhanced oxidation of fatty acids as an alternate food. It is theorized that inhibitors of fatty acid oxidation could reverse the cycle in favor of glucose utilization. **Sodium palmoxirate (19)** was selected as a potential oral antidiabetic agent of a new type based upon this premise. Its synthesis begins by alkylating

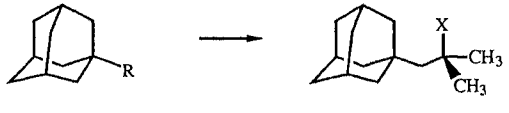
methyl malonate with tridecylbromide (**14**) to give **15** and partially hydrolyzing the product to monoester **16**. Next, treating the monomethylester with diethylamine and aqueous formaldehyde gives the desired alkyl acrylate ester **17**. This is epoxidized with m-chloroperbenzoic acid and the resulting glycidic ester (**18**) is carefully hydrolyzed to give palmoxiric acid as its water soluble sodium salt (**19**). **Palmoxirate** is a potent hypoglycemic agent following oral administration to several animal species [5].



(**14**) (**15**); R = Me (**16**); R = H (**17**) (**18**); R = Me (**19**); R = Na

2. ALICYCLIC COMPOUNDS

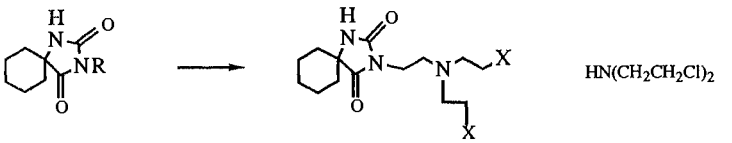
An interesting appetite suppressant very distantly related to hexahydroamphetamines is **somantadine** (**24**). The reported synthesis starts with conversion of 1-adamantanecarboxylic acid (**20**) via the usual steps to the ester, reduction to the alcohol, transformation to the bromide (21), conversion of the latter to a Grignard reagent with magnesium metal, and transformation to tertiary alcohol **22** by reaction with acetone. Displacement to the formamide (**23**) and hydrolysis to the tertiary amine (**24**) completes the preparation of **somantadine** [6].



(**20**); R = CO_2H (**21**); R = CH_2Br (**22**); X = OH (**23**); X = NHCHO (**24**); X = NH_2

Brain tumors are hard to treat in part because many antitumor agents which might otherwise be expected to have useful activity are too polar to pass the blood brain barrier effectively and fail to reach the site of the cancer. Nitrogen mustards are alkylating agents which fall into the category of antitumor agents which do not penetrate into the CNS. It is well known that a number of hydantoins pass through the highly lipid capillary membranes and, indeed, a number of CNS

depressants possess this structural feature. Combination of a hydantoin moiety to serve as a carrier with a latentiated nitrogen mustard results in spiromustine (28). Spiromustine is metabolized in the CNS to the active moiety, bis(chloroethanamine) (29). The synthesis begins with 5,5-pentamethylenehydantoin (25) which is alkylated to 26 by reaction with 1-bromo-2-chloroethane. Reaction of 26 with diethanolamine promoted by in situ halogen exchange with sodium iodide (Finkelstein reaction) leads to tertiary amine 27. The synthesis is completed by reacting the primary alcoholic moieties of 27 with phosphorus oxychloride [7].



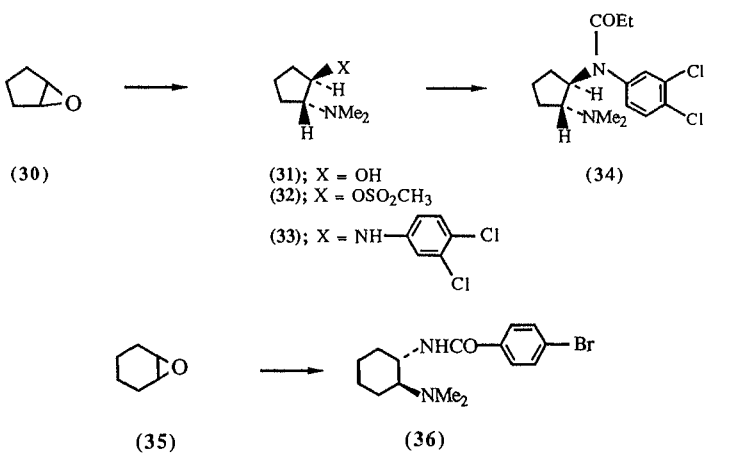
(25); R = H
(26); R = CH_2CH_2Cl

(27); X = OH
(28); X = Cl

$HN(CH_2CH_2Cl)_2$

(29)

Some alicyclic 1,2-diamine derivatives have recently been shown to have interesting CNS properties. For example, eclanamine (34) is an antidepressant with a rapid onset of action. The reasons for its potency are not as yet clear but pharmacologists note that the drug desensitizes adrenergic alpha-2 receptors and antagonizes the actions of clonidine. The synthesis of eclanamine starts with attack of cyclopentene oxide (30) by dimethylamine (to give 31). This product is converted to the mesylate by reaction with sodium hydride followed by mesyl chloride. Attack of



(30)

(31); X = OH
(32); X = OSO_2CH_3
(33); X = NH–

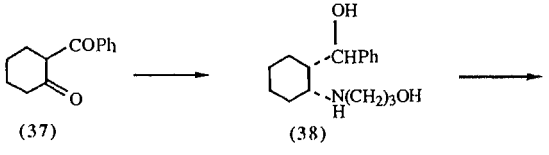
(34)

(35)

(36)

the product (32) by 3,4-dichloroaniline leads to trans-diamine 33. The stereochemical outcome represents a double rear side displacement. The synthesis is completed by acylation with propionic anhydride to give **eclanamine** (34) [8]. A chemically related agent, **bromadoline** (36) is prepared by an analogous series of reactions starting with cyclohexene oxide (35). **Bromadoline** is classified as an analgesic [9].

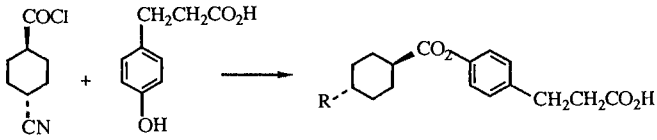
A structurally unrelated agent is **tazadolene** (**40**). The synthesis of **tazadolene** begins with β-keto ester 37 and subsequent enamine formation with 3-amino-1-propanol followed by hydrogenolysis to give 38. This phenylhydroxymethyl compound is then dehydrated with hydrochloride acid to form olefin **39**. Treatment with bromine and triphenylphosphine effects cyclization to form the azetidine ring of **tazadolene** [10].



(37) (38)

(39) (40)

Cetraxate (**44**) is a prodrug of **tranexamic acid**. The latter is a hemostatic agent because it inhibits the activation of plasminogen to plasmin. The result is to prevent excess loss of blood in gastrointestinal ulcers. Prodrugs are of value as they allow greater absorption on oral administration by suppressing, in this case, the amphoteric nature of the drug. The synthesis begins with the esterification of 3-(p-hydroxyphenyl)propionic acid (**42**) by trans-4-cyanocyclohexanecarbonyl chloride (**41**). The product (**43**) is reduced to **cetraxate** by catalytic hydrogenation with hydrogen and Raney nickel [11].



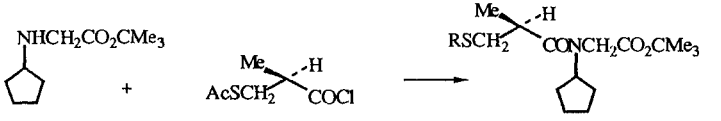
(41) (42)

(43); R = CN
(44); R = CH_2NH_2

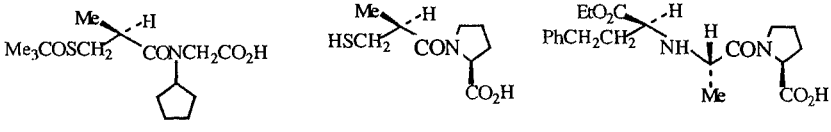
Among the most successful drugs of recent years have been the group of antihypertensive agents which act by inhibition of the important enzyme, angiotensin-converting enzyme (ACE). The renin-angiotensin-aldosterone system exerts an important control over blood pressure and renal function. One of the key steps in the process is the conversion of angiotensinogen to angiotensin I by the enzyme renin. Angiotensin I, an octapeptide (Asp-Arg-Val- Tyr-Ile-His-Pro-Phe-His-Leu), is cleaved of two amino acids by ACE to a hexapeptide, angiotensin II (Asp-Arg-Val-Try-Ile-His- Pro-Phe), a powerful pressor hormone. The majority of the inhibitors of this important enzyme are treated in a later chapter. One of the structurally more interesting representatives, however, is **pivopril** (**50**), an orally active prodrug with a masked sulfhydryl group (protected by a pivaloyl ester moiety) and, instead of possessing the usual chiral C-terminal proline residue, has an achiral N-cyclopentylglycine moiety. The synthesis begins with the reaction of the t-butylester of N-cyclopentyl glycine (**45**) with (S)-3-acetylthio-2-methylpropionyl chloride (**46**) to give amide **47**. The acetyl group is selectively cleaved with ammonia in methanol to give **48**. The thiol group is reprotected by reaction with pivaloyl chloride to give **49** and the carboxyl protecting group is removed by selective reaction with trimethylsilyl iodide to give **pivopril** (**50**) [12].

The structural relationship of **pivopril** to the commercially important analogues **captopril** (**51**) and **enalaprilat** (**52**) is readily apparent.

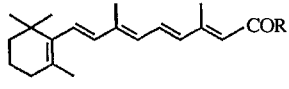
Retinoids are needed for cellular differentiation and skin growth. Some retinoids even exert a prophylactic effect on preneoplastic and malignant skin lesions. **Fenretinide** (**54**) is somewhat more selective and less toxic than **retinyl acetate** (**vitamin A acetate**) for this purpose. It is synthesized by reaction of all trans-retinoic acid (53), via its acid chloride, with p-aminophenol to give ester **54** [13].



(45) (46) (47); R = Ac
(48); R = H
(49); R = Me_3CCO



(50) (51) (52)



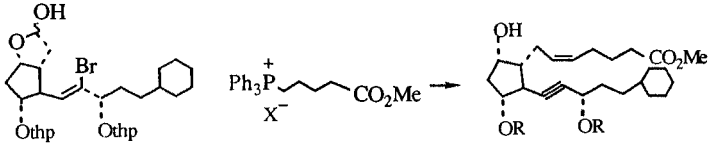
(53); R = OH
(54); R = NH—⟨⟩—OH

3. PROSTAGLANDINS

The prostaglandins continue their stately progress towards clinical use. Their properties as fertility regulators are well established but their use for other therapeutic needs is complicated by their wealth of side effects. Their use as cytoprotective agents and antisecretory agents in gastric ulcers looks promising, however, and there is some hope for the classical agents as transdermal hypotensive agents; otherwise much of the current excitement with these compounds lies in attempts to control the biosynthesis of particular prostanoids or to modulate their action at the receptor level. Most interest centers around the other products of the arachidonic acid cascade such as the thromboxanes and leucotrienes where intervention promises control of disorders of hemodynamics and

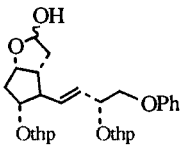
inflammation. Few of these substances have progressed far enough to be the subject of paragraphs in this work as yet.

Alfaprostol (**55**) is a luteolytic agent used injectably for scheduling of estrus in mares for purposes of planned breeding. It is also used for treatment of postweaning anestrus in economically important farm animals. For these purposes, **alfaprostol** is more potent than naturally occurring **prostaglandin F2-alpha**. Notable molecular features of the **alfaprostol** molecule are the acetylenic linkage at C-13, the methyl ester moiety (which is rapidly removed in vivo) and the terminal cyclohexyl moiety which inhibits some forms of metabolic inactivation. The synthesis begins with lactol **56** which undergoes Wittig reaction with methyl 5-triphenylphosphoniumvalerate (**57**) using dimsyl sodium as base. Dehalogenation occurs concomitantly to produce partially protected condensation product **58**. Deblocking to **alfaprostol** is brought about by oxalic acid [14].

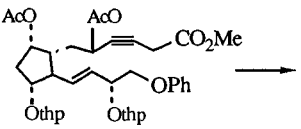


(**56**) (**57**) (**58**); R = thp
(**55**); R = H

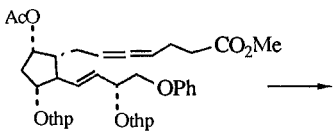
Another luteolytic agent, **fenprostalene** (**62**) contains an alleneic linkage in the upper sidechain and terminates in a phenoxy moiety in the lower. Its synthesis begins with lactol **59** (presumably the product of a Wittig olefination of the Corey lactol and suitable functional group manipulation). Lactol **59** is reacted with lithio 4-carbomethoxybut-1-yne and the resulting secondary carbinol acetylated with acetic anhydride to give substituted acetylene **60**. The allene moiety (**61**) is produced by reaction with copper (II) bromide and methyl lithium. The tetrahydropyranyl ether protecting groups are then removed by treatment with acetic acid, the ester groups are hydrolyzed with potassium carbonate, and the carboxy group is reprotected by diazomethane methylation to give **fenprostalene** [15].



(59)



(60)



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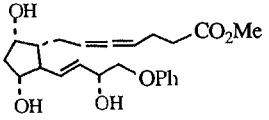
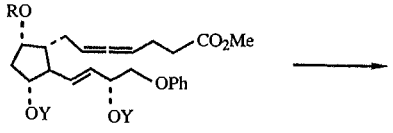


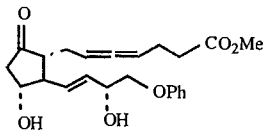
(62)

A prostaglandin closely related to **fenprostalene** is **enprostil** (63). **Enprostil** belongs to the prostaglandin E family and is orally active in humans in reducing gastric acid and pepsin concentration as well as output. It is effective in healing gastric ulcers in microgram doses and is under consideration as an antisecretory, antiulcerative agent. The synthesis begins with intermediate **61** by removing the protecting THP ether groups with acetic acid (**64**) and then replacing them with t-butyldimethylsilyl groups by reaction with t-butyldimethylsilyl chloride and imidazole. This is followed by hydrolysis of the ester moieties with potassium carbonate and reesterification of the carboxy moiety with diazomethane to produce intermediate **65**. The solitary free alcoholic hydroxyl at C-9 is oxidized with Collins' reagent and the silyl ether groups are removed with acetic acid to give **enprostil** (63) [15].

(61)



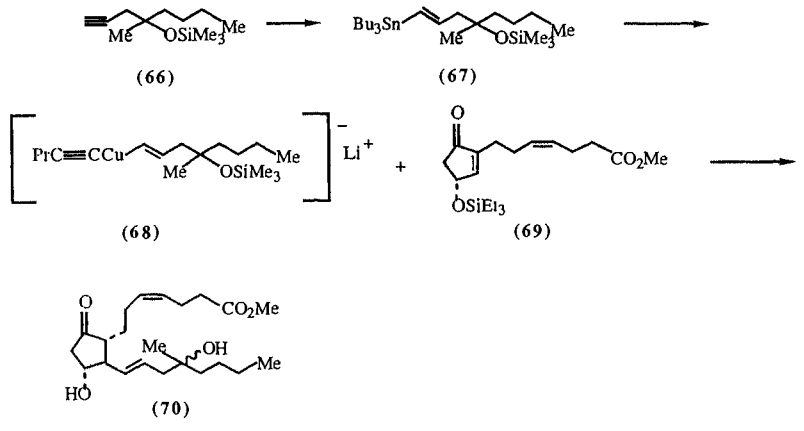
(64) R=Ac; Y=H
(65) R=H; Y=SiMe2t-Bu



(63)

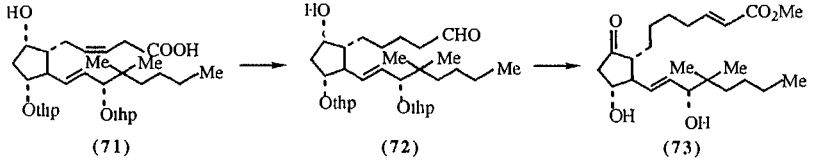
Enisoprost (70) is an antiulcerative/cytoprotective prostaglandin. In addition to the well-known property of E series prostaglandins to inhibit gastric secretion of HCl and pepsin, these agents enhance ulcer healing by stimulating formation of the mucin protective layer over the stomach lining. The well-known ulcer promoting action of nonsteroidal antiinflammatory agents such as aspirin can be rationalized by invoking the reversal of this effect. Thus, useful antiulcer properties can be anticipated at very low doses of certain prostaglandins (offsetting their cost) and this has been confirmed in the clinic. One of the side effects of such prostaglandins which must be minimized is diarrhea and cramps. In the **enisoprost** molecule this has been accomplished by moving the C-15 OH group of ordinary prostaglandins to C-16. This is consistent with antiulcer activity but reduces other side effects. Presumably these results reflect different structural needs of the different receptors. The addition of the methyl group at C-16 prevents oxidative inactivation of the molecule which would involve ketone formation at C-16 otherwise. This devise is a common stratagem used previously, for example, with **methyltestosterone**. The presence of a cis double bond at C-4 is also known to inhibit oxidation beta to the carboxyl group. Thus **enisoprost** carries a number of interesting design features. The synthesis concludes by conjugate addition of mixed cuprate 68 to unsaturated ketone 69. The product, **enisoprost**, is the more stable isomer with the two new side chains trans. The mixed cuprate is made from protected acetylene alcohol 66 by photosensitized trans addition of tri-n-butyltin hydride to give organostannane 67. Successive transmetalations with butyl lithium and then copper 1-pentyne leads to the necessary mixed cuprate (68) for the above sequence [16].

Gemeprost (73; 16,16-dimethyl-trans-Δ^2-prostaglandin-E_1) is dramatically more potent on a dosage basis as an abortifacient than **prostaglandin E_2** itself and has fewer side effects. The gem-dimethyl groups at C-16 protect the alcohol moiety at C-15 from rapid metabolic oxidation.



(66) (67) (68) (69) (70)

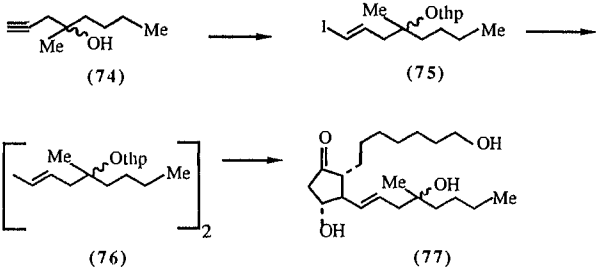
It is synthesized by further transformation of bisnor prostaglandin **71**, itself derived from Corey's lactone by Wittig reactions. Catalytic reduction of the cis double bond using hydrogen and palladium on charcoal is followed by esterification with diazomethane and then DIBAL reduction to the aldehyde **72**. This undergoes Horner-Emmons olefination followed by oxidation of the free alcoholic function at C-9 to the ketone and deblocking with acetic acid to give **gemeprost** (73) [17].



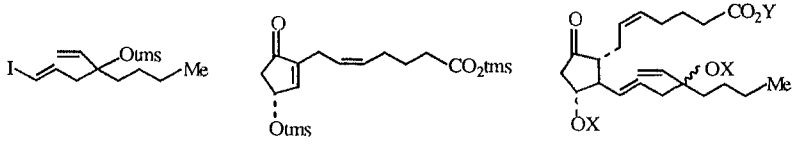
(71) (72) (73)

Rioprostil (77) is also a gastric antisecretory and cytoprotective prostanoid. It is administered as the alcohol and presumably operates as a prodrug, being oxidized in vivo to the acid. An essential step in its synthesis is also a conjugate addition of a suitably substituted organocopper reagent to a suitable unsaturated ketone. The synthesis begins by Grignard addition of propargyl magnesium bromide to 2-hexanone to give alcohol **74** (compare to 66). This is protected as the tetrahydropyranyl (THP) ether in the usual way and then the triple bond is converted to the E-iodoolefin (**75**) by reduction with DIBAL and iodine. This sequence is the equivalent of reverse

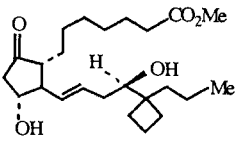
iodoolefin (75) by reduction with DIBAL and iodine. This sequence is the equivalent of reverse addition of HI to protected 74. Mixed lithiocuprate 76 is prepared from 75 by reaction with copper pentyne and tert-butyl lithium. Conjugate addition to the appropriate cyclopentene and deblocking with acetic acid completes the synthesis of **rioprostil** (77) [18].



Viprostol (81) also incorporates a hydroxy group moved to C-16 and protects this from facile metabolic oxidation by vinylation. It is a potent hypotensive and vasodilatory agent both orally and transdermally. The methyl ester moiety is rapidly hydrolyzed in skin and in the liver so it is essentially a prodrug. It is synthesized from protected E-iodo olefin 78 (compare with 75) by conversion to the mixed organocuprate and this added in a 1,4-sense to olefin 79 to produce protected intermediate 80. The synthesis of **viprostol** concludes by deblocking with acetic acid and then reesterification with diazomethane to give 81 [19].



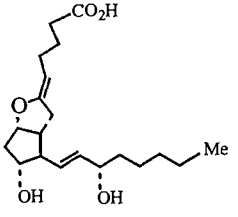
Butaprost (82) not only has the typical C-15 hydroxyl of the natural prostaglandins moved to C-16, as do several of the analogues discussed above, but it has a rather interesting gem dialkyl substitution at C-17, presumably for metabolic protection, in the form of a cyclobutyl ring. It is a bronchodilator and is prepared in a manner analogous to that of **rioprostil** discussed above [17].



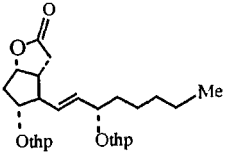
(82)

Prostacyclin (PGI_2) (83) is a naturally occurring bicyclic prostaglandin produced by the vascular endothelium. It is a powerful vasodilator and a potent inhibitor of platelet aggregation. The latter effect makes it of interest in preventing blood clotting. It is too unstable in its own right for therapeutic application, having a biological half-life of seconds to minutes. Much work has been carried out on analogues in an attempt to stabilize the molecule and yet retain significant activity. The carbon bioisostere, **carbacycline** (enol ether oxygen replaced by methylene), has some of these useful properties.

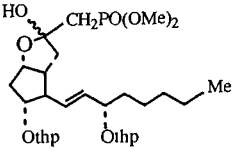
One of the first of the prostacycline analogues to achieve International Nonproprietary Name status is **ciprostene calcium** (**89b**). It is rather less potent as a platelet antiaggregatory agent than **prostacyclin** (83) itself but is still effective in humans in nanogram quantities when given by steady infusion. Its synthesis begins with protected optically active Corey lactone **84** which is reacted with lithium dimethylmethylphosphonate to produce hemiketalphosphonate **85**. Jones' oxidation produces diketone 86 which undergoes an intramolecular Wittig condensation to unsaturated ketone **87** when treated with potassium carbonate and 18-crown-6 in toluene. Conjugate addition of dimethylcopperlithium then leads to saturated ketone 88. The synthesis concludes by Wittig addition of the upper side chain. This step leads to a mixture of 1:1 Z and E olefins which must be separated by chromatography before the right olefin is deblocked in acid and converted to the calcium salt by treatment with CaO in aqueous THF [20].



(83)



(84)



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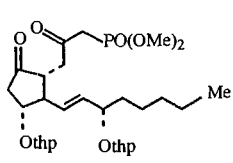

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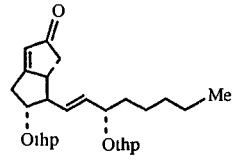

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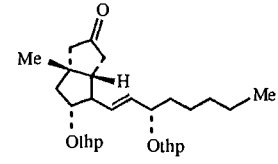

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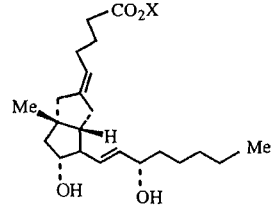
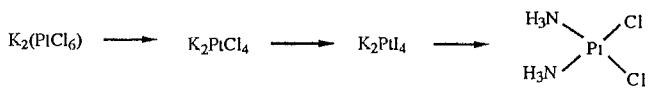


(89a); X = H
(89b); X = 1/2 Ca

4. ORGANOPLATINUM COMPLEXES

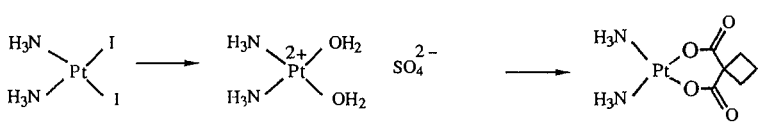
Whereas the medical practice of the Middle Ages contained many inorganic medicaments, modern medicine is dominated by organic drugs. There are, however, notable exceptions. Among these, a number of organoplatinum complexes have shown high potency against a variety of tumors and much work has been carried out in order to reduce their toxicity, enhance their water solubility, and sharpen their anticancer potency. The work has demonstrated that the activity resides in the cis complexes and that the toxicity and pharmacokinetic features of the drugs are manipulable by changing the nature of the organic portion of these agents.

The first of these agents to find use is **cisplatin (93)** itself [21]. Cisplatin was apparently discovered by accident when it was seen that platinum electrodes used in monitoring bacterial cultures leaked platinum and that the consequences were antimicrobial activity. Subsequently, cisplatin was tested in tumor systems also and found to be active. These observations subsequently held up in the clinic but despite marked antitumor activity serious side effects such as kidney damage, damage to the intestinal mucosa, immunosuppression, mutagenicity, and bone marrow depletion, lead to the search for second generation agents. The molecular mode of action of cisplatin and its analogues appears to be cross linking of DNA bases on the same strand rather like some bifunctional alkylating agents. The synthesis proceeds by reduction of potassium hexachloroplatinate (**90**) with hydrazine to give potassium tetrachloroplatinate (**91**). This is converted to potassium tetraiodoplatinate (**92**) by treatment with potassium iodide and then reacted with 6M ammonium hydroxide to give crystals of cisplatin [22]. The iodine exchange enhances the trans effect.



(90) (91) (92) (93)

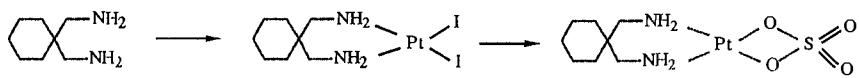
Carboplatin (96) is significantly less toxic in the clinic than cisplatin. Most particularly, it is much less nephrotoxic. Use of a bidentate ligand also ensures formation of a cis complex. Its synthesis begins with cis-diammine platinum diiodide (**94**) which is reacted with silver sulfate to give cis-diaquodiam mine platinum sulfate (**95**). This is reacted with the barium salt of 1,1-cyclobutanedicarboxylic acid to yield **carboplatin** [23].



(94) (95) (96)

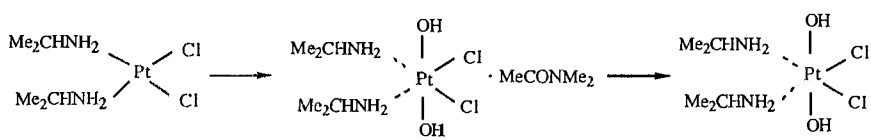
Spiroplatin (99) in animal studies showed excellent antileukemic activity and was less

nephrotoxic than **cisplatin**. Unfortunately when it was tried clinically, little antitumor activity could be demonstrated and it was hard to determine safe doses to use in humans so it was ultimately dropped. Its synthesis starts with potassium tetrachloroplatinate (**91**) which is reacted with spiro-1,3-propanediamine **97** and potassium iodide to give complex platinate **98**. This is treated with silver sulfate to produce **spiroplatin** [24].



(97) (98) (99)

The only prominent antitumor tetravalent platinum complex so far is **iproplatin (102)**. In vitro it has been shown to cause interstrand DNA-breaking and cross linking. Free radical scavengers inhibit these effects. The complex is less neurotoxic and less nephrotoxic than cisplatin. Its synthesis begins with hydrogen peroxide oxidation of cis-dichlorobis(isopropylamine) platinum (**100**) to the dimethylacetamide complex **101**. The latter is heated in vacuum to liberate iproplatin [25].



(100) (101) (102)

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2 Monocyclic Aromatic Compounds

Benzene rings constitute quite rigid, flat, relatively lipophilic moieties with considerable electron density. Groups attached to a benzene ring not only modulate these properties by their relative electron donating or withdrawing character, but also occupy well-defined spatial positions by virtue of the bond angles which form those links. These properties of the aromatic ring enhance uniqueness and fit to receptor sites for endogenous mediators. The benzene ring thus forms the nucleus for a number of pharmacophores.

1. PHENYLPROPANOLAMINES

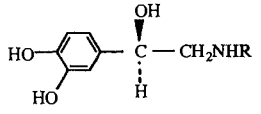
The adrenergic nervous system plays a key role in the regulation of the cardiovascular system. Functions such as performance of the heart muscle and blood pressure are directly affected by levels of the chemical transmitters of the adrenergic system, epinephrine (**1**) and norepinephrine (**2**). Drugs which act on the cardiovascular system by interacting with the adrenergic system have had a major impact on treatment of cardiovascular diseases. These agents range from compounds which act as antagonists at the receptors for beta adrenergic agents (beta blockers) to receptor agonists used to increase contractile force. Effects of epinephrine and norepinephrine result from interaction of those compounds with at least four adrenergic receptors: the alpha 1 and 2 receptors and the beta 1 and 2 receptors.

Some of the side effects due to beta blockers such as the slowing of heart rate can be counteracted by administration of drugs which antagonize the alpha adrenergic receptors. The

antihypertensive agent **labetalol** (3) in fact includes both actions in a single molecule. The presence of two chiral centers in that molecule allows for the existence of two diastereomeric pairs. Preparation and testing of the individual optical isomers showed that each of these had a somewhat different combination of activities. A different conclusion would have been surprising in view of the fact that receptors themselves are made up of chiral molecules. In the event, it was ascertained that the R,R isomer exhibited the best combination of activities.

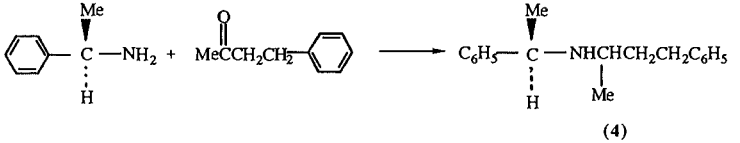
The synthesis starts by condensation of readily available optically active (R)-(+)-alpha-methylbenzylamine with 4-phenyl-2-butanone to form an imine which is itself reduced by hydrogenolysis (Raney nickel) to give a 9:1 mixture of the (R,R)-amine and the (R,S)-amine (**4**). This product (**4**) is then separated into its diastereomers by recrystallization of the corresponding hydrochlorides. Since the amine (**4**) was found to be inert to alkylation with phenacylhalides such as 7, it was debenzylated by hydrogenolysis (Pd/C) to give the primary (R)-amine **5**. Reductive alkylation with benzaldehyde and hydrogen resulted in the formation of the N-benzyl derivative 6. Alkylation of the secondary amine **6** with bromoketone 7, followed by reduction (Pd/Pt/hydrogen) of the ketone group in **8** gives the alcohol **9**. The relative remoteness of the ketone linkage from the chiral center leads to the formation of both diastereomers in a 1:1 mixture. The resulting diastereomers are separated by fractional crystallization. Removal of the benzyl substituents by means of catalytic reduction affords the secondary amine **10**. There is thus obtained the optically active antihypertensive agent **dilevalol** (**10**) [1].

It has by now been well established that Parkinson's disease involves a deficiency of dopamine (**11**) in the brain. It has been further shown that any one of several stratagems for increasing levels of that neurotransmitter near the appropriate receptors will alleviate the symptoms of that disease. For example, a well-absorbed dopamine agonist which reaches the brain should thus be useful in treating that syndrome. Though **ciladopa** (**16**) at first sight closely resembles a beta blocker it should be noted that the presence of the hydroxyl group apparently does not interfere with dopaminergic activity. In addition, the compound lacks the secondary amino group which is thought to be indispensable for interaction with beta adrenergic receptors.

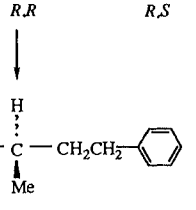


(1); R = H

(2); R = Me

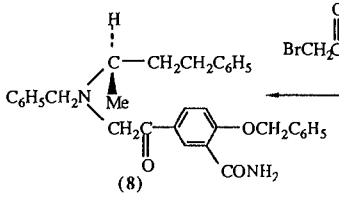


(4)



(5); R = H

(6); R = $CH_2C_6H_5$



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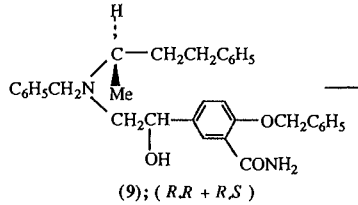
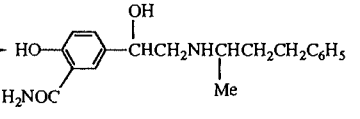


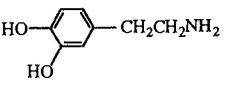
(9); (*R,R* + *R,S*)



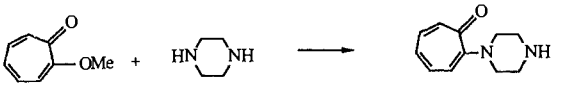
(3); (*R,R* + *R,S* + *S,S* + *S,R*)

(10); (*R,R*)

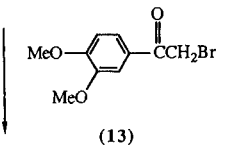
Condensation of piperazine with 2-methoxytropone gives the addition-elimination product **12** [2]. Alkylation of the remaining secondary amino group with bromoketone **13**, itself the product from acylation of dimethyl catechol, gives aminoketone **14**. Reduction of the carbonyl group with sodium borohydride leads to secondary alcohols **15** and **16**. Resolution of these two enantiomers was achieved by recrystallization of their tartrate salts to give ciladopa (**16**) [3].



(**11**)



(**12**)



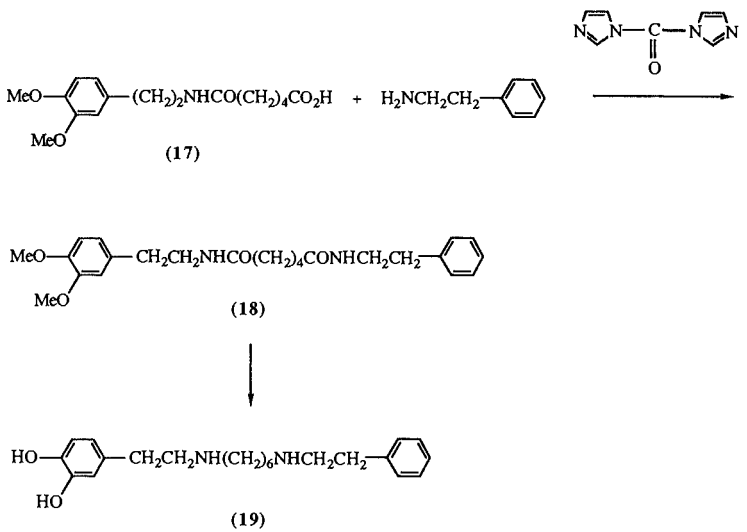
(**13**)

(**14**)

(**15**); (*S*)

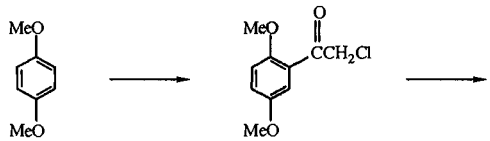
(**16**); (*R*)

Condensation of adipic acid derivative **17** with phenylethylamine in the presence of carbonyldiimidazole affords the bis-adipic acid amide **18**. The synthesis is completed by reduction of the carbonyl groups with diborane followed by demethylation of the aromatic methoxy groups with hydrogen bromide the afford dopexamine (**19**) [3].

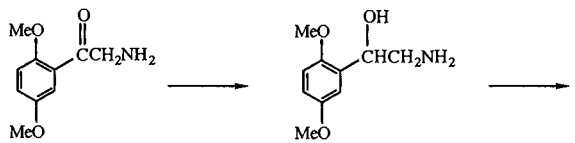


Interposition of an amide function in the norepinephrine-like side chain in midodrine (25) affords a compound which retains a good measure of adrenergic activity. Acylation of dimethylhydroquinone with chloroacetyl chloride gives the chloroketone **20**. The halogen is then converted to the amine **21** by any of a set of standard schemes, and the ketone reduced to an alcohol with borohydride (**22**). Acylation of the amino group in this last intermediate with chloroacetyl chloride affords the amide **23**. The halogen is then displaced by azide and the resulting product (**24**) reduced catalytically to the glycinamide, midodrine (25) [4].

A compound closely related to classical adrenergic agonists in which the para hydroxy function is however replaced by an amino group has been investigated for its activity as a growth promoter in domestic animals. Acylation of the aniline derivative 26 with chloracetyl chloride will afford acetophenone **27**; the amino-ketone 28 is obtained on reaction with isopropylamine. Removal of the protecting group (**29**) followed by reduction of the ketone affords cimaterol (30) [5].



(20)

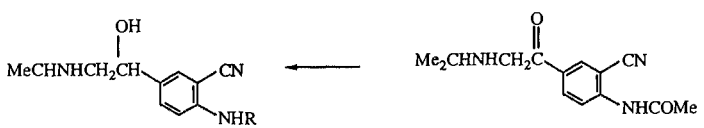


(21) (22)

(23); X = Cl
(24); X = N_3

(25)

(26) (27)



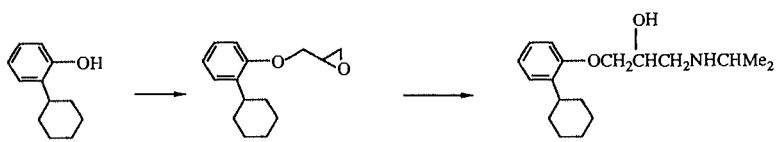
(28)

(29); R = COMe
(30); R = H

2. PHENOXYPROPANOLAMINES

Compounds which act as antagonists at the receptors for beta sympathetic transmitters (beta blockers) have gained very wide acceptance as antihypertensive agents. It was found subsequent to their introduction that there are two populations of beta receptors; the beta-1 receptors are richest in the cardiovascular system; whereas beta-2 receptors are mostly found in the bronchi. Lack of receptor-type specificity led to bronchial spasm in some asthmatic individuals on ingestion of the earlier beta blockers. Much of the work outlined below had as its goal the preparation of agents which showed selectivity for beta-1 receptors.

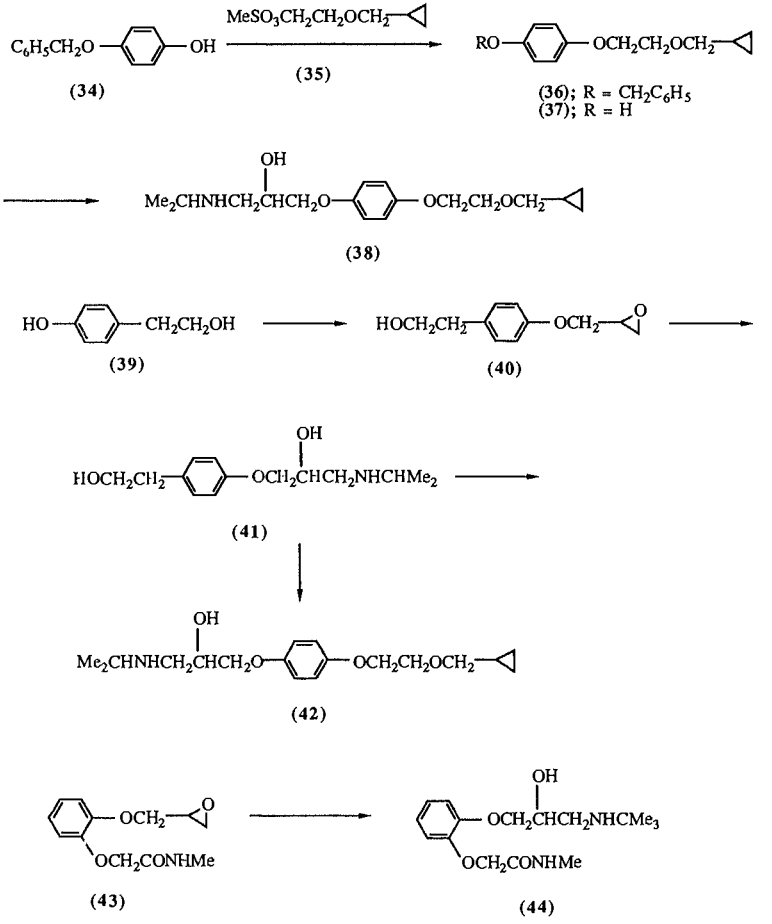
It will be noted that the great majority of beta blockers consist of phenoxypropanolamines. Many of the agents incorporate substituents ortho to the side chain in response to the observation that such groups increase potency; this is thought to be due to the bulk of that substituent, encouraging productive conformations. The synthetic schemes for these agents as a rule culminate in the introduction of the aminoalcohol side chain. The first step often consists in reaction of the appropriate phenolate with epichlorohydrin to give a glycidic ether such as **32**; reaction with a primary amine, usually isopropylamine or tert-butylamine, leads to the amino alcohol. Application of this scheme to o-cyclohexylphenol (**31**), leads to **exaprolol** (33) [6].



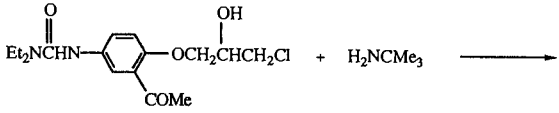
(31) (32) (33)

Alkylation of the monobenzyl ether of hydroquinone **34** with mesylate **35**, gives ether 36. Hydrogenolytic removal of the benzyl group gives phenol 37. This affords **ciclo**prolol (38) when subjected to the standard alkylation scheme [7]. In much the same vein, alkylation of p-hydroxyphenylethanol **39**, obtainable from the corresponding phenylacetic acid, with epichlorohydrin

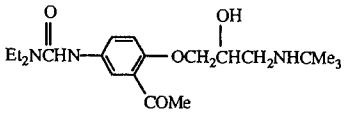
gives ether **40**. Aminolysis with isopropylamine produces **41** which was alkylated with cyclopropylmethyl bromide to give **betaxolol (42)** [8]. Aminolysis with t-butylamine of epoxide **43** gives the beta blocker **cetamolol (44)** [9].



Alkylation of tert-butylamine (**46**) with **45** affords **celiprolol** (**47**) [10].

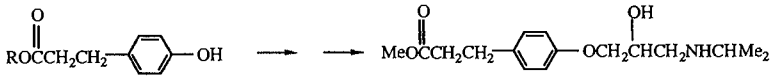


(45) (46)



(47)

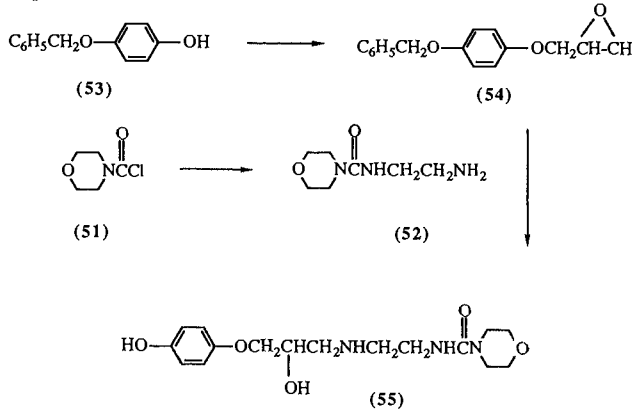
The medicinal chemist is only too familiar with the exciting lead which fails due to too short a duration of action caused by rapid metabolic destruction *in vivo*. Though a number of approaches have been developed for protecting compounds against such destruction these are not universally successful. It is thus refreshing to note a successful program in which a drug was carefully designed to be quickly inactivated by inclusion of a function which is a metabolic weak link. The profound effect of beta adrenergic agonists on cardiac function has led to the use of beta blockers in the treatment of heart diseases. Blood levels which are too low will fail to have a therapeutic effect while levels which are too high may cause excessive suppression of heart function. Careful adjustment of circulating levels of the drug is thus quite important in acute cardiac crises. Parenteral administration of the drug allows rough adjustment of blood levels; infusion of a drug which is quickly inactivated allows fine tuning of those levels. It will be noted that **esmolol** (**50**) incorporates a carboxylic ester on one of the pendant side chains; saponification by the ubiquitous serum esterase enzymes affords the corresponding carboxylic acid; this is rapidly excreted through the kidneys terminating activity. The compound is prepared in straightforward fashion by adding the propanolamine side chain to the methyl ester (**49**) of p-hydroxyphenylpropionic acid (**48**) [11] as detailed above (see the synthesis of **33** in Scheme 2-6).



(48); R = H
(49); R = Me

(50)

Inclusion of one of the phenolic groups present in epinephrine in a compound which otherwise looks like a classic beta blocker, leads to an agent which displays agonist rather than antagonist activity [12]. This agent **xamoterol** (**55**) can, in principle, be prepared by a convergent synthesis which starts by reaction of the chloroformamide of morpholine (**51**) with ethylenediamine to give **52**. Reaction of a singly protected derivative of hydroquinone (53) with epichlorohydrin will give epoxide **54**. Condensation of **54** with **52** followed by removal of the protecting group on the phenol will afford **xamoterol** (**55**).

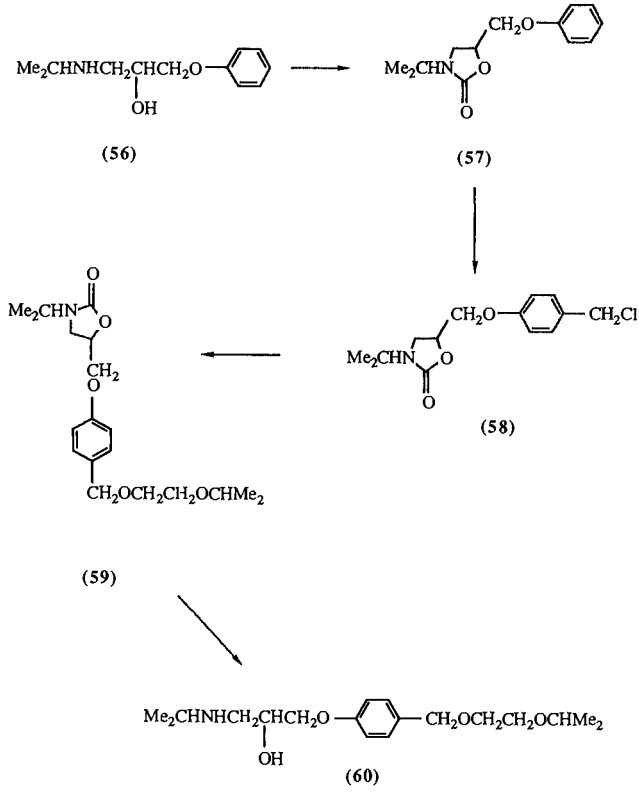


(53) (54)

(51) (52)

(55)

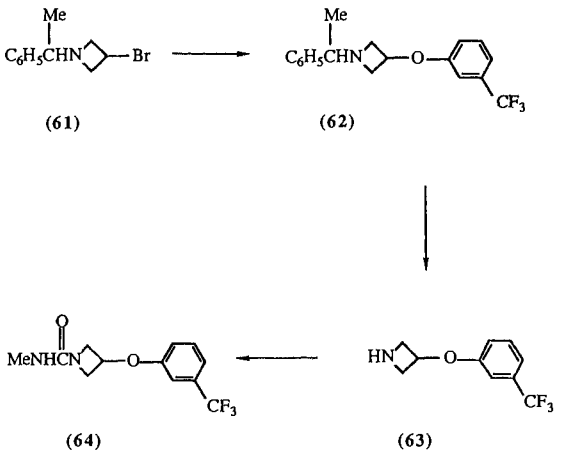
One of the reasons for adding the propanolamine side chain at the last step in the syntheses described above is the reactive nature of that functional array. It is however possible to protect that side chain to permit modification of the aromatic ring in a preformed phenylpropanolamine. For example, reaction of aminoalcohol **56** with phosgene or ethyl orthoformate gives the cyclic carbamate **57**. Chloromethylation by means of paraformaldehyde and hydrogen chloride gives derivative **58**. Displacement of halogen with the anion from isopropoxyethanol leads to the ether **59**. Removal of the carbamate protecting group by reaction with aqueous base affords **bisoprolol** (**60**) [13].



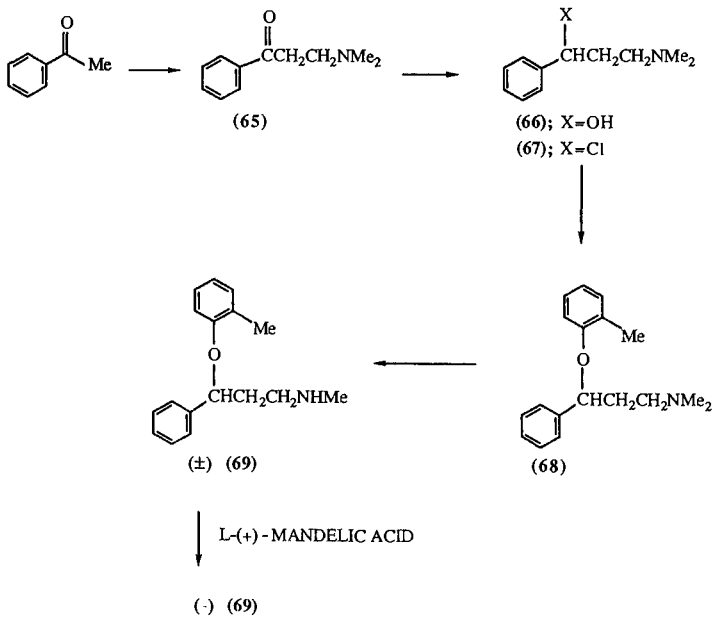
3. ALKYLBENZENES AND ALKOXYBENZENES

The role of the aromatic ring in the alkoxy- and alkylbenzenes which follow is not nearly as well defined as it is with the adrenergic and antiadrenergic drugs.

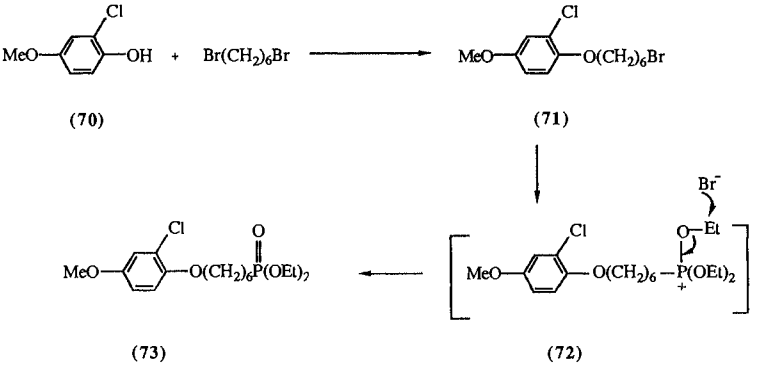
Alkylation of the protected azetidinyl bromide **61** with the anion from m-trifluormethylphenol gives ether **62**. Removal of the N-(alpha-methylbenzyl)- protecting group by catalytic hydrogenation gives the secondary amine 63. Reaction of that compound with methyl isocyanate gives the anticonvulsant urea **fluzinamide (64)** [14].



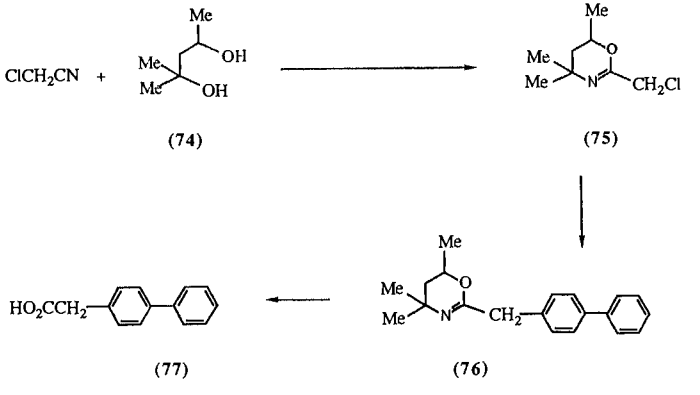
The very slow onset of action and side effects which follow from the anticholinergic side effects characteristic of the tricyclic antidepressants has led to a continuing effort to find replacements from other structural classes which might thus be devoid of this defect. A series of alkoxy phenylpropylamines has been investigated extensively in this search for non-tricyclic antidepressants. The most recent analogue, **tomoxetine** (**69**), is accessible by the same route [15] used to prepare the earlier analogue, **nisoxetine**, in which methoxyl replaces the ortho methyl group. Thus, reduction of the Mannich reaction product (**65**) from acetophenone leads to alcohol **66**. Replacement of the hydroxyl group by chlorine (**67**) followed by displacement of halogen with the anion from o-cresol affords the ether **68**. Removal of one of the methyl groups on nitrogen by means of the von Braun reaction or its modern equivalent (reaction with alkyl chloroformate followed by saponification) leads to racemic **69** which is then resolved with L-(+)-mandelic acid to give the levorotary antidepressant **tomoxetine** (**69**) [16].



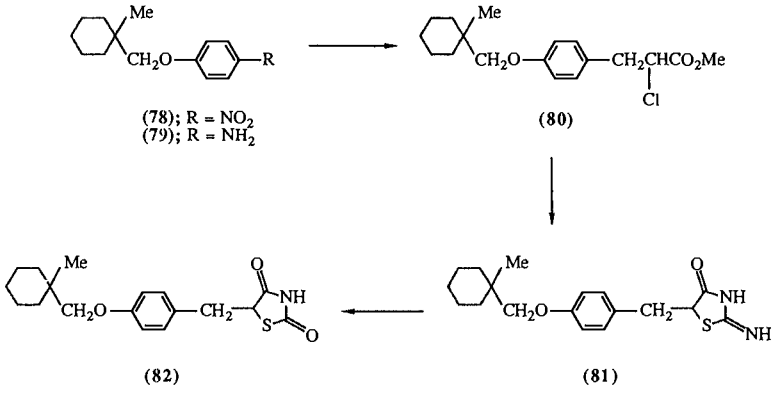
Phosphorus ranks with carbon, hydrogen, oxygen, nitrogen and sulfur as one of the key elements involved in the structure of compounds involved in vital processes. It is thus somewhat surprising to find few drugs that contain phosphorus. Important exceptions involve antiviral agents and some antineoplastic compounds. As an example though the antiviral compound **acyclovir** is itself devoid of phosphorus, it is phosphorylated in vivo within virus-infected cells to the active agent. If phosphorylated before administration, the compound fails to enter the cell and so is inactive. A recent antiviral candidate **fosarilate** (73) incorporates phosphorus in the form of a phosphite ester group. This function is electrically neutral, permitting ready entry into cells across typical lipid membranes. Alkylation of hydroquinone derivative **70** with 1,6 dibromohexane gives the ether **71**. Reaction with triethyl phosphite gives initially the product from direct alkylation (72). In a classical Arbuzov reaction, the bromide counterion displaces one of the ethyl groups by attack on carbon. There is thus obtained **fosarilate** (73) [17].



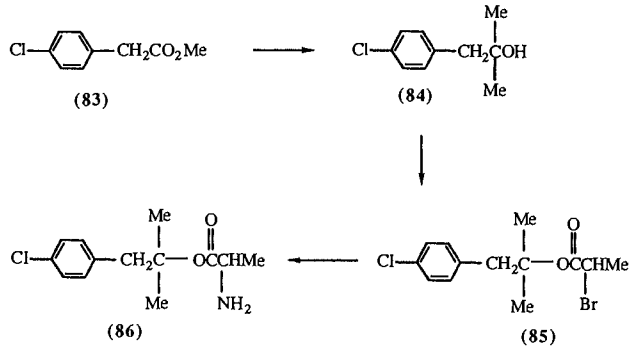
Arylacetic and 2-arylpropionic acids have been extensively investigated as potential nonsteroidal antiinflammatory agents (NSAIDs). A wide range of substituents have been shown to be consistent with the prostaglandin synthetase blocking activity to which this class of drugs owes its activity. **Felbinac** (77) [18] represents possibly the ultimate structural simplification in this therapeutic category. One of the more interesting routes to this compound starts with the condensation of chloroacetonitrile with glycol **74** to give the oxazine **75**. This heterocycle contains both a carboxyl group in its latent form and an activated allylic halogen. Displacement of the latter with the Grignard reagent from 4-bromobiphenyl leads to intermediate 76. Acid hydrolysis leads to **felbinac** (77) [19].



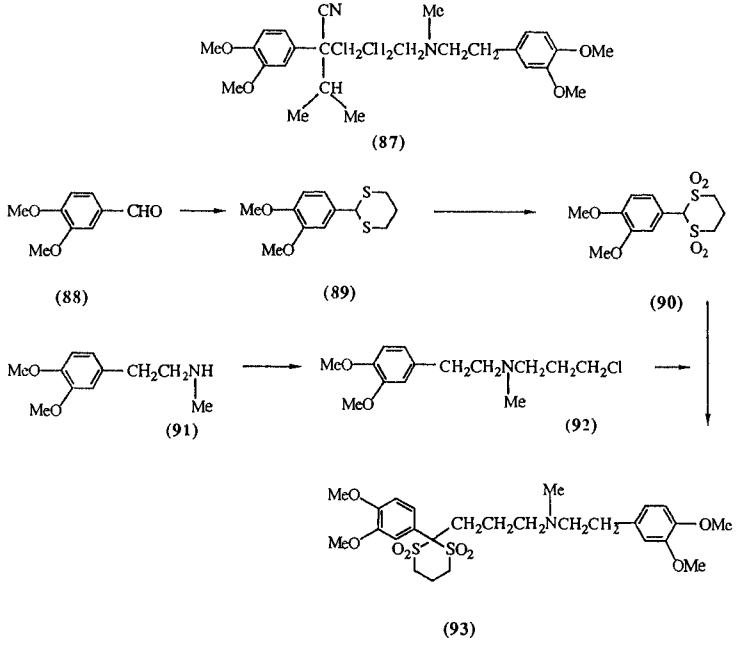
Virtually all drugs which have proven useful in the treatment of adult onset diabetes (also known as non-insulin dependent diabetes) contain sulfonylurea or biguanide functions. The thiazolidinedione function present in **ciglitazone** (82) represents a marked departure from the previous pattern. The synthesis of **ciglitazone** (82) starts with 4-(1-methylcyclohexylmethoxy)nitrobenzene (78) which was probably obtained by alkylation of p-nitrophenol with 1-bromomethyl-1-methylcyclohexane. Hydrogenation of 78 yielded the aniline derivative 79. Diazotization of 79 in the presence of copper (I) oxide followed by addition of methyl acrylate (Meerwein arylation) produced the alpha-chlorinated ester 80. Reaction of the chloro ester with thiourea probably proceeds through initial displacement of halogen by the nucleophilic sulfur; displacement of ethoxide by urea nitrogen leads, after bond reorganization, to the heterocycle 81. Acid hydrolysis of the exocyclic imine affords the target compound (82) [20].



An ester of alanine with an arylaliphatic alcohol has shown promise as a non-tricyclic antidepressant. It may be speculated that the hindered milieu of the ester linkage protects the compound from hydrolysis by endogenous esterases. The preparation starts by reaction of phenylacetate 83 with methyl magnesium iodide to give tertiary carbinol 84. Acylation with 2-bromopropionyl bromide leads to ester 85; displacement of halogen with ammonia leads to **alaproclate** (86) [21].

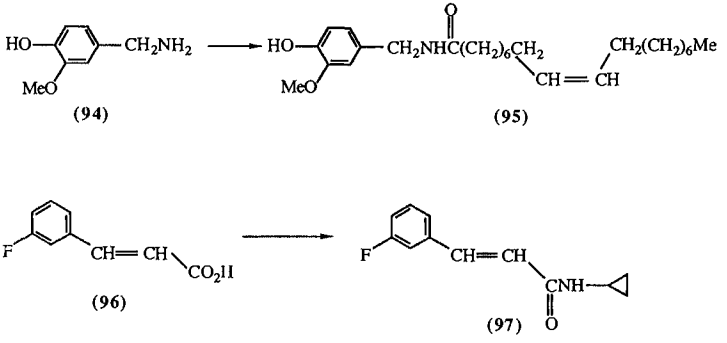


Verapamil (87) probably ranks chronologically as the first antianginal compound which acts by blocking the so-called slow calcium channels. It is of passing interest that elucidation of the drug's mechanism of action awaited the discovery, some years later, of the dihydropyridine antianginals. Replacement of the quaternary center by an oxidized dithiane ring interestingly leads to retention of activity. Acetal formation of benzaldehyde **88**, with 1,3-propanedithiol leads to dithiane **89**; treatment with hydrogen peroxide gives the bis-sulfone **90**. The side chain intermediate **92** is obtained by alkylation of phenethylamine **91** with 1-bromo-3-chloropropane. Treatment of the anion from **90** with the side chain intermediate affords tiapamil (93) [22].



Reductive amination of vanillin with ammonia leads to benzylamine **94**. Acylation of that compound with (Z)-9-octadecenoyl chloride affords the analgesic **olvanil (95)** [23].

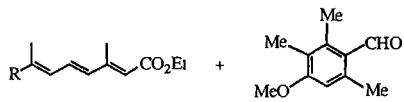
Condensation of m-fluorobenzaldehyde with malonic acid leads to the trans cinnamic acid **96**; acylation of the acid chloride with cyclopropylamine leads to amide **97** (**cinflumide**), a muscle relaxant [24].



The free acid analogue of the antipsoriatic agent **etretinate (103)** is prepared in substantially the same way as the parent compound. Thus, the aldehyde group in **98** is converted finally to the phosphonate (**101**) by sequential reduction (**99**), conversion to the chloride (**100**), and finally reaction with triethyl phosphite. Condensation of the ylide from **101** with the benzaldehyde **102** gives **etretinate (103)**; saponification affords **acitretin (104)** [25].

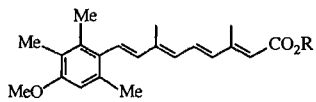
4. DERIVATIVES OF ANILINE

The broad category of helminths includes a host of parasitic worms such as tapeworms and flukes; infestations in domestic animals can have serious negative consequences on growth. Anthelmintic drugs as a result occupy an important place in the practice of veterinary medicine. **Febantel (108)** is representative of this class of agents. Acylation of nitroaniline **105** with methoxyacetyl chloride gives the corresponding amide **106**. Reduction of the nitro group leads to the aniline **107**. Reaction of that intermediate with the thiourea S-methyl ether probably proceeds by initial addition of the amine to the imine; loss of methylmercaptan gives the substituted guanidine function. There is thus obtained **febantel (108)** [26].



(98); R = CHO
(99); R = CH_2OH
(100); R = CH_2Cl
(101); R = $CH_2PO(OEt)_2$

(102)

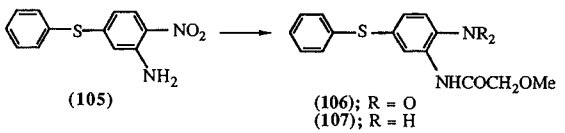


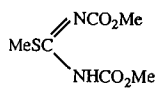
(103); R = Et
(104); R = H

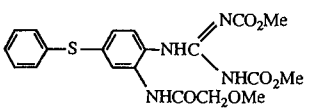
In a somewhat similar vein, alkylation of the urea derivative **109** with methyl iodide affords the S-methyl ether **110**. Condensation of that with taurine (**111**), leads to the guanidine **112**, again by an addition elimination process. The product is the anthelmintic agent **netobimin** (**112**) [27].

Nucleophilic aromatic substitution of the anion from arylacetonitrile **113** on the dichloronitrobenzene **114** results in replacement of the para halogen and formation of **115**. Reduction of the nitro group gives the corresponding aniline (**116**). Acylation of the amine with 3,5-diiodoacetylsalicylic acid **117** by means of the mixed anhydride formed by use of ethyl chloroformate, gives, after alkaline hydrolysis, the anthelmintic agent **closantel** (**118**) [28].

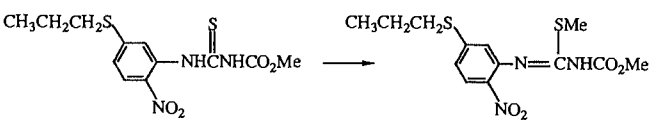
Reaction of 2,4-xylidine with methylamine and ethyl orthoformate leads to the amidine **119**; condensation of that product with a second mole each of orthoformate and 2,4-xylidine gives the scabicide **amitraz** (**120**) [29].

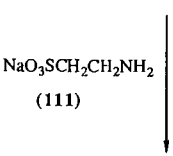


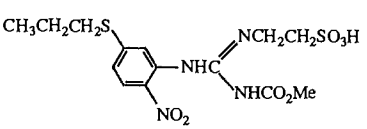




(108)

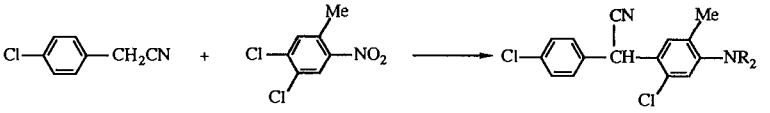




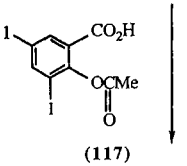


(112)

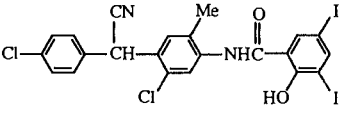
Treatment of 2,6-dimethylaniline (**121**) with phosgene and triethylamine affords the corresponding isocyanate (**122**). Condensation of that reactive intermediate with N-isopropylpropylene-1,3-diamine leads to formation of urea **123**. This product, **recainam** (**123**), acts as membrane stabilizing agent and thus exhibits both local anesthetic and antiarrhythmic activity [30].



(113) (114) (115); R = O (116); R = H_2

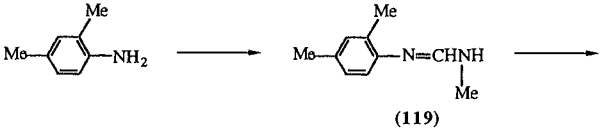


(117)

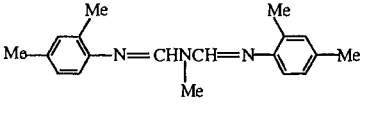


(118)

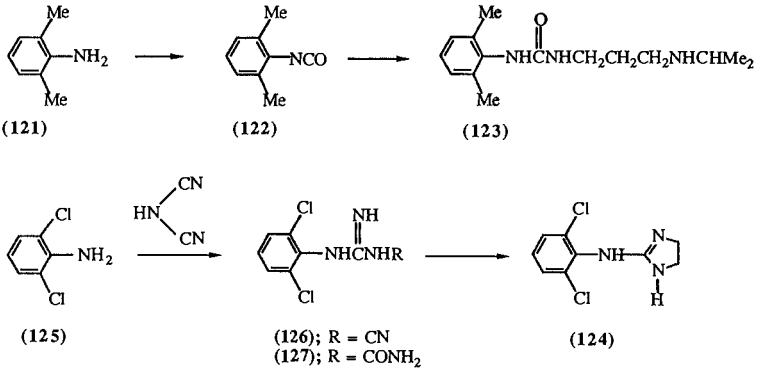
Centrally acting alpha blocking agents such as **clonidine (124)** have proven useful as antihypertensive agents. Side effects of this drug have led to the search for better tolerated analogues. This effort has shown that there is considerable flexibility in the specific nature of the guanidine function. Preparation of a noncyclic analogue starts with reaction of aniline **125** with dicyanamine to give **126**. Hydrolysis under strongly acidic conditions, interestingly, leads to hydrolysis of the nitrile without affecting the guanidine function. There is thus obtained biclodil (127) [31].



(119)



(120)

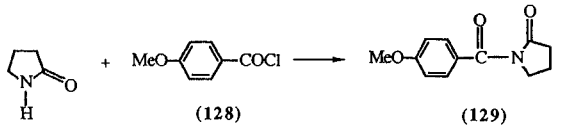


5. BENZOIC ACID DERIVATIVES

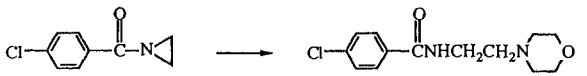
Pyrrolidone derivatives substituted on nitrogen with alkyl groups have shown some activity as cognition enhancing agents in the aged. It is thus of some interest that acylation on nitrogen also leads to active compounds. Thus, treatment of anisoyl chloride **128** with the anion from 2-pyrrolidinone affords **aniracetam (129)** [32]. Aniracetam is the product of an effort to discover agents to treat precocious senility (Alzheimer's disease).

Yet another nontricyclic antidepressant consists of a relatively simple morpholine derivative. Acylation of aziridine with p-chlorobenzoyl chloride gives the amide **130**. This intermediate is sufficiently reactive to undergo ring opening on treatment with morpholine. The product is the antidepressant agent **moclobemide** (131) [33].

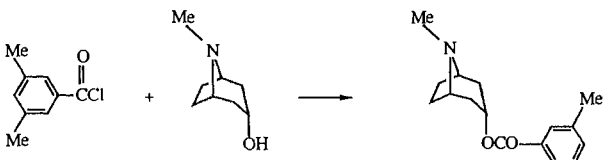
Esters of tropine have a venerable place in medicinal chemistry. One such compound, **cocaine**, the object of some current interest, was the natural product lead which led eventually to most of today's local anesthetics. A distantly related analogue is prepared by reaction of tropine (132) with 3,5-dimethylbenzoyl chloride. This leads to an ester structurally related to another prominent natural product, **atropine (133)**. The product, **tropanserin (134)**, is described as an antiserotonergic agent intended for antimigraine use [34].



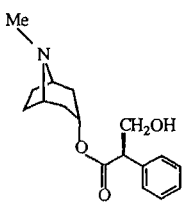
(128) (129)



(130) (131)



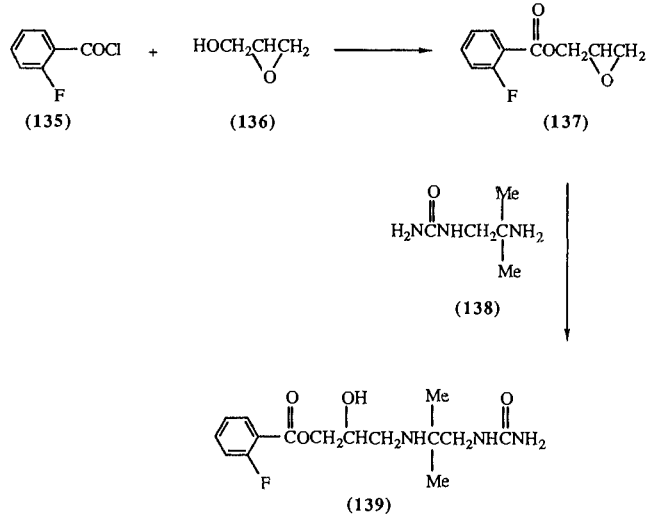
(132) (134)



(133)

It has by now been reasonably well established that an ethanolamine function appropriately linked to an aromatic ring is a prerequisite for beta adrenergic activity and/or antagonism. Examples have been met above where those two moieties are attached directly as well as examples where the functions are separated by an oxymethylene fragment. It has recently been found that beta blocking activity is retained even when a carbonyl is inserted between the extra oxymethylene

group and the aromatic ring. Activity is lost once the ester linkage is broken. These compounds will also thus serve as short acting beta-blockers since they will be expected to be substrates for serum esterases. Acylation of glycidol **136** with acid chloride **135** proceeds in straightforward fashion to give the ester **137**. Condensation of that intermediate with amine **138**, obtained by reaction of 1,1-dimethyl ethylenediamine with urea gives the short acting betablocker **flestolol (139)** [35].



(135) (136) (137) (138) (139)

The classical antipsychotic agents, such as the phenothiazines and butyrophenones, owe much of their efficacy to their dopamine antagonist activity. A number of these agents find some utility as antiemetic compounds since emesis is also at least partly mediated by dopaminergic nerves. A dopamine antagonist from a quite different structural class seems to show some selectivity for those GI functions which involve dopamine receptors. The prototype, **metoclopramide (140)**, has been found useful as an antiemetic compound as well as an agent for the control of the motility of the upper GI system. The finding that this drug controls emesis not effected by earlier dopamine antagonists, for example, that induced by chemotherapeutic agents used in cancer patients, has led to increased interest in the benzamide class.

The benzoic acid moiety common to many of the benzamides is prepared in straightforward manner from the methyl ether of p-aminosalicylic acid **141**. Acylation on nitrogen (**142**) followed by chlorination gives intermediate **143**; benzoic acid **144** is then obtained by removal of the acetyl group. Condensation of this acid with an aminopiperidine could be achieved by means of the mixed anhydride (prepared by reaction with ethyl chloroformate), which affords **clebopride** (**145**). Reaction with 3-aminoquinuclidine (**146**) of the intermediate prepared from acid **144** with carbonyldiimidazole affords **zacopride** (**147**) [36].

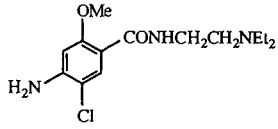
Activity is apparently retained when the aromatic amino group is deleted. Bromination of acid **148** followed by reaction of the product (**149**), as its acid chloride, with the (S)-(-)-aminomethylpyrrolidine **150**, gives the dopamine antagonist, **remoxipride** (**151**) [37] with (S)-configuration.

The synthesis of a benzamide with a somewhat more complex side chain starts by condensation of acid **144** with racemic cis-aminopiperidine **152**. Removal of the benzyl group of **153** by hydrogenolysis gives the secondary amine **154**. Alkylation on nitrogen with the halide **155** gives finally the dopamine antagonist, **cisapride** (**156**) [38,39].

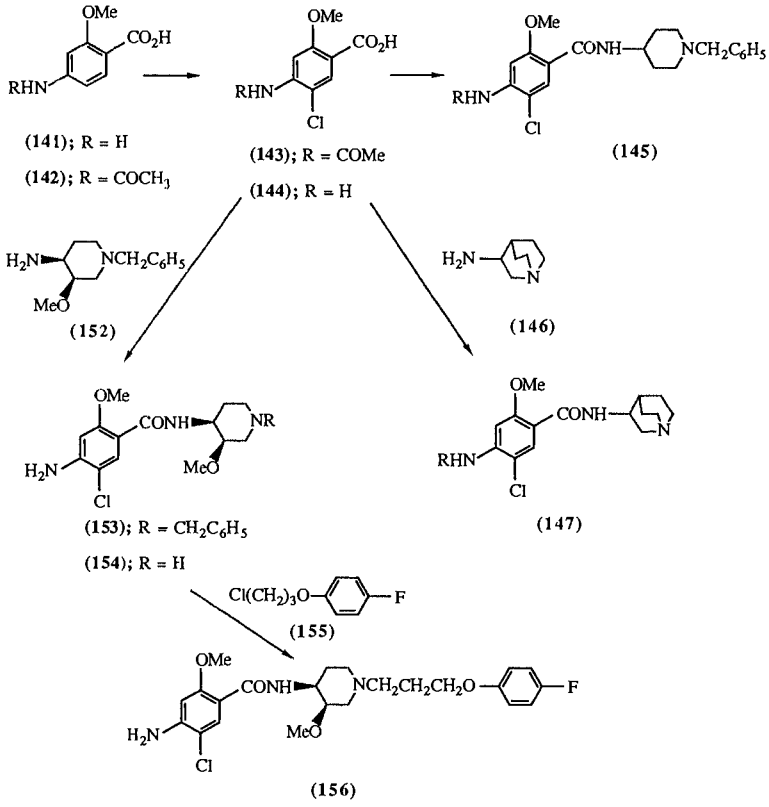
Sulfasalazine (157) is one of the few drugs useful in the treatment of ulcerative colitis. It is well established that the compound undergoes reductive cleavage in the gut to p-aminosalicylic acid and sulfapyridine; the former is actually the active agent. **Sulfasalazine** thus serves as a site-directed prodrug for the salicylate. A newer agent for this indication consists of two salicylates linked by an azo linkage; reductive cleavage should thus yield only salicylate. Treatment of methyl aminosalicylate **158** with nitrous acid leads to diazonium salt **159**. Reaction of that with methyl salicylate gives the diazonium coupling product **160**. Saponification then yields **olsalazine** (**161**) [40].

Flufenamic acid (**162**) is a reasonably well-established NSAID; (Non Steroidal Anti Inflammatory Drug). Alkylation of its potassium salt with the hydroxyethyl ethyl ether of ethylenechlorohydrin affords the latentiated derivative **etofenamate** (**163**) [41]. Antiinflammatory activity is apparently retained when both rings in the fenamate series carry carboxyl groups. Thus, condensation of dichlorobenzoic acid **164** with anthranilic acid (**165**) by means of nucleophilic aromatic

substitution, gives the NSAID **lobenzarit (166)** [42].



(140)



(141); R = H

(142); R = $COCH_3$

(143); R = COMe

(144); R = H

(145)

(146)

(147)

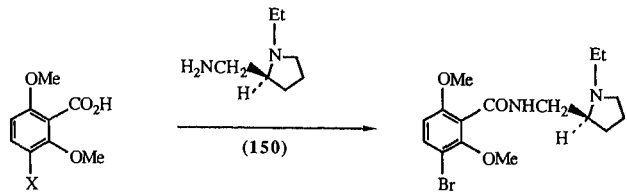
(152)

(153); R = $CH_2C_6H_5$

(154); R = H

(155)

(156)

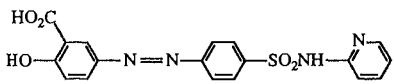


(148); X = H

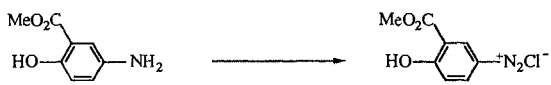
(149); X = Br

(150)

(151); (*S*)



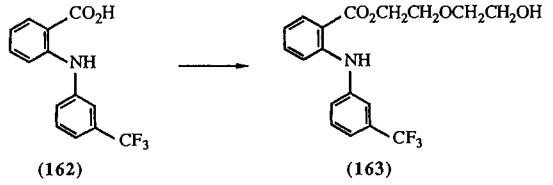
(157)



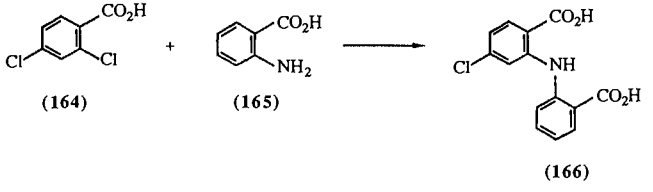
(158) (159)

(161) (160)

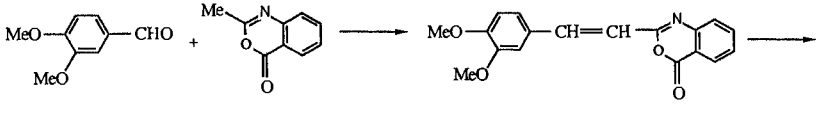
One of the early steps in an allergic reaction consists in the release of a series of endogenous compounds referred to as mediators from sensitized cells. The finding in the early 1960s that **cromolyn sodium**, still the only approved drug of this class, blunts this reaction has led to an intense search for additional examples. It is of interest that a relatively simple anthranilic acid derivative has shown mediator-release inhibiting activity. Reaction of 3,4-dimethoxybenzaldehyde (**167**) with isatoic anhydride **168** gives the condensation product **169**, which, upon hydrolysis, affords **tranilast (170)** [43].



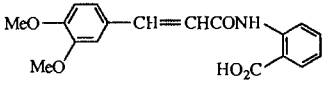
(162) (163)



(164) (165) (166)

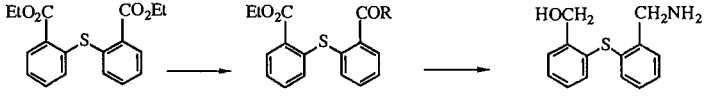


(167) (168) (169)



(170)

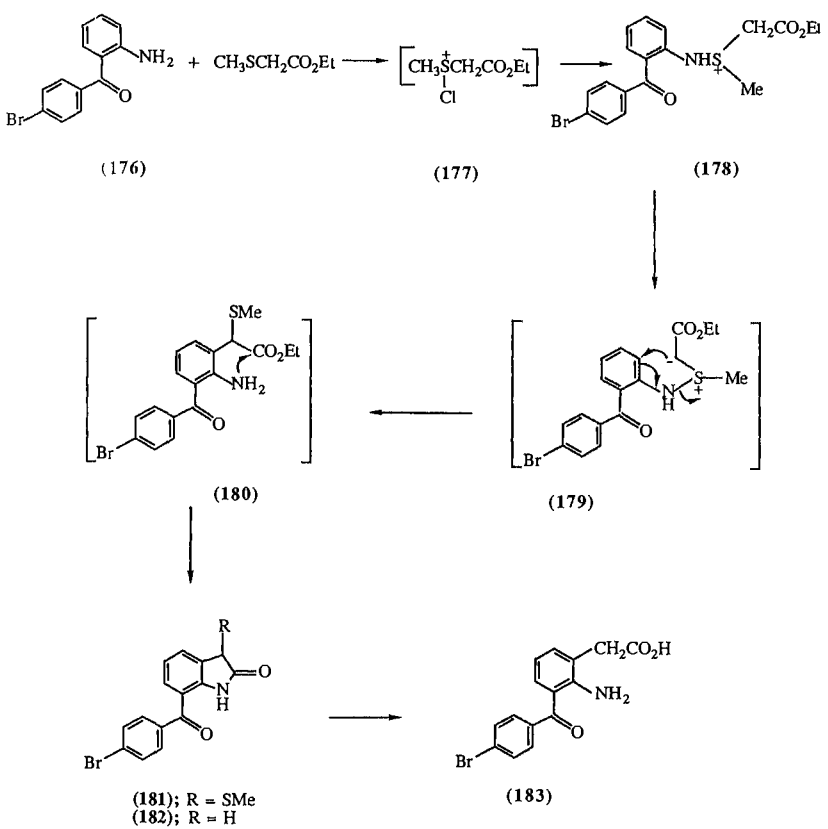
A substituted benzoic acid serves as precursor for the nontricyclic antidepressant **bipenamol** (**175**). Selective saponification of ester **171** affords the half-acid **172**. Reaction of the acid chloride derived from this intermediate (**173**) with ammonia gives the amide **174**. Reduction of the last by means of lithium aluminum hydride gives **bipenamol** (**175**) [44].



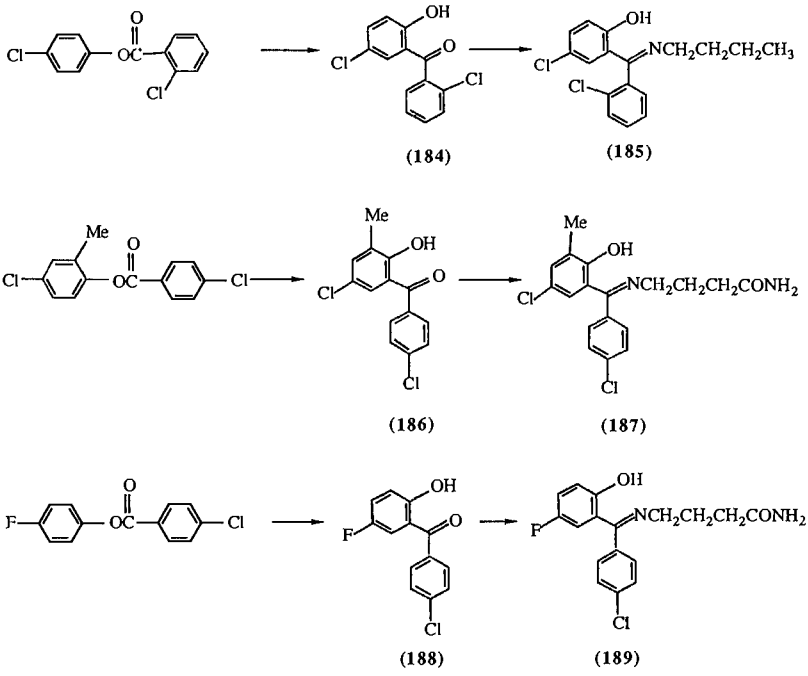
(171) (172); R = OH (173); R = Cl (174); R = NH_2 (175)

6. DIPHENYLMETHANES

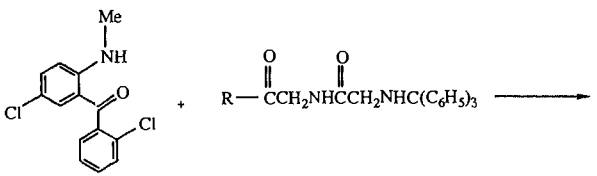
The sulfur analogue of the Hauser ortho-substitution rearrangement provides access to an arylacetic NSAID. Reaction of the aminobenzophenone **176** with ethyl methylthioacetate and tert-butyl hypochlorite gives the intermediate **178**. The reaction probably proceeds by way of formation of the S-chlorinated sulfonium derivative **177**; displacement on sulfur will lead to the salt **178**. Treatment with triethylamine leads initially to the betaine **179**. Electrocyclic rearrangement of that transient intermediate leads, after rearomatization, to the homoanthranilic acid **180**. Internal ester-amine interchange leads then to indolone **181** [45]. The thiomethyl group is then removed with Raney nickel. Saponification of intermediate **182** affords **bromfenac (183)** [46].



Gamma-aminobutyric acid (GABA) ranks among the numerous brain neurotransmitters; it exerts inhibitory activity on certain pathways and abnormalities in levels of GABA or in its transport and/or metabolism have been implicated in various CNS diseases including convulsions. Attempts to treat such disorders by administration of exogenous GABA are rendered difficult by the compound's poor penetration of the blood brain barrier. A series of imines of GABA or its potential metabolic precursors with phenolic benzophenones are apparently well enough absorbed to show antiepileptic and anticonvulsant activity. Acylation of p-chlorophenol with o-chlorobenzoyl chloride gives, after Fries rearrangement, phenol **184**; formation of the imine between this ketone and butylamine affords **fengabine** (185) [47]. In a similar vein, acylation of 2,4-dichlorophenol with p-benzoyl chloride gives the benzophenone **186**, after Fries rearrangement; acylation of p-fluorophenol with the same acid chloride gives the rearranged benzophenone **188**. Formation of the imines of these ketones with the amide of GABA gives respectively **tolgabide** (**187**) [48], and **progabide** (**189**) [49].



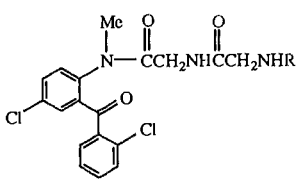
It has been shown that glycine amides of aminobenzophenones are readily converted to the corresponding benzodiazepines in vivo. Peptides which terminate in such a moiety should thus serve as a benzodiazepine prodrug after hydrolysis by peptidases. One of the glycine residues in **lorzafone (194)**is presumably removed metabolically in this manner to give a benzodiazepine precursor which spontaneously cyclizes. Acylation of benzophenone **190** with the trityl protected dipeptide **191**, as its acid chloride **192**, affords the amide **193**. Removal of the trityl protecting group with acid yields **lorzafone (194)** [50].



(190)

(191); R = OH

(192); R = Cl

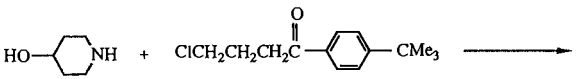


(193); R = $C(C_6H_5)_3$

(194); R = H

The sedation side effect commonly observed on administration of classical antihistaminic drugs has been attributed in part to the ease with which many of these compounds cross the blood brain barrier. There have been developed recently a series of agents, for example, **terfenadine** (198), which cause reduced sedation by virtue of decreased penetration into the CNS. This is achieved by making them more hydrophilic. Synthesis of a related compound, **ebastine (197)**,

starts by alkylation of 4-hydroxypiperidine with butyrophenone **195**. Alkylation of the alcohol **196** at the 4 position with benzhydryl bromide leads to **ebastine (197)** [51].



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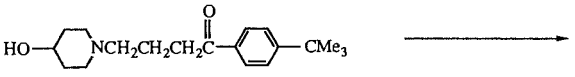

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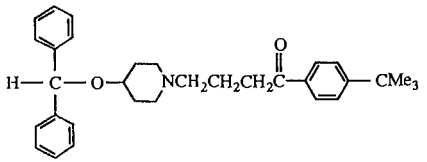

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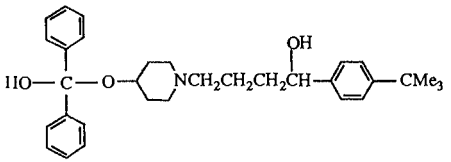
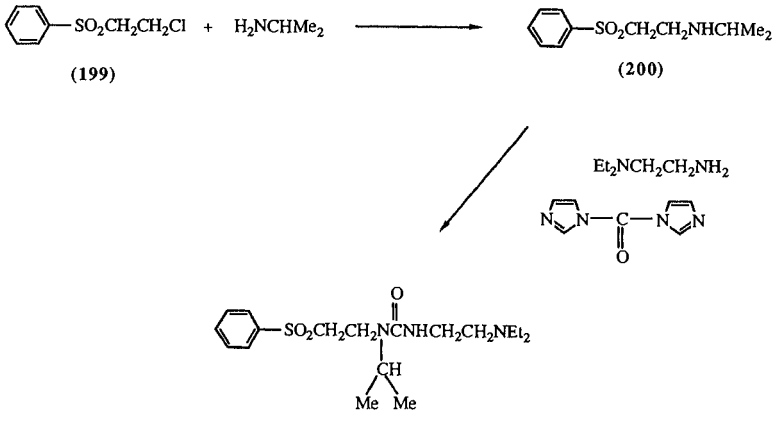


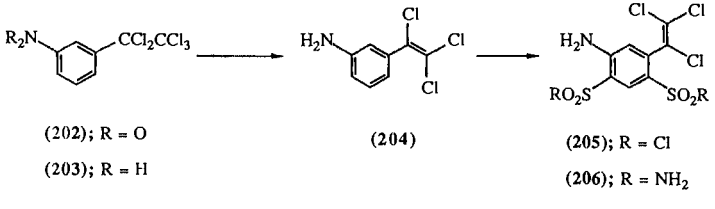
(198)

7. MISCELLANEOUS COMPOUNDS

The antiarrhythmic activity of local anesthetics has been noted several times previously. Another such agent is prepared by first alkylating isopropylamine with sulfone **199**. Reaction of the product (**200**) with diethylethylenediamine and carbonyldiimidazole results in transfer of the CDI carbonyl group and formation of the urea suricainide (**201**) [52]. The transform in all likelihood involves stepwise replacement of the imidazole groups by the basic groups in the other reactants.

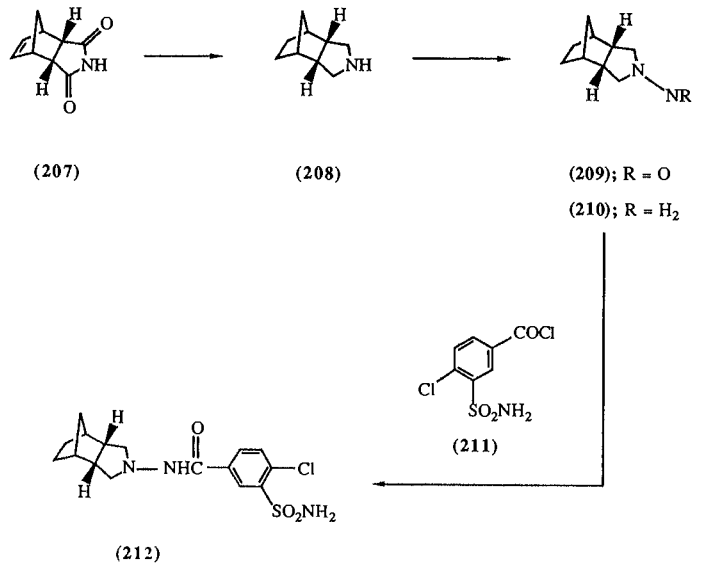


The antiparasitic drug **clorsulon (206)**, contains a rather unusual trichloroethylene group. This function is established early in the synthesis by treatment of the perhalogenated compound **203** obtained from reduction of **202** with iron powder. Chlorosulfonation of **204** by means of chlorosulfonic acid, followed by conversion of sulfonyl chloride **205** to the amide, gives **clorsulon (206)** [53].

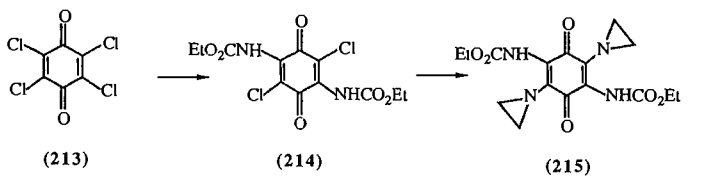


Thiazide diuretics have a venerable history as antihypertensive agents; until the advent of the angiotensin-converting enzyme (ACE) inhibitors this class of drugs completely dominated first line therapy for hypertension. The size of this market led until surprisingly recently to the syntheses of new sulfonamides related to the thiazides. Preparation of one of the last of these compounds starts by exhaustive reduction of the Diels-Alder adduct from cyclopentadiene and maleimide (207). Nitrosation of the product (208), followed by reduction of the nitroso group of **209**,

gives the corresponding hydrazine (**210**). Acylation with acid chloride **211** gives **tripamide** (**212**) [54].



Cancer chemotherapeutic agents as a rule poorly penetrate the blood brain barrier. Brain tumors are thus not readily treatable by chemotherapy. **Diaziquone** (at one time known as AZQ) is an exception to this generalization. Treatment of chloranil (**213**) with the anion from urethane gives intermediate **214**, probably by an addition elimination scheme. Displacement of the remaining halogen with aziridine yields diaziquone (**215**) [55].



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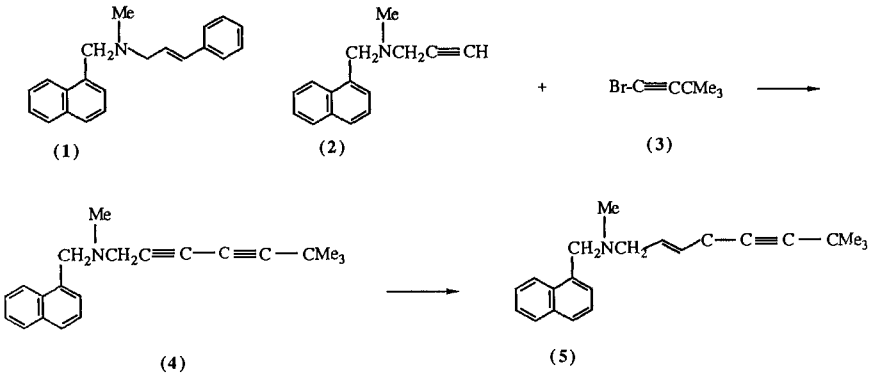
3 Polycyclic Aromatic Compounds and Their Reduction Products

1 NAPHTHALENES AND TETRALINS

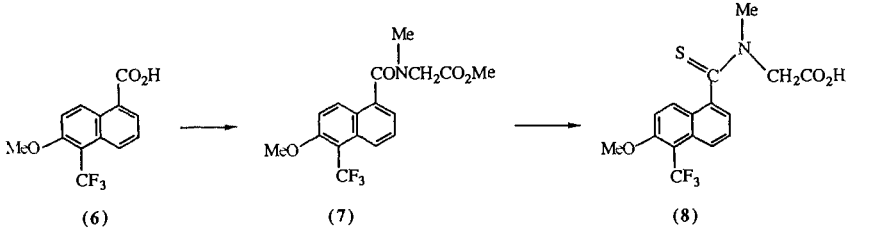
The diverse range of pharmacological actions of this structural class documents the belief that the naphthalene nucleus consists of a scaffold upon which various functional groups can be arranged and that the action elicited is a consequence of receptor response to the kind and spatial arrangement of these functions

Terbinafine (5) (formerly SF 86327) is an antidermatophytic (antifungal) agent apparently owing its selective action to an inhibition of squalene epoxidation Ergosterol is one of the possible end products of the pathway requiring squalene epoxide Ergosterol is an essential component of fungal membranes so a deficiency in its production brought about by **terbinafine** creates a serious problem for fungi Mammalian cell membranes are not as efficiently inhibited by **terbinafine** accounting for the useful selective toxicity of this agent

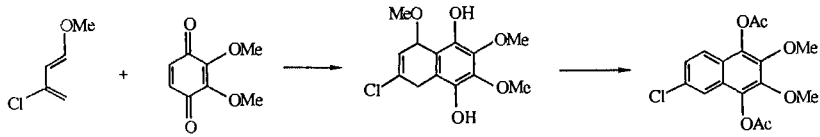
The original lead substance for this fungal class, **naftifine** (1) was discovered during routine screening and a derivative generating program eventually led to **5** [1] The synthesis of **terbinafine** begins by alkylation of the allyl acetylene derivative **2** with bromoacetylene derivative **3** mediated by CuBr and base The asymmetrically coupled diyne (**4**) was reduced to the trans eneyne **terbinafine** (**5**) with diisopropyl aluminum hydride Such reduction is a characteristic feature of tertiary 2-propyneamines and contrasts with the better known production of cis olefins by hydride reduction of simpler acetylenes The selectivity of the reduction also follows from this nitrogen based directing influence



The complex thioamide **tolrestat** (8) is an inhibitor of aldose reductase. This enzyme catalyzes the reduction of glucose to sorbitol. The enzyme is not very active, but in diabetic individuals where blood glucose levels can spike to quite high levels in tissues where insulin is not required for glucose uptake (nerve, kidney, retina and lens) sorbitol is formed by the action of aldose reductase and contributes to diabetic complications very prominent among which are eye problems (diabetic retinopathy). **Tolrestat** is intended for oral administration to prevent this. One of its syntheses proceeds by conversion of 6-methoxy-5-(trifluoromethyl)naphthalene-1-carboxylic acid (6) to its acid chloride followed by carboxamide formation (7) with methyl N-methyl sarcosinate. Reaction of amide 7 with phosphorous pentasulfide produces the methyl ester thioamide which, on treatment with KOH, hydrolyzes to **tolrestat** (8) [2].



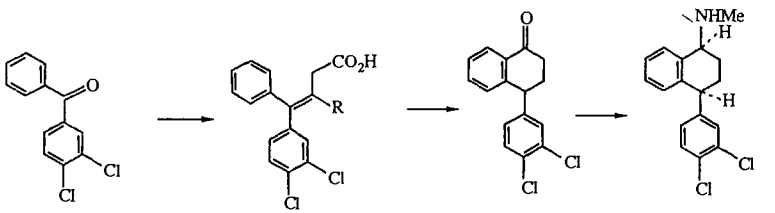
The hydroquinone derivative **lonapalene (12)** is intended to be used topically for the treatment of the skin disease psoriasis in place of classical treatments such as coal tar, anthralin, and cortical steroids. These suffer from the defects of staining the skin and/or causing atrophy. **Lonapalene** inhibits 5-lipoxygenase in vitro and is believed to exert its effects by blocking leucotriene formaiion in vivo. A short synthesis [3] starts by Diels-Alder reaction of 3-chloro-1-methoxy-1,3-butadiene (**9**) and 2,3-dimethoxybenzoquinone (**10**) to give adduct 11 under defined conditions in which the air sensitive hydroquinone is intercepted by addition of acetic anhydride to give **12** in a one-pot reaction. Concomitant aromatization through loss of methanol occurs. A somewhat more involved synthesis is also available [4].



(9) (10) (11) (12)

Sertraline (17) is a tetralin analogue possessing nonsedative antidepressant activity. At subtherapeutic doses it potentiates the action of a subthreshhold dose of morphine in the classic tail flick model for analgesia. This effect is apparently mediated through serotonin and adrenergic neurones and apparently therefore satisfies the stated goals of the program by possessing antidepressant activity by a different pharmacological mechanism than the classical agents (which appear to inhibit norepinephrine uptake at certain receptors).

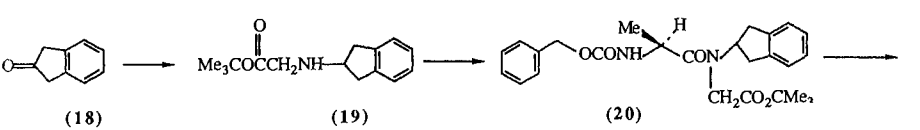
The synthesis starts with the Stobbe condensation of diethylsuccinate and 3,4-dichlorobenzophenone (13). The product (**14**) is hydrolyzed and decarboxylated to a cis-trans mixture of olefins (**15**). This last is reduced using a Pd/C catalyst and then undergoes unidirectional Friedel-Crafts intramolecular acylation into the more reactive ring to produce substituted tetralone **16**. This was converted to its imine with methylamine catalyzed by titanium tetrachloride and then sodium borohydride reduction produced **17** as a mixture of diastereomers. This was resolved by column chromatography to give **sertraline** [5]. Dextrorotatory cis **sertraline** is substantially more potent than its isomers.



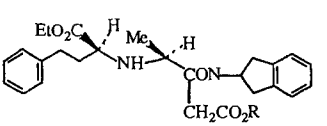
(13) (14), R = CO_2Et (15), R = H (16) (17)

2 INDANES AND INDENES

Following the development and introduction of captopril and enalapril, a great many investigations have resulted in a wide variety of hypotensive agents which exert their effects by inhibition of angiotensin converting enzyme (ACE) One such is the rather potent orally active and long acting agent **delapril** (**22**) One of its syntheses starts with reductive amination of 2 indanone (18) with the t butylester of glycine by use of $NaCNBH_3$ The product (**19**) undergoes peptide bond formation with N carbobenzyloxy L alanine using carboxyl activation through use of the mixed anhydride method (ethyl chlorocarbonate) The optically active product (**20**) is hydrogenolized to free the primary amino group of the alanyl moiety before undergoing reductive (Raney nickel) alkylation with ethyl 2 oxo 4 phenylbutyrate to give ester **21** as a diastereoisomeric mixture resolvable by chromatography The synthesis of **delapril** (**22**) is completed by taking the major product and selectively removing the t butylester moiety with HBr in acetic acid [6] Other syntheses are available [7]



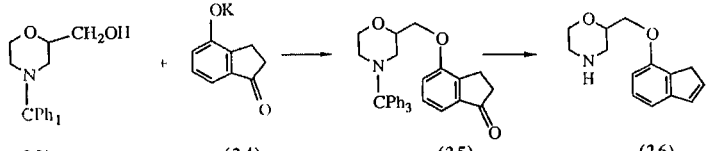
(18) (19) (20)



(21), R = CMe_3
(22), R = H

As a representative of the indenes, **indeloxazine (26)** is an antidepressant and a cognition activator. With an increasingly aged population, a significant amount of research is being devoted to finding compounds which enhance learning and memory by a believable mode of action. Cholinergic agents are receiving the most attention at present. **Indeloxazine**, on the other hand, has very little effect on known receptors but increases intrasynaptic norepinephrine and serotonin concentrations. The meaning of this is unclear, however, in clinical trials this compound has brought about improvement in patients with traumatic brain injury.

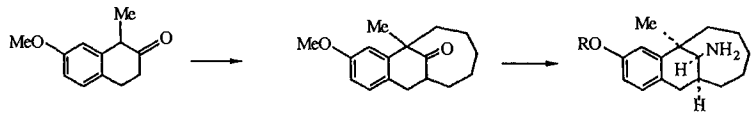
In order to avoid as far as possible double bond positional isomers, a problem quite common in drugs with indene moieties, N-trityl-2-hydroxymethylmorpholine (23) was reacted with the potassium salt of 4-hydroxy-1-indanone (**24**) in DMSO solvent to give condensation product **25** in good yield. Reduction of **25** with $LiAlH_4$ produced the hydroxyindane which was dehydrated and deprotected with HCl to give **indeloxazine (26)** [8].



(23) (24) (25) (26)

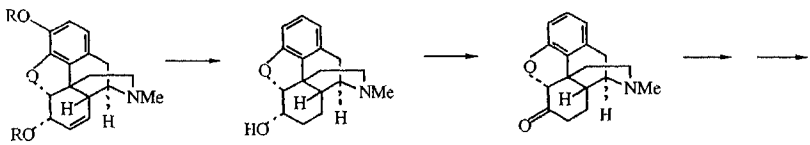
Dezocine (30) represents a class of bridged aminotetralins possessing morphine-like analgesic properties. It appears to be roughly equivalent in potency and addiction potential to morphine. The molecule combines molecular features of precedent aminotetralins and benzomorphans and its structure fits the classical Morphine Rule. The l-enantiomer is the more active and the β-epimer (equatorial NH_2) is the active diastereomer.

The synthesis begins with the 1-methyl-7-methoxy-2-tetralone (**27**) which undergoes a two stage reaction with 1,5-dibromopentane and sodium hydride to give **28**. The 1-hydrogen atom of **27** is the more acidic and, presumably, the reaction initiates by alkylation here. Vigorous reaction of **28** with hydroxylamine and pyridine followed by Raney nickel-catalyzed hydrogenation gives a mixture of amines which can be fractionally crystallized to give racemic **tricycloamine 29**. The ether linkage is then hydrolyzed with 48% HBr to give **dezocine (30)** [9].



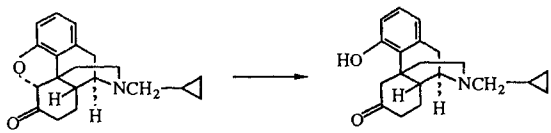
(27) (28) (29); R = Me
(30); R = H

Ketorphanol (36) contains a more usual morphine skeleton and, indeed, this analgesic agent is prepared from **morphine** (31) itself. The synthesis begins by treatment of **morphine** with diethyl chlorophosphate to produce diphosphonyl ester **32**. This is converted to its dihydroanalogue by saturation of its olefinic linkage with 10% Pd-C. Cleavage of the phosphoryloxy ester moiety at C-3 and hydrolysis of the aliphatic phosphate ester group was achieved by dissolving metal reduction with Li in liquid ammonia to give **33**. This selective oxyphosphoryl cleavage reaction is one of the few convenient methods for removal of phenolic OH groups from polyfunctional molecules. The synthesis proceeds by Oppenauer oxidation (benzophenone-t-BuOK) to the corresponding ketone (**34**). This intermediate requires three steps for transformation to its cyclopropylmethyl analogue (**35**). First, N-methyl group exchange for N-cyano is accomplished by the von Braun reaction (with cyanogen bromide). Hydrolysis to the secondary amine requires 2N HCl treatment during which the intermediate N-carboxyamine decarboxylates spontaneously. Finally, alkylation with cyclopropylmethyl bromide gives **35**. Reaction of **35** with Zn dust in ammonium chloride brings about the anticipated cleavage of the C-O bond alpha to the ketone to produce ketorphanol (36) [10]. An alternative synthesis is available [11].



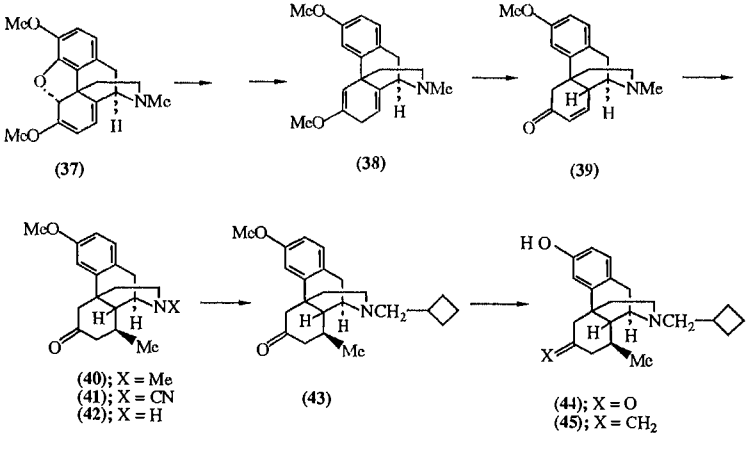
(31); R = H
(32); R = $PO(OEt)_2$

(33) (34)

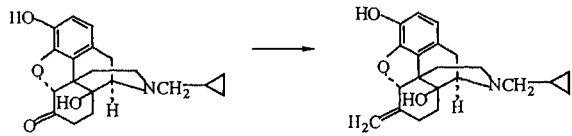


(35) (36)

A somewhat related molecule, **xorphanol (45)**, is an analgesic which possesses at the same time partial antagonist properties. For example, it antagonizes morphine's action when given in suitable doses and it precipitates the morphine abstinence syndrome. Its most interesting molecular feature is the alkylation pattern in the terminal alicyclic ring. The synthesis begins from the clinically useless but relatively abundant alkaloid **thebaine** (37). Sodium and liquid ammonia reduction cleaves the dihydrofuran ring on the aliphatic side; the phenolic product is converted to its 4-phenylether and this is also cleaved with dissolving metal to produce unconjugated dihydrothebaine analogue **38** and phenol. Acid (HCl) hydrolysis converts the enol ether grouping to a saturated ketone followed by olefin migration via enolization to give the conjugated ketone **39**. The stereochemistry at the ring juncture is dictated by the geometric needs of the bridged tetracyclic ring system. Reaction of **39** with lithium dimethylcuprate results in the usual conjugate addition to give **40** as a single isomer which in tum undergoes the von Braun N-dealkylation procedure to give secondary amine **42** via the intermediate cyanogen bromide exchange product **41**. Alkylation of **42** with cyclobutylmethyl bromide produces **43** which undergoes methoxy ether cleavage with HBr to give ketone 44. The synthesis of **xorphanol (45)** concludes by Wittig methylenation of this last with methylenetriphenylphosphorane in DMSO [12,13].



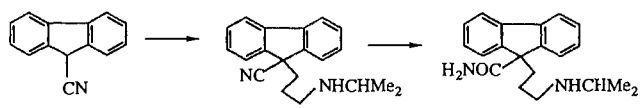
Another agent of this general type is **nalmefene (47)** Despite their useful characteristics, opiates display tolerance, addiction, abuse, and some toxic side effects Antagonists combat some of these effects, most notably respiratory depression and addiction **Nalmefene** reputedly has significant oral activity as a narcotic antagonist The synthesis of **nalmefine** concludes by Wittig olefination of **naltrexone (46)** to **nalmefene (47)** This molecular transformation resulted in a significant increase in oral potency as well [14]



(46) (47)

3 FLUORENES

A very significant mortality in Western countries is associated with cardiac arrhythmias Consequently an intensive search is underway for agents to combat this condition - particularly for compounds with an unusual mode of action A class Ic (local anesthetic-like) agent of interest in this context is **indecainide (50)** One of several routes to this compound covered by patents begins with sodium amide mediated alkylation of 9 cyanofluorene **(48)** with 3 isopropylamino-1 chloropropane to give amine **49** The synthesis concludes by partial hydrolysis of the nitrile function to a carboxamide linkage with sulfuric acid to produce **indecainide (50)** [15]

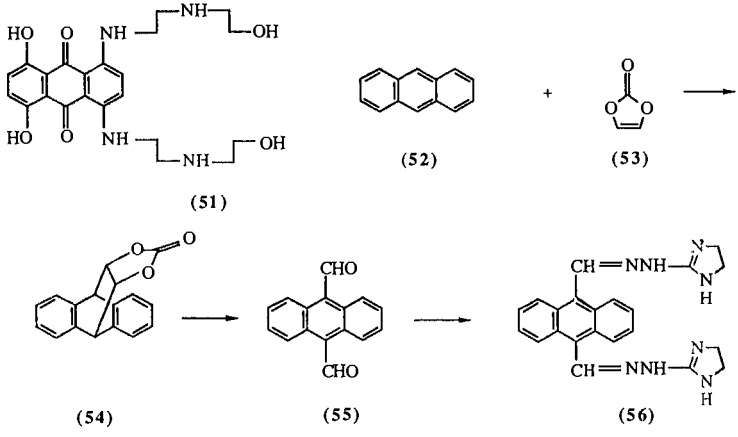


(48) (49) (50)

4 ANTHRAQUINONES

Bisantrene (56), also known as **' orange crush"**, is a broad spectrum intercalating antitumor agent competing with **doxorubicin** and the somewhat more closely related quinone **mitoxantrone (51)**

The synthesis of **bisantrene** begins with Diels-Alder reaction of anthracene (**52**) and ethylene carbonate (**53**) to produce adduct **54**. Hydrolysis and glycol cleavage lead to bis-carboxaldehyde **55**. This readily forms a bis-hydrazone with guanylhydrazine [16].

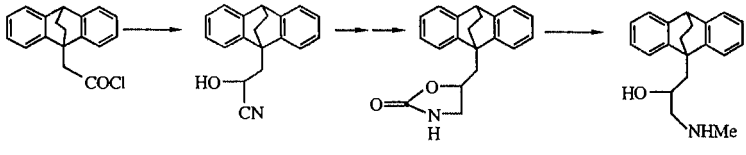


(51) (52) (53)

(54) (55) (56)

5. REDUCED ANTHRACENES

Oxaprotiline (60) is an antidepressant possessing an unusual structure. The clinically useful isomer is the S-(+)-analogue. Several routes are available in patents for producing this agent. For example, acid chloride **57** (prepared by autoclaving anthracene-9-acetic acid with ethylene and then conversion to the acid chloride) undergoes Rosenmund reduction with partially poisoned Pd-C and hydrogen to produce the corresponding aldehyde linkage followed by cyanohydrin formation to produce **58**. $LiAlH_4$ reduction produces the primary amine which is converted to the corresponding oxazolidone (**59**) with phosgene. Strong base (NaH) mediated alkylation of the oxazolidone with iodomethane and hydrolysis follows. Alternatively the synthesis can conclude with $LiAlH_4$ reduction. These last steps are clever means of achieving clean monoalkylation [17].



(57) (58) (59) (60)

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4 Steroids

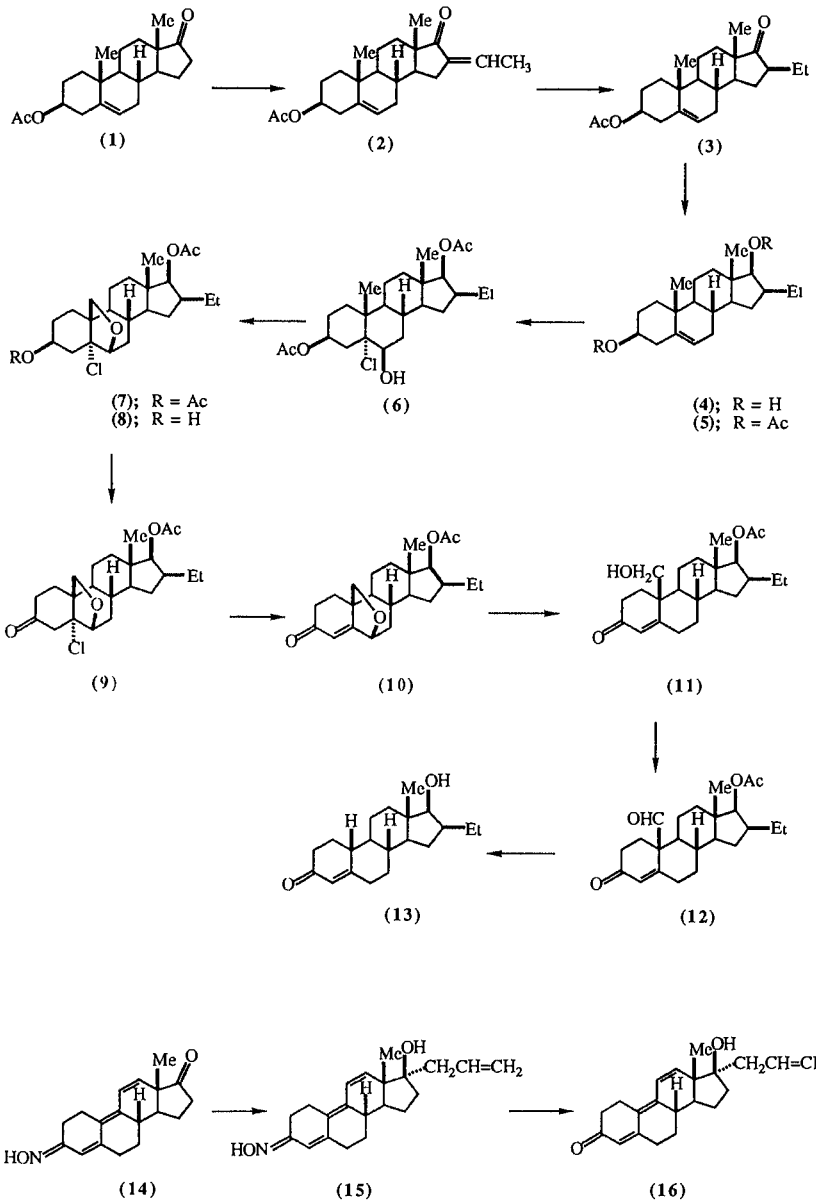
A quick glance at the various chapter titles which have occupied the pages in this series shows a high turnover rate in some of the more specialized structural classes. Some headings as, for example, "Phenothiazines" and "Tetracyclines" occur in the first volume only; "Benzodiazepines" merited separate sections in Volumes 1 and 2. Sufficient work has been devoted over the years to the steroid class, on the other hand, to occupy continuing discrete chapters in each volume. The profound biological activities of appropriately substituted steroids in large part account for the long-term interest in this structural class. The mid 1950s saw an impressive amount of work devoted to the synthesis of compounds related to cortisone for their antiinflammatory activity. This class is revisited in the current chapter as laboratories attempt to develop corticoids which have topical antiinflammatory activity but are devoid of side effects stemming from parenteral activity.

1. ESTRANES

One of the key functions of the steroid sex hormones involves maintenance of gonads and secondary sexual characteristics. Excessive levels of the hormones or increased sensitivity on the part of the target organs can lead to hypertrophy of those targets. In addition, there exist at the extreme a series of malignant tumors which contain sex hormone receptors and are thus stimulated by those hormones. Hormone antagonists should thus be useful in the therapy of both benign and malignant hypertrophies. The utility of a series of synthetic antagonists to the estrogen receptor in the treatment of certain breast cancers (see, for example, **tamoxifen, nafoxidine, and nitromifene** in previous volumes) has led to the search for corresponding antagonists to the androgen receptor(s).

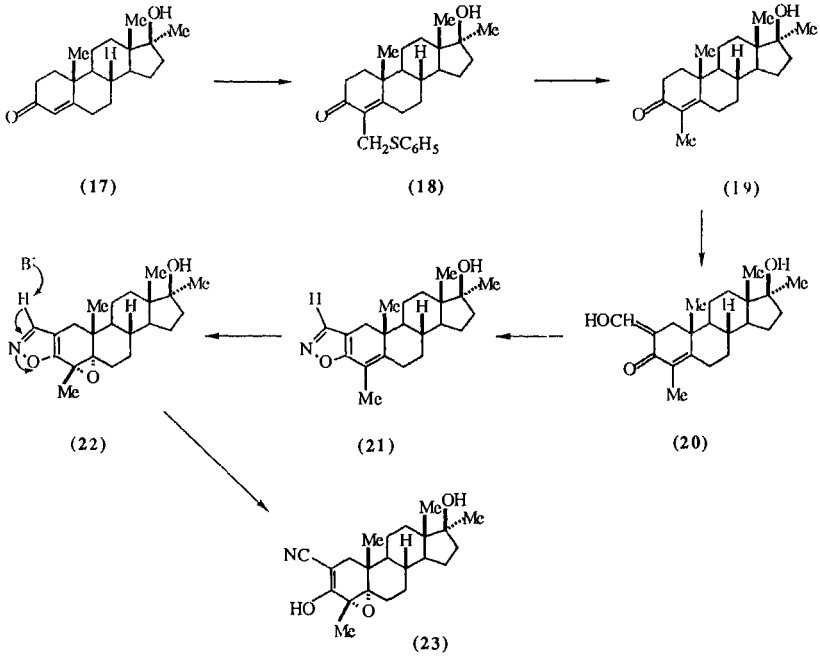
The synthesis of the androgen antagonist **oxendolone** (**13**) starts with Knoevenagel condensation of acetaldehyde with dehydroepiandrosterone acetate (**1**) to give enone **2**. Catalytic reduction proceeds by attack from the less hindered side to give what is in essence the product, 3, which would be obtained from a thermodynamically disfavored alkylation. Treatment of the ketone **3** with lithium aluminum hydride leads to reduction to the 17-β alcohol and reductive loss of the acetate at the 3 position to give the 3,17-diol **4**; acetylation leads to diacetate **5**. Addition of the elements of hypochlorous acid proceeds by the stereochemistry predicted by initial formation of a 5,6-α chloronium ion followed by diaxial ring opening by hydroxide to produce 6. The next step consists in oxidative functionalization of the methyl group at the 10 position so as to permit its elimination. Thus, treatment of the chlorohydrin with lead tetraacetate leads to attack of the methyl group at the 10 position by oxygen, probably by a free radical reaction and formation of the cyclic ether 7. The alcohol at the 3 position is then selectively saponified, and the resulting alcohol, 8, oxidized (**9**). The conjugated ketone in **10** is then established by base catalyzed beta elimination of chloride. Reductive cleavage of the cyclic ether by means of zinc leads to formation of the 10-hydroxymethyl derivative **11**. Oxidation of the primary alcohol with pyridine chlorochromate gives the vinylogous β-ketoaldehyde **12**. Decarbonylation by means of base finally affords **oxendolone** (**13**), [1].

Most of the current oral contraceptives consist of combinations of estrogens and progestational 19-nor steroids. Some of the more potent 19-nor progestins can be used for estrus cycle regulation in their own right. (It may be speculated that a sufficient fraction of these drugs is converted metabollically to the aromatized derivative to provide the estrogenic component in vivo.) Compounds in this class have proven particularly useful in veterinary applications. Condensation of the 19-nor trienedione **14**, in which the 3 ketone is protected as its oxime [2], with allylmagnesium bromide leads to the product of addition from the alpha side of **15**. Removal of the protecting group by transoximation with pyruvic acid affords **altrenogest** (16) [3].

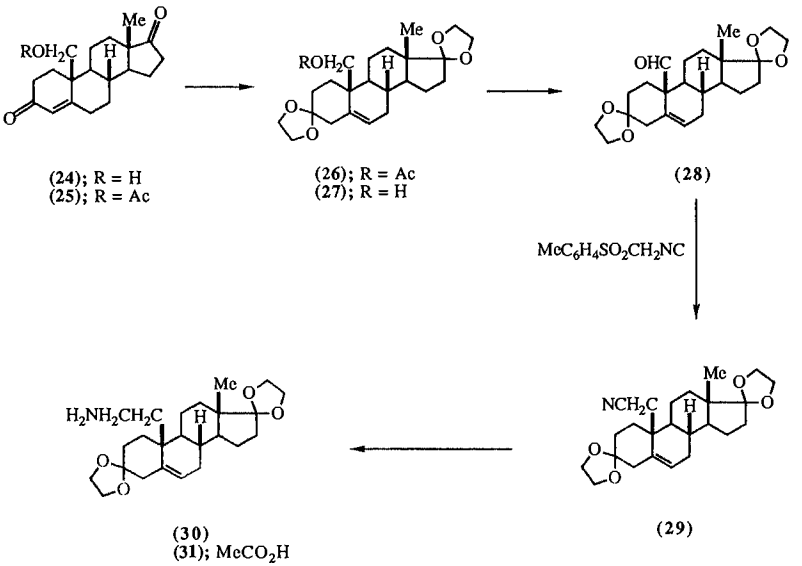

(1)
(2)
(3)
(4); R = H
(5); R = Ac
(6)
(7); R = Ac
(8); R = H
(9)
(10)
(11)
(12)
(13)
(14)
(15)
(16)

2. ANDROSTANES

The familiar estrogen-progestin oral contraceptives owe their activity largely to inhibition of ovulation. Several other series of compounds have been identified which have potential as contraceptives at a later stage in the reproductive process. As interceptive agents these compounds inhibit further development of a fertilized ovum. A highly modified testosterone derivative, **epostane (23)** shows this activity. Reaction of methyltestosterone **17** with formaldehyde and thiophenol leads to the 4-thiomethyl derivative **18**; removal of sulfur by means of Raney nickel gives the 4-methyl compound **19**. Condensation of that intermediate with ethyl formate gives the 2-formyl derivative **20**. Reaction of the beta dicarbonyl function with hydroxylamine affords isoxazole **21**. Epoxidation with peracid (mCPBA) proceeds as expected from the alpha side to give **22**. Treatment of 22 with sodium methoxide leads initially to removal of the sole proton on the isoxazole moiety. Ring opening of the resulting carbanion gives, after protonation of the enol oxygen at the 3 position, the enol-nitrile array in **epostane** (23) [4].

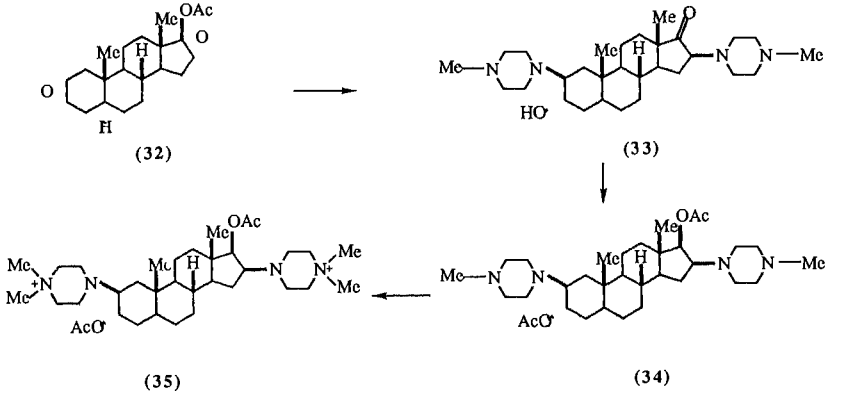


By far the greatest number of medicinal agents based on the steroid nucleus have been designed as agonists or antagonists for endogenous steroid hormones. There do however exist scattered examples of potential drugs which use the steroid nucleus as a nonspecific, rigid, and relatively lipophilic framework. The antiarrhythmic agent **edifolone** (**31**), for example, combines the androstane nucleus with a basic nitrogen. Acetylation of 19-hydroxy-4-androstene-3,17-dione **24**, obtainable by a route analogous to that shown in Scheme 4.1, followed by reaction of **25** with ethylene glycol gives the bis-ketal **26**. The acetate is then removed (**27**) and the alcohol oxidized to the aldehyde **28**. Reaction of the aldehyde **28** with tosylmethyl isocyanide produces the nitrile derivative **29**; which, followed by reduction by means of LAH, leads to the primary amine **30** [5].



Yet another steroid-based pharmacological agent uses the nucleus as a framework for locating two quaternary nitrogen groups in the spatial positions required for curare-like neuromuscular blocking activity. Reaction of N-methylpiperazine with bis-epoxide **32**, used also as starting material for the closely related agent **pancuronium chloride** [6], leads to the product 33 predicted from diaxial opening of the oxiranes **32**; the hemiacetal produced at the 17 position reverts to a

ketone under the reaction conditions Reduction of that ketone followed by acetylation gives diacetate **34** Reaction with bromomethane leads to alkylation of the sterically more accessible N-methyl piperazine nitrogens There is thus produced **pipecuronium bromide (35)** [7]

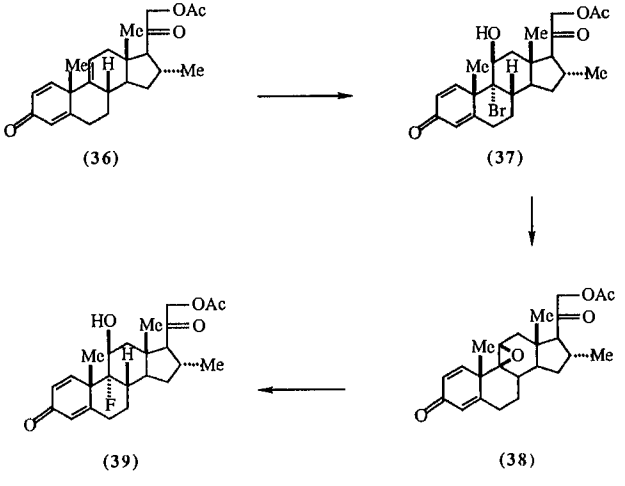


(32) (33) (34) (35)

3 PREGNANES

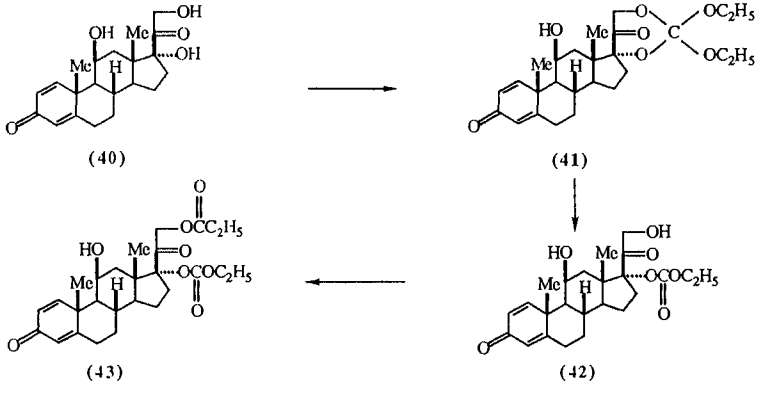
Endogenous corticosteroids such as cortisone are potent hormonal substances involved in the regulation of a host of biological parameters such as mineral and glucose balance The serendipitous discovery that these agents possessed marked antiinflammatory activity when given in supra hormonal doses, led as noted above, to an enormous amount of synthetic work aimed at separating the antiinflammatory activity from the hormonal activity dubbed 'side effects The potency of the later analogues often represented increases of orders of magnitude over the lead compounds, the goal of separating activity from side effects was never quite achieved

More recent work in the corticosteroid series has involved modification of the dihydroxyacetone side chain at the 17 position Activity is retained, for example, when the hydroxyl group at the 17 position is omitted Thus, addition of the elements of hypobromous acid to triene **36** [8], gives the bromohydrin **37**, treatment with base leads to internal elimination to form the β-epoxide **38**, opening of the oxirane with hydrogen fluoride gives **desoximetasone, 39**, [9]



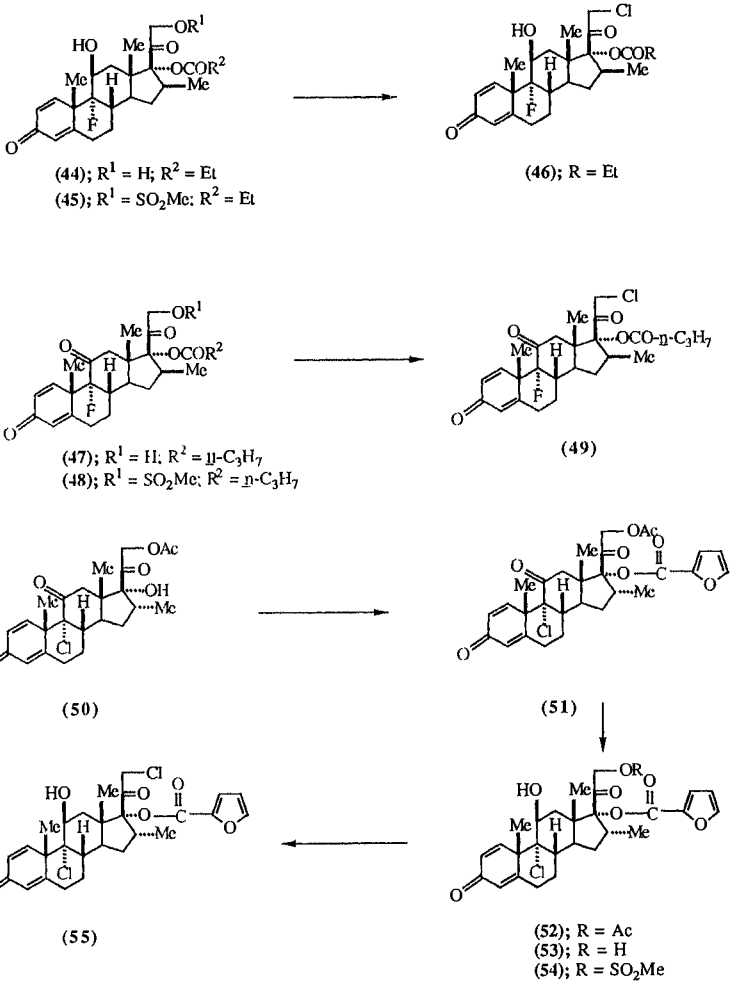
(36) (37) (38) (39)

Condensation of **prednisone, 40** with tetraethyl orthocarbonate leads to the cyclic orthocarbonate **41**; hydrolysis proceeds by protonation on the most accessible ether oxygen (that on carbon 21) to give the 17 mixed carbonate ester **42**. Acylation with propionyl chloride proceeds on the remaining hydroxyl group to afford **prednicarbate (43)** [10].



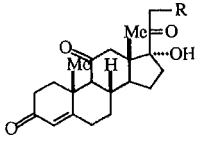
(40) (41) (42) (43)

Activity is also retained when the hydroxyl group at the 21 position is replaced by chlorine. Reaction of corticoid **44** with methanesulfonyl chloride proceeds preferentially at the 21-hydroxyl (**45**) due to the hindered nature of the 11-alcohol. Replacement of the mesylate by means of lithium chloride in DMF affords **clobetasol propionate (46)**; a similar sequence starting with the 17- butyrate ester **47**, via mesylate **48**, should give **clobetasone butyrate, (49)** [11].

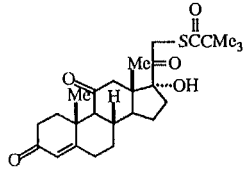


In a similar vein, acylation of the corticoid **50** with furoyl chloride gives the diacyl derivative **51**. Reduction with sodium borohydride serves to convert the 11-ketone to the alcohol **52**. Hydrolysis under mild acid conditions preferentially removes the acyl group at the less hindered 21 position. The hydroxyl group in that derivative (**53**) is then converted to the mesylate **54**. Replacement by chlorine affords **mometasone** (**55**) [12].

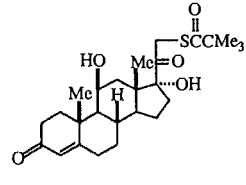
Activity is also retained when oxygen at the 21 position is replaced by sulfur. Preparation of one of these compounds follows a route quite analogous to the foregoing; thus, displacement of the mesylate group in the cortisone (**56**) derivative **57** with the anion from thiopivalic acid affords thioester **58**. Reduction of the 11-ketone by means of borohydride affords **tixocortol pivalate** (**59**) [13].



(56); R = OH
(57); R = OSO_2Me



(58)



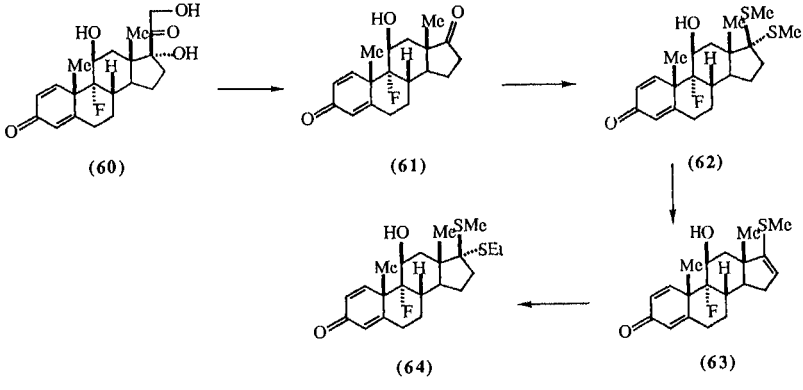
(59)

Further clinical investigations on corticosteroids revealed that these compounds had very useful activity against various inflammatory skin conditions when applied locally. A drawback to this form of therapy consisted in the fact that these drugs tend to be well absorbed through the skin into the blood stream; circulating levels of corticoids can lead to the typical side effects. This occasioned a second wave of research on corticosteroids; the goal of that work is to develop steroids which have potent topical activity and are so designed that they will be deactivated once they are absorbed parenterally, so as to avoid the typical corticoid side effects.

Classical corticosteroids have in common an unsaturated ketone at the 3 position, oxygen at the 11 position and a dihydroxy-acetone side chain at the 17 position (see, for example, **56**).

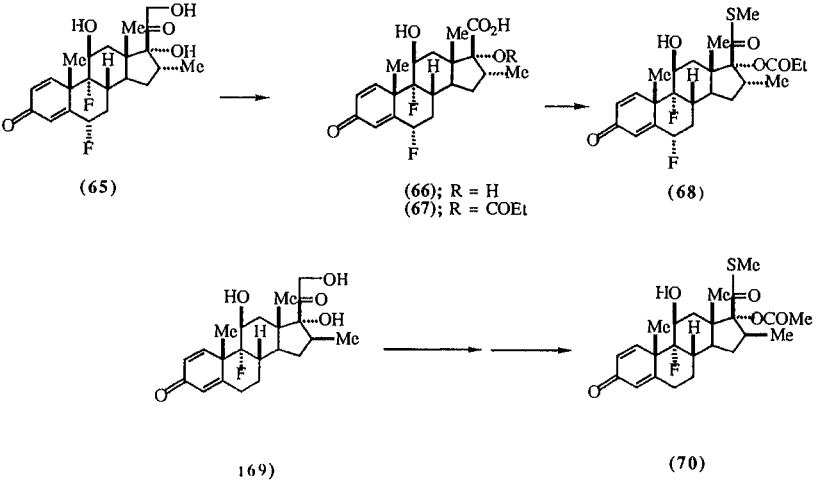
Much of the current work is based on the fact that the side chain can be replaced by an alternative functionality, which contains sulfur. Metabolic destruction presumably involves the readily oxidized thioether groups.

It is of passing interest that the preparations of these modified corticoids use classical corticoids as starting materials and involve degradation of the side chain as a first step. This is probably due in large part to the fact that those classical steroids are today available in abundant supply. Thus removal of the side chain in **60** by oxidation with sodium bismuthate gives the corresponding 17 keto derivative **61**. Treatment with methyl mercaptan gives thioacetal **62**. Elimination of methy mercaptan under acidic conditions leads to the enol thioacetal 63. When this last is exposed to ethyl mercaptan under acetal forming conditions, that reagent adds from the less hindered alpha face to give unsymmetrical thioketal **64**. There is thus obtained the topical corticoid **tipredane (64)** [14].



Somewhat milder oxidative conditions lead to loss of but one carbon. Periodic acid cleavage of the side chain in **65**, leads to the so-called etio acid (66). Reaction with propionic anhydride leads to acylation of the 17-hydroxyl group (67). Possibilities for neighboring group participation severely limit the methods available for activating the acid for esterification. Best results seemed to have been obtained by use of a mixed anhydride from treatment with diphenyl chloro-

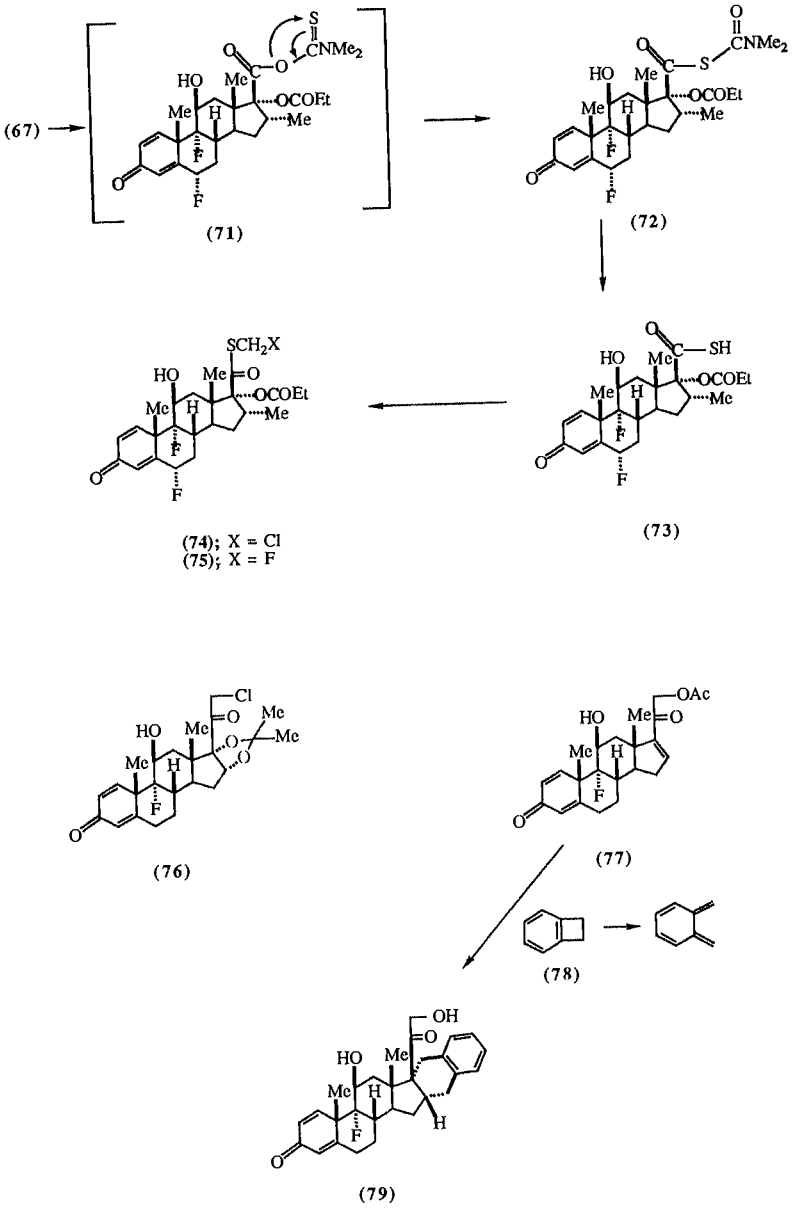
phosphate. Reaction of the intermediate 67 with the salt from methyl mercaptan gives **ticabesone propionate** (68). The related 16-β methyl isomer **timobesone acetate** (70) is obtained by subjecting the corticoid 69 to the same scheme [15].



(65) (66); R = H (67); R = COEt (68) (69) (70)

Reaction of etio acid 67 with N,N-dimethylthioformamidoyl chloride probably gives initially the mixed anhydride 71; this is not isolated but undergoes O to S carbonyl migration to the anhydride 72. Saponification then leads to the thioacid 73. Reaction of the sodium salt of the acid with bromochloromethane affords **cloticasone propionate** (74). The corresponding reaction with bromofluoromethane leads to **fluticasone propionate** (75) [16].

It has long been assumed that the activity of corticoids which contain an additional ring annulated to the 16,17 positions such as **halcinonide** (76), owed their activity to the hydrolyzed product. It is thus of note that full activity seems to be retained by a compound which incorporates a ring at that position held in place by carbon-carbon bonds. Diels-Alder condensation of halcinonide precursor 77, with benzocyclobutadiene, obtained by heating benzocyclobutane 78, leads after hydrolysis of the acetate to **naflocort** (79) [17].


(67)
(71)
(72)
(73)
(74); X = Cl
(75); X = F
(76)
(77)
(78)
(79)

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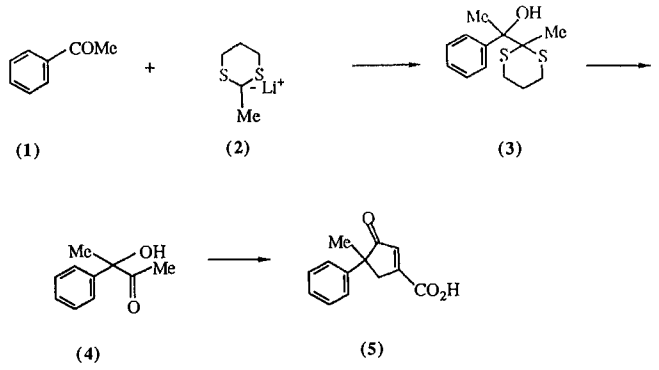
5 Five-Membered Ring Heterocycles

1. ONE HETEROATOM

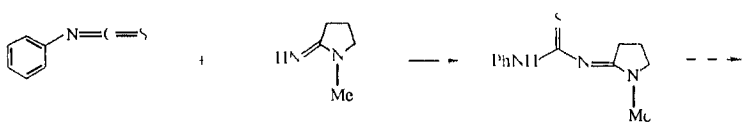
Cardiovascular disease is a major killer. Although it has proven difficult to make a clear causative association of dietary and blood levels of cholesterol with this condition, the evidence cumulatively makes this a reasonable assumption. In any case, most physicians now ask patients at risk to lower their blood cholesterol levels by diet, if possible, or with drugs if need be. A dihydrofuranone, **acifran (5)**, is a potential antihyperlipoproteinemic drug. Cholesterol is carried in the blood in various forms and in experimental animals oral **acifran** decreases total blood cholesterol levels as well as those of low-density lipoprotein and triglycerides. It is synthesized from acetophenone (1) and the anion of 1-methyl-2,6-dithiolane (2) (prepared using n-BuLi). The latter is a reversed polarity version of acetaldehyde (Umpolung) whose condensation with 1 produces tertiary alcohol 3 by carbonyl addition. Acid-catalyzed dithiolane exchange with pyruvate leads to α-hydroxyketone **4**. This last undergoes base-catalyzed oxalylation on the methyl ketone moiety and cyclodehydration and ester hydrolysis to produce **acifran (5)** [1]. This synthesis is satisfactory for producing radiolabeled drug.



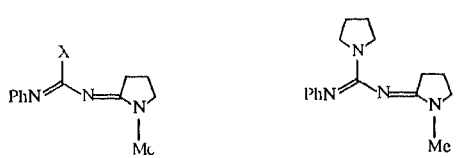
(1) (2) (3)

(4) (5)

Pyrrolidine containing **linogliride(10)** is a structural analogue of the clinically used oral antidiabetic agent **pirogliride (11)** **Linogliride**, on oral administration, stimulates the secretion of insulin in noninsulin dependent patients and the mechanism by which this is brought about, in experimental animals, is apparently different from that involved in the action of sulfonylureas and biguanides **Linogliride** is 2 8 fold more potent than **pirogliride** The synthesis of **linogliride** begins by condensation of phenyl isocyanate (6) with 2 imino 1 methylpyrrolidine (7) to give complex thiourea **8** The latter undergoes alkylation on S as expected on treatment with MeI to give **9** An addition elimination reaction with morpholine concludes this synthesis of **linogliride** (10) [2]



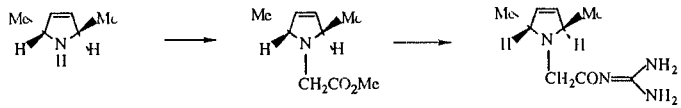
(6) (7) (8)



(9) , X = MeS (11)

(10) , X = -N O

Rolgamidine (14) is a dihydropyrrole derivative which has antidiarrheal activity It can be synthesized by alkylation of trans 2,5-dimethyl-3 pyrroline (12) with methyl bromoacetate to give 13 An amide-ester exchange reaction with guanidine hydrochloride completes the synthesis of **rolgamidine (14)** [3]

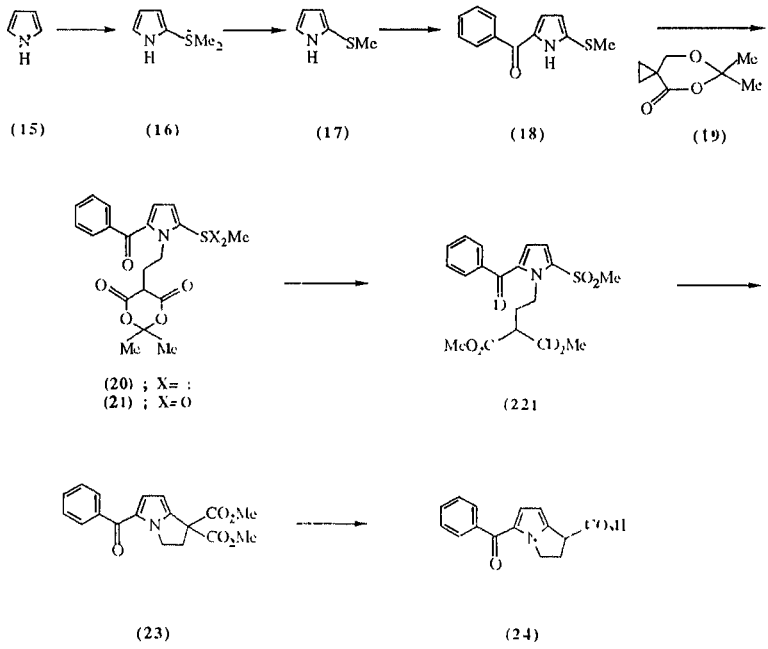


(12) (13) (14)

Ketorolac (24) is a nonsteroidal antiinflammatory and analgesic agent possessing dramatically greater oral activity than aspirin or acetaminophen In early clinical trials the drug was effective against mild and acute postoperative pain The molecular mode of action appears to be inhibition of arachidonic cyclooxygenase The active enantiomer is (l) S The synthesis of **ketorolac** (24) involves some nonstandard pyrrole chemistry of interest Pyrrole (15) is electrophilically substituted by reaction with the adduct of N chlorosuccinimide and dimethyl sulfide to give 16 This on thermolysis dealkylates to 2 thiomethylpyrrole (17) Under Vilsmeier Haack reaction conditions acylation to **18** occurs using N,N dimethylbenzamide Diarylketone **18** reacts readily with Danishefsky's reagent (19) to produce N alkylated product **20** This Meldrum's acid analogue is converted to the sulfone (21) by oxidation with m chloroperbenzoic acid The anion of **21** did not cyclize readily until it was converted by methanolysis to substituted malonate 22 Heating this with sodium ethoxide gives an intramolecular nucleophilic aromatic displacement reaction to give malonate derivative 23 The synthesis of **ketorolac (24)** concludes by saponification, acidification and heating to decarboxylate the auxiliary carboxyl group [4]

The dramatic clinical success of the orally active angiotensin converting enzyme inhibitor, **captopril (25)** as an antihypertensive agent has led to preparation of a large number of analogues **Enalapril (28)**, introduced to the market as an orally active prodrug, is the most successful of these to date Enalapril differs most significantly from **captopril** in that it has a carboxy group, after metabolic unmasking, in place of the SH group of **captopril**

The synthesis of **enalapril** follows the normal course for such compounds in that L alanyl-L proline (27) was reductively alkylated with ethyl 2-oxo 4 phenylbutyrate (**26**) using sodium cyanoborohydride as the reducing agent (catalytic reduction may also be used) The product is



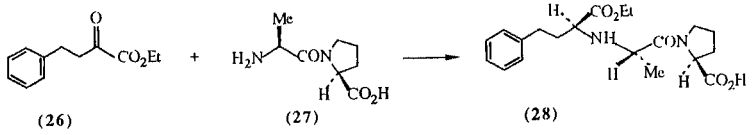
(15) (16) (17) (18) (19)

(20) ; X= :
(21) ; X= O

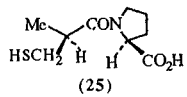
(22)

(23) (24)

enalapril (28). A new asymmetric center is generated in this process, and, as these are diastereoisomers, they can be resolved by column chromatography or by fractional crystallization of the maleate salt [5]. The corresponding diacid is the ultimately bioactive species and is known as **enalaprilat.** Alternate syntheses are also available [6-8].

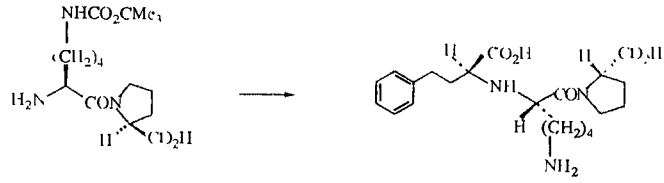


(26) (27) (28)



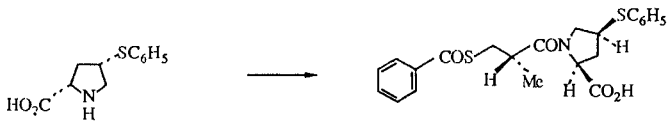
(25)

Lisinopril (30) is the lysine analog of enalapril and is prepared by an analogous process beginning with L-lysyl-L-proline protected at the terminal amino group by a T-BOC (tert-butoxycarbonyl) moiety (29). After reductive alkylation, the blocking group is removed and the diasteriomers separated to give lisinopril (30) [9]. Lisinopril has been shown to be an effective antihypertensive agent in the clinic.



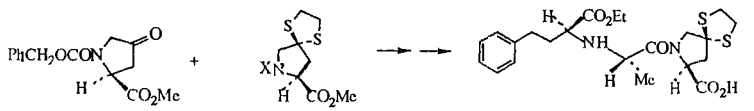
(29) (30)

Zofenopril (32) is constructed from hydroxyproline by conversion first to the cis-3-thiophenylproline analogue (31). Esterification with the appropriate acid analogue produces zofenopril (32) [10].



(31) (32)

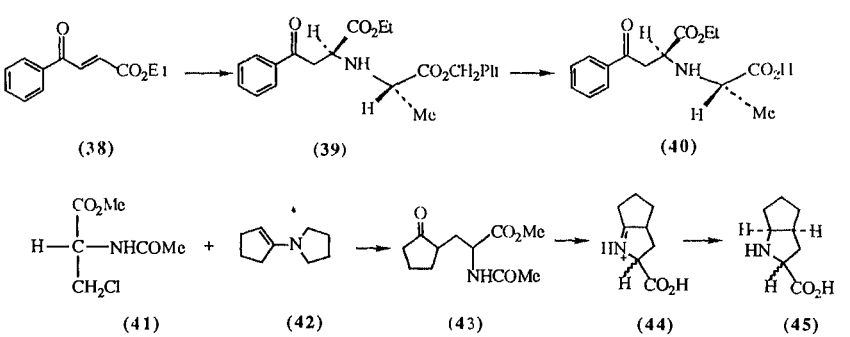
Spirapril (37) is a clinically active antihypertensive agent closely related structurally and mechanistically to enalapril. Various syntheses are reported with the synthesis of the substituted proline portion being the key to the methods. This is prepared from 1-carbobenzyloxy-4-oxoproline methyl ester (33) by reaction with ethanedithiol and catalytic tosic acid. The product (34) is deprotected with 20% HBr to methyl 1,4-dithia-7-azospiro[4.4]nonane-8-carboxylate (35). Condensation of this with N-carbobenzyloxy-L-alanyl-N-hydroxysuccinate leads to the dipeptide ester which is deblocked to 36 by hydrolysis with NaOH and then treatment with 20% HBr. The conclusion of the synthesis of spirapril (37) follows with the standard reductive alkylation [11].



(33) (34); X = $PhCH_2OCO$ (35); X = H (36); X = L-Ala (37)

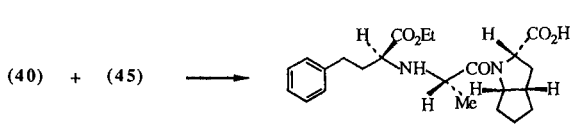
Ramipril (46) is another analogue in the **enalapril** class whose structure indicates that considerable leeway exists for modification at the L-prolyl end. This clinically active antihypertensive agent shows a number of interesting actions in vitro and in animals in addition to ACE inhibition. For example, the compound shows some antiinflammatory activity due to inhibition of PGI_2 biosynthesis in vascular tissue, inhibits adrenergic action in the CNS and heart, and inhibits enkephalinase. All of these effects may contribute to its clinical activity.

In a convergent synthesis, L-alanyl benzyl ester undergoes conjugate addition to the unsaturated keto group in ethyl 4-phenyl-4-oxo-but-2-enoate (38) to give diester **39** as a diastereoisomeric mixture. This is separated by fractional crystallization and hydrogenated to give **40** by loss of the benzyloxy moiety. The other piece required is assembled starting with enamine alkylation of cyclopentenopyrrolidine (**42**) with chloromethylene reagent **41** (prepared from N-



(38) (39) (40)

(41) (42) (43) (44) (45)

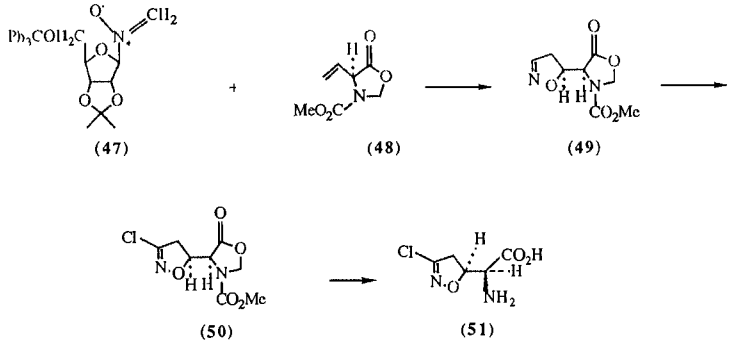


(46)

acetylserine methyl ester). The product, ketone **43**, undergoes cyclization to the deblocked imine (**44**) on treatment with dilute HCl. Hydrogenation with a Pt catalyst gives the diastereoisomeric endo, cis-bicyclo amino acid **45**. The latter is resolved as its benzyl ester. The synthesis of **ramipril (46)** concludes by peptide bond formation between **40** and **45** [12,13].

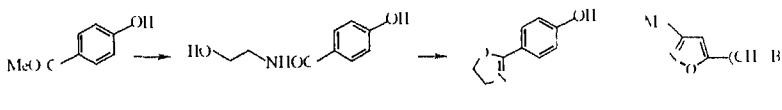
2. TWO HETEROATOMS

Acivicin (51) is a fermentation-derived antitumor agent possessing a highly reactive iminochloride linkage. The clinical use of this agent is limited by the usual toxicities associated with alkylating agents as well as by neurologic problems. The molecular mode of action of **acivicin** appears to involve irreversible inhibition of glutamate-requiring pathways needed for de novo nucleoside synthesis. The CNS toxicity most likely involves this also. The unusual structure of **acivicin** has inspired a number of synthetic attempts. A rather short process involves a 1,3-nitrone cycloaddition reaction using a chiral auxiliary to achieve chirality transfer. Nitrone **47** was prepared in situ from 2,3-O-isopropylidene-5-O-trityl-D-ribose oxime by reaction with paraformaldehyde. This was reacted with vinylglycine analogue **48**. The resulting N-substituted isoxazolidine was freed of its auxiliary by formic acid hydrolysis and this was oxidized to **49** with N-chlorosuccinimide. Chlorine in t-BuOH produced the desired chloroisoxazoline **50**. The synthesis was finished by removing the protecting groups with BCl_3 [14]. Some other syntheses are noted [15-17].

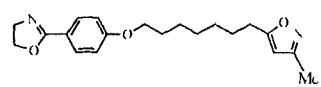


(47) (48) (49) (50) (51)

It has proven to be difficult to find broad spectrum antiviral compounds which are satisfactorily nontoxic A substituted isoxazole, disoxaril (56), has proven effective in vitro and in vivo against a great many rhinovirus serotypes It has been shown to exert its effects by inhibiting the uncoating of the virus after it has been absorbed into the target cell The coated virus cannot reach the cell nucleus, thus effectively preventing viral replication The synthesis begins by ester amide interchange of methyl p hydroxybenzoate (52) with ethanolamine to give substituted amide 53 This could be cyclodehydrated with thionyl chloride to give the dihydrooxazole 54 This is reacted in the usual way with alkyl bromide 55 and base to complete the synthesis of disoxaril (56) [18 19]

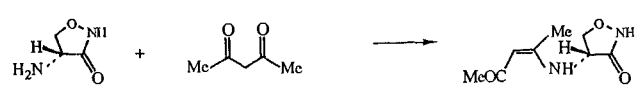


(52) (53) (54) (55)



(56)

One of the problems with cycloserine (57) as an antibacterial agent is its tendency to dimerize In an attempt to overcome this, the prodrug pentizidone (59) has been prepared The primary amino group essential for the dimerization reaction is reversibly blocked to prevent this Pentizidone is synthesized conveniently from cycloserine (57) by merely mixing it with acetyl acetone (58) and stirring for two days to achieve the dehydration The resulting pentizidone apparently requires enzymic assistance to release cycloserine in vivo [20]

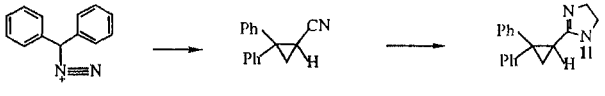


(57) (58) (59)

The pyrrazole analogue **fezolamine (61)** does not possess the classical fused tricyclic structure classically associated with such activity but nonetheless possesses antidepressant activity in animal models, but with an apparently different side effect profiles as compared to precedent drugs Its synthesis is accomplished by reacting 3,4 diphenylpyrazole (**60**) with acrylonitrile under base catalysis The resulting mixture (both N atoms react but the desired N 1 substitution greatly predominates under these conditions) is separated by crystallization Conversion to **fezolamine** was accomplished by Pd C catalyzed reduction in the presence of dimethylamine Presumably the intermediate imine undergoes imine exchange and then reduction to achieve this result [21]

(60) (61)

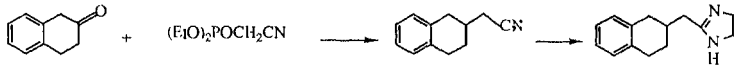
The imidazoline derivative **cibenzoline (64)** is a class I antiarrhythmic agent which has undergone clinical trials in the United States with apparently satisfactory results It is synthesized by diphenylcyclopropanation of acrylonitrile by thermal carbene generation from diphenyldiazo methane (62) to give 1 cyano 2,2 diphenylcyclopropane (63) Reaction of this with ethylenedia mine tosylate completes the synthesis of **cibenzoline (64)** [22]



(62) (63) (64)

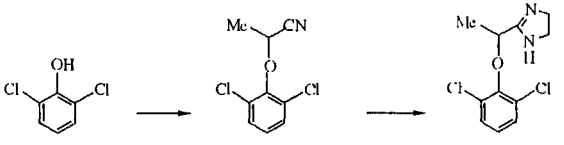
Napamezole (68) is a dihydroimidazole derivative with antidepressant activity probably as a result of its combined α 2 adrenergic receptor blocking and serotonin uptake blocking proper ties It can be synthesized by Wittig olefination of β-tetralone (65) with diethyl (cyanomethyl) phosphonate (66) and base to give nitrile 67 Imidazoline construction on the latter was smoothly

accomplished by reaction with ethylenediamine and trimethylaluminum. The product (68) is **napamezole** [23].



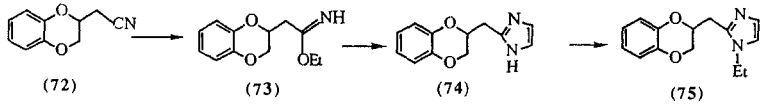
(65) (66) (67) (68)

Another imidazoline derivative, **lofexidine** (71), has different pharmacological properties, being an antihypertensive. It is pharmacologically reminiscent of **clonidine**. As expected for a central adrenergic α-blocker, a major side effect in the clinic was orthostatic hypertension. The compound has been marketed. Its synthesis begins with alkylation of 2-chloropropionitrile with 2,6-dichlorophenol (69), KI, and base. The ether produced (70) is converted to **lofexidine** by reaction with ethylene diamine and catalytic carbon disulfide [24]



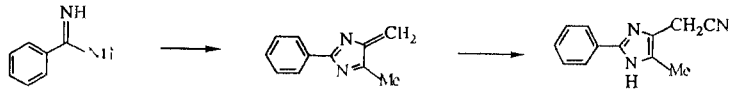
(69) (70) (71)

An imidazole derivative which is also a hypotensive agent by virtue of adrenergic α-2-receptor blockade is **imiloxan** (75). Its synthesis begins by conversion of 2-cyanomethyl-1,4-benzodioxane (72) to its iminoethylether with anhydrous HCl in ethanol (73). Reaction of the latter with aminoacetaldehyde diethylacetal and subsequent acid treatment produces the imidazole ring (74). Alkylation of 74 with ethyl iodide mediated by sodium hydride completes the synthesis [25].



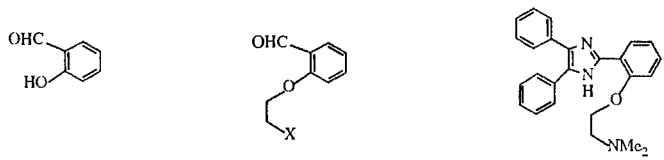
(72) (73) (74) (75)

Mefenidil (78) is a cerebral vasodilator which may be of value in treating geriatric cerebral circulatory problems. It can be synthesized by reacting benzamidine (**76**) with biacetyl to produce the highly reactive methylene benzimidazole adduct **77**. Reaction of the latter with sodium cyanide completes the synthesis [26].



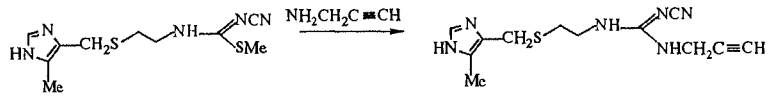
(176) (77) (78)

Trifenagrel (82) is an antithrombotic agent which also has analgesic, antiinflammatory, and antipyretic properties and so is classed as a nonsteroidal antiinflammatory agent. Its synthesis begins by ether formation between o-hydroxybenzaldehyde (**79**) and ethylenedibromide to give **80**. Displacement with dimethylamine produces aminoether **81**. The synthesis is completed by reacting **81** with benzil ($C_6H_5COCOC_6H_5$) and NH_4OAc/NH_4OH [27].



(179) (80); X = Br (81); X = NMe_2 (82)

Etintidine (84), an imidazole-containing histamine H-2 receptor antagonist, is an antiulcer agent conceptually related to **cimetidine** and **ranitidine**. It can be synthesized by various routes one of which terminates by an addition-elimination reaction of propargylamine with substituted N-cyano-S-methylisothiourea derivative 83 to give **etintidine** (**84**) [28].

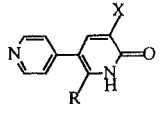


(83) (84)

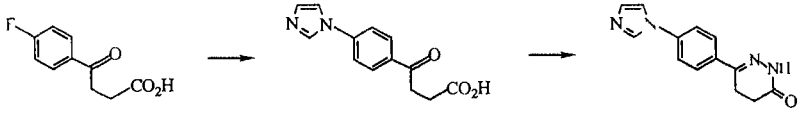
Lofemizole (86) is an arylalkylimidazole-containing agent with antiinflammatory, analgesic, and antipyretic properties It is conveniently synthesized from 1 (4 chlorobenzoyl)ethanol (85) by reaction with ammonium formate or formamide [29]

(85) 186)

Imazodan (also known as Cl 914) (91) is a cardiotonic agent related conceptually to the established agents amrinone (87) and milrinone (88) Thus, it is considered as a potential substitute for the use of digitalis glycosides in congestive heart failure Systemic vasodilators reduce the work load on the heart and are increasingly favored in such patients The synthesis of **imazodan** (91) begins with γ oxo p fluorobenzenebutanoic acid (89) which is reacted with imidazole to displace the fluoro group (which is activated by the p-keto moiety) to give **90** This is reacted with hydrazine to produce the dihydropyridazinone ring of **imazodan** (91) [30,31]

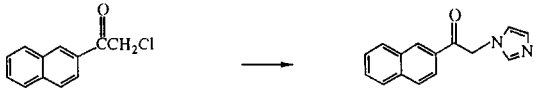


(87), R = H X= NH_2
(88), R = Me X = CN



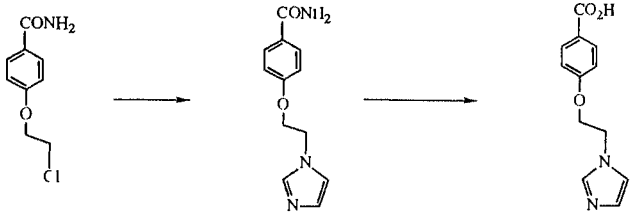
(89) (90) (91)

Nafimidone (93), an anticonvulsant compound, also contains an imidazole moiety It seems to have been discovered by accident during a search for antifungal agents Its synthesis is straightforward involving displacement with imidazole of the activated chlorine atom of chloromethyl-β-naphthylketone (92) [32]



(92) (93)

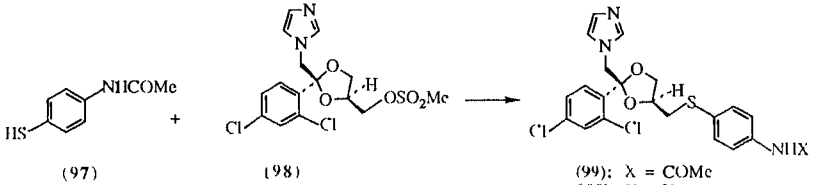
We continue to document the point that the imidazole ring per se though common enough in drugs, is not a general pharmacophore by considering the antithrombotic agent **dazoxiben (96)** Imidazole itself has some thromboxane B 2 inhibitory action but is dramatically less active than analogues such as da**zoxiben** Inhibition of this important enzyme in the arachidonic acid cascade results in a surplus of prostacycline and net inhibition of blood clotting One convenient synthesis starts with the O chloroethylether of p hydroxybenzamide (94) and proceeds by displacement with imidazole to give **95** Hydrolysis of the amide function completes the synthesis of **dazoxiben (96)** [33 34]



(94) (95) (96)

Tubulozole (101) is an antineoplastic agent by virtue of its ability to inhibit microtubule formation Microtubules are a sort of cellular scaffolding and cellular reproduction is impossible without the ability to make microtubules Thus, i a , tumor cell growth is inhibited by **tubulozole** Interestingly, only the cis isomer is active The structure of **tubulozole** is such as to suggest that it was originally prepared as a potential antifungal agent One of the syntheses starts with p thio acetanilide (97) which condenses with complex methanesulfonate **98** in the presence of K_2CO_3 in acetone to produce acetanilide **99** Deblocking by hydrolysis via **100** followed by reaction with

ethylchloroformate completes this synthesis [35]. The synthesis of requisite intermediate **98** is straightforward from 2,4-dichloroacetophenone.

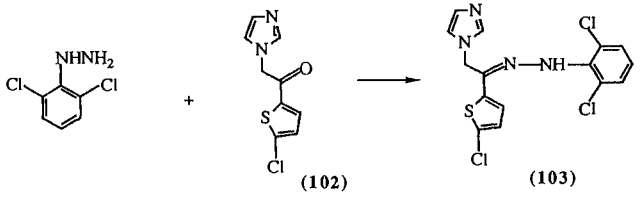


(97) (98) (99): X = COMe (100); X = H (101): X = CO_2Et

Infections by fungi are becoming increasingly prominent as more individuals undergo immunesuppression following intensive corticoid therapy, organ transplantation, anticancer therapy, or infection by the dreaded AIDS virus. Consequently an intensified search for relatively non-toxic, broad spectrum, and orally active antifungal agents has been undertaken. Many appropriately substituted imidazole derivatives, known collectively as the 'conazoles, have been prepared and some have found clinical use.

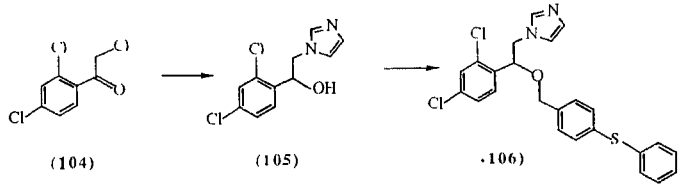
Zinoconazole (103) is a typically complex example of the second generation of such compounds but is notable for its oral activity and for being fungicidal at realistic doses. In common with the other 'conazoles, **zinoconazole** blocks the enzymic demethylation of lanosterol by a cytochrome P-450 enzyme thus, preventing the formation of ergosterol, an important cell membrane constituent of many pathogenic fungi. **Zinoconazole** seems also to damage membranes, directly thereby exerting a 'cidal rather than a 'static effect.

It is made readily by hydrazone formation between ketone 102 and 2,6-dichlorophenylhydrazone [36].

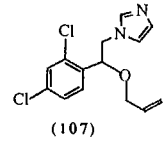


(102) (103)

Fenticonazole (106), on the other hand, is used topically to combat a wide variety of dermatophytes and yeasts, particularly *Candida albicans*. It can be synthesized from 2,4-dichlorophenacyl chloride (**104**) by reduction with borohydride and subsequent displacement with imidazole to give **105**. This last undergoes ether formation with p-thiolphenylbenzyl chloride mediated by NaH to produce **fenticonazole (106)** [37].



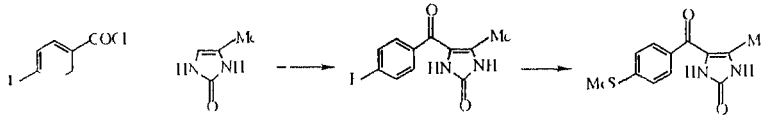
Enilconazole (107) has been marketed for antifungal use in plants and animals. It can be synthesized in a variety of ways including one closely analogous to that used for **fenticonazole** except that the alkylating group is allyl chloride [39].



Bifonazole (109) is claimed to be remarkably non-toxic and is marketed as a topical antifungal agent overseas. It can be conveniently synthesized in the by now familiar way by reduction of p-phenylbenzophenone (**108**) with borohydride, conversion to the chloride with thionyl chloride, and then imidazole displacement to **bifonazole (109)** [39].

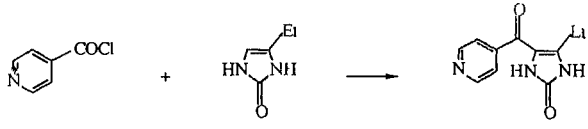
Enoximone (113), an imidazolinone-containing molecule, is a cardiotonic molecule like **imazodan** above. Its mechanism of action is still not established but it is reported to be a potent

inhibitor of a cAMP phosphodiesterase isoenzyme It is synthesized by Friedel Crafts acylation of 4 methylimidazolin 2 one (111) with 4 fluorobenzoyl chloride (110) to give unsymmetrical bi aryl ketone **112** The synthesis is concluded by a nucleophilic aromatic displacement reaction with methyl mercaptan to give **enoximone (113)** [40]



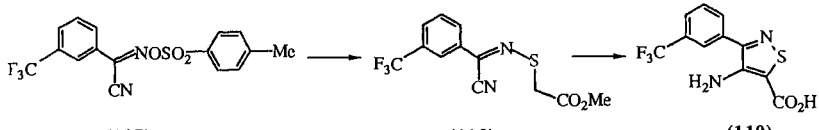
(110) (111) (112) (113)

A related agent piroximone (116) is also an active cardiotonic agent by virtue of marked strengthening of the force of the heart beat and reducing after load Its synthesis is accomplished by Friedel Crafts acylation of 4 ethylimidazolin 2 one (115) with the acid chloride of isonicotinic acid (114) [41]



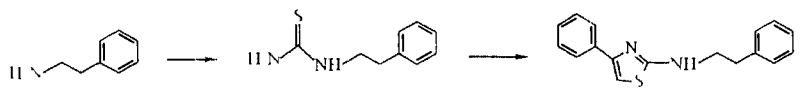
(114) (115) (116)

Amflutiazole (119) is an isothiazole containing gout suppressant by virtue of its inhibitory action against xanthine oxidase, an important enzyme in the catabolism of uric acid Gout is characterized by crystallization of sharp needles of excess uric acid in joints Decreasing its metabolic formation relieves this condition The drug is synthesized by reaction of the tosyloxime derivative **117** with methyl thioacetate to give **118** by addition elimination The latter undergoes intramolecular cyclization between the active methylene and the electrophilic CN moiety on treatment with base to produce **amflutiazole** [42]



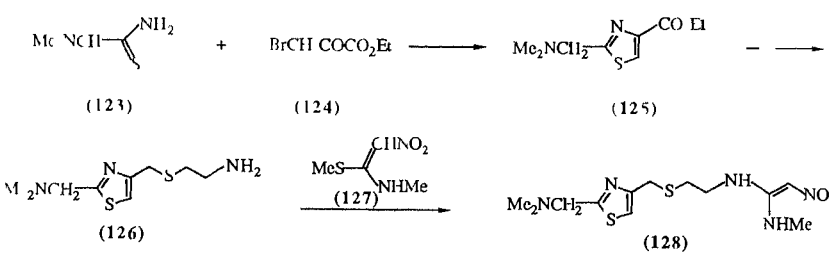
(117) (118) (119)

Fanetizole (122) is a biological response modifier with significant immunosuppressant activity It can be synthesized by conversion of 2 phenylethylamine (**120**) with ammonium thio cyanate to the corresponding thiourea analogue 121 The synthesis of **fanetizole (122)** concludes by thiazole ring formation of **121** by reaction with phenacylbromide Thus its synthesis involves use of the classic Hantzsch procedure in which a bromoacetone analogue and an appropriate thio urea derivative are reacted [43]



(120) (121) (122)

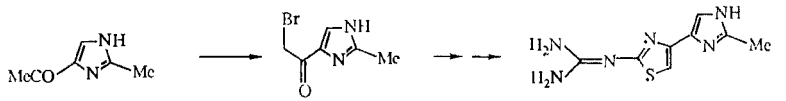
Another thiazole containing drug nizatidine (**128**) is an antagonist of histamine at H_2 receptors and thus is an antiulcer agent related to cimetidine It has shown oral activity in the clinic **Nizatidine** can be synthesized by reaction of ethyl bromopyruvate (**124**) with dimeth ylaminothioacetamide (**123**) Presumably halide displacement is followed by cyclodehydration in producing thiazole **125** Hydride reduction and HBr mediated displacement with 2 aminoethan ethiol gives **126** This last is reacted with 1 (methylthio) 2 nitro 1 N methylethylene (**127**) to give **nizatidine (128)** [44]



(123) (124) (125)

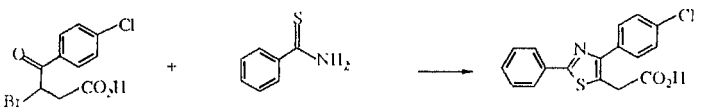
(126) (127) (128)

Another antiulcer histamine H_2 receptor antagonist containing a thiazole moiety is **zaltidine (131)** Its synthesis can be accomplished readily by brominating 4 acetyl 2 methylimidazole (**129**) to give haloketone **130** Displacement with amidinothiourea completes the synthesis of **zaltidine (131)** via a displacement cyclodehydration sequence [45]



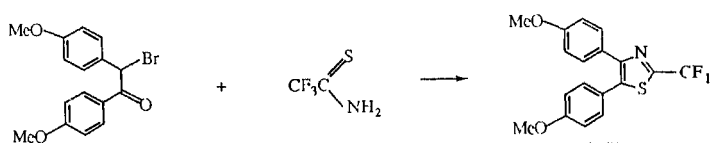
(129) (130) (131)

Fentiazac (134) is a member of the biarylacetic acid class of nonsteroidal antiinflammatory agents. Its synthesis also involves the Hantzsch reaction. Thiobenzamide (**133**) is reacted with 3-(4-chlorobenzoyl)-3-bromopropionic acid (**132**) to give **fentiazoc** (134) [46].



(132) (133) (134)

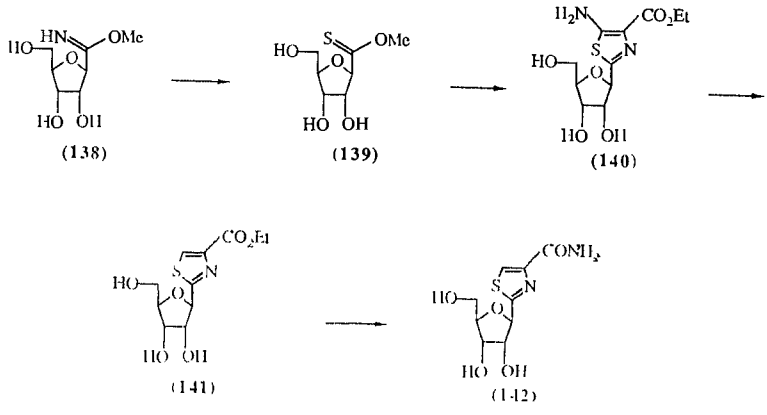
Itazigrel (137) is an antithrombotic compound because of its inhibition of platelet aggregation induced by collagen. It is synthesized from 1-bromo-1-(4-methoxy)benzoyl-4-methoxytoluene (135) by reaction in the usual way with trifluorothioacetamide (**136**) to give **itazigrel** [47].



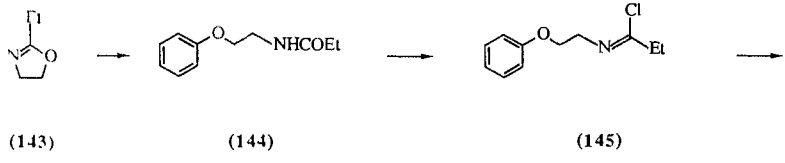
(135) (136) (137)

Tiazofurine (142) is an antimetabolite with antineoplastic activity. It preferentially affects leukemic lymphocytes over normal cells due to selective activation by formation of its adenine dinucleotide by transformed cells. Of the syntheses available, one starts by conversion of inidate 138 to methyl 2,5-anhydroallonothioate (**139**). Next, condensation with ethyl 2-amino-2-cyanoacetate leads to the thioamide which undergoes thiol addition to the nitrile function to produce the amminothiazolecarboxyester system of **140** directly. Sodium nitrite in aqueous hypophosphorus acid eliminates the superfluous amino group via the diazonium transformation to give **141**. This synthesis of **tiazofurine (142)** concludes by ester amide exchange in methanolic ammonia [48].

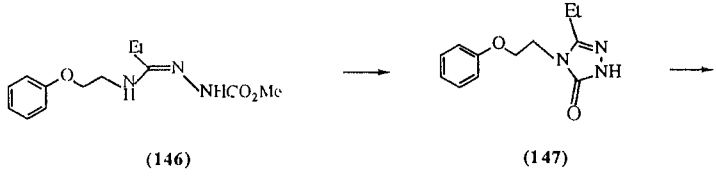
Other syntheses can be consulted [49,50].



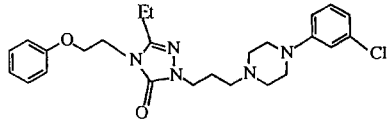
(138) (139) (140) (141) (142)



(143) (144) (145)



(146) (147)



(148)

3 THREE HETEROATOMS

Triazolone containing **nefazodone (148)** is an antidepressant agent It is of particular interest because of its unusual spectrum of receptor interactions It interacts with both adrenergic and serotonin receptors but not with muscarinic acetylcholine receptors or monoamine oxidase Of the various syntheses one of the more interesting starts with 2 ethyloxazoline (143) which reacts with phenol to produce the propionamide ether **144** This is converted to the iminochloride (**145**) with phosgene Reaction of the latter with methyl carbazate produces **146** The latter cyclizes to the triazolone **147** by ester amide interchange in base The sequence terminates with alkylation of **148** by 1 (3 chlorophenyl) 4 (3 chloropropyl)piperazine [51]

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6 Six-Membered Heterocycles

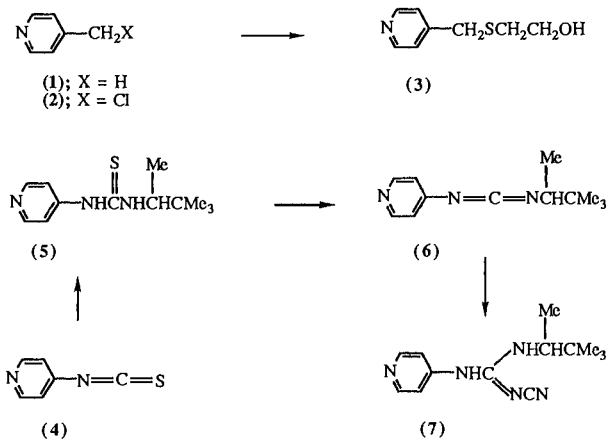
As noted earlier, benzene rings in biologically active compounds act largely as centers of defined electron density and as rigid nuclei for attachment of groups which have pharmacophoric action. Aromatic, monocyclic heterocycles often play a similar role. It is, for example, often possible to replace a benzene ring by a heterocycle such as pyridine without markedly affecting biological activity even in face of the presence of the unshared basic pair of electrons in pyridine. There are, however, cases where the heterocycle forms an indispensable part of the chromophore; for example, a dihydropyridine is, as far as is known, an absolute requirement for calcium channel blocking activity. In a similar vein, 2-amino-4-pyridones form an essential part of those histamine H-2 antagonists lacking the cyano- or nitroguanidine functions.

1. PYRIDINES

A rather simple pyridine derivative shows activity as an immunoregulator. Alkylation of 4-chloromethylpyridine (2), available from 4-picoline (**1**), with 1-hydroxyethane-2-thiol affords **ristianol** (3) [1].

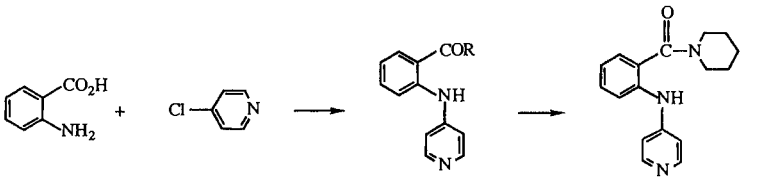
One of the first classes of compounds which provided practical chemical control of hypertension was guanidine derivatives. The mechanism of action of these agents, peripheral sympathetic blockade, resulted in side effects which led the class to be superseded by agents which acted by more acceptable means. A recent guanidine antihypertensive, which incorporates a cyano group on one of the nitrogens - making the functionality more akin to a thiourea - may act by a different mechanism. Condensation of the isothiocyanate **4** from 4-aminopyridine with the appropriate sec-amine gives thiourea **5**. Treatment of that intermediate with a mixture of triphenylphos-

phine, carbon tetrachloride, and triethylamine leads to the unsymmetrical carbodiimide **6**. Addition of cyanamid affords **pinacidil** (7) [2].

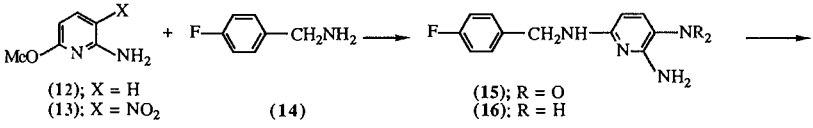


Replacement of one of the benzene rings in a fenamic acid by pyridine interestingly leads to a compound which exhibits antihypertensive rather than antiinflammatory activity. Preparation of this agent starts with nucleophilic aromatic substitution of anthranilic acid (**8**) on 4-chloropyridine. The product (**9**) is converted to its acid chloride (**10**), and this is condensed with piperidine. There is thus obtained **ofornine** (**11**) [3].

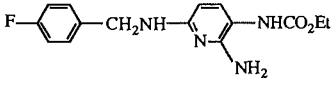
The majority of analgesics can be classified as either central or peripheral on the basis of their mode of action. Structural characteristics usually follow the same divisions; the former show some relation to the opioids while the latter can be recognized as NSAID's. The triamino pyridine **17** is an analgesic which does not seem to belong structurally to either class. Reaction of substituted pyridine **13** (obtainable from **12** by nitration) with benzylamine **14** leads to the product from replacement of the methoxyl group (**15**). The reaction probably proceeds by the addition elimination sequence characteristic of heterocyclic nucleophilic displacements. Reduction of the nitro group with Raney nickel gives triamine **16**. Acylation of the product with ethyl chloroformate produces **flupirtine** (**17**) [4].



(8) (9) ; R = OH (10): R = Cl (11)



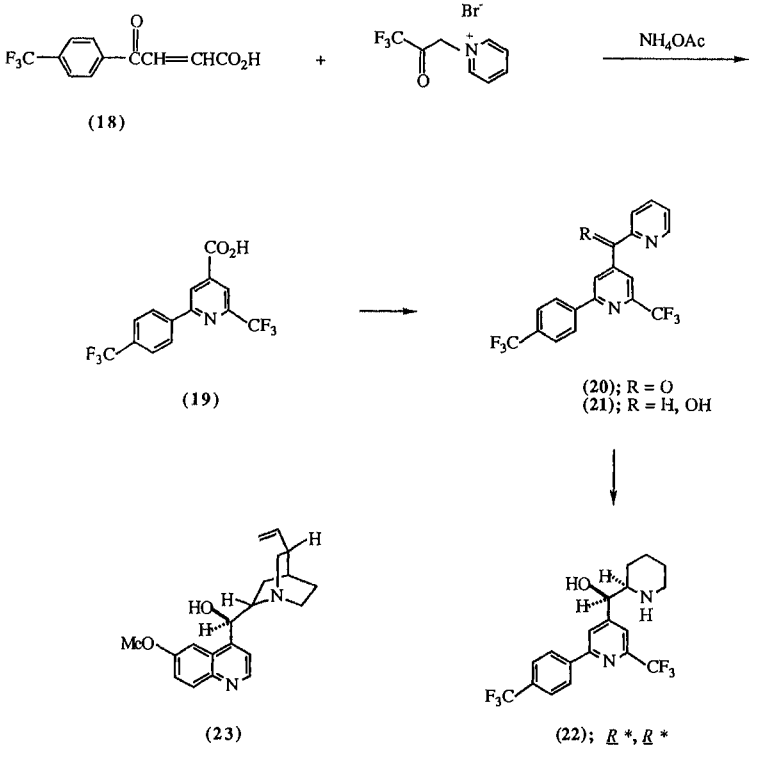
(12); X = H (13): X = NO_2 (14) (15); R = O (16): R = H



(17)

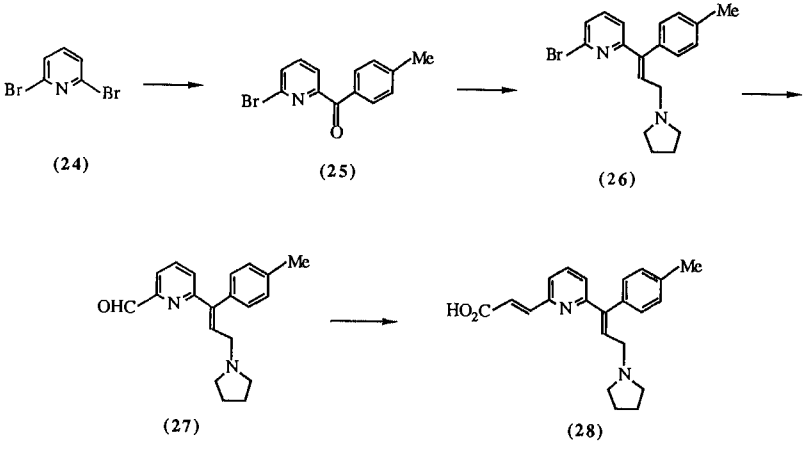
The causative agents of malaria, the *plasmodia*, have, in common with virtually all other microorganisms, developed tolerance to the chemotherapeutic agents which at one time seemed ready to wipe them from the face of the earth. Successful treatment of malaria has thus demanded a continuing effort to develop ever newer agents. The incentive for developing new antibiotics lies in the enormous market for these drugs in the so-called developed nations. No such incentive exists for research on new antimalarial drugs, since this is largely a disease of the third world. This accounts in part for the few entries in this category in recent volumes in this series. One of the newer drugs for treating malaria, **enpiroline** (22), interestingly incorporates a great many structural features of **quinine** (23). It is of note that this drug owes its existence to research sponsored by the U.S. Army's Walter Reed Institute rather than a pharmaceutical company. The starting nicotinic acid derivative **19** is the product of the rather complex condensation of keto-acid 18 with 1-trifluoroacylmethylpyridinium bromide and ammonium acetate patterned on the work of Kroehnke [5]. Condensation of the product with an excess of 2-lithiopyridine gives the ketone **20**.

Treatment with sodium borohydride leads to the alcohol **21**. Catalytic reduction of the product in the presence of acid leads to preferential hydrogenation of the monosubstituted ring. Selectivity is probably due to the fact that pyridine rings must be protonated in order to be reduced; the larger number of electron withdrawing substituents on the disubstituted ring will reduce basicity of the nitrogen and favor protonation of the alternate pyridine nitrogen. Separation of the R*,R* isomer from the diastereomeric mixture affords **enpiroline** (22) [6].



The search for nonsedating H-1 antihistamines met its first success in **terfenadine** (see **198**, Chapter 2). A different approach aimed at keeping such agents out of the CNS, by prevent-

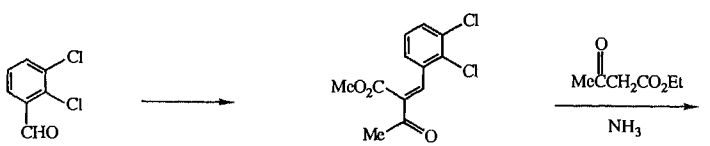
ing their crossing the blood brain barrier, consists in converting some known antihistamine to a zwitterion by incorporating a carboxyl group. Application of this strategy to **triprolidine** (28 minus the pendant acrylic acid chain) results in the antihistamine **acrivastine** (28). Synthesis of this compound starts by reaction of the mono lithio derivative from pyridine **24** with p-toluonitrile. Hydrolysis of the intermediate imine affords the benzophenone **25**. Condensation of the carbonyl group with the ylide from triphenyl(2-N-pyrrolidinoethyl)phosphonium chloride gives the intermediate **26**, probably as a mixture of geometric isomers. The remaining halogen on the pyridine ring is then converted to the lithio reagent by halogen metal interchange with an alkyl lithium. Condensation of the resulting organometallic with dimethylformamide gives, after hydrolysis, the aldehyde 27. This is again subjected to a Wittig type reaction, this time with the ylide from triethylphosphono acetate. This last reaction leads almost exclusively to the trans double bond isomer. Saponification of the ester group affords the amino acid. Separation of the E,E isomer affords **acrivastine** (28) [7].



2. DIHYDROPYRIDINES

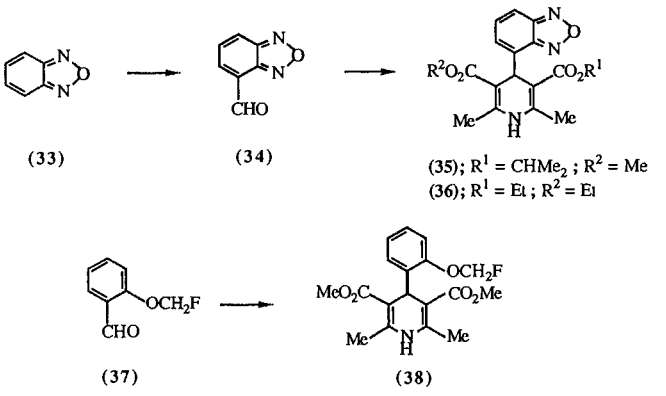
The calcium channel blocking agents, typified by the dihydropyridine **nifedipine**, were approved initially for use in cases of atypical, nonexercise induced angina. Continued clinical investigations have shown these agents to be useful for a variety of additional indications, including all types of angina as well as hypertension. This resounding commercial success has spurred work in numerous laboratories in order to develop their own proprietary dihydropyridine calcium channel blocking agents.

The Hantsch pyridine synthesis provides the final step in the preparation of all dihydropyridines. This reaction consists in essence in the condensation of an aromatic aldehyde with an excess of an acetoacetate ester and ammonia. The need to produce unsymmetrically substituted dihydropyridines led to the development of modifications on the synthesis. (The chirality in unsymmetrical compounds leads to marked enhancement in potency.) Methyl acetoacetate forms an aldol product (**30**) with aldehyde **29**; conjugate addition of ethyl acetoacetate would complete assembly of the carbon skeleton. Ammonia would provide the heterocyclic atom. Thus, application of this modified reaction affords the mixed diester **felodipine 31** [8].



(29) (30)

(31) (32)



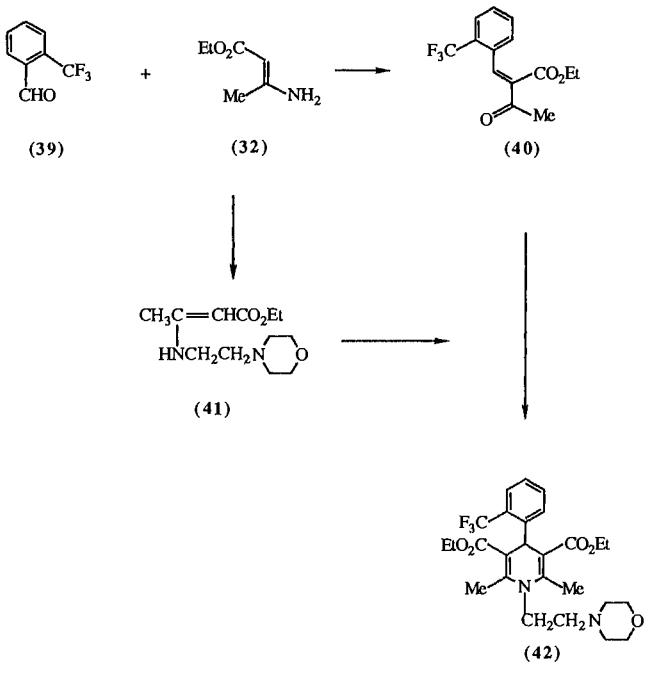
(33) (34) (35); $R^1 = CHMe_2$; $R^2 = Me$
(36); $R^1 = Et$; $R^2 = Et$

(37) (38)

Random incorporation of two different acetoacetates can also be avoided by converting one of the acetoacetates to a derivative which carries the future pyridine nitrogen. For example, treatment of ethyl acetoacetate with ammonia gives the corresponding β-aminocrotonate **32**. The aldehyde (**34**) required for preparation of such an unsymmetrical compound is prepared by reaction of the product from direct metallation of 33 with dimethylformamide. Condensation of that aldehyde with methyl acetoacetate and the β-aminocrotonate from isopropyl acetoacetate leads to **isradipine** (**35**) [9]. The same aldehyde with ethyl acetoacetate and the β-aminocrotonate from ethyl acetoacetate gives **darodipine** (36) [10]. In much the same vein, condensation of the benzaldehyde **37** with methyl acetoacetate and its β-aminocrotonate derivative affords **riodipine** (38) [11].

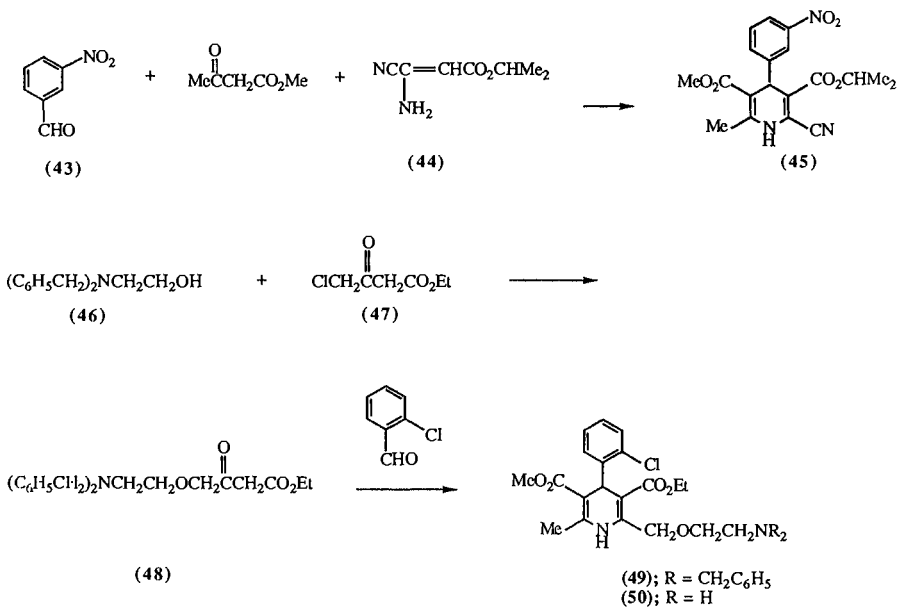
Activity is apparently retained when the ring nitrogen is alkylated as in **flordipine** (**42**). Aldol condensation of the benzaldehyde **39** with ethyl acetoacetate gives the unsaturated ester **40**. The nitrogen containing reaction partner **41** is obtained by condensation of **32** with 2- morpholinoethylamine. Reaction of **40** with **41** leads to **flordipine** (**42**) [12].

The methyl groups adjacent to the pyridine nitrogens can also be modified without changing calcium channel blocking activity. The most significant change involves replacement of methyl by a nitrile group. Hantsch type condensation of the nitrobenzaldehyde **43** with methyl acetoacetate and the vinyl amine **44** from isopropyl 3-cyano-3-ketopropionate leads directly to **nilvadipine** (**45**) [13].



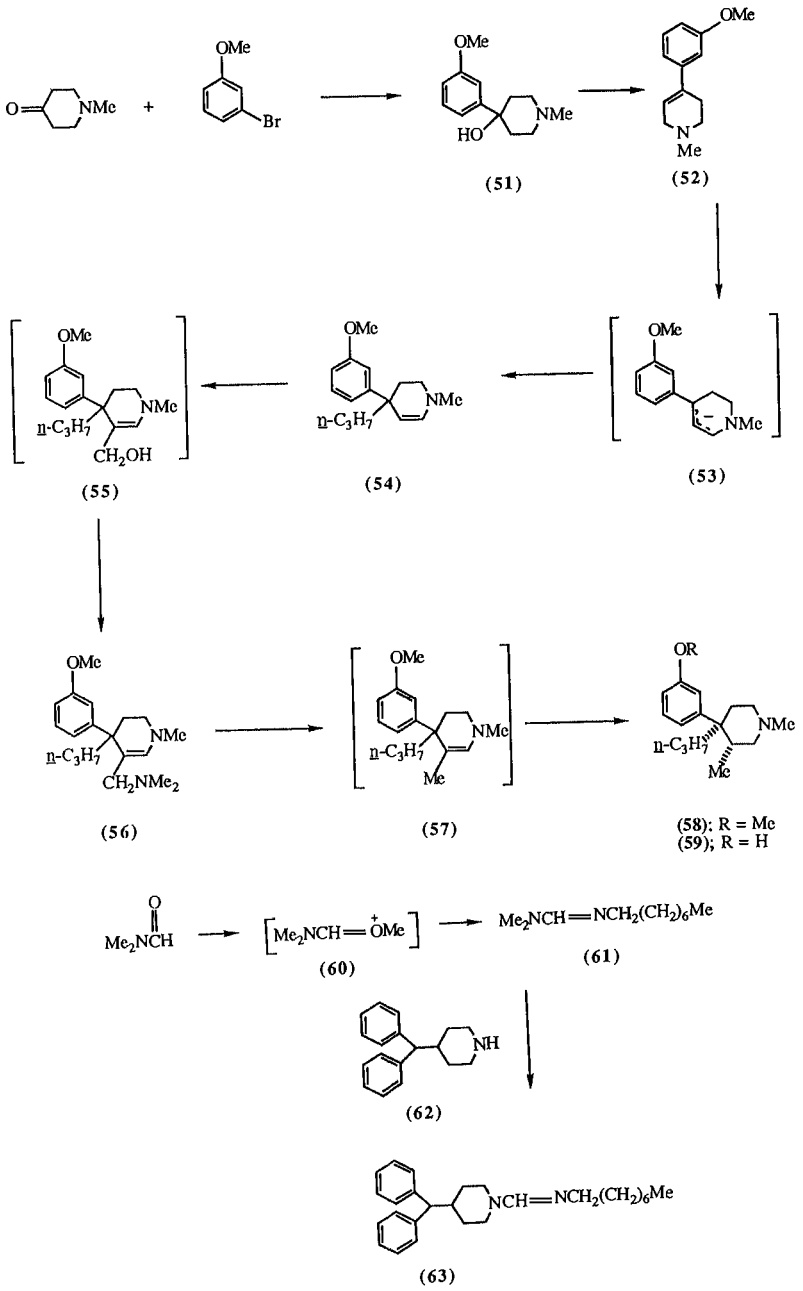
The preparation of an analogue containing an oxygenated methyl group starts by the displacement of halogen on the chloro acetoacetate **47** by the protected ethanolamine derivative **46**. Condensation of the product (**48**) with the vinyl amine derivative of methyl acetoacetate and o-chlorobenzaldehyde gives the dihydropyridine **49**. Removal of the benzyl protecting groups by catalytic hydrogenation, affords **amlodipine (50)** [14].

The search for opioid analgesics which show reduced addiction liability has centered largely on benzomorphan and morphinan derivatives. Some research has, however, been devoted to derivatives of the structurally simpler **meperidine** series. The preparation of one such compound, **picenadol (59)**, starts with the reaction of N-methyl-4-piperidone with the lithium derivative from m-methoxybromobenzene. Dehydration of the first formed carbinol **51** gives the intermediate **52**. Deprotonation by means of butyl lithium gives an anion which can be depicted in the ambident form **53**. In the event, treatment of the anion with propyl bromide gives the product **54** from reaction of the benzylic anion. Treatment of that product, which now contains an eneamine function,

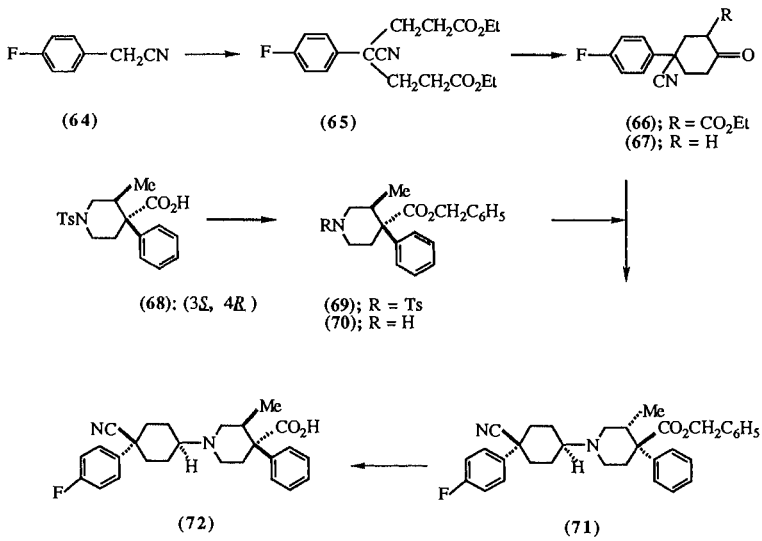


under Mannich reaction conditions (formaldehyde, dimethylamine) leads to the aminomethyl derivative **56**. It may be speculated that the reaction proceeds initially through the methyl carbinol **55**. Hydrogenolysis of **56** involves initially removal of the allylic amino group to afford a transient intermediate such as **57**, followed by reduction of the enamine to produce **58**. Demethylation of the phenolic ether by means of hydrogen bromide and fractional crystallization to obtain the derivative with cis configuration of the two ring alkyl groups completes the synthesis of the analgesic **picenadol** (**59**) [15].

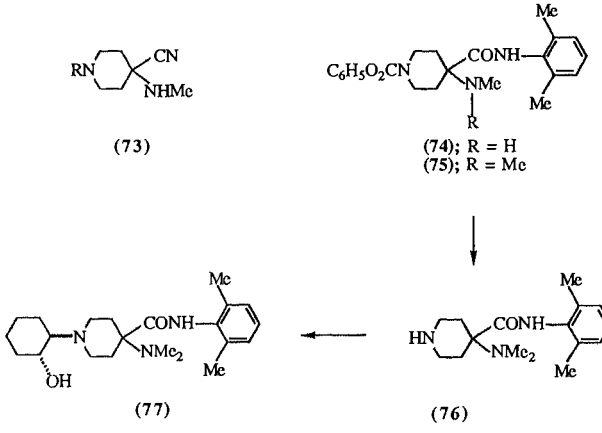
Reaction of dimethylformamide with dimethyl sulfate leads to the highly reactive O-methyl ether **60**. Exposure of this reagent to n-octylamine leads to the amidine **61**. An exchange reaction between this last intermediate and the piperidine derivative **62**, results in displacement of dimethylamine by the piperidine nitrogen. There is thus obtained the gastric antisecretory agent **fenoctimine** (**63**) [16]. The structural fragment represented by **62** is often used in H-1 antihistamines; the fact that those compounds often exhibit some anticholinergic activity may account for the activity of **63**.


OMe
NMe
HO
Br
N
Me
n-C3H7
CH2OH
CH2NMe2
OR
(51)
(52)
(53)
(54)
(55)
(56)
(57)
(58): R = Me
(59); R = H
Me2NCH
(60)
Me2NCH=NCH2(CH2)6Me
(61)
NH
(62)
NCH=NCH2(CH2)6Me
(63)

A rather more complex compound, **levocabastine (72)**, is described as an extremely potent, selective, H-1 antihistaminic agent. The presence of a free carboxyl group suggests that this compound may have difficulty in crossing the blood brain barrier and may thus show reduced sedating activity. One leg of the convergent synthesis starts with the double conjugate addition of ethyl acrylate to the anion from p-fluorophenylacetonitrile (**64**). Base catalyzed cyclization of the product (**65**) affords the keto ester **66**. Decarboethoxylation of that intermediate gives the cyanocyclohexanone **67**. Esterification of the carboxyl group in the optically active meperidine-related compound **68** with benzyl chloride leads to ester **69**. The tosyl protecting group is then removed by means of electrolytic reduction. Condensation of the ketone **67** with secondary amine **70**, under reductive alkylation conditions affords predominantly (9:1 ratio) the intermediate **71**, which is purified by recrystallization. The trans stereochemistry of the cyclohexane amino group and the aromatic ring result from the tendency to form equatorial nitrogen in the reduction of the intermediate imine. The benzyl protecting group is then removed by means of a second, more drastic hydrogenation step. The product of that reaction is then the levorotatory isomer, **levocabastine (72)** [17].



Treatment of the piperidine **74**, obtainable from an aminonitrile such as **73**, under N-methylation conditions leads to the dimethylamino derivative **75**. The carbobenzoxy protecting group is then removed by catalytic hydrogenation. Reaction of the resulting secondary amine **76** with cyclohexene oxide leads to the alkylated trans aminoalcohol. There is thus obtained the anti-arrhythmic agent **transcainide (77)** [18].

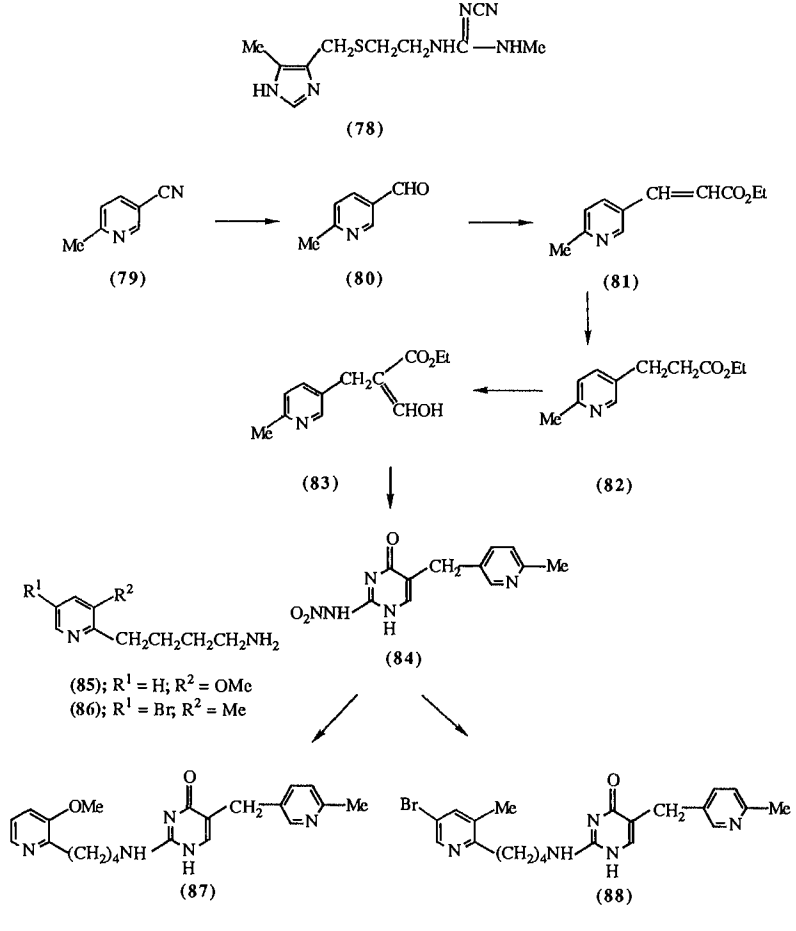


3. PYRIMIDINES

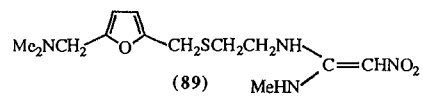
The discovery of the histamine H-2 blocking agents has virtually revolutionized the treatment of ulcers of the upper GI tract. Drugs such as **cimetidine (78)** and **ranitidine (89)** have proven so safe and effective that serious consideration is being given to granting approval for sale of these without prescriptions. This very success has engendered considerable work aimed at exploring the limits of the SAR. It was found early on that the cyanoguanidine function could be replaced by a pyrimidone (see *The Organic Chemistry of Drug Synthesis*, Volume 3). Most of the recent work in this series has apparently focused on such pyrimidones.

Catalytic reduction of the nitrile **79** in the presence of semicarbazide affords initially the semicarbazone of **80**. Hydrolysis-interchange, for example in the presence of pyruvic acid, gives the aldehyde **80**. Condensation with the half ester of malonic acid leads to the acrylic ester **81**; the double bond is then removed by means of catalytic reduction (82). Base catalyzed reaction of the

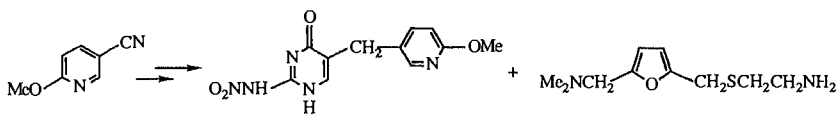
ester with ethyl formate gives the corresponding formyl derivative **83**. Condensation of this beta dicarbonyl compound with N-nitroguanidine leads to the pyrimidone **84**. The reaction involves, as expected, the more nucleophilic (i.e., nonnitrated) guanidine nitrogens; the product, in addition, contains a built in good leaving group. Thus, displacement of the leaving group with pyridylpropylamine **85**, affords the H-2 blocker **icotidine** (**87**) [19]. The same reaction using the bromopyridine **86** as the nucleophile, gives the H-2 blocker **temelastine** (**88**) [20].



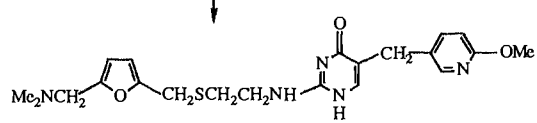
Ranitidine (89), in which the imidazole ring has been replaced by a furylmethyl moiety has proven a particularly successful drug. Several pyrimidones thus incorporate that ring system. Repetition of the scheme used to prepare the pyrimidone intermediate **84**, starting with the oxygenated pyridine **90** instead of **79**, affords the key synthon **91**. Displacement of the leaving group by the primary amine from the furyl alkylamine **92** leads to **93**. Treatment of this last compound with dry hydrogen chloride leads to cleavage of the pyridine O-methyl ether and formation of the corresponding hydroxy derivative. This function is more usually depicted as a pyridone. There is thus obtained donetidine (**94**) [21].



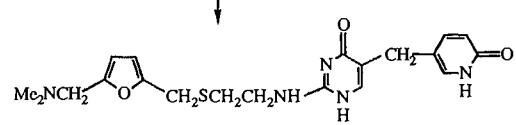
(89)



(90) (91) (92)

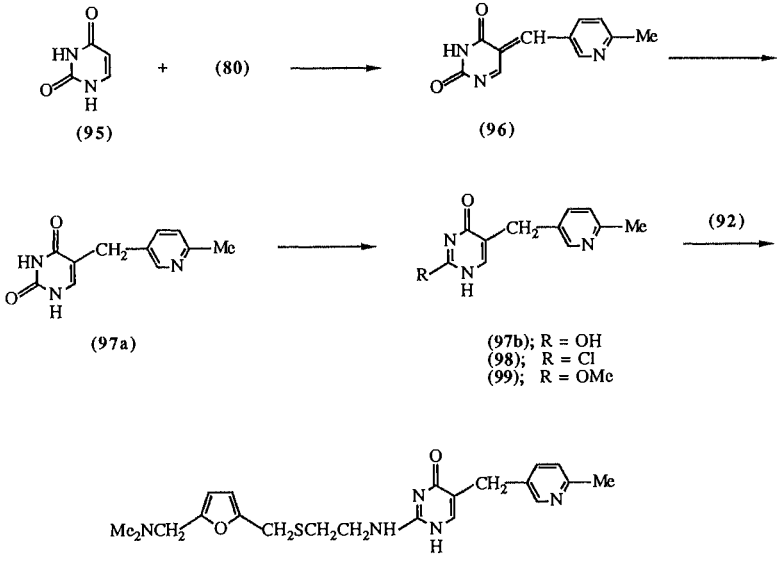


(93)



(94)

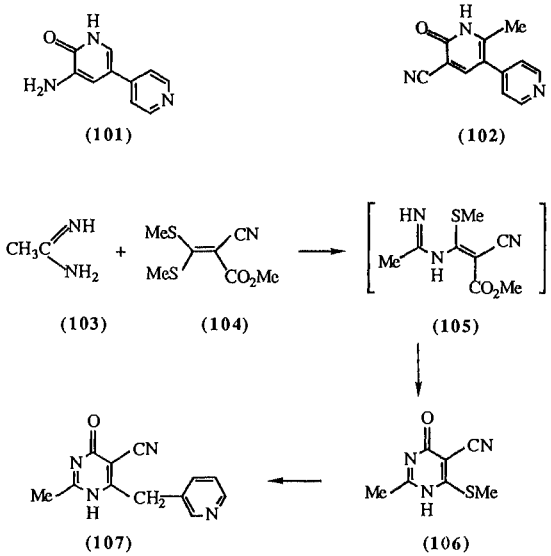
An alternate scheme for preparing these compounds starts with a prefabricated pyrimidone ring. Aldol condensation of that compound (**95**), which contains an eneamide function, with pyridine-3-aldehyde (**80**), gives the product **96**. Catalytic hydrogenation gives the product of 1,4 reduction. The resulting pyrimidinedione, of course exists in the usual tautomeric keto (**97a**) and enol (**97b**) forms. Reaction with phosphorus oxyxchloride leads to the chloro derivative **98**. Displacement with methoxide gives **99**. Reaction of this last intermediate with the furylalkylamine derivative **92** leads to the H-2 blocker lupitidine (**100**) [22].



(100)

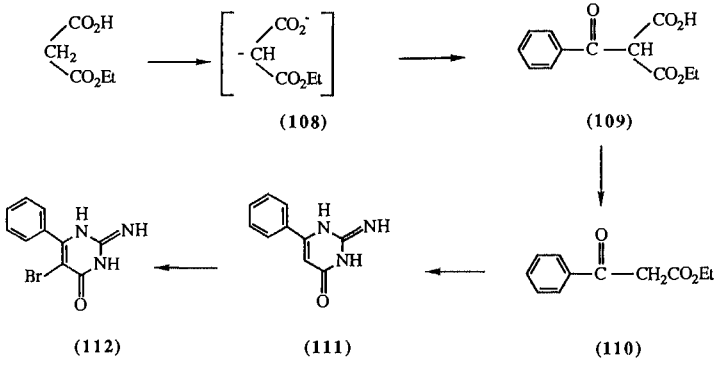
Pyridones such as **amrinone (101)** and **milrinone (102)** have proven to be very effective cardiotonic agents. It is of interest that activity is retained when an additional nitrogen is inserted into the ring to form a pyrimidone. Condensation of amidine **103** with intermediate **104** can be visualized as involving initially addition elimination of basic nitrogen to the highly electrophilic double bond and loss of the good, though odiferous, leaving group, methyl mercaptide (**105**). Cyclization by replacement of the ester methoxide group will then give pyrimidone **106**. Re-

placement of the remaining thiomethyl group by 3-methylaminopyridine affords the cardiotonic agent pelrinone (**107**) [23].



Chemotherapy of diseases caused by microorganisms is at least conceptually very straightforward since it depends on deepseated metabolic differences between eukariotic and prokariotic species; it has as consequence usually been possible to identify compounds which are uniquely toxic to disease causing organisms. In contrast to this, viral and neoplastic diseases have in common a derangement of the host cells' mechanism for replication; this process is taken over by the virus in one case and is no longer under tight genetic control in the other. The clean differences in metabolism simply do not exist. The fact that both disease types involve nuclear processes and thus also nucleosides has led to a long-term research effort to synthesize modified purines and pyrimidines in the hope that some subtle differences may exist between healthy and diseased cells. The success of the modified nucleoside, **acyclovir**, suggests that this approach has considerable merit.

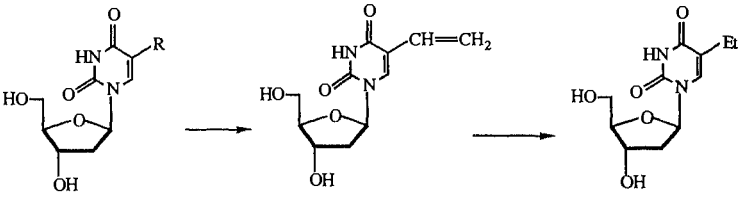
One such compound, **bropirimine (112)**, is described as an agent which has both antineoplastic and antiviral activity. The first step in the preparation involves formation of the dianion **108** from the half ester of malonic acid by treatment with butyllithium. Acylation of the anion with benzoyl chloride proceeds at the more nucleophilic carbon anion to give **109**. This tricarbonyl compound decarboxylates on acidification to give the beta ketoester **110**. Condensation with guanidine leads to the pyrimidone **111**. Bromination with N-bromosuccinimide gives **bropirimine (112)** [24].



Compounds prepared from naturally occurring nucleosides are of course more closely related to genetic material and may have a better chance of interacting with infected cells. Mercuration of the 2'-deoxyuridine **113** leads to the organometallic derivative **114**; reaction of that with ethylene in the presence dilithio palladium tetrachloride gives the alkylation product **115**; this is reduced catalytically *in situ*. There is thus obtained the antiviral agent edoxudine (116) [25].

Todays' most famous virus is probably that which is responsible for AIDS. Though an actual cure is not yet in sight, a drug which slows progression of the disease by inhibiting replication of the virus was recently introduced. The published synthesis for the drug, known trivially as **AZT**, starts from thymidine, possibly accounting for its very high cost when initially made available. Thus, treatment of thymidine (**117**) with chloropentafluorotriethylamine leads to the product from displacement of the sugar ring hydroxyl by the hydroxyl from the pyrimidone eno-

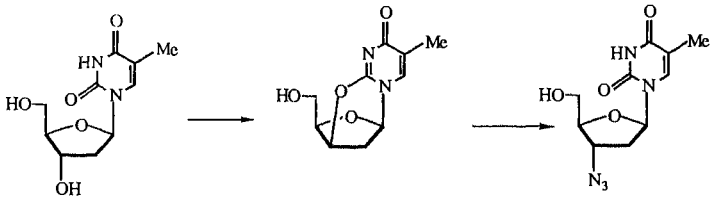
late (**118**). The potent nucleophile, azide, serves to open the somewhat strained bridging ring; this involves a second inversion and restoration to the natural stereochemistry. There is thus obtained zidovudine (**119**), formerly known as **AZT** [26].



(**113**); R = H
(**114**); R = HgCl

(**115**)

(**116**)



(**117**)

(**118**)

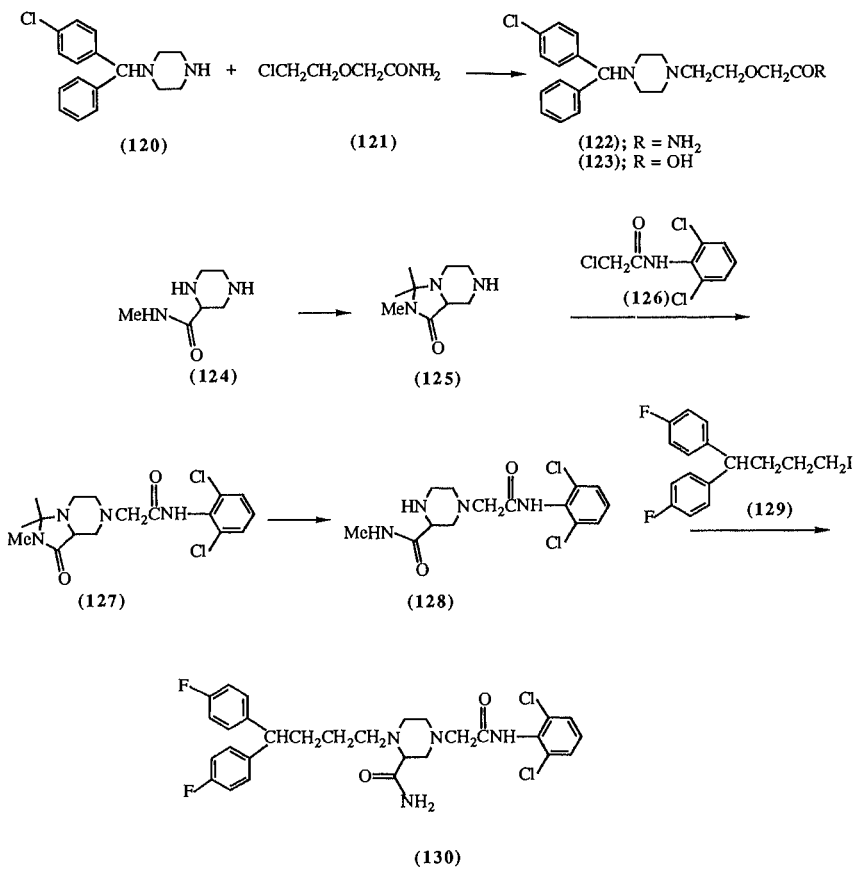
(**119**)

4. PIPERAZINES

Yet another nonsedating zwitterionic H-1 antihistamine consists of the product from metabolism of the terminal hydroxyl of the potent antihistamine hydroxyzine terminating in hydroxymethyl instead of a carboxylic acid. This compound, cetirzine (**123**), can be obtained in straightforward fashion by alkylation of the monosubstituted piperazine **120** with halide **121**, via the amide **122** [27].

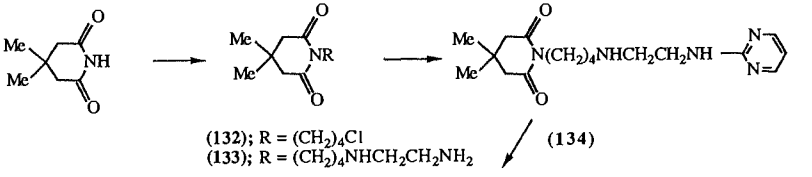
A number of diarylmethyl alkylpiperazines, such as, for example lidoflazine, have found use as coronary vasodilators for the treatment of angina. The most recent of these interestingly incorporates a 2,6-dichloroaniline moiety reminiscent of antiarrhythmic agents. Treatment of the piperazine carboxamide **124** with acetone leads to formation of the nitrogen analogue of an acetal, the aminal **125**. Alkylation of the remaining secondary nitrogen with chloroamide **126** leads to the intermediate **127**. Exposure to aqueous acid leads to hydrolysis of the aminal function

and restoration of the secondary amine **128**. Alkylation of that center with iodide **129** followed by N-demethylation leads to the formation of **mioflazine (130)** [28].



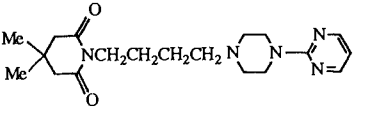
The anxiolytic agent **buspirone (131)** is notable for the fact that it does not interact with the receptor for the benzodiazepines. This difference in biochemical pharmacology is reflected in the fact that **buspirone (131)** seems to be devoid of some of the characteristic benzodiazepine side effects. The spiran function is apparently not required for anxiolytic activity. Alkylation of 3,3-dimethylglutarimide with dichlorobutane in the presence of strong base yields the intermedi-

ate **132**; treatment of that with ethylenediamine leads to **133**. Use of this diamine to alkylate 2-chloropyrimidine proceeds at the terminal amino group to afford the open chain compound **134**. Bisalkylation with 1,2-dichloroethane leads to ring closure to a piperazine. There is thus obtained gepirone (**135**) [29].

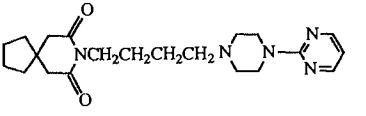


(132); R = $(CH_2)_4Cl$
(133); R = $(CH_2)_4NHCH_2CH_2NH_2$

(134)



(135)

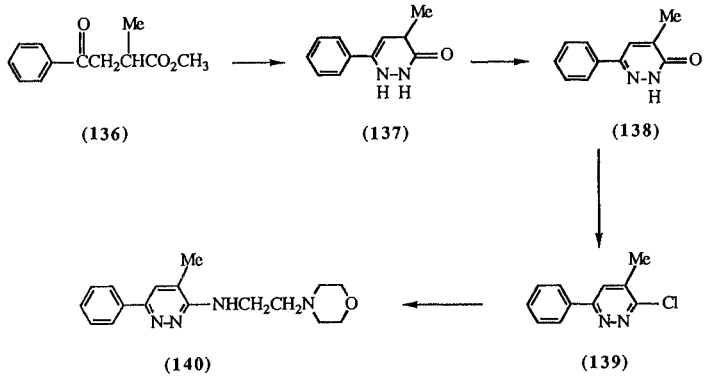


(131)

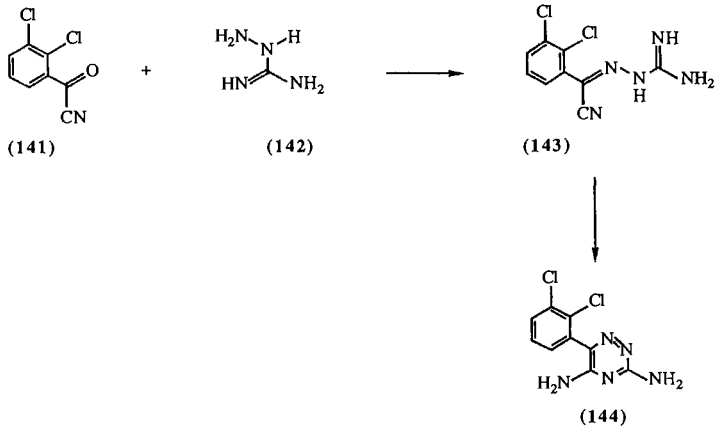
5. MISCELLANEOUS COMPOUNDS

A piridazine ring forms the nucleus for a rather unusual nontricyclic antidepressant. Condensation of the keto ester **136** with hydrazine leads to the cyclic hydrazide **137**. Oxidation, for example with bromine, gives the corresponding pyridazone **138**. The oxygen is then replaced by chlorine by reaction with phosphorus oxychloride. Displacement of the halogen in **139** with N-ethylaminomorpholine affords minaprine **140** [30].

Reaction of 2,3-dichlorobenzoyl chloride with cyanide ion leads to the corresponding benzoyl cyanide (**141**). Condensation of that reactive intermediate with aminoguanidine **142** leads to the hydrazone-like product **143**. Treatment with base results in addition of one of the guanidine amino groups to the nitrile function and formation of the 1,2,4-triazine ring. The product, lamotrigine (**144**), is described as an anticonvulsant agent [31].



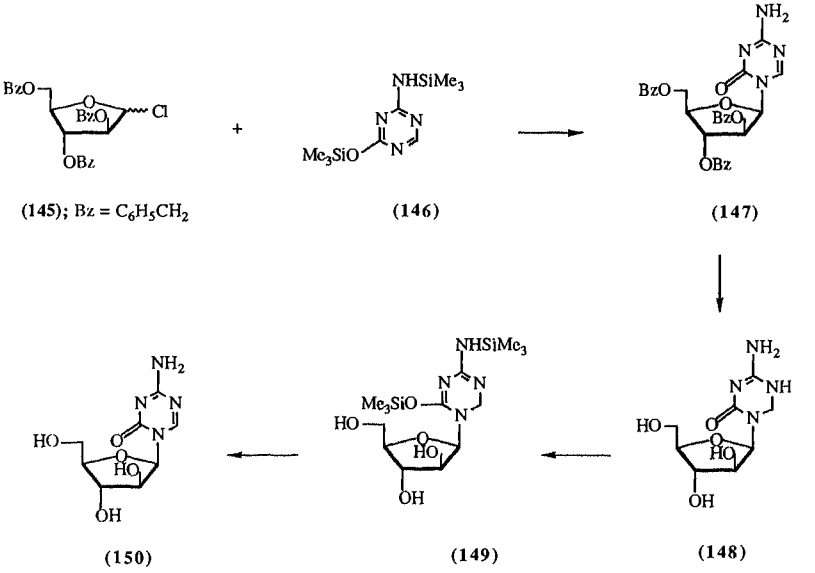
(136) (137) (138) (139) (140)



(141) (142) (143) (144)

Replacement of heterocyclic rings in nucleosides by ring systems which do not occur in nature represents another approach to compounds which may have activity against viral and neoplastic diseases. One of the early successes in this category involves replacement of a pyrimidine ring by a triazine. The synthesis starts with a now classical glycosidation of a heterocycle as its silylated derivative (**146**) with a protected halosugar (**145**), in this case a derivative of arabinose

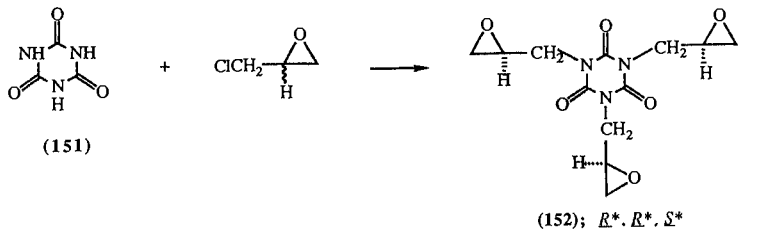
[32]. Hydrogenation of the product **147** removes the benzyl protecting groups and at the same time reduces the triazine to its dihydro derivative **148**. A roundabout scheme is required for dehydrogenation due to the sensitivity of the intermediates. The product is thus converted to its silyl ether **149**; exposure to air results in oxidation and desilylation. There is thus obtained the antineoplastic agent **fazarabine (150)**, also known as **ara-A C**.



(145); Bz = $C_6H_5CH_2$ (146) (147)

(150) (149) (148)

Alkylating agents represent the oldest class of antineoplastic agents. These compounds, whose actions are somewhat indiscriminate, disrupt genetic material by forming covalent bonds with the bases in DNA. Polydentate alkylating agents may be more effective, it is thought, due to their ability to crosslink adjacent DNA chains. One such compound is available from the reaction of cyanuric acid (**151**) with epichlorohydrin [33]. Each of the three epoxypropyl side chains contains a chiral center. The product will thus consist of a mixture of 4 enantiomers (2 diastereomers) [34]. The drug, **teroxirone (152)**, in fact consists of the separated racemic (R S, R S, S R)-isomer.



(151)

(152); *R**, *R**, *S**

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7 Five-Membered Ring Benzofused Heterocycles

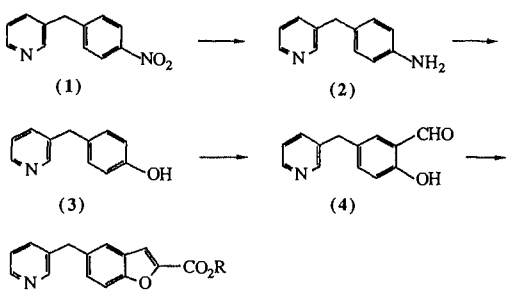
The vast majority of drugs contain an aromatic ring of some type or other as an important structural element. Biological systems are often quite forgiving in their acceptance of interchange of certain heteroatoms for carbon in such rings [e. g., N (benzene to pyridine), O (furan for pyrrole), S (thiophene for furan)] as shown by the popularity of the stratagem of bioisosteric replacement as an element of drug design. In this context, the heteroaromatic ring often appears to serve as a flat, electron rich framework upon which to attach functionality which may interact with specific receptors. These factors, the relative ease of construction of heterocycles, and the huge numbers of isomers this makes possible account for many of the very large family of drugs incorporating this structural feature. In such molecules the specific aromatic moiety is rarely essential for activity. As one consequence, the drugs discussed in this chapter display a very wide range of bioactivities.

1. BENZOFURANS

Thromboxane A-2 has been implicated in a number of disorders of the circulatory system including coronary artery spasms, unstable angina pectoris, traumatic and endotoxic shock, and heart attacks. It is formed normally very near its receptors and is rapidly deactivated by metabolizing enzymes so circulating levels are quite low. Furthermore, it is opposed in its actions by the prostacyclins. When these controls are defective, pathology results and drugs can be the resort in attempts to restore the normal healthy balance. For one example, **furegrelate** (6) is a throm-

boxane synthetase inhibitor which can reestablish homeostasis by banking down the synthesis of thromboxanes. A useful ancillary characteristic of this type of drug is that the precursor prostaglandin endoperoxides are largely diverted to the biosynthesis of prostanoids whose pharmacological actions antagonize those of thromboxanes. Thus, both of its major actions operate in the same direction and the drug has shown clinical value in some life-threatening conditions [1].

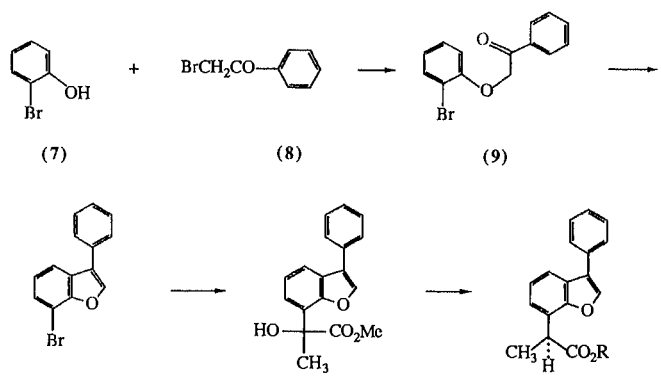
One of the syntheses of **furegrelate** begins by catalytic hydrogenation (Pd/C) of 3-(4-nitrobenzyl)pyridine (**1**) to the corresponding aminobenzylpyridine (2). This is followed by diazotization in the usual fashion; the diazonium salt is transformed to the corresponding phenol (3) by heating with hot aqueous acid. A formyl group is then introduced ortho to the phenolic function by use of hexamethylene tetramine in anhydrous trifluoroacetic acid (the Duff reaction). The key intermediate in this interesting transformation is believed to be the substituted benzylmethylene imine formed by interception by the phenol of the highly reactive intermediate formed by partial depolymerization of the hexamethylene tetramine reagent. The resulting substituted benzylmethyleneimine is in turn thought to undergo double bond isomerization to the corresponding substituted benzaldehyde methylimine. Hydrolysis during workup gives the final product. Treatment with base and diethyl bromomalonate produces the desired benzofuran ring system of **5**. It seems likely that this reaction proceeds by ether formation followed by cyclization to the 3-hydroxy-2,2-dicarbethoxydihydrofuran system which, on saponification undergoes decarboxylative ejection of hydroxyl giving aromatic ester **5**. The synthesis concludes by saponification to **furegrelate** (6) [2].



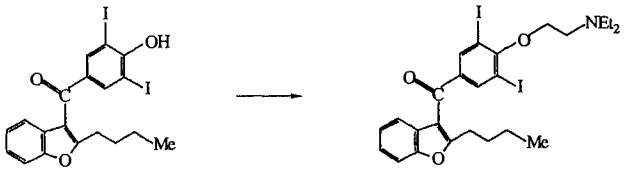
(1) (2) (3) (4)

(5); R = Et
(6); R = H

A somewhat related nonsteroidal antiinflammatory agent, **furaprofen (14)**, is much more active as its S-enantiomer. Its patented preparation depends upon a chiral enzymic hydrolysis in a late step. One synthesis begins by ether formation between 2-bromophenol (7) and phenacyl bromide (8) to give the aryloxyacetophenone **9**. Treatment of **9** with polyphosphoric acid leads to cyclodehydration to benzofuran **10**. The later is converted to the Grignard reagent and condensed with methyl pyruvate to give tertiary carbinol **11**. Deoxygenation is accomplished by sequential dehydration with tosic acid and subsequent hydrogenation to produce racemic ester **12**. Saponification produces racemic **furaprofen (13)**. The use of a hydrolytic enzyme from *Bacillus subtilis* to convert **12** to **13** produces the optically active drug [3].



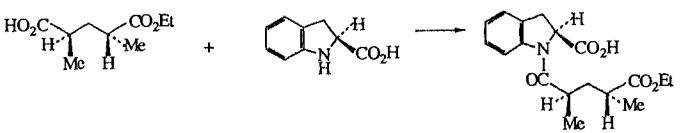
Amiodarone (16) has been the center of much interest because of its activity as a cardiac depressant useful in treating ventricular arrhythmia and many analogues have been prepared [4]. The originally patented procedure concludes simply by etherification of benzofuran-containing iodonated phenol **15** with 2-halodiethylaminoethane to give **amiodarone (16)** [5]. The synthesis of **15** is not detailed in the reference but the synthesis of **benzbromarone** contains closely analogous steps [6].



(15) (16)

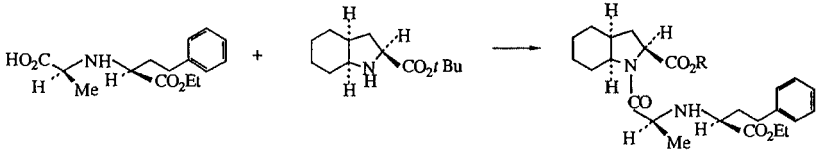
2. INDOLINES

One of the many angiotensin-converting enzyme (ACE) inhibitors covered in this volume contains an indoline residue instead of a pyrrolidine. As such, it may be considered as a benzo analogue of the captopril series. The synthesis of **pentopril** (19) follows the classical amide forming condensation of hemiester 17 (itself prepared by alcoholysis of the corresponding 2,4-dimethylglutaric anhydride) with (S)-indoline-2-carboxylic acid (**18**), using 1-[3-(dimethylamino)propyl)]-3-ethylcarbodiimide as condensing agent, in order to produce **pentopril** [7].



(17) (18) (19)

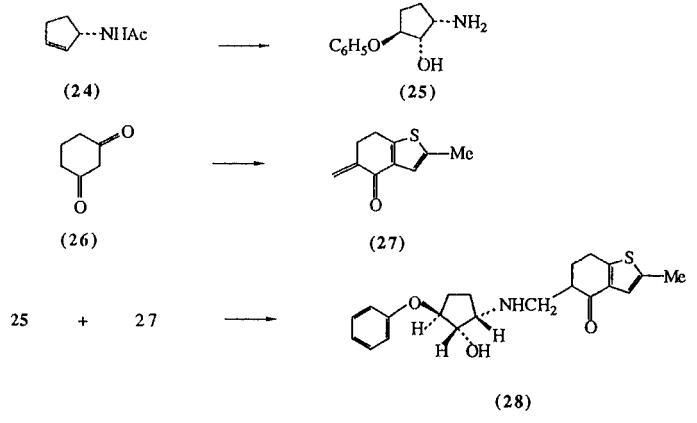
Saturation of the aromatic ring of **pentopril** analogues is also consistent with ACE inhibition as demonstrated by the oral activity of **indolapril** (23). The necessary heterocyclic component (21) can in principle be prepared by catalytic perhydrogenation (Rh/C, HOAc) of the corresponding indole. A single isomer predominates. The product is condensed by amide bond formation with the appropriate alanylhomophenylalanyl dipeptide ester **20** to give **22**. Selective saponification to 23 could be accomplished by treatment with HCl gas. Use of the appropriate stereoisomers (prepared by resolution processes) produces chiral **indolapril** [8].



(20) (21) (22); R = *t*-Bu
(23); R = H

3. BENZOTHIOPHENES

Tipentosin (28) contains a partially reduced benzothiophene ring system and is of interest as an antihypertensive agent. Its synthesis begins with epoxidation of 3-acetamidocyclopentene (24) followed by epoxide opening with phenol, and then deacetylation to give amino alcohol **25**. The second half of the molecule is prepared from 1,3-cyclohexanedione (26) by sequential alkylation with chloroacetone, isopropylidenation of the product (to the bisenolether), and cyclization to a thiophene moiety with hydrogen sulfide. The latter reaction appears to involve a sequential double Michael addition of hydrogen disulfide with consequent elimination of the acetonide in the form of acetone and water. Synthesis of this component is concluded by aminomethylation via a Mannich reaction followed by reverse Michael loss of dimethylamine to give **27**. The synthesis of lipentosin (28) concludes by Michael addition of the amino group of **25** to the conjugated linkage of 27 [9].



(24) (25)

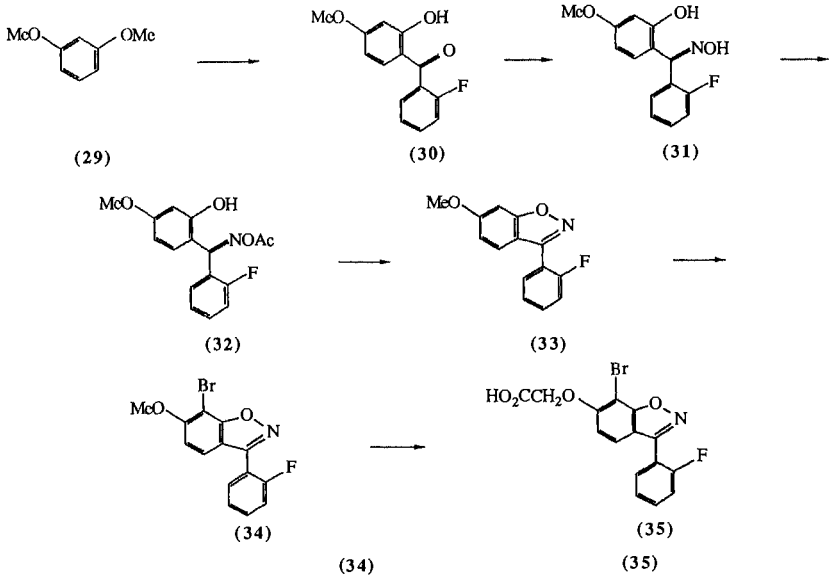
(26) (27)

25 + 27

(28)

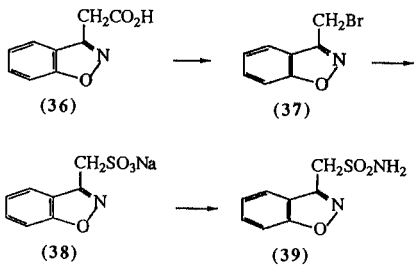
4. BENZISOXAZOLES

A diuretic of the phenoxyacetic acid class is **brocrinat (35)**. Its synthesis begins with Friedel-Crafts acylation of resorcinol dimethyl ether (**29**) with 2-fluorobenzoyl chloride to give unsymmetrical benzophenone **30**. The ortho-phenolic ether moiety is cleaved selectively in this acylation reaction. The product is converted predominantly to its E-oxime analogue (**31**) in the usual fashion and then acetylated (Ac_2O) to its acetyl ester 32. This synthesis of the benzisoxazole ring concludes by NaH treatment leading to cyclization to 33 involving an internal displacement reaction. Metallation with n-BuLi followed by bromination produced **34**. Ether cleavage with pyridine hydrobromide followed by alkylation with NaH and ethyl bromoacetate and hydrolysis lead to the oxyacetic acid containing **brocrinat (35)**. [10].



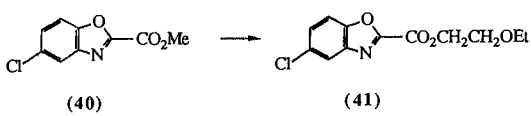
The anticonvulsant activity of some 1,3-benzisoxazoles was discovered in routine testing. One of the more interesting of the subsequent analogues prepared was **zonisamide (39)**. One of its syntheses starts with 1,2-benzisoxazole-3-acetic acid (**36**) which is brominated and subsequently decarboxylated to give 37. Displacement of halogen in **37** with sodium bisulfite interestingly

proceeds by reaction on sulfur to produce 1,2-benzisoxazole-3-methane sulfonic acid (38). Chlorination of 38 with phosphorous oxychloride to the corresponding sulfonyl chloride followed by reaction with ammonia gives the sulfonamide, **zonisamide (39)** [11]. Alternate syntheses are available [12].



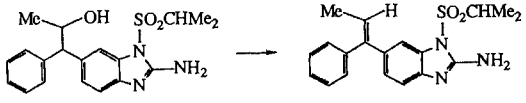
5. BENZOXAZOLES

Eclazolast (41) is an antiallergy compound which inhibits release of mediators of allergy. One reported synthesis involves the simple ester exchange of methyl 2-benzoxazolecarboxylate (**40**) with 2-ethoxyethanol catalyzed by sulfuric acid [13].



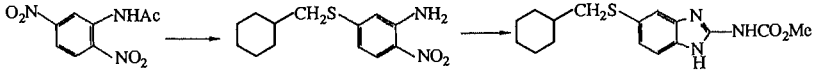
6. BENZIMIDAZOLES

The last step in one reported preparation of the antiviral agent **enviradene (43)** involves dehydration of 6-(1-hydroxy-1-phenylpropyl)-2-amino-1-isopropylsulfonyl-benzimidazole (**42**). The E-product predominates [14]. Precedent for this chemistry and a description of related intermediates can be found in Volume 3, p. 177 of this work.



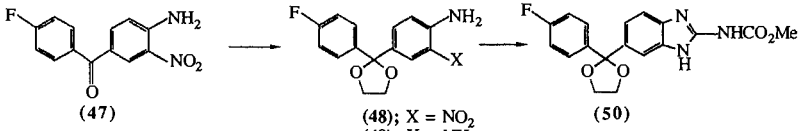
(42) (43)

Benzimidazoles bearing a carboxamide function at the 2-position have provided the nucleus for a significant number of anthelmintic agents. (See Chapter 11 of Volume 2 and Chapter 10 of Volume 3 of *The Organic Chemistry of Drug Synthesis* for examples.) The high rate at which resistant strains of parasites have developed has led to the need for ever newer drugs. Preparation of **dribendazole (46)** begins by reaction of the acetate of 2,5-dinitroaniline with cyclohexylmethylthiol; the product from the unusual displacement of one of the nitro groups (**45**) is then reduced to the diamine. Reaction of this intermediate with N,N-dicarbomethoxy-S-methylthiourea leads to the cyclized product [15].



(44) (45) (46)

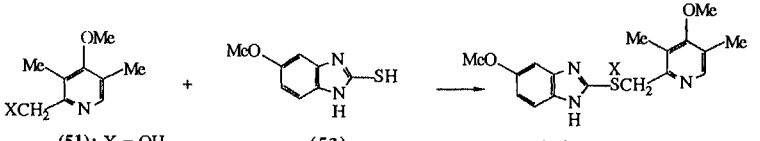
An analogous sequence leads to the anthelmintic agent, **etibendazole (50)**. Reaction of the benzophenone **47**, which can be obtained by acylation of o-nitroaniline with p-fluorobenzoyl chloride, with ethylene glycol leads to acetal **48**. Sequential reduction of the nitro group and cyclization of the resulting diamine (**49**) with N,N-dicarbomethoxy-S-methylthiourea gives the benzimidazole **etibendazole (50)** [16].



(47) (48); X = NO_2 (49); X = NH_2 (50)

The discovery of the antiulcer activity of H2 antihistamine antagonists has revolutionized the treatment of that disease. A benzimidazole, **Omeprazole (55)**, inhibits gastric secretion and subsequent ulcer formation by a quite different mechanism. Studies at the molecular level suggest that this compound inhibits K^+/H^+ dependent ATPase and consequently shuts down the proton pumping action of this enzyme system.

Treatment of pyridyl carbinol **51** with thionyl chloride leads to the corresponding chloride (52). Treatment of that intermediate with 5-methoxy-2-mercaptobenzimidazole (53), obtained from reaction of 4-methoxy-o-phenylenediamine with potassium ethylxanthate leads to displacement of halogen and formation of the sulfide (**54**). Finally, oxidation with 3-chloroperbenzoic acid produces the sulfoxide **omeprazole (55)** [17].

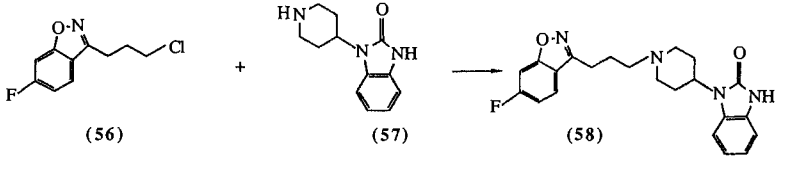


(51); X = OH
(52); X = Cl

(53)

(54); X = :
(55); X = O

The p-fluorobutyrophenone group is one of the hoary traditions in the field of antidopaminergic antipsychotic drugs. First introduced in the neuroleptic **haloperidol**, this group has appeared in numerous drugs or drugs-to-be. It is of interest that an isoxazole serves as a surrogate for the carbonyl group in some p-fluorobutyrophenones. Alkylation of 1-(4-piperidinyl)-2-benzimidazolinone (**57**), an intermediate closely related to one used for **domperidone** (see Volume 3, p. 174) with 3-(3-chloropropyl)-6-fluoro-1,2-benzisoxazole (**56**) affords **neflumozide (58)** [18,19].



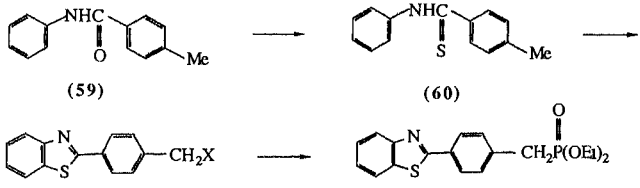
(56)

(57)

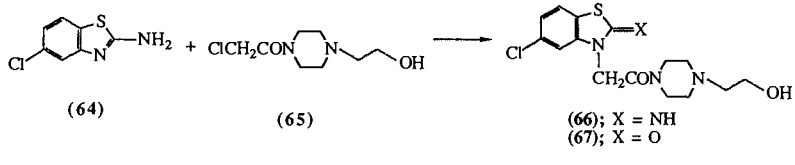
(58)

7. BENZOTHIAZOLE

Calcium channel antagonists have proven of great value as antianginal and antihypertensive agents. Most of these agents fall into one of three rather narrow structural classes. It is thus of interest to find that a structurally quite different benzothiazole shows the same type of activity. It is of note too that the agent in question, **fostedil** (63), is one of the very few phosphorous containing agents to be developed for the clinic. Treatment of benzanilide **59** with phosphorous pentasulfide or Lawesson's reagent gives thioamide **60**. Oxidative ring formation by reaction with potassium ferricyanide and base (presumably involving a free radical intermediate) constructs the benzothiazole ring of **61**. Bromination of this compound with N-bromosuccinimide produces bromomethyl intermediate **62**. The synthesis of **fostedil** (63) concludes with a Michaelis-Arbuzov reaction of 62 with triethyl phosphite [20].



Tiaramide (67) is a benzothiazolinone containing antiasthmatic agent. One of its syntheses begins with alkylation of 5-chloro-2-aminobenzothiazole (**64**) by 4-(2-hydroxyethyl)-1-piperazinylcarbonylmethyl chloride (**65**) to give 66 and concludes by gentle hydrolysis with methanolic hydrogen chloride to convert the imino moiety to the carbonyl of **tiaramide** [21].



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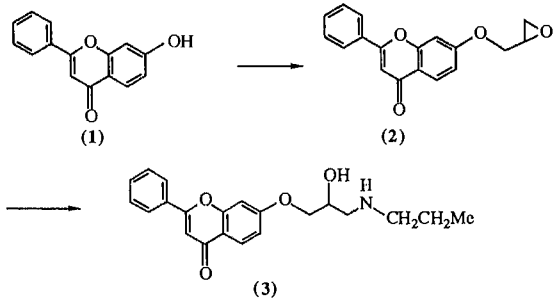
8 Six-Membered Ring Benzofused Heterocycles

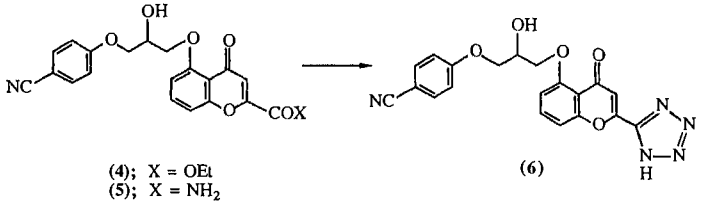
1. CHROMONES

The great commercial success of the adrenergic β-receptor blockers has led to the synthesis of many other potential drugs by the incorporation of an oxypropanolamine functionality into a wide variety of aromatic rings. This has lead to the preparation of thousands of such analogues. An example of this is **flavodilol** (3), an antihypertensive agent, which is synthesized using chemistry standard for the purpose by starting with 7-hydroxyflavone (**1**). The side chain scaffolding is assembled by reaction with epichlorohydrin to give glycidylether **2** and this is in turn reacted with propylamine to give **flavodilol** (3) [1]. Surprisingly, **flavodilol** does not block the effects of norepinephrine at either adrenergic α or β receptors, despite its formal structural similarity to the classical β-blockers.



The attractive properties of **cromolyn** as an inhibitor of the release of mediators of anaphylaxis has inspired many attempts to improve on the antiasthmatic characteristics of that substance. One such agent is **cromitrile** (6). In this case, a tetrazolyl unit is introduced as a carboxy group

bioisostere and the two aromatic ring systems are different from one another. One synthesis concludes in the classic manner by converting chromone ester **4** to the carboxamide (**5**) by ammonolysis, dehydrating the latter functionality to the nitrile with tosyl chloride in pyridine and adding sodium azide selectively across this functionality to produce the antiasthmatic agent **cromitrile (6)** [2]. The chemical basis for the selectivity of the last reaction is not obvious.

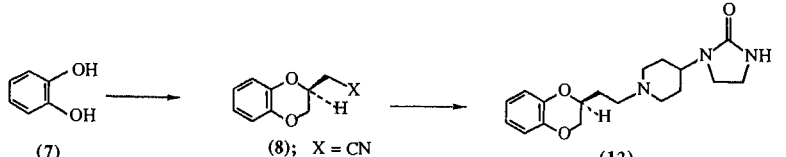


(4); X = OEt
(5); X = NH_2

(6)

2. BENZODIOXANES

Azaloxan (12) is an antidepressant agent. Its synthesis can be accomplished starting with the reaction of catechol (**7**) and 3,4-dibromobutyronitrile (obtained by addition of bromine to the olefin) to give 1,4-benzodioxan-2-ylacetonitrile (8). A series of functional group transformations ensues [hydrolysis to the acid (**9**), reduction to the alcohol (**10**) and conversion to a tosylate (**11**)] culminating in an SN-2 displacement reaction on tosylate **11** with 1-(4-piperidinyl)-2-imidazolidinone to give **azaloxan (12)** [3].



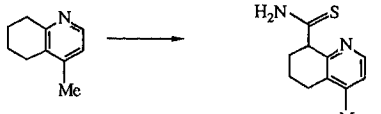
(7)

(8); X = CN
(9); X = CO_2H
(10); X = CH_2OH
(11); X = CH_2OTos

(12)

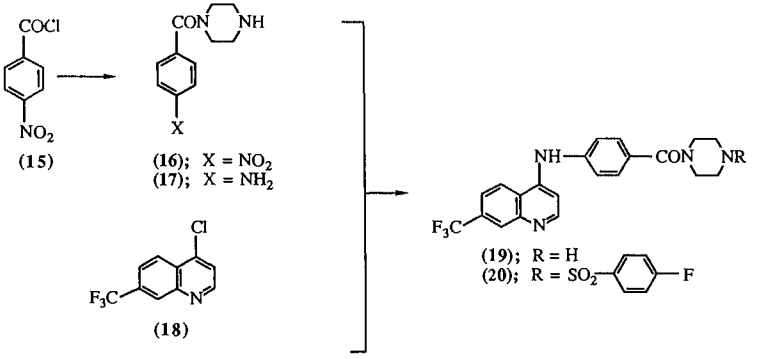
3. QUINOLINES AND CARBOSTYRILS

A partially reduced quinoline derivative with antiulcerative and antisecretory activities is isotiquimide (**14**). It may be synthesized by metallating (with n-BuLi) 4-methyl-5,6,7,8-tetrahydroquinoline and condensing this with dimethylmethoxysilylisothiocyanate to produce the desired thioamide isotiquimide (**14**) [4].



(**13**) (**14**)

Losulazine (**20**) is an orally and parenterally active antihypertensive agent apparently acting on peripheral postganglionic sympathetic nerve terminals to deplete norepinephrine stores. This prevents vasoconstriction by reducing levels of that neurotransmitter available following stimulation of adrenergic nerves. In this sense its calming action mimics that of reserpine. In a convergent synthesis, 4-nitrobenzoyl chloride (**15**) is used to monoacylate piperazine to give amide **16**; the nitro moiety of this is then reduced to give substituted aniline synthon **17**. A nucleophilic aromatic displacement reaction between **17** and 4-chloro-7-trifluoromethylquinoline (**18**) leads to **4**-aminoquinoline derivative **19**. The synthesis of losulazine concludes by formation of the sulfonamide (**20**) by reaction of the remaining secondary piperazine nitrogen with 4-fluorobenzenesulfonyl chloride [5].



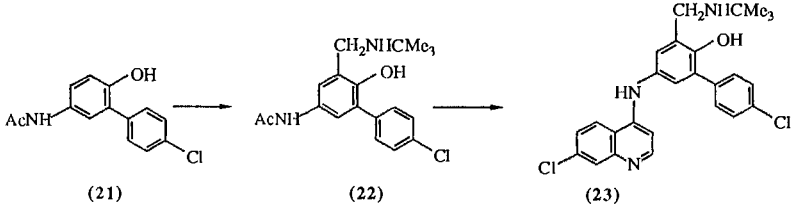
(**15**)

(**16**); X = NO_2
(**17**); X = NH_2

(**18**)

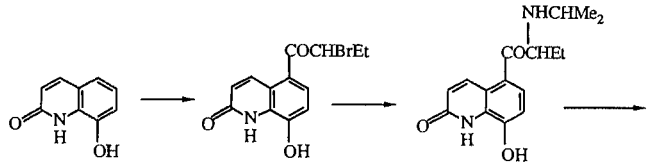
(**19**); R = H
(**20**); R = SO_2

The continuing development of resistant strains by the malaria parasite to chemotherapeutic agents has led to an ongoing, though sporadic, synthesis of new chemical entities aimed at that target in the hope of finding drugs which will overcome resistance. That there is still interest in the classical 4-aminoquinolines (see *The Organic Chemistry of Drug Synthesis*, Volume 1, p. 343) is attested to by the preparation of **tebuquine** (23), a hybrid compound combining structural elements of **amodiaquine** and some 2-(dialkylamino)-o-cresols which have shown antimalarial activity. The synthesis is closely analogous to the original method used for **amodiaquine**. It starts by reacting 4'-chloro-N-(6-hydroxyl[1,1'-biphenyl]-3-yl) acetamide (21) with formaldehyde and t-butylamine in an aromatic version of the Mannich reaction to give acetanilide 22. Hydrolysis to the free aniline with HCl is followed by the standard nucleophilic aromatic displacement reaction with 4,7-dichloroquinoline to complete the synthesis of the antimalarial agent **tebuquine** (23) [6].

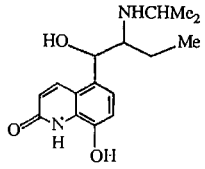


(21) (22) (23)

Procaterol (27) is a β-adrenergic agonist with bronchodilatory action intended for use in bronchial asthma. A carbostyril NH group in this molecule is used as part of a bioisostere replacing the catechol moiety of epinephrine. Pharmacologically it is of special interest in that it is said to selectively stimulate adrenergic β-2 receptors without much effect on β-1 receptors, minimizing cardiac stimulation. Friedel-Crafts reaction between 8-hydroxycarbostyril (**24**) and 2-bromobutyryl bromide leads to the expected acylation at C-5 in the more activated ring (**25**). Halide displacement with isopropylamine (to give **26**) is followed by borohydride reduction to the mixture of diastereoisomeric arylethanolamines. The erythro-isomer is **procaterol** (27) [7].



(24) (25) (26)



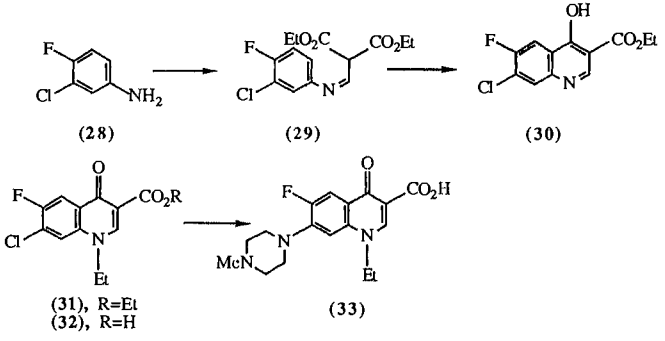
(27)

4. QUINOLONES

Intense synthetic activity has resulted centered about congeners of the quinolone-3-carboxylic acids when it was found that certain analogues, notably those with 6-fluoro-7-piperazinyl moieties (now known collectively as the fluoroquinolones) possess broad spectrum oral antimicrobial activity with potencies in the range of fermentation-derived antibiotics. Additional interest in these molecules was inspired by the discovery of their unusual molecular mode of action; strongly selective inhibition of the action of bacterial DNA gyrase, a type II (double strand DNA breaking) topoisomerase essential for dictating the conformation of bacterial circular DNA. The activity of DNA gyrase is essential for the orderly processing of DNA as several important enzymes are sensitive to the topological arrangement of the molecule. Several thousand furoquinolone analogues have been prepared and several (including **norfloxacin, ciprofloxacin,** and **ofloxacin**) have been introduced clinically and several others are advancing toward commercial use.

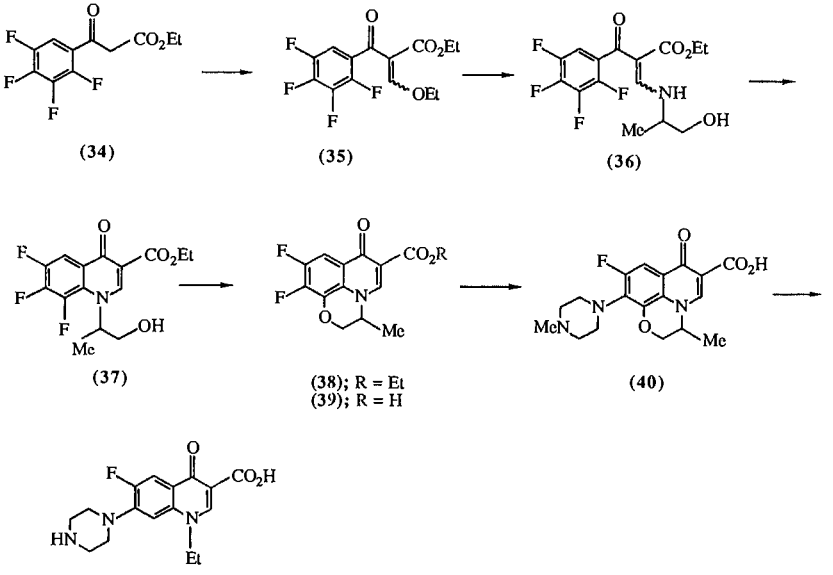
Pefloxacin (33) is the N-methyl analogue of **norfloxacin** (58) and is at least partly converted to it by metabolic enzymes in vivo. It has been launched in France for the treatment of a number of infections including those caused by sensitive strains of *Pseudomonas aeruginosa.* It can be synthesized starting with the Gould-Jacobs reaction of 3-chloro-4-fluoroaniline (28) and diethyl ethoxymethylenemalonate in an addition-elimination sequence leading to 29 which undergoes

thermal cyclization to hydroxyquinoline ester **30**. Despite the apparent asymmetric substitution pattern of **29** which might lead one to believe that mixtures would result from the pericyclic reaction, only one product is observed in any quantity. It is rationalized that the buttressing effect of the aryl chlorine atom is the cause of the observed steric preference. Next, alkylation on nitrogen with EtI leads to quinolone ester **31** which is itself readily hydrolyzed to the corresponding carboxylic acid **32**. A nucleophilic aromatic displacement reaction of the 7-chloro moiety, activated by the pyridone carbonyl as a sort of vinylogous acid chloride, with N-methylpiperazine completes a synthesis of **pefloxacin** (**33**). This synthetic sequence is the classic route to this series of antimicrobial agents [8].



One of the most promising newer members of the fluoroquinolone family is **ofloxacin** (**40**). In this case, the N-ethyl moiety has been made rigid by incorporation into a heterocyclic ring. This creates a chiral center and subsequent chiral synthesis reveals that the S-enantiomer is significantly more potent than its antipode and is rather more water soluble than the racemate. Of the various syntheses of **ofloxacin**, the more recent chiral process is illustrated. Starting with ethyl (2,3,4,5-tetrafluoro)-3-oxopropionate (**34**), the ethoxymethylene function is introduced by cross condensation with ethylorthoformate and acetic anhydride to give **35**. Alaninol, prepared by reduction of optically active alanine, is incorporated in an addition-elimination reaction to give **36**. Treatment of the latter with non-nucleophilic base leads to a nucleophilic aromatic displacement of fluorine and thus ring closure to give **37**. The geometry of **36** appears to be unimportant as it is lost in the intermediate anion. Condensation, of course, depends upon proximity. Repetition of the base

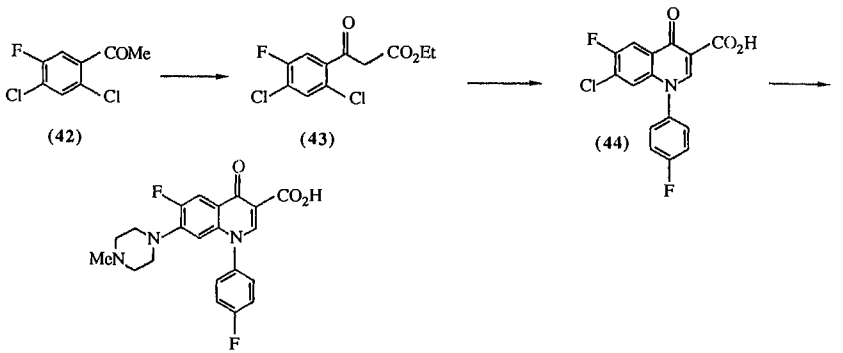
treatment and/or use of forcing conditions leads to a second displacement of aromatic fluorine and the closure of the second heterocyclic ring of 38. The remainder of the sequence follows the standard quinolone synthetic route in which saponification (to **39**) and nucleophilic aromatic displacement with N-methylpiperazine leads to **ofloxacin (40)**. The chirality of the alanine derivative employed dictates the stereochemistry of the final product [9,10,11].



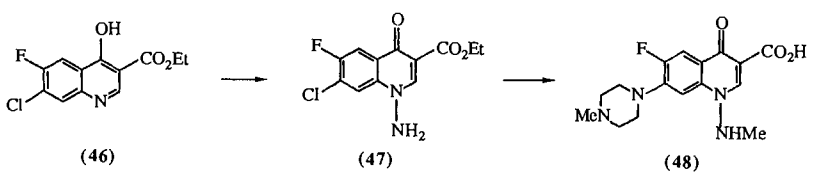
Norfloxacin (41), the substance which triggered this avalanche of activity, has recently been introduced into clinical practice in the United States. Its synthesis parallels closely that of its N-methyl analogue, **pefloxacin**, except that the nucleophilic aromatic displacement reaction of **32** is carried out with mono-N-carboethoxypiperazine instead and the final step encompasses deblocking of this carbamoyl ester moiety [8].

The generally accepted structure-activity relationships developed in the early work in the quinolone series held that the N-1 substituent needed to be small and aliphatic. This picture was upset in a dramatic way with the discovery of the excellent potency and antimicrobial spectrum of **difloxacin (45)** and its congeners in which the substituent on N-1 is an aromatic ring. The synthe-

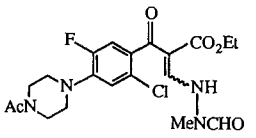
sis of **difloxacin** begins with 2,4-dichloro-5-fluoroacetophenone (**42**) which is carbethoxylated by reaction with diethyl carbonate and base to give ester **43**. The rest of the synthesis parallels that described above for **ofloxacin** except that the addition-elimination reaction is carried out with 4-fluoroaniline and **44** is the resulting product after cyclization and hydrolysis. Conclusion of the synthesis of **difloxacin** (**45**) involves displacement of the activated 7-chloro atom by N-methylpiperazine [12].



Amifloxacin (**48**) demonstrates that the methylene group of the N-ethyl substituent can be replaced successfully by a bioisosteric NH group in the fluoroquinolone series. In one of two interesting syntheses, 4-hydroxyquinoline ester **46** is reacted with O-(2,4-dinitrophenyl)hydroxylamine with the aid of potassium carbonate to give the hydrazine analogue **47**. Next, N-formylation is accomplished with aceticformic anhydride (formed in situ by reaction of $Ac_2O + HCO_2H$). The formamide thus produced is methylated with iodomethane and base. This sequence allows for clean monoalkylation. The N-formyl group is hydrolyzed with NaOH and N-methylpiperazine displacement of the activated C-7 chloro atom completes the synthesis of **amifloxacin** (**48**) [13].

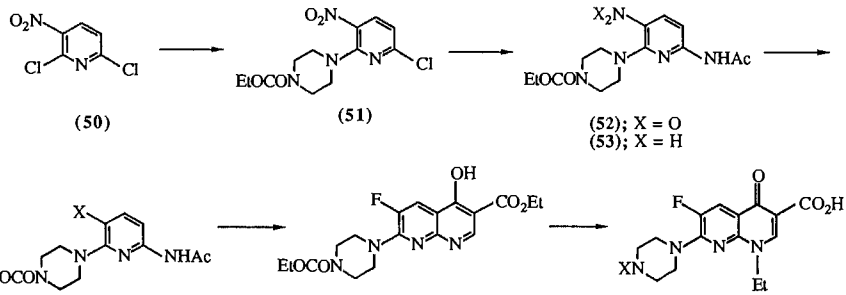


Alternately, amifloxacin can be prepared *via* the ofloxacin/difloxacin route using an addition-elimination reaction with unsymmetrical N-methyl-N-formyl hydrazone to give **49** [14].



(49) (48)

Enoxacin (58) is an analogue of the quinolones based on the 1,8-naphthyridine ring system. The drug is available commercially in Japan. The naphthyridine analogues of the fluoroquinolones, generally speaking, are not as potent as the quinolones in vitro but have favorable pharmacokinetic characteristics which help compensate for this in vivo. The synthesis of **enoxacin** begins by reaction of 2,6-dichloro-3-nitropyridine (**50**) with N-carboethoxypiperazine to give **51**. The second, less reactive, halo group is then displaced with ammonia, and the resulting amine acetylated to **52**, the nitro group is then reduced to give triaminopyridine derivative **53**. Diazotization to **54** with sodium nitrite plus tetrafluoroboric acid, followed by heating in xylene, results in displacement of the diazonium salt by fluorine to give **55**. The rest of the synthesis follows the well trodden path of acid hydrolysis followed by Gould-Jacobs reaction to **56**. The alternate ortho-closure onto pyridine nitrogen does not take place presumably due to the steric interference by the piperazinyl group at C-7. Sequential hydrolyses to **57** and then **58** concludes the synthesis of **enoxacin** [15,16].



(50) (51) (52); X = O (53); X = H

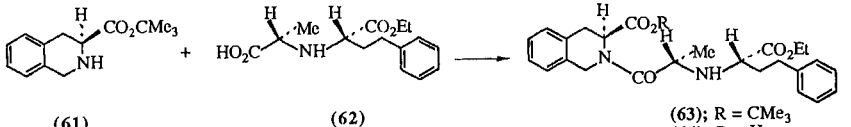
(54); X = N_2 (55); X = F (56) (57); X = CO_2Et (58); X = H

5. TETRAHYDROISOQUINOLINES

Most of the widely used antidepressants are tricyclics related to imipramine. A 1-phenyltetrahydroisoquinoline analogue, nomifensine (60), departs from this structural pattern. Pharmacologically it inhibits the reuptake of catecholamines such as dopamine at neurons. It can be synthesized by alkylation of 2-nitrobenzyl-methylamine with phenacyl bromide followed by catalytic reduction of the nitro group (Pd-C) and then hydride reduction of the keto moiety to give **59**. Strong acid treatment leads to cyclodehydration to nomifensine (60) [17].

(59) (60)

Given the well-established structural forgiveness available among angiotensin-converting enzyme (ACE) inhibitors, it is not surprising to find a tetrahydroisoquinoline analogue represented. Quinapril (64) is synthesized from the t-butyl ester of tetrahydroisoquinoline-3-carboxylic acid (61) by amide formation with 62 using mixed ester methodology. Subsequent partial deblocking of 63 upon acid treatment leads to quinapril (64) [18]. This is by now a familiar reaction sequence for construction of molecules in this class.

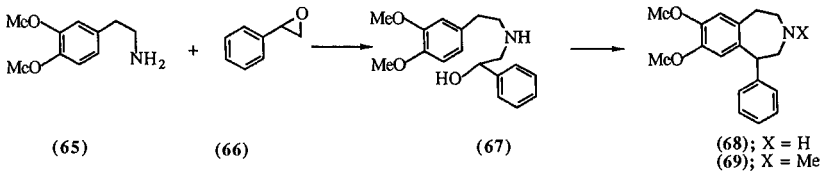


(61) (62)

6. BENZAZEPINES

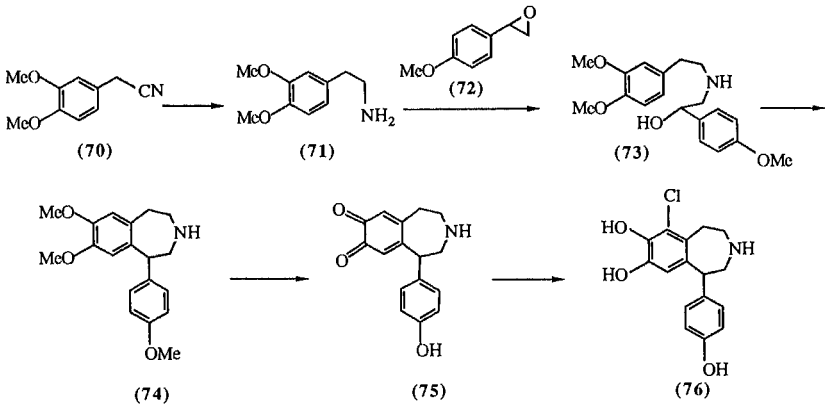
Trepipam (69) is a sedative agent apparently acting *via* dopaminergic mechanisms. It can be synthesized by attack on the less hindered terminus of styrene oxide (66) by 4,5-dimethoxyphenethylamine (65) to give 67. Cyclodehydration catalyzed by strong acid then leads to 68 and N-

methylation with formic acid and formaldehyde (Eschweiler-Clarke reaction) completes the synthesis of **trepipam** (**69**) [19].



(65) (66) (67) (68); X = H (69); X = Me

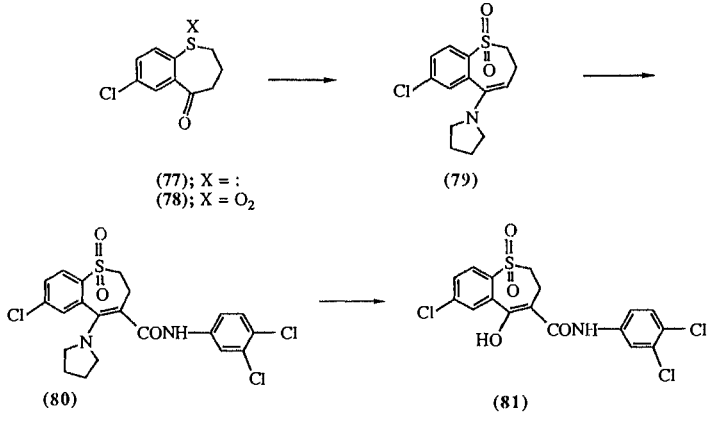
Fenoldopam (76) is an antihypertensive renal vasodilator apparently operating through the dopamine system. It is conceptually similar to **trepipam**. **Fenoldopam** is superior to dopamine itself because of its oral activity and selectivity for dopamine D-1 receptors (D-2 receptors are associated with emesis). It is synthesized by reduction of 3,4-dimethoxyphenylacetonitrile (**70**) to dimethoxyphenethylamine (**71**). Attack of this last on 4-methoxystyrene oxide (**72**) leads to the product of attack on the epoxide on the less hindered side (73). Ring closure with strong acid leads to substituted benzazepine **74**. O-Dealkylation is accomplished with boron tribromide and the catechol moiety is oxidized to the ortho-quinone **75**. Treatment with 9N HCl results in conjugate (1,6) chloride addition and the formation of **fenoldopam** (76) [20,21].



(70) (71) (72) (73) (74) (75) (76)

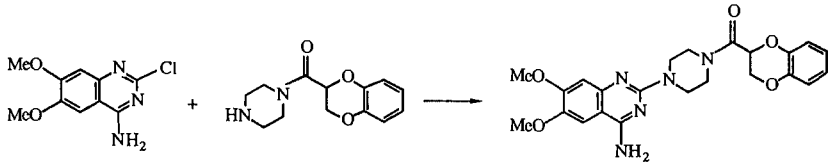
7. BENZOTHIEPINS

Enolicam (**81**) is a nonsteroidal antiinflammatory agent which may be viewed as a higher homologue of compounds in the **pyroxicam** series (see *The Organic Chemistry of Drug Synthesis*, Volume 2, p. 394). It is intended for use in the treatment of psoriasis and arthritis. It is active both orally and topically. Oxidation of 7-chlorotetrahydro-1-benzothiepen-5-one (**77**) with hydrogen peroxide leads to the sulfone **78**. This is converted to the pyrrolidine enamine (**79**) using tosic acid as catalyst and this is then reacted at its electron rich center with 3,4-dichlorophenylisocyanate to give amide **80**. The synthesis concludes with hydrolysis of the enamine function with HCl to produce **enolicam** (**81**). **Enolicam** is sufficiently acidic to be used primarily as its sodium salt [22].



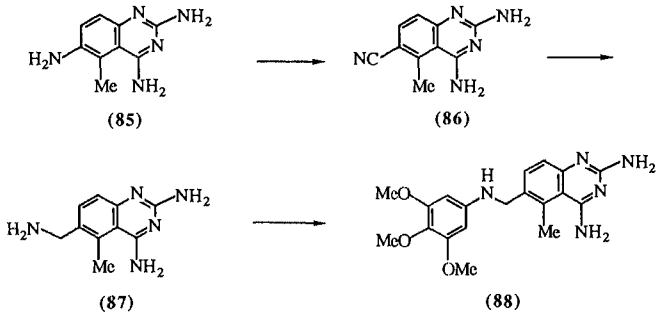
8. QUINAZOLINES AND QUINAZOLINONES

Doxazosin (**84**) is an adrenergic postsynaptic α-1 receptor antagonist with antihypertensive properties. The discerning eye will recognize a structural resemblance to the antihypertensive quinazoline **prazosin**, also an α-1 receptor antagonist. **Doxazosin** was produced in an attempt to develop agents which could be administered once daily to combat hypertension. It is synthesized by reacting 4-amino-2-chloro-6,7-dimethoxyquinazoline (**82**) with (1,4-benzodioxan-2-ylcarbonyl)piperazine (**83**) in an addition-elimination sequence leading to **84** [23].



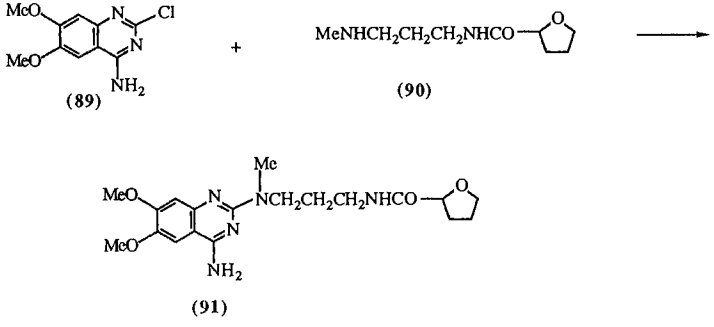
(82) (83) (84)

Trimetrexate (88) is an antineoplastic agent related to the well-established folic acid antimetabolite **methotrexate**. It can be synthesized by selective diazotization of the most basic amino group of 2,4,6-triamino-5-methylquinazoline (85) followed by a Sandmeyer displacement with CuCN to give nitrile 86. Careful reduction using Raney nickel produces the aminomethyl intermediate 87 or, if the reaction is carried out in the presence of 3,4,5-trimethoxyaniline, **trimetrexate** (88) [24]. One presumes that that outcome is a consequence of amine exchange at the partially reduced imine stage and further reduction.

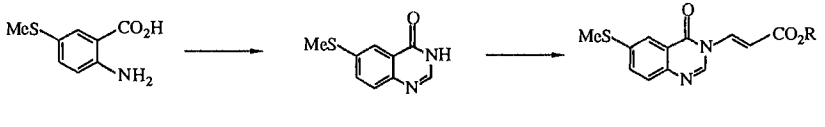


(85) (86) (87) (88)

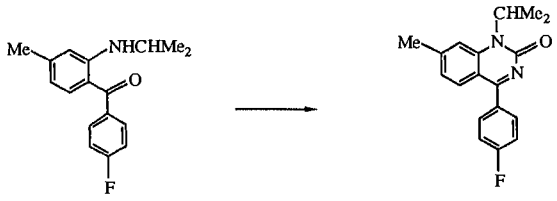
Alfuzosin (**91**) is a **prazosin**-like hypotensive adrenergic α-1 receptor blocker with the special structural feature that two carbons have been excised conceptually from the piperazine ring normally present in this series. Following the usual sequence for this series, reaction of 4-amino-2-chloro-7-dimethoxyquinazoline (89) with the tetrahydro-2-furyl amide of 3-methylaminopropylamine (90) gives **alfuzosin** (**91**) [25]. **Alfuzosin** is claimed to cause less orthostatic hypotention (dizziness or fainting upon sudden rising) than **prazosin**.



The quinazolinone-containing antiallergic agent **tiacrilast (95)** has many of the pharmacological properties of the mediator release inhibitor **cromolyn sodium** for treatment of bronchoconstriction and seems in animal models to be orally active as well. Its structure embodies a molecular simplification (molecular dissection strategm) of a lead series of pyrido[2,1-b]quinazolinecarboxylic acids. It is synthesized in straightforward fashion by reacting 5-methylthioanthranilic acid (**92**) with formamide to form the quinoxalone ring of **93**. This is then subjected to an addition-elimination reaction with E-3-chloroacrylate to give methyl ester **94** which itself is then hydrolyzed to produce **tiacrilast (95)** [26].

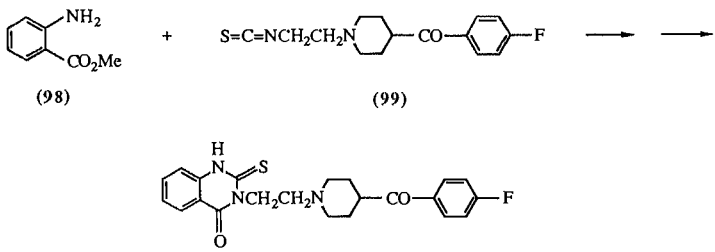


Fluproquazone (97) contains a 2-quinazolinone nucleus and is found to be an analgetic agent useful in mild to moderate pain. One of the preparations involves reaction of 2-isopropylamino-4-methyl-4'-fluoro-benzophenone (**96**) with potassium cyanate in hot acetic acid [27].



(96) (97)

Altanserin (100) is a representative of the thiaquinazolinones. This serotonin antagonist is said to prevent gastric lesions. One method for preparation of this compound involves first preparation of isothiocyanate derivative **99**, by reacting 4-fluorobenzoylpiperidine with 2-bromoethylamine and then converting the intermediate to the isothiocyanate with thionyl chloride and base. Condensation of **99** with methyl anthranilate (**98**) probably proceeds initially to a thiourea. Cyclization by ester-amide interchange leads to **altanserin (100)** [28].



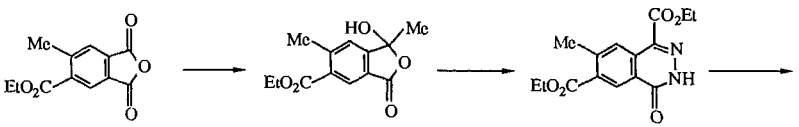
(98) (99)

(100)

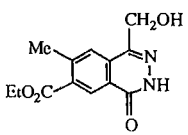
9. PHTHALAZINES

Oxagrelate (104) is of interest as a platelet antiaggretory agent and is thus of potential value in preventing thrombus formation in blood vessels. It may also be of potential value in preventing arteriosclerotic lesions in coronary arteries - a substantial cause of morbidity and mortality in

western countries. It is synthesized by reacting 4-ethoxycarbonyl-5-methylphthalic anhydride (**101**) (itself derived from the Diels-Alder product of dimethylacetylenedicarboxylate and ethyl isodehydroacetate) with excess malonic acid in pyridine to give phthalide **102**; the reaction apparently proceeds by attack of malonate on the more electrophilic carbonyl group. The methyl group introduced into **101** is the remnant of the malonic acid moiety after decarboxylation. Oxidation of of the newly introduced methyl group of **102** with aqueous permanganate produces the keto acid; this is converted to the phthalazine carboxylic acid with hydrazine and that esterified to **103**. Treatment of this last with sodium borohydride completes the synthesis of **oxagrelate** [29].

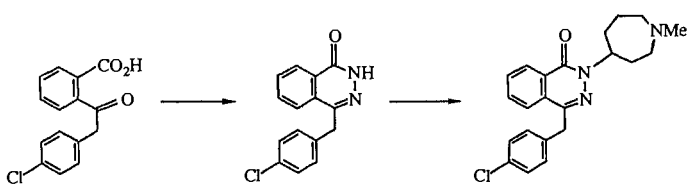


(101) (102) (103)



(104)

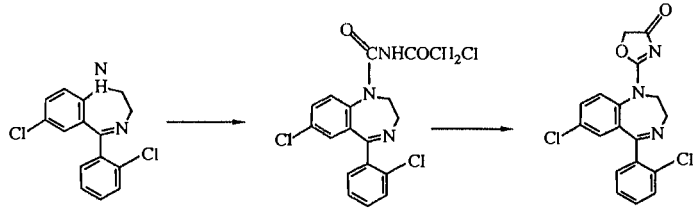
Azelastine (**107**) is an antiallergic/antiasthmatic agent prepared from 4-chlorobenzyl-2'-carboxyphenylketone (**105**) by condensation with hydrazine to give the phthalazinone (**106**) followed by reaction of the sodium salt of this last with 2-(2-chloroethyl)-N-methylpyrrolidine (presumably involving nucleophilic ring expansion of the bicyclic quaternary salt putatively formed as a first product) to complete the synthesis [30].



(105) (106) (107)

10. BENZODIAZEPINES

That once well-represented class of compounds, the benzodiazepine anxiolytic agents, has declined precipitously in numbers in consecutive volumes of this series. Preparation of the sole classical representative in the present volume starts with the preformed 7-chloro-5-(o-chlorophenyl)-2,3-dihydro-1H-1,4-benzodiazepine (**108**) (see *The Organic Chemistry of Drug Synthesis,* Volume 1, page 369). Condensation of that with 2-chloroacetylisocyanate proceeds on the more basic nitrogen of **108** to afford urea **109**. Reaction of that with sodium iodide and base probably proceeds initially by halogen exchange of iodine for chlorine (Finkelstein reaction). Subsequent replacement of iodide by the enol anion of the urea oxygen results in formation of the oxazolone ring. There is thus obtained **reclazepam (110)** [31].



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9 Bicyclic Fused Heterocycles

A large number of benzo-fused heterocyclic nuclei are of course possible in theory. This number is, however, dwarfed by the structural possibilities brought into play by fusing two heterocyclic rings. A large number of such structures have in fact been synthesized in the search for therapeutic agents. Part of the impetus probably comes from the fact that half the bases involved in genetic material, the purines, in fact consist of fused heterocycles, specifically imidazo[1,2-a]- pyrimidines. Another motivation comes from the fact that the large number of structural possibilities opens the way for good patent exclusivity.

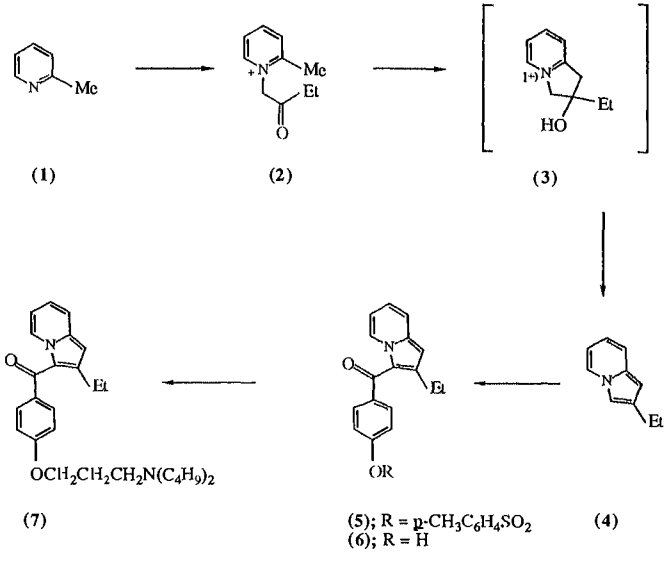
1. INDOLIZINES

Aminoalkyl ethers of 3-benzoyl benzofurans such as **amiodarone** have been found to be very effective antiarrhythmic agents. Biological activity is retained when the heterocyclic nucleus is replaced by the nearly isosteric indolizine system. Reaction of 2-picoline (**1**) with ethyl chloroacetate leads to the acyl pyridinium salt **2**; reaction of that with propionic anhydride leads to the indolizine **4**, possibly via intermediate 3 (Chichibabin synthesis). Friedel-Crafts acylation of **4** with the p-toluenesulfonate ester of p-hydroxybenzoyl chloride gives the ketone **5**. The p-toluenesulfonate protecting group is then removed by saponification. Treatment of the resulting phenol 6 with 1,3-dibromopropane and dibutylamine gives the antiarrhythmic agent **butoprozine** (7) [1].

2. PYRROLIZINES

Incorporation of the 2-aryl-2-methylacetic acid moiety characteristic of NSAID's as part of

a fused heterocyclic ring is consistent with good activity. A number of syntheses have been described for compounds in the **anirolac** series [2,3,4]. One of the more interesting preparations starts by acylation of 2-(methylthio)pyrrole 8 with anisoyl chloride (**9**). Oxidation of the product **10** with peracid leads to the sulfone **11**. The nitrogen anion obtained from treatment of **11** with



(1) (2) (3)

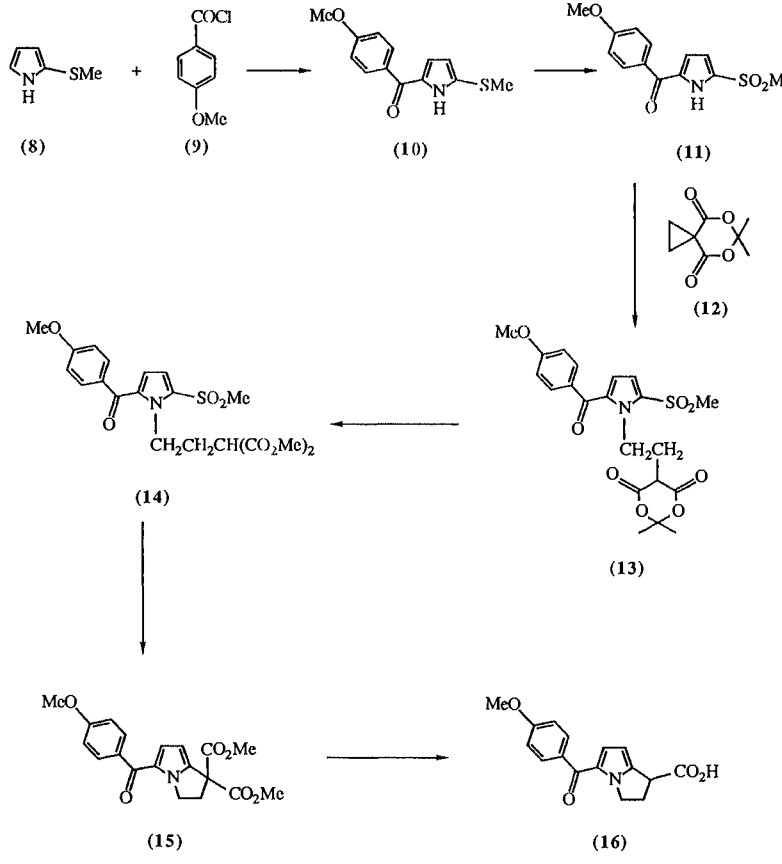
(7) (5); R = p-$CH_3C_6H_4SO_2$ (6); R = H (4)

base is then allowed to react with the Meldrum ester **12**. Attack of the anion on the cyclopropyl carbon leads to ring opening and formation of the alkylation product **13**. It was found empirically that the next step proceeds in better yield with a methyl ester; this intermediate (**14**) is obtained by ester interchange with methanol. The anion from malonate **14** then displaces the pyrrole sulfone group to give the cyclization product 15. Saponification, followed by decarboxylation of the resulting diacid, affords **anirolac** (16) [3,4].

3. CYCLOPENTAPYRROLES

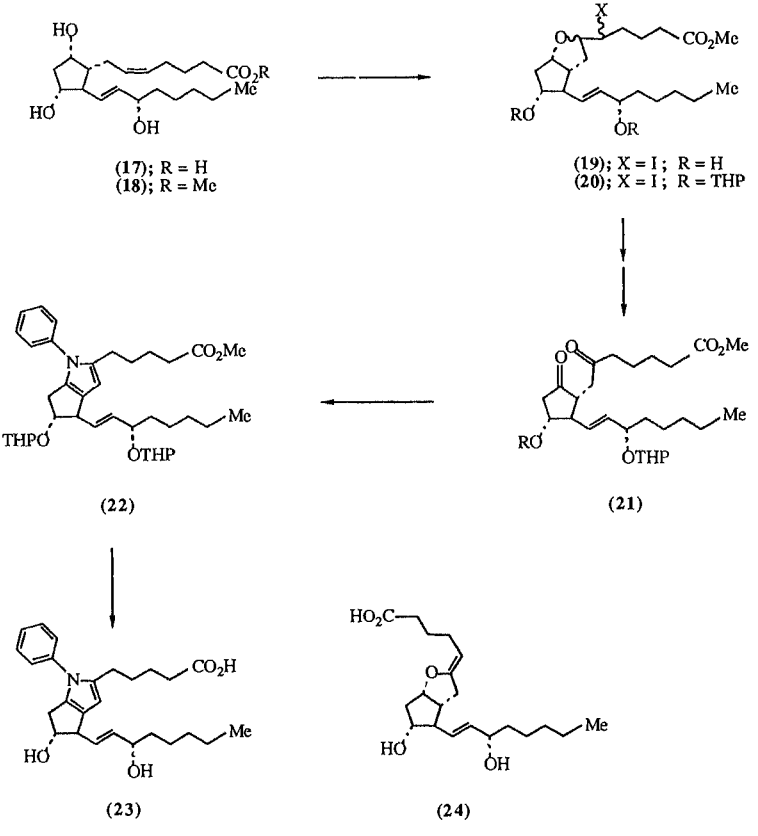
The majority of endogenous prostaglandins tend to exert undesirable effects on the cardiovascular system. These compounds as a rule tend to cause vasoconstriction and promote platelet aggrega-

tion. An important exception to this trend is the last prostaglandin derivative to be discovered, PGI_2, or prostacyclin, (**epoprostenol, 24**). Use of this compound in therapy is severely limited by its short biological half-life, which is measured in minutes. It has been found that compounds in which the ring containing the enol ether function is replaced by some more stable ring system retain a considerable portion of the activity of the endogenous compound. The starting material for an analogue in which that ring is replaced by a pyrrole, $PGF_{2\alpha}$ (**17**), is interestingly the natural precursor for **24** as well. Treatment of $PGF_{2\alpha}$ methyl ester (**18**) with base and iodine, gives



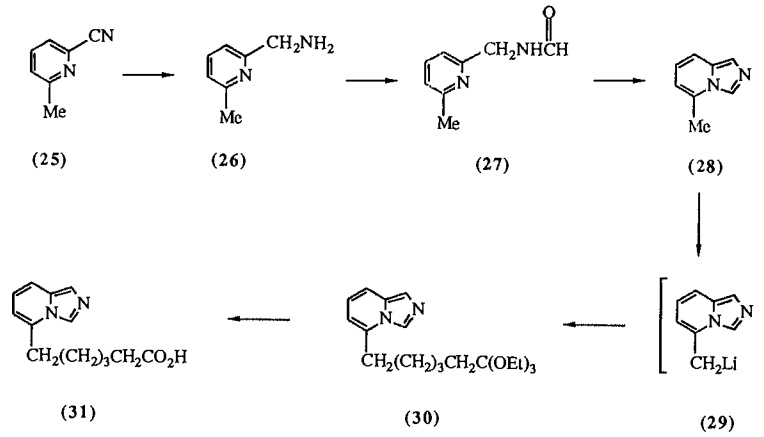
the iodolactonization product **19**. Regiochemistry is controlled by the close approach which is

possible between the ring hydroxyl and the isolated olefin. The remaining free hydroxyl groups are then protected as their tetrahydropyranyl ethers (**20**). Dehydroiodination with DBN, followed by hydrolysis and then by oxidation of the C-9 hydroxyl group gives diketone **21**. Condensation of 1,4 diketones with secondary amines is one of the classical methods for forming pyrroles. Reaction of **21** with aniline thus proceeds to give the highly substituted pyrrole **22**. Saponification of the ester and removal of the tetrahydropyranyl groups completes the preparation of the antiasthmatic agent piriprost (23) [5].



4. IMIDAZOPYRIDINES

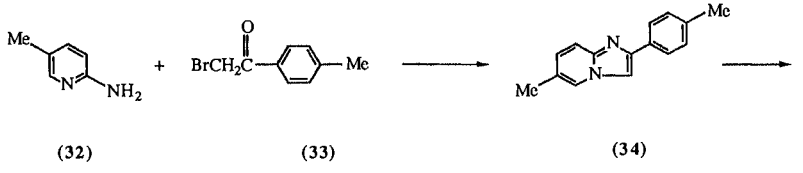
The continuing search for effective platelet aggregation inhibitors has covered a wide variety of structural types. One such candidate consists of a fatty acid chain attached to a fused heterocycle. (A somewhat fanciful relation to **24** can be imagined.) Reduction of cyanopicoline 25 leads to the primary amine 26; treatment of the corresponding formamide **27**, with phosphorous oxychloride results in cyclodehydration and formation of the imidazo[1,5-a]pyridine 28. The pendant methyl group readily forms an organometallic derivative with n-butyllithium. Treatment of that with the orthoester from 6-bromohexanoic acid gives the alkylation product **30**. Hydrolytic removal of the orthoester grouping, leads to **pirmagrel (31)** [6].



The derivative from an isomeric fused system has been described as a sedative-hypnotic compound. The synthesis starts by condensation of the aminopicoline **32** with the haloketone 33. The resulting pyrrolo[1,2-a]pyridine **34** then undergoes a Mannich reaction with formaldehyde and dimethylamine to give the aminomethylated derivative **35**. After quaternization of the dimethylamino group in **35** with methyl iodide, the ammonium group is displaced by cyanide to

produce **36**. Standard conversion of the nitrile to the amide concludes the synthesis of zolpidem (37) [7].

Selected modified pyrimidines which are closely related to nucleotides have, as noted in Chapter 6, shown therapeutic utility as antiviral and/or antineoplastic agents. Much the same rationale has been used to support the synthesis of compounds related to the purine nucleotides. An analogue of guanine which lacks one of the ring nitrogens, dezaguanine, (**47**) is, for example, used as an antineoplastic agent. Nitrosation of dimethyl acetone dicarboxylate (38) with nitrous acid gives the derivative **39**. This is then reduced to the amine **40**. Treatment of the latter with potassium thiocyanate leads initially to addition of the thiocyanate group to the amine to give the thiourea **41**. That newly formed function, or more likely an intermediate toward its formation,



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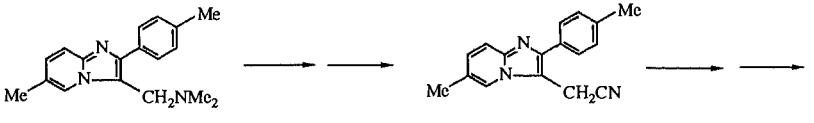

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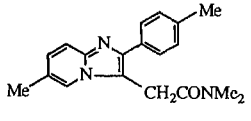
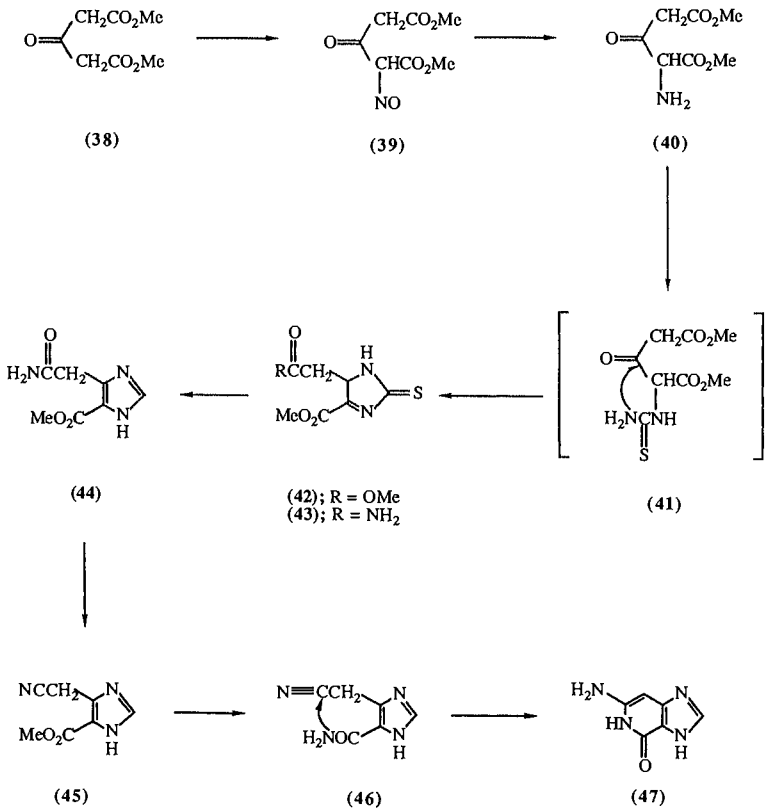


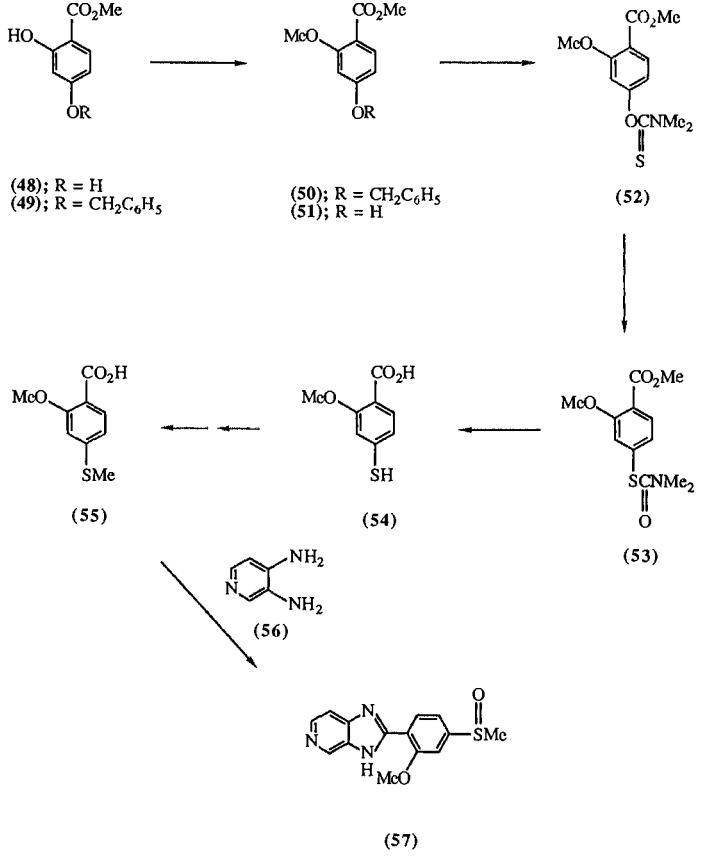
(37)

condenses intramolecularly with the ketone. There is thus obtained the imidazolethione **42**. Ammonolysis proceeds preferentially at the ester on the longer chain to give **43**. Treatment of **43** with Raney nickel gives imidazole **44**. Exposure of that compound to phosphorus oxychloride serves to convert the amide to the nitrile **45**. Exposure of the ester-nitrile to liquid ammonia leads to the amide **46**, which is cyclized with sodium carbonate. There is thus obtained **dezaguanine**, (**47**) [8].

The narrow therapeutic range of digitalis related cardiotonic agents has resulted in an extensive effort to identify compounds in other structural classes which will improve cardiac function. The discovery of the heterocyclic cardiotonic drug, **amrinone**, led to research on other heterocyclic compounds for that indication. The imidazopyridine, **isomazole** (**57**), is representa-



tive of some of the newer active compounds. Alkylation of the phenolic ester derivative **48** proceeds selectively at the least hindered phenol to give the monobenzyl ether **49**. Methylation of the free hydroxyl group (**50**), followed by removal of the benzyl group by hydrogenolysis gives the phenol **51**. This intermediate is then acylated with dimethylthioformamidoyl chloride to afford the thiocarbamate **52**. This compound, on heating, undergoes an O to S migration of the aryl group to afford the product of replacement of aromatic oxygen by sulfur (**53**). Removal of the acyl group with aqueous base (**54**) is followed by methylation of both the thiophenol group and the benzoic acid. Hydrolysis of the methyl ester then gives the benzoic acid **55**. Reaction of the carboxyl function with the amino groups in **56**, leads to the formation of an imidazole ring. Oxidation of the sulfide moiety to the sulfoxide by MCPBA at low temperature gives isomazole (**57**) [9].



5. PURINEDIONES

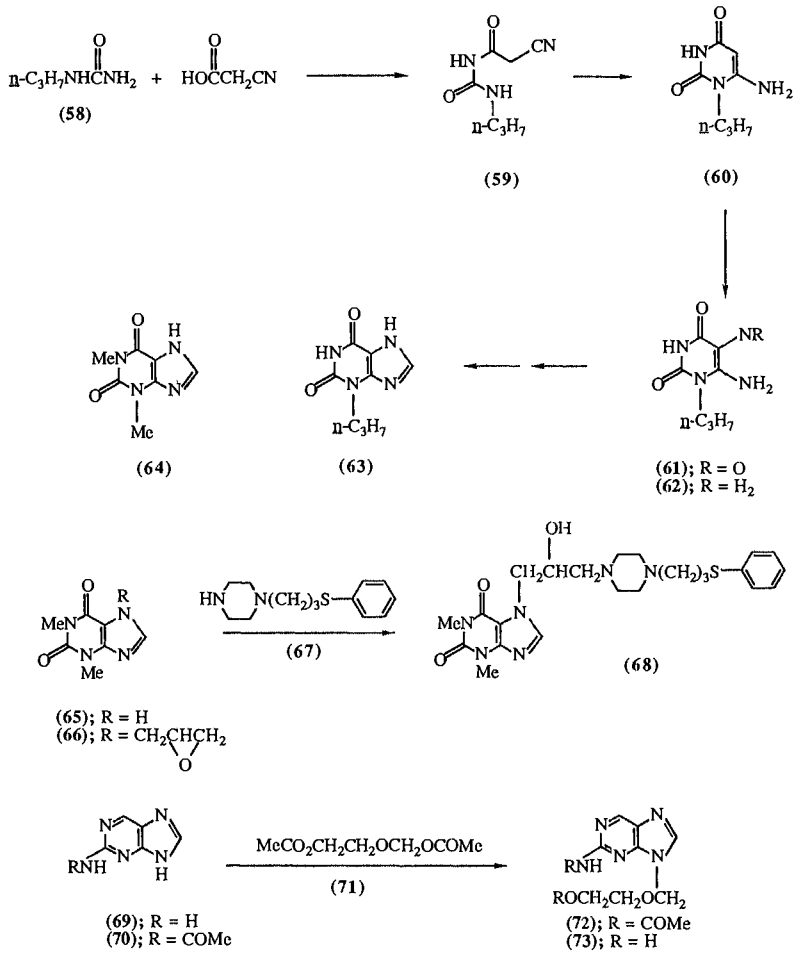
The purinedione, **theophylline** (**64**) has been the mainstay for the treatment of asthma for the better part of a century. Few other drugs rival **theophylline** for its efficacy as a bronchodilating agent. This drug is, however, noted for its very narrow therapeutic window. Blood levels associated with efficacy range between 10 and 20 mcg/mL; toxic effects start to be seen when those blood levels exceed 25 mcg/mL. A considerable amount of research has thus been devoted to preparing analogues in the hopes of developing a safer agent. The synthesis of one such agent involves a variation on the classical method for the construction of purinones. Condensation of n-propylurea **58** with cyanoacetic acid gives product **59**. Treatment of that intermediate with aqueous base leads to addition of urea nitrogen to the nitrile group and consequent formation of the aminouracil **60**. Treatment with nitrous acid leads to nitrosation at the only open position on the ring (**61**); reduction of the newly introduced nitroso group leads to the 1,2 diamine **62**. The required remaining carbon atom is then introduced by reaction with formic acid followed by cyclization with sodium hydroxide; there is thus obtained **enprofylline** (**63**) [10].

A somewhat more complex **theophylline** derivative includes both the purinone nucleus and a piperazine side chain more commonly associated with H1 antihistaminic compounds. The starting epoxide, **66**, is available from treatment of the anion of purinone **65** with epichlorohydrin. Alkylation of the epoxide with monosubstituted piperazine derivative **67**, leads to **tazifylline** (**68**) [11].

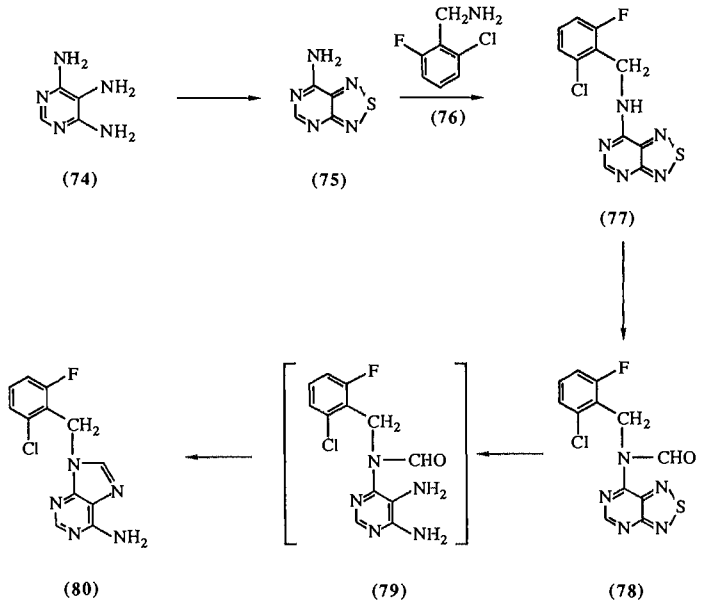
6. PURINES

The deoxyguanine analogue of **acyclovir**, apparently retains the antiviral activity of the parent compound. Preparation of that agent starts by acylation of the amino group on purine **69**. Treatment of that with diacetate **71** under typical glycosidation conditions leads to displacement of the reactive acetal acetate by imidazole nitrogen and the formation of the intermediate **72**; removal of the acetate protecting groups with aqueous base affords **desciclovir** (**73**) [12].

Preparation of the coccidiostat **arprinocid** (**80**) starts by protection of two of the three amino groups on the pyrimidine **74**; thus, reaction of **74** with thionyl chloride leads to reaction of

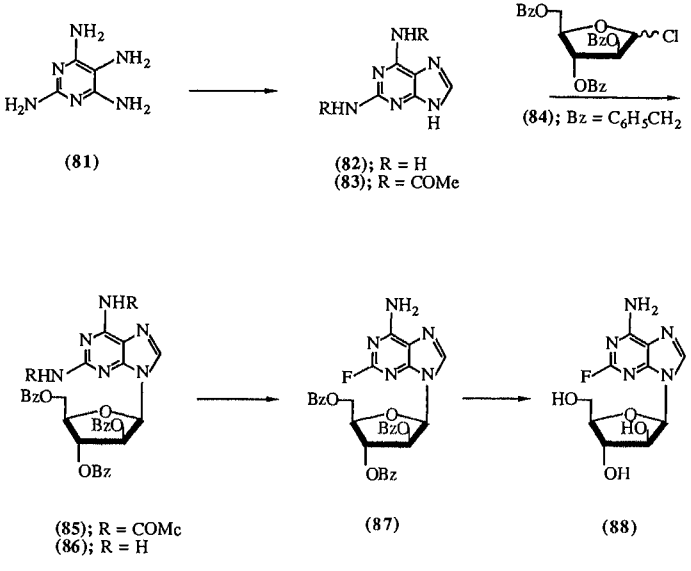


adjacent amino groups with the bidendate reagent to form a fused thiadiazole ring 75. The symmetry of the starting material guarantees regiochemistry. Reaction of the product with the benzylamine 76 gives product 77 by apparent displacement of an amino group; it is very probable that the reaction in fact involves addition of benzylamine to the pyrimidine 6 position, followed by loss of ammonia from the same center. Acylation of the newly introduced nitrogen gives the formamide 78. Desulfurization of this last compound with Raney nickel will afford initially the transient formyl-diamine 79. Cyclization of the formamide with the adjacent amino group leads to



formation of an imidazole ring; there is thus obtained **arprinocid** (80) [13].

The fluorinated derivative of an adenine arabinose glycoside, has shown useful antineoplastic activity. The requisite heterocyclic nucleus is obtained in classic fashion by reaction of the peraminated pyrimidine **81** with formamide. In this case too, the symmetry of the starting material means that only a single product, 82, is possible. The remaining free amino groups are then protected by acetylation (83). Glycosidation of the diacyl compound with the protected chlorinated arabinose derivative **84** affords the protected nucleoside 85. The free diamine 86 is obtained on saponification. Diazotization of this intermediate in the presence of fluoroboric acid in THF gives the fluorinated derivative 87. The regiochemistry of that reaction can probably be attributed to the greater reactivity of the amino group at the 2-position as a consequence of the higher electron density and basicity at that position compared to the 4-amino group. Treatment of the fluorination product with boron trichloride leads to removal of the benzyl protecting groups and the formation of **fludarabine** (88) [14].

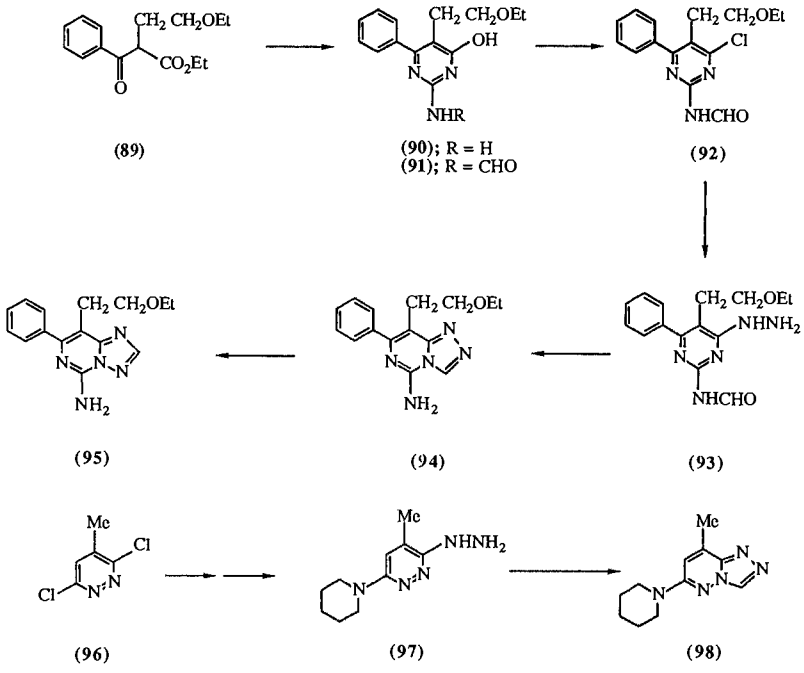


7. TRIAZOLOPYRIMIDINES

Inclusion of yet another nitrogen in the aromatic nucleus gives a product, **bemitradine** (**95**), described as a diuretic agent. The starting pyrimidine **90** is obtainable in straightforward fashion from condensation of the β-keto ester **89** with guanidine. After protection of **90** as its N-formyl derivative **91**, chlorination with phosphorous oxychloride yields **92**. Reaction of chloropyrimidine **92** with hydrazine produces hydrazinopyrimidine **93**, which is then cyclized in the presence of ethyl orthoformate to give the bicyclic compound **94**. Subsequent heating produces the Dimroth type rearrangement product **bemitradine** (**95**) [15].

8. TRIAZOLOPYRIDAZINES

A derivative of an isomeric azapurine ring system interestingly exhibits bronchodilator activity, possibly indicating interaction with a target for **theophylline**. The starting pyridazine **97** is available from dichloro compound **96** by sequential replacement of the halogens. Treatment of **97** with formic acid supplies the missing carbon and cyclizes the intermediate formamide with consequent formation of **zindotrine** (**98**) [16].

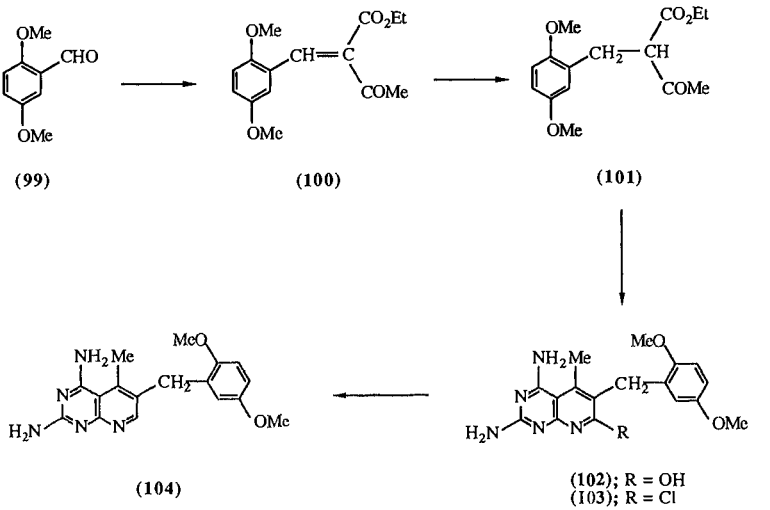


9. PYRIMIDINOPYRAZINES

Pyrimidinopyrazines related to folic acid have been investigated in some detail for their antimetabolic and antineoplastic activities. A related compound, which lacks one nitrogen atom, has been described as an antiproliferative agent, indicating it too has an effect on cell replication. Aldol condensation of the benzaldehyde **99** with ethyl acetoacetate gives the cinnamate **100**. This is then reduced catalytically to the acetoacetate **101**. Reaction of that keto ester with 2,4,6- triaminopyrimidine gives the product **102** which is subsequently chlorinated (**103**) and subjected to hydrogenolysis. There is thus formed **piritrexim** (**104**) [17].

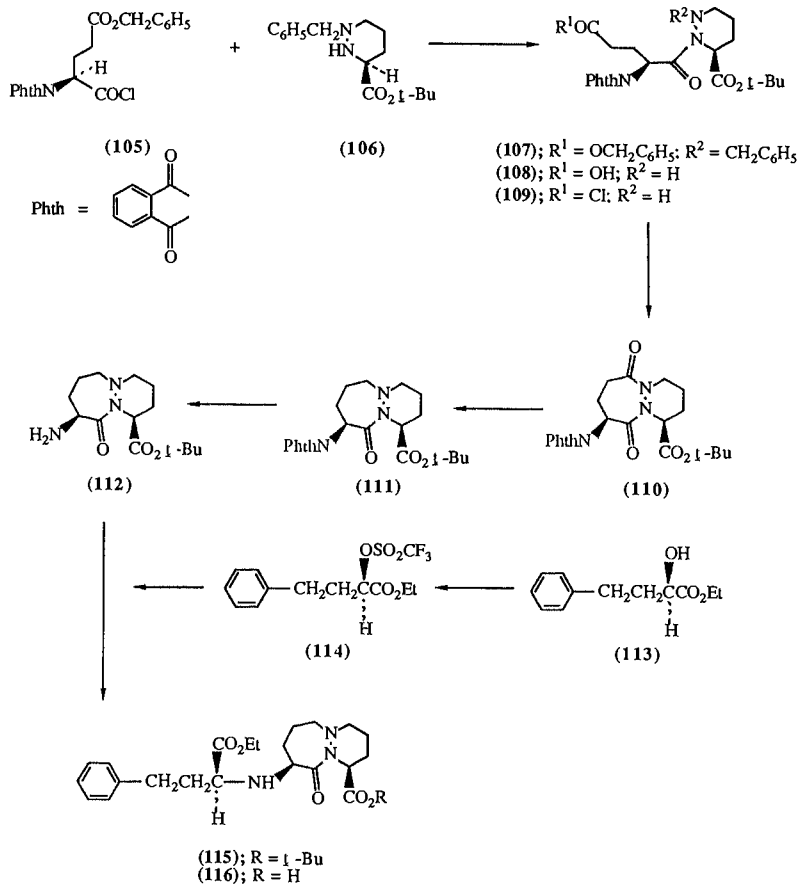
10. PYRIDAZINODIAZEPINES

The ready acceptance of angiotensin converting enzyme inhibitors as antihypertensive agents has, as noted previously in this volume, engendered intensive investigation into the limits of the



SAR in this series. A fused heterocycle ranks among the more unexpected nuclei for an ACE inhibitor. The fact that the end product interacts with a receptor site on an enzyme means that a single enantiomer will be responsible for the activity of the drug. The synthesis takes cognizance of this fact by choosing that enantiomer as the target; the precursors for both starting materials (**105, 106**) thus consist of S enantiomers. The amino group further removed from the carboxyl in the precursor to **106** is sufficiently more reactive to afford the monobenzylation product on alkylation. Acylation of that intermediate with the mono acid chloride of the protected glutamic acid **105** leads to amide **107**. Hydrogenolysis then serves to remove the benzyl protecting groups so as to afford the aminoacid **108**. This is then cyclized to the bicyclic amide **110** via the acid chloride **109**. Reduction of the diamide with diborane interestingly occurs selectively at the less hindered amide grouping to afford **111**. The phthaloyl (Phth) protecting group is then removed in the usual way by reaction with hydrazine to afford **112**. Construction of the remainder of the molecule consists in the conversion of the R enantiomer of the hydroxy acid **113**, to its triflate derivative **114**. This very reactive leaving group is readily displaced by the primary amino group in **112** with inversion of configuration; the three chiral centers in the product thus all have the S configuration. Brief exposure of the alkylation product to anhydrous strong acid serves to remove

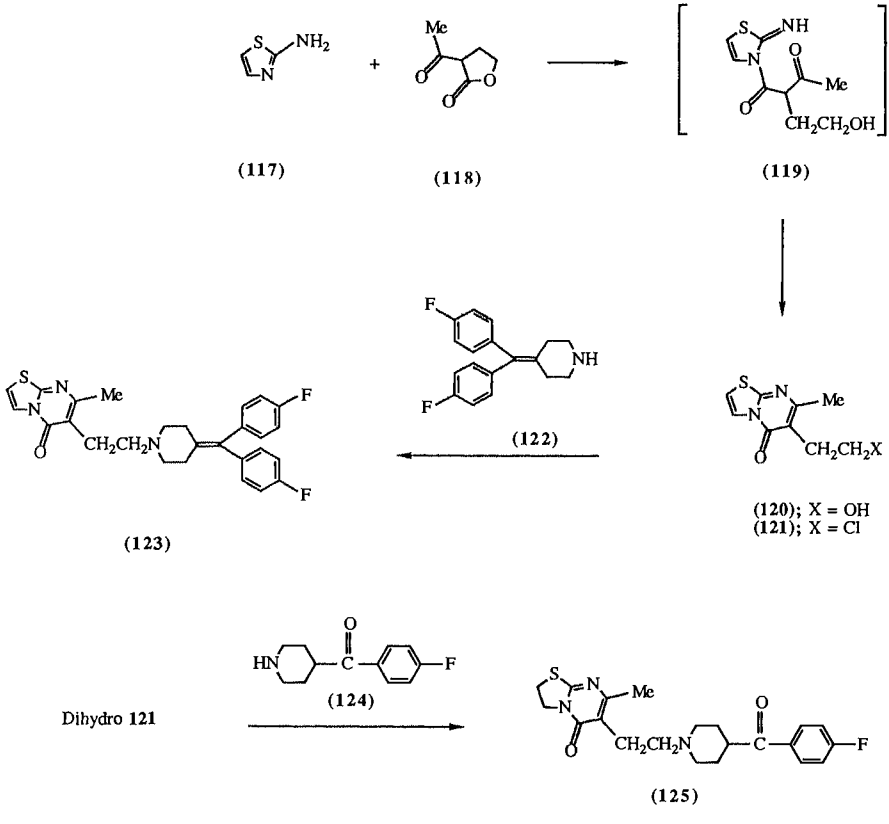
the tert-butyl protecting group. There is thus obtained **cilazapril (116)** [18].



11. THIAZOLOPYRIMIDONES

The involvement of serotonin (5-hydroxytryptamine) in disease states has been recognized for several decades. Research on antagonists awaited the recent development of methodology involving serotonin receptors. A thiazolopyrimidone serves as the nucleus for a pair of serotonin antagonists. The key intermediate **118** is in fact simply the lactonized form of 2-hydroxyethyl acetoacetate. Condensation of this β-keto ester can be visualized to involve initial attack on the reactive

butyrolactone by the ring nitrogen of thiazole **117**; cyclodehydration of that hypothetical intermediate **119** gives the fused heterocycle **120**. The terminal hydroxyl group is then converted to the corresponding chloride **121**. Displacement of the halogen by piperidine **122** affords **ritanserin (123)** [19]; the analogous reaction with the related dihydrothiazolopyrimidone using piperidine **124** leads to **setoperone (125)** [20].



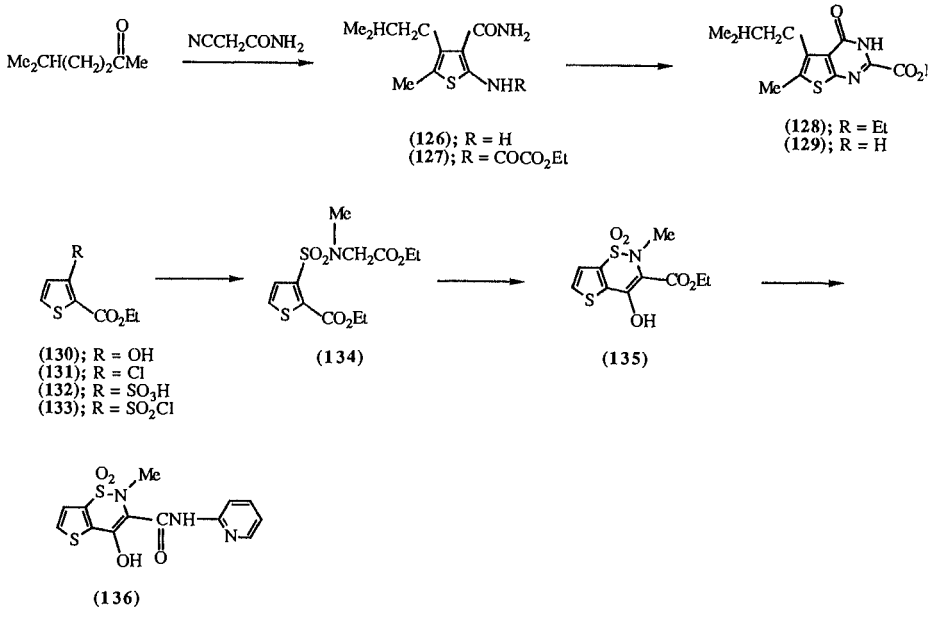
12. THIENOPYRIMIDINES

The carboxylic acid derivative of an isomeric fused thienopyrimidine exhibits mediator release inhibiting activity. The apparently complex thiophene **126** can be obtained in a single step by

reaction of methyl isoamyl ketone with cyanoacetamide and sulfur. Acylation of the product with the acid chloride from the half ester of oxalic acid leads to the oxamate **127**. This last cyclizes on heating to afford the pyrimidone **128**. Saponification to the acid gives **tiprinast (129)** [21].

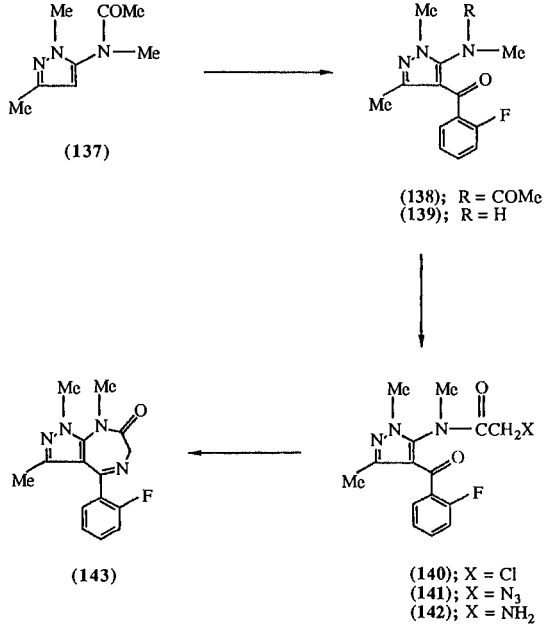
13. THIENOTHIAZINES

Replacement of a benzene ring by its isostere, thiophene, is one of the more venerable practices in medicinal chemistry. Application of this stratagem to the NSAID **piroxicam**, gives **tenoxicam, 136**, a drug with substantially the same activity. The synthesis of this compound starts by a multi-step conversion of hydroxythiophene carboxylic ester **130**, to the sulfonyl chloride **133**. Reaction of that with N-methylglycine ethyl ester, gives the sulfonamide **134**. Base-catalyzed Claisen type condensation serves to cyclize that intermediate to the β-keto ester **135** (shown as the enol tautomer). The final product **tenoxicam (136)** is obtained by heating the ester with 2-aminopyridine [22].



14. PYRAZOLODIAZEPINONES

A more unusual strategy, which has proven particularly fruitful in the benzodiazepine series, involves replacement of benzene by pyrazole. One route to such an analogue involves first Friedel-Crafts acylation of **137** with o-fluorobenzoyl chloride. The acetyl protecting group on product **138** is then removed and the product **139** acylated with chloroacetyl chloride to give chloroacetamide **140**. Halogen is then displaced with azide (**141**), and the newly introduced function reduced to an amine (**142**). This last readily cyclizes with the aroyl keto group to form zolazepam (143) [23].



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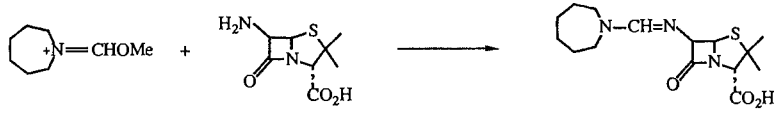
10 β-Lactam Antibiotics

In the relatively few years since the preparation of the previous volume in this series, the explosion of synthetic and clinical experimentation on the semi and totally synthetic antibacterial β-lactam antibiotics has continued, providing a rich body of literature from which to assemble this chapter. The search for utopiasporin, the perfect cephalosporin, continues. The improvements in spectrum and clinical properties achieved to date, however, are largely incremental and have been achieved at the price of substantially higher costs to the patient. Nonetheless, these newer compounds are truly remarkable when compared with the properties of the fermentation-derived substances from which they have sprung.

1. PENICILLINS

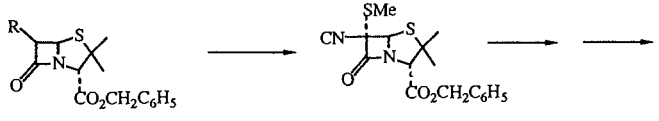
The vast majority of the β-lactam antibiotics contain an amide side chain attached to the β-lactam ring. A clear exception to this is amdinocillin (also known as mecillinam) (3). This parenterally active anti Gram-negative antibiotic has a formiminoyl moiety at C-6. Mecillinam is primarily used to treat urinary tract infections, particularly those caused by *Escherichia coli*. It is synthesized simply by reaction of 6-amino penicillanic acid triethylammonium salt (2) with imino ether **1** [1]. A slightly different synthesis of this agent was described in *The Organic Chemistry of Drug Synthesis*, Volume 3, page 208.



(1) (2) (3)

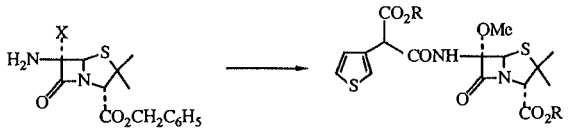
Resistance to β-lactam antibiotics by bacteria is a complex function of the elaboration of β-lactamases which hydrolyze penicillins and cephalosporins before they can reach their receptors, the ability of some bacteria to exclude these antibiotics from their cells, and a decreased tendency to bind β-lactams to the penicillin binding proteins which are their intercellular targets. Various devices have been developed to deal with these factors. For example, increased steric bulk strategically placed near the side chain amide linkage often conveys greater stability against β-lactamases without significant loss of potency. Temocillin (**11**) is an embodiment of this stratagem in that it has a C-7 α-methoxy moiety to perform this service and it demonstrates nearly the same potency against many strains of Gram-negative bacteria which do and do not elaborate β-lactamases. It does, however, have relatively little activity against Gram-positive bacteria and pseudomonads.

One of the syntheses of temocillin begins by reaction of benzyl 6-aminopenicillanate (**4**) with formic acid and dicyclohexylcarbodiimide to give the corresponding formamide (**5**) and this is next dehydrated to the isocyanate (6) by reaction with phosgene. Reaction of 6 with methyl methoxycarbonyl disulfide and mild base introduces the 6-α-methylthio moiety (7). Reaction of 7 with tosic acid hydrate in chloroform hydrolyzes the isocyanate moiety back to the primary amine (8). Reaction of 8 with mercury (II) chloride/pyridine and methanol results in replacement of the methylthio moiety by a methoxyl group (9). Mercury II ion has a strong affinity for sulfur, converting it to an excellent leaving group. The particular selectivity between sulfurs seen here stems from causes which are not so obvious. Acylation of **9** with 2-benzyloxycarbonyl-2-(thien-3-yl)acetyl chloride produces dibenzyl ester **10**. This synthesis of temocillin (**11**) then concludes by hydrogenolysis of the benzyl groups (Pd/C-hydrogen) [2].



(4); R = NH_2
(5); R = NHCHO
(6); R = CN

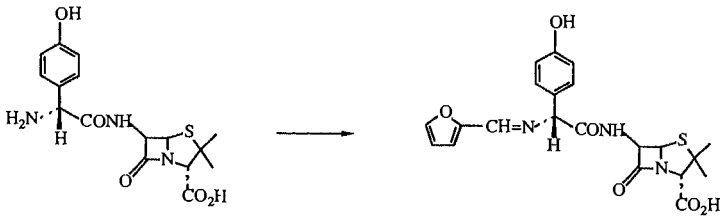
(7)



(8); X = SMe
(9); X = OMe

(10); R = $CH_2C_6H_5$
(11); R = H

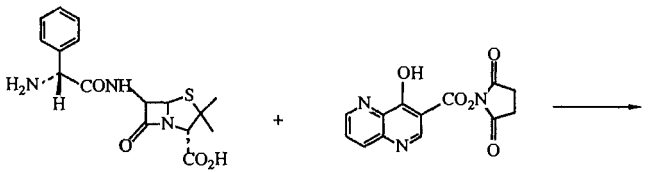
One of the most popular orally active penicillins in present clinical use is amoxicillin (12). Its oral effectiveness and broad spectrum of activity against common pathogens as well as its better absorption than its closest precedent competitor, ampicillin (14), largely accounts for this. Higher blood and tissue levels of antibiotics is another means of dealing with resistance. In an attempt to achieve yet further improvements in oral bioavailability and hence blood and tissue levels of amoxicillin, the prodrug fumoxicillin (13) is prepared from amoxicillin (12) by treatment with furfural [3]. The imine moiety is less basic than the primary amine so that the isoelectric point of fumoxicillin is more on the acid side than is that of amoxicillin.



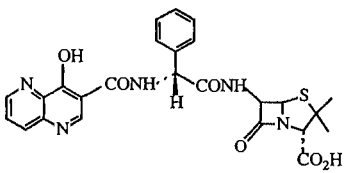
(12)

(13)

Acylation of the primary amino group of ampicillin (14) with suitable acids leads to penicillins with activity against pseudomonads. Azlocillin, mezlocillin, and piperacillin are well-known examples of this. A newer derivative in this subclass is apalcillin (16). In this case, the acid is a 4-hydroxy-1,5-naphthyridine derivative. The synthesis is carried out by acylation of ampicillin (14) with the N-hydroxysuccinimide ester of 4-hydroxy-1,5-naphthyridine-3-carboxylic acid (15) to give apalcillin (16) [4]. The use of N-hydroxysuccinimide esters in amide bond forming reactions, including peptide synthesis, is becoming increasingly popular.

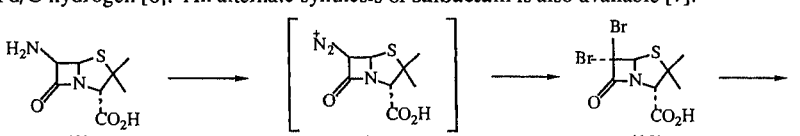


(14) (15)

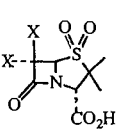


(16)

Another device for dealing with the β-lactamase problem is to prepare substances which deactivate this class of enzyme. The chemical mechanisms by which this takes place are rather interesting [5]. These substances can be administered conjointly with an otherwise susceptible antibiotic and, if the pharmacokinetic characteristics match, protect the antibiotic from premature hydrolysis. The clinical success of the natural product **clavulanic acid** in a fixed ratio combination with **amoxicillin** demonstrates clearly the utility of this approach. **Sulbactam** (**20**) is a partially synthetic agent possessing this type of activity. Its synthesis begins with diazotization of 6-aminopenicillanic acid (**2**) to give unstable 6-diazopenicillanic acid (**17**); this can be brominated without isolation to produce relatively stable dibromide **18** by carrying out the diazotization in the presence of bromine. Formation of the corresponding sulfoxide (**19**) can be carried out subsequently or in situ with potassium permanganate. The synthesis concludes by hydrogenolysis with 5% Pd/C-hydrogen [6]. An alternate synthesis of **sulbactam** is also available [7].



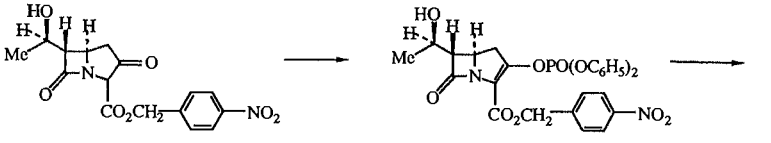
(2) (17) (18)



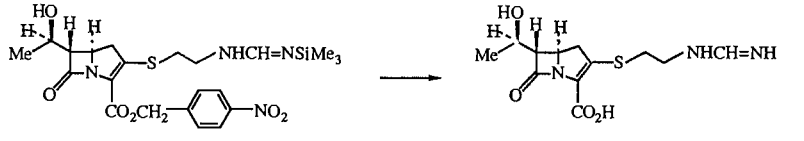
(**19**); X = Br
(**20**); X = H

2. CARBAPENEMS

The exceptional potency and breadth of spectrum of the naturally occurring carbon bioisostere of the penicillins, thienamycin (the primary amine corresponding to formiminoyl derivative **24**), makes this a truly exciting substance. One of its unfortunate properties, however, is its pronounced chemical instability. This is attributed in part to self-condensation between the primary amino moiety and the β-lactam ring of another molecule leading to inactive polymers. To avoid this complication, and yet retain bioactivity, it was decided to reduce the nucleophilicity of the amino moiety. This was accomplished by formation of the N-formiminoyl linkage of imipenem (**24**). One preparation of imipenem begins with p-nitrobenzyl 6-(1')-hydroxyethyl)-1-azabicyclo(3.2.0)heptane-3,7-dione-2-carboxylate (**21**) rather than unstable thienamycin itself. This is converted to the diphenoxyphosphate enol ester **22** and this in turn reacted with N,S-bis-trimethylsilyl-N- formimidoylcysteamine with Hunnig's base (diisopropylethylamine) or DMAP (dimethylaminopyridine) to produce **23**. Use of the bistrimethylsilylated reagent was necessary in order to avoid side reactions caused by cyclization reactions. Removal of the protecting groups completes the synthesis of imipenem [8]. Alternate syntheses are available [9]. For commercial purposes, premature in vivo hydrolysis of the β-lactam ring by a kidney enzyme is prevented by coadministration of the inhibitor cilastatin.



(21) (22)



(23) (24)

3. CEPHALOSPORINS

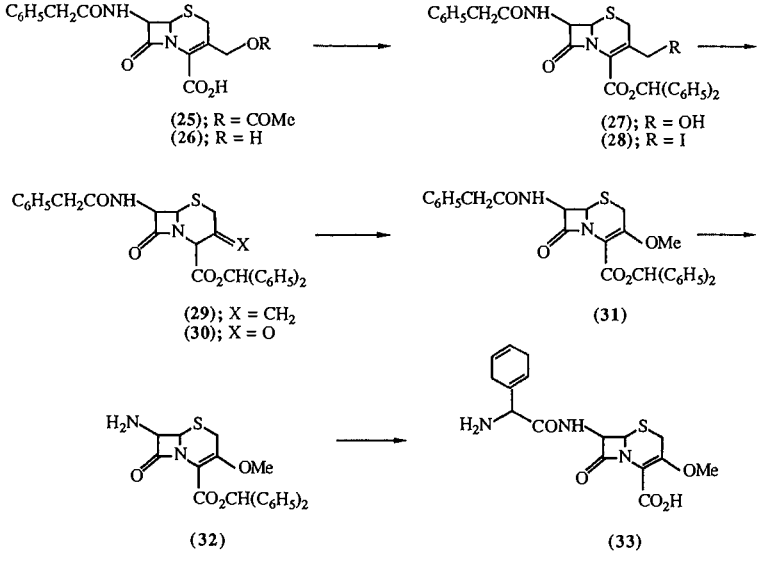
The past 10 years have seen the synthesis and evaluation of an exceptionally large number of cephalosporins. At least 16 cephalosporin type antibiotics are now commercially available in the United States and a larger number are available overseas. An even larger number have received generic names and so have made significant progress toward possible clinical use. Many of these agents possess exceptional stability toward β-lactamases and extraordinarily broad spectrum activity against pathogens. The very number of these agents suggests that the search for the perfect cephalosporin antibiotic is not yet over.

The cephalosporins are classified for commercial reasons by so-called "generations." The distinction between the generations is not sufficiently clear cut that all compounds can be classified easily except by experts. Briefly, the oldest or first discovered substances largely comprise the first generation. The second generation agents have a broader activity spectrum than those of the first generation. The third generation cephalosporins have broader spectra than any of the preceding agents. Many more Gram-negative pathogens are now sensitive but usually at the cost of lesser potency against Gram-positive pathogens.

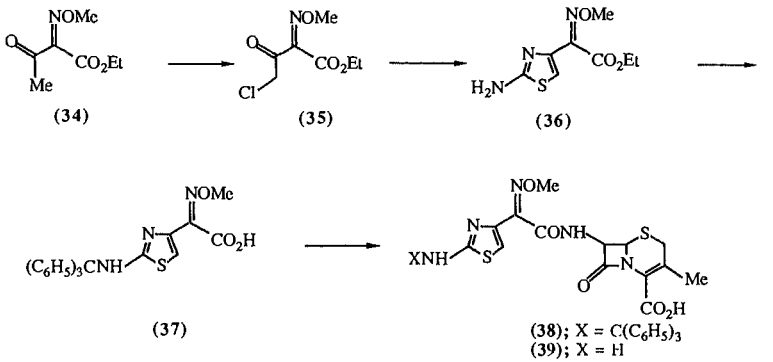
Aside from their great expense to the patient and their general lack of oral efficacy for systemic infections, the best of these so-called "third generation" cephalosporins possess significant advantages including activity against a great many of the serious pathogens encountered in a hospital setting and have remarkably little toxicity. These come close to the ideal cephalosporin antibiotic being sought. Frenetic activity characterizes this area of medicinal chemistry.

Cefroxadine (33) possesses an activity spectrum rather similar to that of **cephalexin** and so can be placed generally in the first generation of cephalosporins. Structurally, it has a side chain at C-7 identical with that of **cephradine** (D-absolute stereochemistry) so its oral efficacy is predictable. The side chain at C-3 of cephalosporins is significant not only for potency but also controls many pharmacokinetic features of these drugs. In the case of **cefroxadine**, an unprecedented (in these pages) enol methyl ether moiety is found. Of the various syntheses, **cefroxadine** can be made starting with the phenacetyl amide of 7-aminocephalosporanic acid (**25**). This is deacetylat-

ed to the alcohol (26) using an immobilized bacterial enzyme to avoid damaging the other solvolytically sensitive molecular features and this is converted to the diphenylmethyl ester (27) by reaction with diphenyldiazomethane. The hydroxyl linkage is exchanged for an iodo (28) by reaction with N-methyl-N,N'-dicyclohexylcarbodiimidium iodide and the iodo group is then ejected to produce olefin 29 by reaction with zinc in 90% acetic acid. Double bond migration accompanies this transformation. Ozonolysis at low temperature produces ketone 30 (accompanied by some of the sulfoxide). Next, conversion to the enol ether (31) with diazomethane sets the stage for side chain exchange at C-7. Removal of this amide function in the presence of the more labile β-lactam bond requires a roundabout process which exploits the secondary amide character of the C-7 substituent as compared with the tertiary amide character of the β-lactam moiety. Thus, reaction with phosphorous pentachloride in pyridine produces the side chain iminochloride; this is intercepted with alcohol to produce the iminoether and careful hydrolysis produces the 7-aminocephalosporanic acid analogue (32). Amide formation with D-tert-butoxycarbonylamino-(1,4)-cyclohexadienyl) acetic acid is brought about by isobutyl chloroformate and N-methylmorpholine treatment and this is followed by deblocking with trifluoroacetic acid to complete the synthesis of **cefroxadine** (33) [10].



Many newer cephalosporins incorporate a 2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetic acid side chain at C-7. The syn oximino ethers convey high level resistance to β-lactamases (the anti oximino ethers are much more susceptible) and the aminophenyl bioisostere seems to convey the ability to penetrate well into bacterial cells of species which would otherwise be expected to be resistant. This moiety is frequently found in third generation cephalosporins. An example is the parenteral agent **cefetamet** (39) whose synthesis starts with ethyl syn-2-methoxyimino-3-oxobutyrate (**34**); this is chlorinated (chlorine) to chloroketone **35** and this is subjected to the Hantzsch reaction with thiourea to give the desired aminothiazole (36). This is followed by protection of the amino group as the trityl amine and hydrolysis of the ethyl ester function to produce the necessary protected acid (37) for the side chain. Amide formation in the usual way with 7-amino-3-desacetoxycephalosporanic acid gives protected antibiotic **38** and deblocking with acid completes this synthesis of **cefetamet** (39) [11].

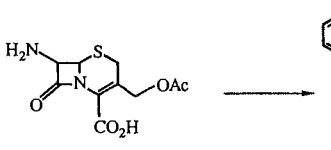


Cefixime (**47**) is another cephalosporin antibiotic with an aminothiazole ring attached to an oximinoether containing side chain at C-7. An interesting and novel side chain is attached to C-3. The cephalosporins derived from naturally occurring 7-aminocephalosporanic acid have an acetyl function attached to the C-3 methylene. Esterases cleave this in the body and the resulting alcohols are less potent as antibiotics. One way of dealing with this undesirable metabolic transformation is to hydrogenolyze this moiety to a methyl function such as is seen with **cefetamet** above. In an apparent attempt to prepare homologues, transformation to an aldehyde followed by Wittig reactions produces a series of vinyl analogues with interesting properties in their own right.

One of these is **cefixime**. The reader will also note that the oximino ether moiety of **cefixime** is an acetic acid function rather than the methyl ether seen above. This substitution not only retains the β-lactamase resistance intended but also alters the isoelectric point of the drug allowing for more efficient absorption. This agent is found to have rather good activity against Gram-negative microorganisms, is resistant to many β-lactamases and is orally active. It does, however, have somewhat less potency against Gram-positives. This would apparently lodge it among the second generation cephalosporins. One of the syntheses of this agent starts with 7-aminocephalosporanic acid (**40**) which is hydrolyzed to the alcohol with base, converted to its Schiffs' base with salicylaldehyde, and esterified to its diphenylmethyl ester with diphenyldiazomethane to give protected intermediate **41**. Reaction of this with phosphorous pentachloride and pyridine exchanges the hydroxyl function for a chlorine (**42**). The olefinic linkage of **43** is introduced by reaction with triphenylphosphine and NaI to produce the Wittig reagent; reaction with formaldehyde gives the methylene derivative. Careful acid treatment of **43** selectively removes the salicyl protecting group from C-7 and the desired side chain is put in place by reaction with blocked synthon **45** (prepared by activation of the carboxyl group by reaction with phosphoryl chloride and DMF [Vilsmeier reagent]). The resulting blocked C-3 vinyl analogue (**46**) is deprotected at the primary aromatic amino group by reaction with methanolic HCl and the remaining protecting groups are removed by reaction with trifluoroacetic acid in anisole to complete this synthesis of **cefixime** (**47**) [12]. Other syntheses have been described for this agent and its analogues [13-15].

Cefpimizole (**51**) appears to be less active in vitro than **cefotaxime** and **cefoperazone** and to have a somewhat narrower activity spectrum although some strains of *Pseudomonas* are susceptible. It is not orally active, but its performance in vivo appears superior to what would be expected from its in vitro data. Its synthesis begins by acylation of **cephaloglycin** (**48**) with the bis acid chloride of imidazole-4,5-dicarboxylic acid (**49**) to give amide **50**. The acetyl moiety at C-3 of this intermediate is displaced with 4-pyridineethanesulfonic acid and sodium iodide to give **cefpimazole** (**51**) [16].

Just as with **cefpimazole**, **cefepime** (**54**) has a quatemary nitrogen substituent at C-3 whose electron withdrawing character and excellent nucleofugic properties increases the reactivity of the



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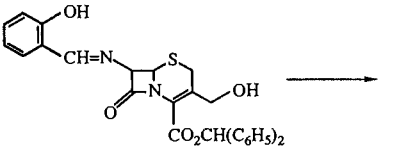

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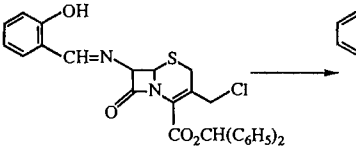

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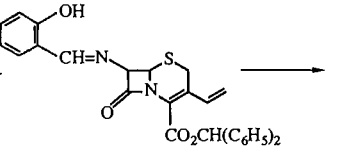

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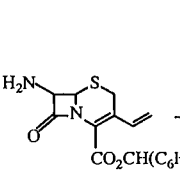

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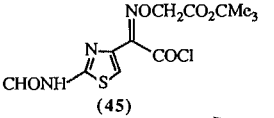

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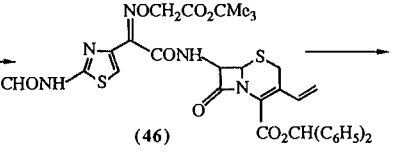

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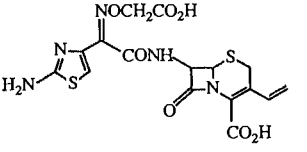

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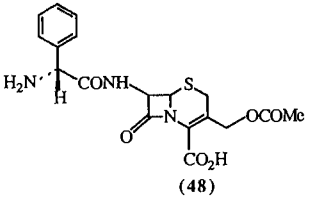

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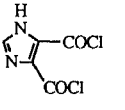

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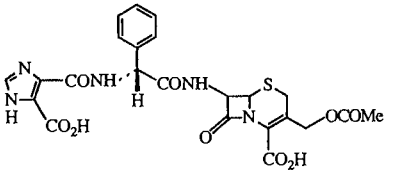

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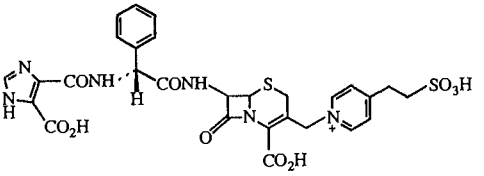
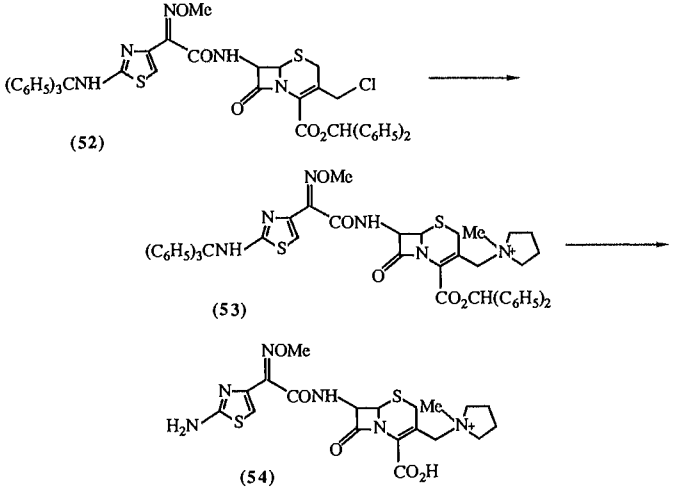


(51)

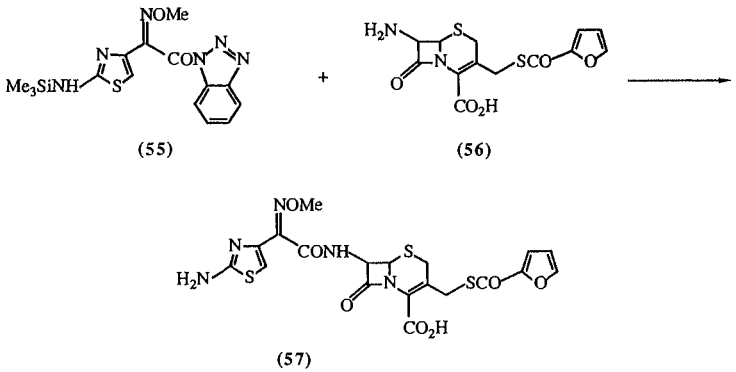
β-lactam bond and also the antibacterial potency of the molecule. This derivative is prepared simply by displacement of the C-3 chloro moiety of suitably blocked cephalosporin 52 with N-methylpyrrolidine to give intermediate 53 and this is deblocked with trifluoroacetic acid in the usual manner to give **cefepime (54)** [17].



(52) (53) (54)

Ceftiofur (57) differs from the preceding cephalosporin derivatives in that it has a thioester moiety at C-3. This can be introduced by displacement of the C-3 acetyl group of 7-aminocephalosporanic acid (**40**) with hydrogen sulfide and esterification with 2-furylcarboxylic acid to give synthon **56**. This can in turn be reacted with trimethylsilylated oximinoether derivative **55** (itself obtained from the corresponding acid by reaction with dicyclohexylcarbodiimide and 1-hydroxybenzotriazole) to produce, after deprotecting, **ceftiofur (57)** [18].

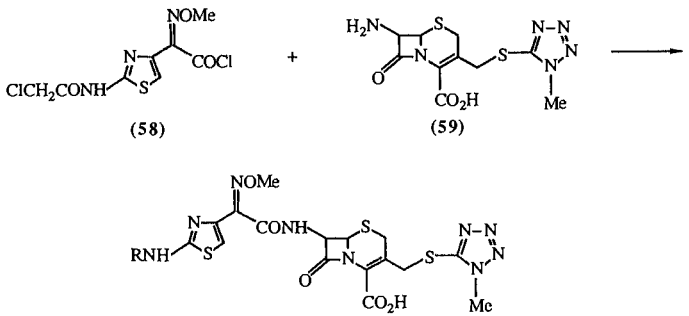
Cefmenoxime (61) is a third generation parenteral cephalosporin whose in vitro antimicrobial spectrum approximates that of **cefotaxime**. Its side chains consist of the common methyltetrazolylthio group at C-3 and the familiar oximinoether aminothiazole moiety at C-7. It is synthesized



(55) (56)

(57)

from acid chloride **58** and 7-aminocephalosporin synthon **59** to produce blocked amide **60**. The utility of this blocking group is demonstrated by its ease of removal to give **cefotaxime** (61) by reaction with thiourea (displacement of chloride by sulfur and internal cyclization to remove the protecting group from the amine) [19].

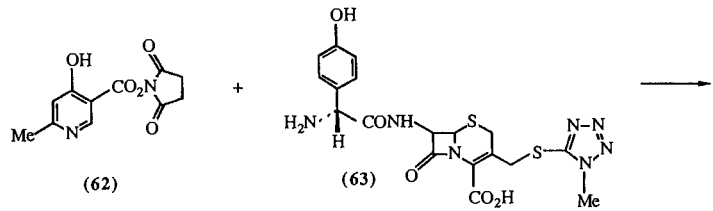


(58) (59)

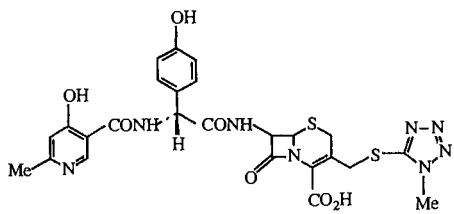
(60); R = $ClCH_2CO$
(61); R = H

Cefpiramide (**64**) is a third generation cephalosporin with a 1-methyl-[1H]-tetrazol-5-ylthiomethyl moiety at C-3 and an acylated p-hydroxyphenylglycine moiety at C-7. It includes in its activity spectrum reasonable potency in vitro against many strains of *Pseudomonas*. It can be synthesized in a variety of ways including condensation of cephalosporin antibiotic **63** with 6-methyl-4-(1-H)-pyridone-3-carboxylic acid in the form of its active N-hydroxysuccinimide ester (**62**) to produce **cefpiramide** (**64**) [20,21].

Cefoperazone (66) is a third generation parenteral antipseudomonal cephalosporin containing an acylated C-7 side chain reminiscent of that of **piperacillin**. One of the simplest syntheses

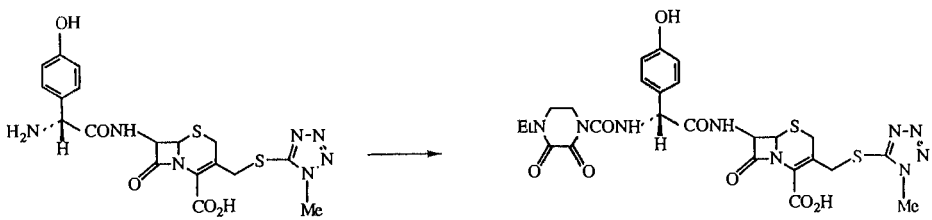


(62) (63)



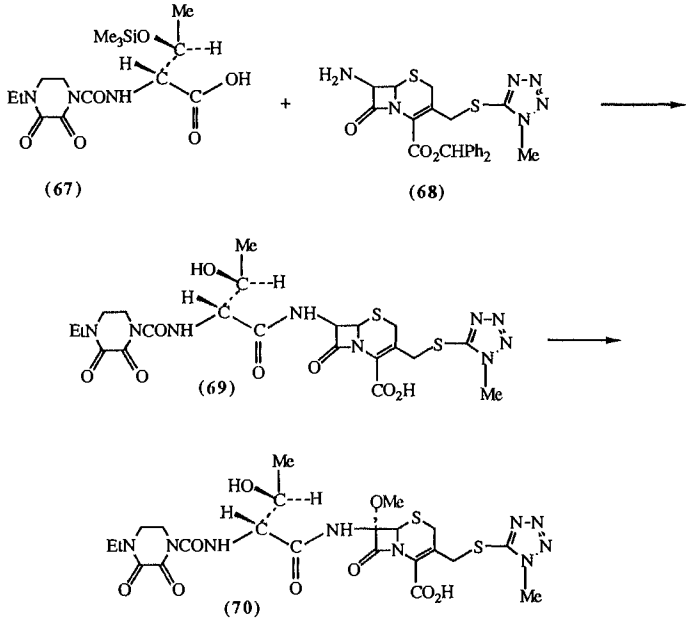
(64)

involves acylation of antibiotic 65 with 4-ethyl-2,3-dioxo-1-piperazinecarbonyl chloride and triethylamine to give **cefoperazone** (66) [22].



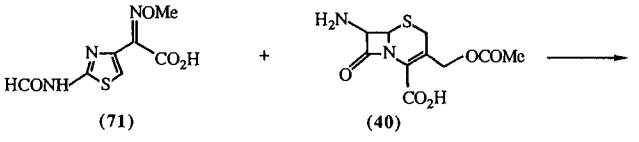
(65) (66)

The chemical structure of **cefbuperazone** (70) is somewhat analogous to that of **cefoperazone**, however, the C-7 side chain ureido function is attached to an aliphatic amino acid rather than an aromatic one and in fact consists of the amino acid threonine. β-lactamase resistance of this agent is enhanced further by incorporation of a C-7 methoxyl moiety derived conceptually from the cephamycins. One of the syntheses of this agent starts with reaction of threonine and 4-ethyl-2,3-dioxo-1-piperazinecarbonyl chloride and subsequent trimethylsilylation to give synthon 67. This is condensed with protected 7-aminocephalosporanic acid ester 68 by means of ethyl chloroformate and N-ethylmorpholine. After deblocking, the product (69) is converted to its C-7 methoxy analogue by protection with ethylvinyl ether and acid and sequential reaction with lithium methoxide and t-butylhypochlorite followed by deblocking in acid to produce **cefbuperazone** (70) [23].

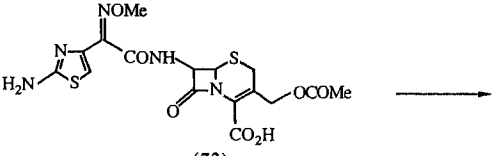


Cefotriaxone (73) has a 2,5-dihydro-6-hydroxy-2-methyl-3-thia-5-oxo-1,2,4-triazine moiety at C-3 in order to avoid some of the side effects of cephalosporins attributed to the presence of an alkylthiatetrazolyl moiety at C-3 (antabuse-like acute alcohol intolerance and prolonged blood clotting times). In animal studies, **cefbuperazone** has been shown to be more effective than **cefmetazole** and **cefoperazone** in infected mice. Of the various syntheses, one proceeds from 7-aminocephalosporanic acid itself (**40**) by condensation with (formamidothiazolyl)(methoxyimino)acetic acid (**71**) promoted by 1,1'-(carbonyldioxy)dibenzotriazole (formed by reaction of 1-hydroxybenzotriazole with trichloromethylchlorocarbonate--this converts the carboxylic acid moiety to the activated 1-hydroxybenzotriazole ester of **71**) to give cephalosporin **72**. This synthesis of **ceftriaxone** (73) concludes by displacement of the acetoxyl moiety of **72** with 2,5-dihydro-6-hydroxy-2-methyl-3-mercapto-5-oxo-1,2,4-triazine and sodium bicarbonate [24].

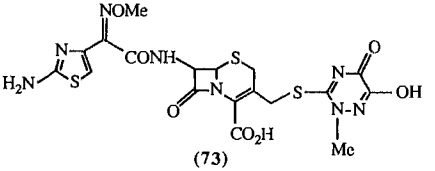
Cefmetazole (78) is a cephamycin-inspired cephalosporin differing from the mainstream compounds in having an aliphatic amide moiety attached to C-7. Its antibacterial spectrum is similar to the second generation agent **cefoxitin**. The synthesis starts with 7-aminocephalosporan-



(71) (40)

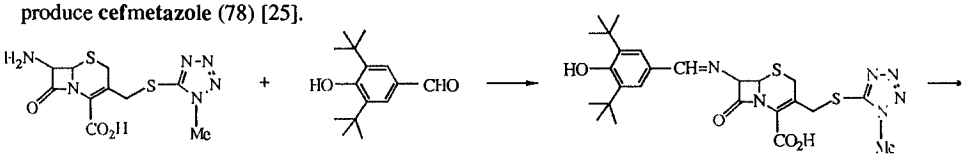


(72)

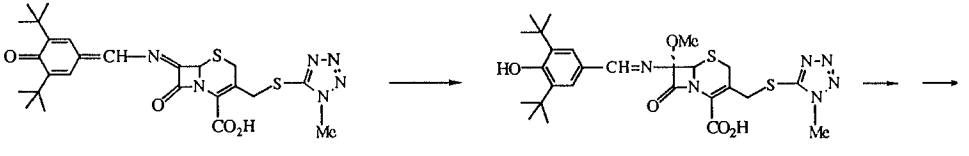


(73)

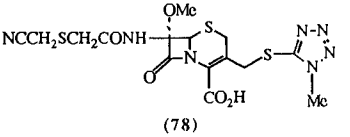
ic acid derivative **59** which is converted to its Schiff's base (**75**) with 3,5-di-t-butyl-4-hydroxybenzaldehyde (**74**). The imine (**75**) is oxidized to the iminoquinonemethide (**76**) with lead dioxide. Methanol is added 1,8 to this conjugated system to produce desired intermediate **77**. The protecting Schiff's base is removed by exchange with Girard T reagent and the 7-aminocephalosporanic acid derivative so produced is acylated with cyanomethylthioacetic acid as its acid chloride to produce **cefmetazole** (78) [25].



(59) (74) (75)

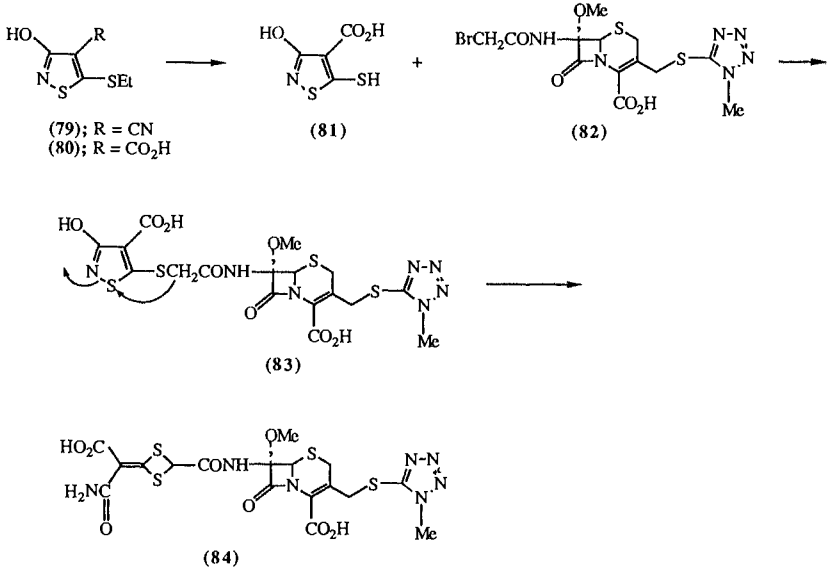


(76) (77)



(78)

Cefotetan (84) stands out from the other cephalosporin antibiotics in that it possesses the unusual 1,3-dithietan side chain at C-7. This was introduced initially as the result of a molecular rearrangement and this interesting moiety was found to be consistent with excellent activity against many Gram-negative microorganisms (although not pseudomonads). Methods were developed for the deliberate incorporation of this functionality into molecules. The drug is rather similar to **ceftazidime** in its in vitro antimicrobial spectrum. Its synthesis begins with hydrolysis of 4-cyano-5-ethylthio-3-hydroxyisothiazole (**79**) with sodium hydroxide to produce acid **80**. Reductive cleavage to thiol **81** was accomplished in good yield by reaction with sodium in liquid ammonia. This synthon was used to displace the bromo atom of cephalosporin antibiotic **82** to give antibiotic 83. Treatment of the latter with aqueous sodium bicarbonate leads to a facile rearrangement of the isothiazole, presumably by intramolecular displacement. The mechanism of this interesting reaction is not certain but may involve the process indicated by the arrows in formula 83. The product is in any case the antibiotic **cefotetan** (84) [26].

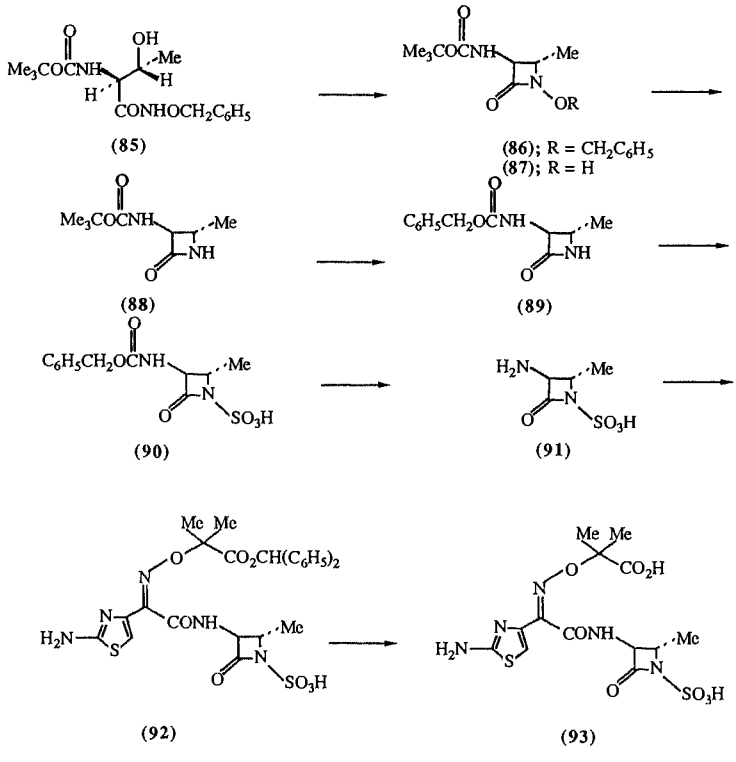


4. MONOBACTAMS

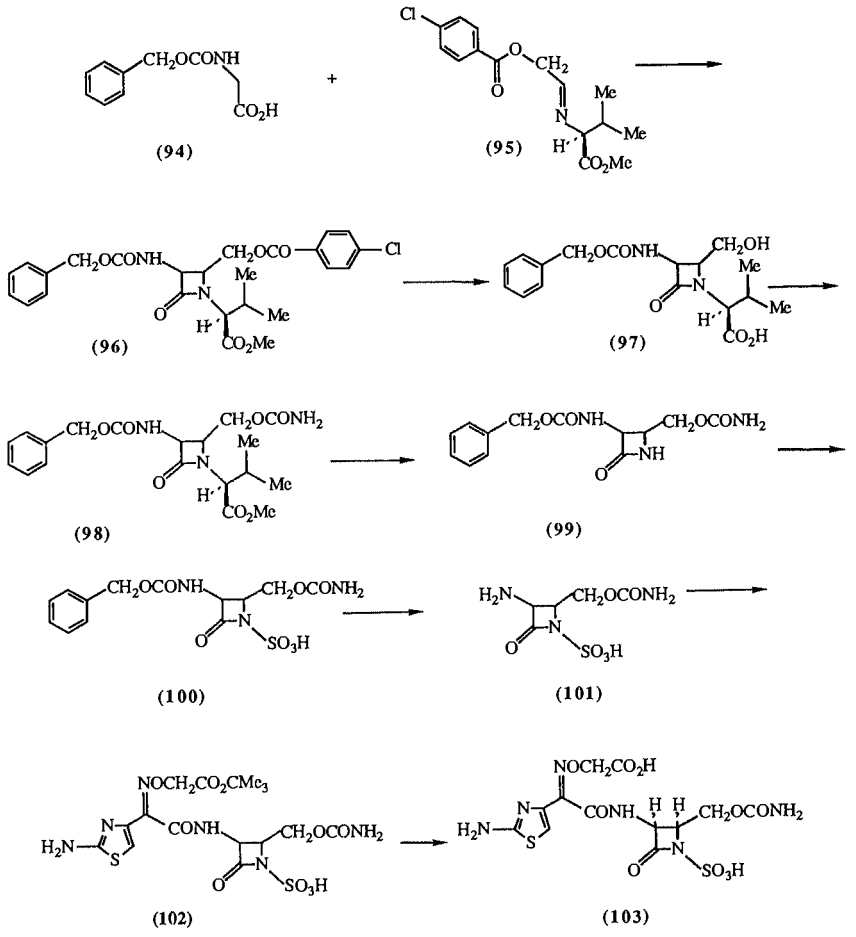
Utilizing a specially designed and intensive screen for novel β-lactam antibiotics from bacterial species, a series of monobactams (monocyclic β-lactam antibiotics) were ultimately discovered which not only possessed interesting anti-Gram-negative activity but possessed an intriguing N-sulfonic acid moiety attached to the nitrogen of the β-lactam ring. This group mimics the function of the carboxyl moiety of penicillins and cephalosporins. Previously it had also been believed that a fused strained bicyclic β-lactam system was necessary for significant antibacterial activity. While the natural monobactams do not appear to have clinically useful activity, a number of their totally synthetic analogues do. This field has been explored intensively in recent years and some of the fruits of this work are reported here.

Aztreonam (**93**) is a wholly synthetic agent directed primarily against Gram-negative bacteria. The total chemical synthesis of **aztreonam** begins with N-t-butoxycarbonyl threonine-O-benzylhydroxylamide (**85**) which cyclizes to the monocyclic β-lactam intermediate (**86**) by use of an intramolecular Mitsunobu reaction with triphenylphosphine and diethylazodicarboxylate ("DEAD"). Careful hydrogenolysis is employed to remove the benzyl protecting group without cleaving the N-O bond to give intermediate **87**. The now superfluous N-hydroxyl group is removed by reduction with titanium trichloride to give azetidin-2-one **88**. The t-BOC protecting group is removed by hydrolysis with trifluoroacetic acid and then replaced by a carbobenzyloxy moiety by reaction with benzyl chloroformate. The protected intermediate (**89**) is sulfonated with sulfur trioxide in DMF to give sulfonamide **90**. The CBZ protecting group is removed by hydrogenolysis to produce amphoteric azetidinone **91**. The desired acyl side chain is installed in the form of its diphenylmethyl ester using N-hydroxybenzotriazole as condensing agent to produce **92**. Hydrolysis with trifluoroacetic acid leads finally to **aztreonam** (**93**) [27].

Carumonam (**103**) differs from **aztreonam** structurally in having an acetic acid function attached as an ether to the oximino moiety in the side chain and a carbamoylmethyl group in place of the methyl group at C-3. Like **aztreonam** it is primarily effective against Gram-negative bacteria. An interesting synthesis starts with a 2 + 2 cycloaddition reaction using carbobenzoxyglycine

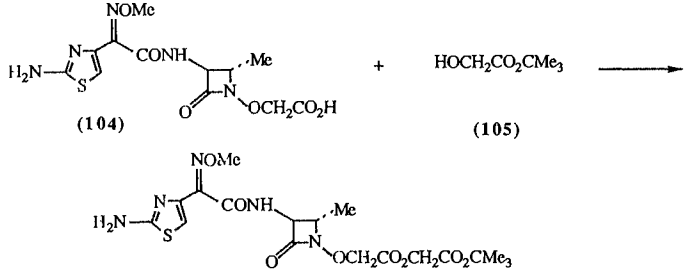


(**94**) and a complex imine prepared from methyl L-valinate (**95**). The requisite ketene derivative is made in situ by reacting CBZ-glycine (**94**) with i-butyl chloroformate or i-propyl chloroformate. The product of cycloaddition is primarily cis (**96**) and can be separated from the mixture by fractional crystallization. Careful hydrolysis with potassium carbonate removes the two ester groups (**97**) and then the carbamoyl moiety is introduced by reaction with dichlorophosphoryl isocyanate followed by reaction with aqueous bicarbonate to give **98**. The chiral auxiliary now having served its purpose can best be removed by anodic oxidation in acetic acid-triethylamine solution followed by hydrolysis with potassium carbonate to give partially deblocked monobactam **99**. The remainder of the steps to **carumonam** consist of reaction with sulfur trioxide to the N-sulfonate (**100**), hydrogenolytic deblocking of the primary amine to amphoteric **101**, addition of the protected side chain to give **102**, and deblocking with trifluoroacetic acid to produce **carumonam** (**103**) [28]. Other conceptually interesting syntheses are available to the interested reader [29,30].



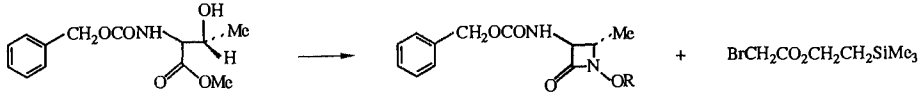
A number of monobactams have been prepared in which the N-sulfonic acid moiety has been replaced by various other acidic groups. One means of closing the β-lactam ring in this drug class invokes the normally suppressed nucleophilicity of the N-atom of the oxime moiety. This leaves an oxygen atom which is either replaced by a sulfonic acid group (as with **aztreonam**) or utilized as a functional group to which a bioisosterically equivalent appendage, such as an acetic acid moiety is attached. This works in part because the electronic character of the bridging oxygen is somewhat analogous to that of the sulfur but also because the molecular size of the oxygen and the methylene carbon are roughly equivalent to that of sulfur so that the position in space of the acidic

moiety is roughly the same in **aztreonam** and in **gloximonam** (after deblocking to **oximonam**). In order to enhance the oral bioavailability of **oximonam** (**104**), a prodrug has been made by esterification of the carboxyl group with the t-butyl ester of hydroxyacetic acid (**105**). The product is prodrug **gloximonam** (**106**) [31]. **Gloximonam** is efficiently converted to **oximonam** in the body by metabolic processes.

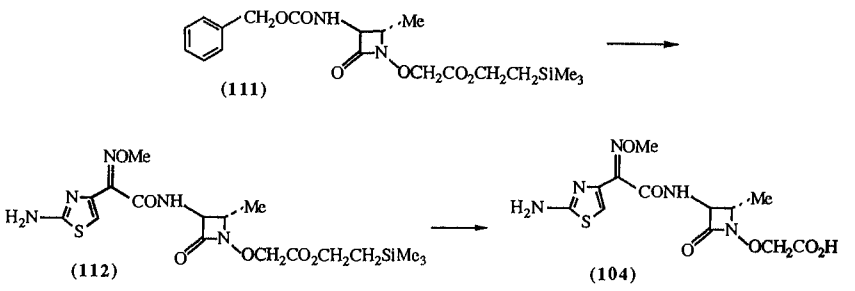


(104) (105) (106)

The drug latentiated in the previous paragraph is the parenteral antibacterial monobactam **oximonam** (**104**). Its subclass of monobactams is sometimes referred to as the monosulfactams. As with the other monobactams, **oximonam** is primarily active against Gram-negative microorganisms. The synthesis begins with methyl N-carbobenzoxythreonine (**107**) which is converted to its oximinoyl amide with hydroxylamine then acetylated and finally cyclized to protected monobactam **108** under modified Mitsunobu conditions (triphenylphosphine and dimethyldiazodicarboxylate). Deacetylation with sodium carbonate produces **109**. Ether formation, aided by a water soluble carbodiimide, with 2-trimethylsilylethylbromo acetate (**110**) leads to ether-ester **111**. Hydrogenolytic deblocking of the primary amino group (hydrogen, Pd-C, HCl) and acylation leads as in previous examples to **112**. Final deblocking to **oximonam** (**113**) is carried out with tetrabutylammonium fluoride [32].



(107) (108); R = COMe (109); R = H (110)



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11 Miscellaneous Heterocycles

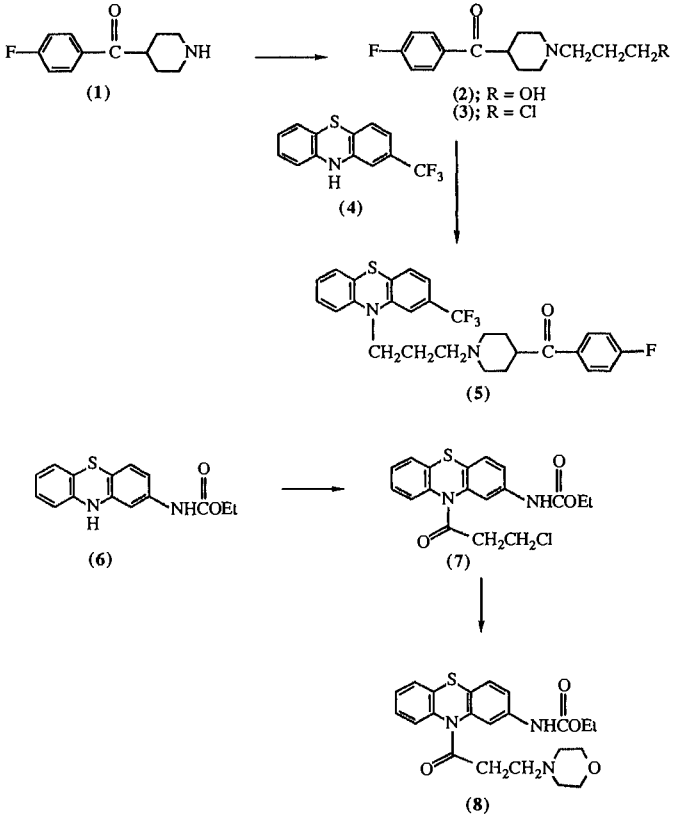
The classification of medicinal agents in terms of their chemical structures has been a hallmark of this series. This system proves readily applicable for the majority of structural types. Rather complex structures which might strain such a scheme, such as for example, β-lactams, are often represented by a sufficient number of examples so that they can be collected in a special chapter. Some structures however, perhaps inevitably, do not readily fall into any neat category, hence this chapter on " Miscellaneous Heterocycles ." It is of passing interest that a number of the entries, such as, for example, the phenothiazines and benzodiazepines, belong to structural classes which merited chapters in their own right in previous volumes. The fact that the references to the preparation of these compounds tend to be somewhat old, suggest that they were in fact first prepared when those fields were under intensive investigation. The granting of an USAN to those agents in the much more recent period covered by this book (1982-1987) probably means that, for one reason or another, that they have been taken off the shelf for clinical development.

1. PHENOTHIAZINES

The phenothiazine **duoperone (5)** combines structural elements found in phenothiazine and butyrophenone antipsychotic agents. Alkylation of substituted piperidine **1** with 3-chloropropanol affords the intermediate **2**; treatment of this with thionyl chloride converts the terminal hydroxyl to chloride. Alkylation of the phenothiazine **4** with halide **3** affords the antipsychotic agent **duoperone (5)** [1].

A more polar phenothiazine derivative in which the side chain consists of an amino amide

exhibits the antiarrhythmic activity often found in such hindered amides. Acylation of phenothiazine 6 with 2-chloropropionyl chloride gives the haloamide 7; displacement of halogen with morpholine gives moricizine (8) [2].

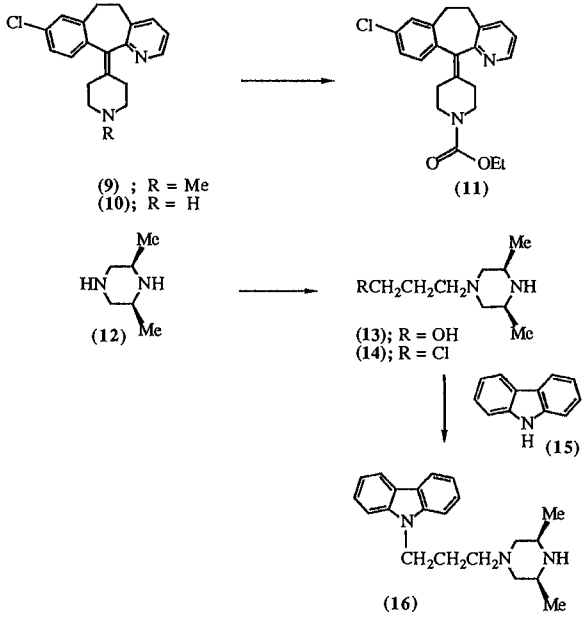


2. BENZOCYCLOHEPTAPYRIDINES

Demethylation of the tricyclic antihistamine **9**, with cyanogen bromide gives the secondary amine **10**; acylation of that intermediate with ethyl chloroformate affords the nonsedating H-1 antihistaminic agent **loratidine (11)** [3]. It is of interest that this compound does not contain the zwitterionic function which is thought to prevent passage through the blood-brain barrier, characteristic of this class of compounds.

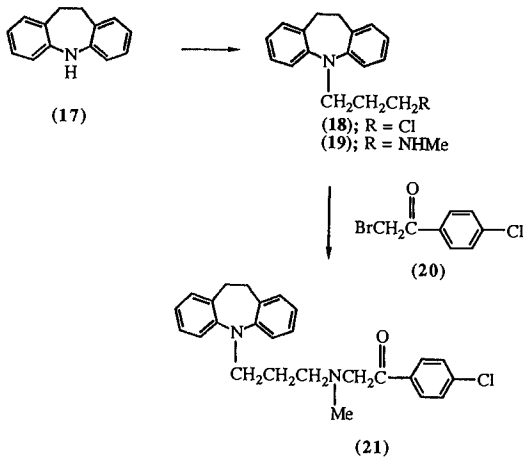
3. CARBAZOLES

Alkylation of the dimethylpiperazine **12** with 3-chloropropanol followed by treatment of the product **13** with thionyl chloride gives the halide **14**. Alkylation of the anion from carbazole (**15**) with that halide leads to the tricyclic antipsychotic agent **rimcazole (16)** [4].



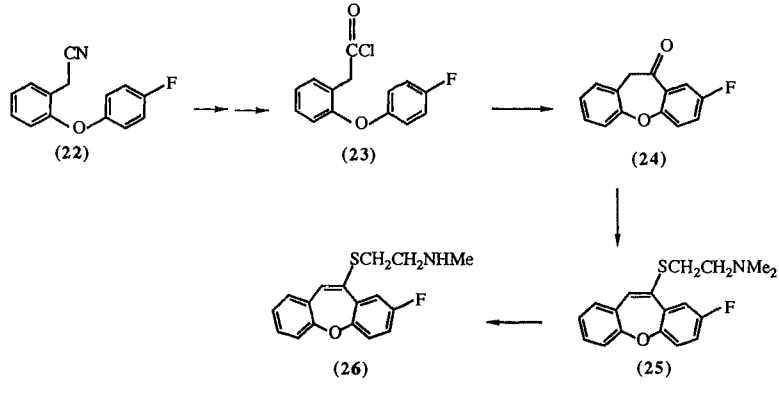
4. DIBENZAZEPINES

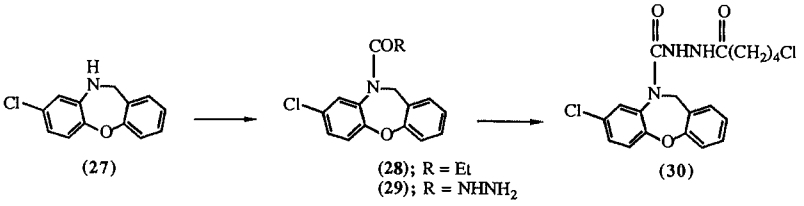
The **imipramine** analogue in which one of the methyl groups on the side chain nitrogen is replaced by a phenacyl group retains antidepressant activity. The starting material for this analogue, **desipramine (19)**, interestingly is an antidepressant drug in its own right. Alkylation of **19** with p-chlorophenacyl bromide (**20**) leads to **lofepramine (21)** [5].



5. DIBENZOXEPINES

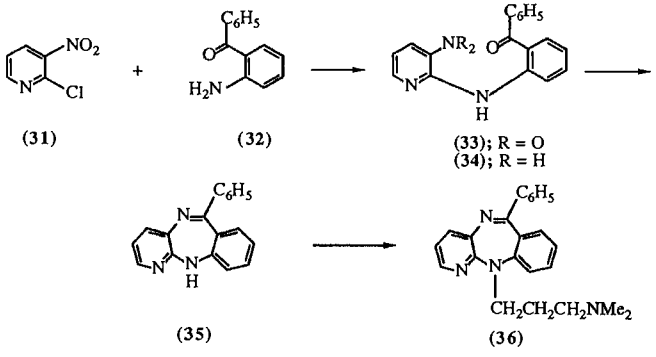
Two related tricyclic heterocyclic systems provide the nuclei for analgesic compounds which are not related structurally to either NSAIDs or opioids. Saponification of the nitrile group in **22** leads, via the corresponding acid, to acid chloride **23**. Friedel-Crafts cyclization of **23** affords the ketone **24**. Reaction of that ketone with 2-dimethylamino ethanethiol in the presence of boron trifluoride leads to formation of the enol thioether. Demethylation with phenylchloroformate gives **fluradoline (26)** [6]. Acylation of the dibenzoazaoxepin **27** with ethylchloroformate leads to the carbamate **28**. Hydrazinolysis of the ester gives the hydrazide **29**. Acylation of the remaining basic nitrogen on that intermediate with 5-chloropentanoic acid affords **pinadoline (30)** [7].





6. PYRIDOBENZODIAZEPINES

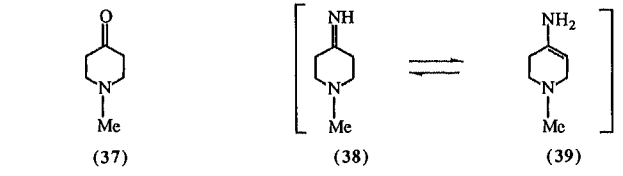
Antidepressant activity is retained when the two carbon bridge in imipramine is replaced by a larger, more complex, function. Nucleophilic aromatic substitution on chloropyridine **31** by means of o-aminobenzophenone (**32**) gives the bicyclic intermediate **33**. Reduction of the nitro group (**34**), followed by intramolecular Schiff base formation gives the required heterocyclic ring system **35**. Alkylation of the anion from **35** with 1-dimethylamino-3-chloropropane leads to tampramine **36** [8].



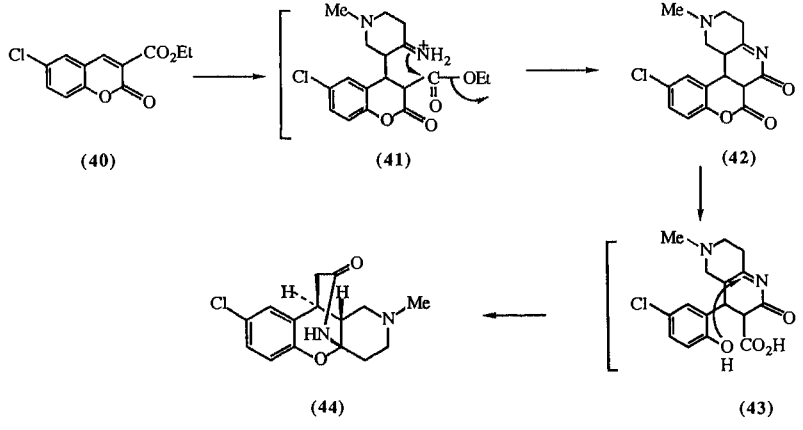
7. BENZOPYRANOPYRIDINES

The reaction of relatively simple starting materials, coumarin **40**, piperidone **37** and ammonium acetate, leads in a single step to the complex bridged tetracyclic compound **44**. The reaction can be rationalized by assuming formation of the imine **38** from reaction of **37**, with ammonia. Conjugate addition of the eneamine-like tautomer **39** to the excellent Michael acceptor **40** will

lead to the adduct **41**. This last is perfectly set up for intramolecular cyclization to the imide **42** by attack of imine nitrogen on the adjacent ester function. Ring opening of the lactone in **42** would afford the phenolic acid **43**. This last intermediate is shown in neutral form; the reaction can be rationalized just as well by using the charged intermediate ions. Addition of the phenol (or phenoxide) oxygen to the imide serves to close the last ring. Decarboxylation of the beta dicarbonyl grouping in **43** completes the reaction sequence. This last step can be visualized to occur either prior to or after the last ring is closed. The stereochemistry is probably thermodynamically controlled since the last ring closure in fact consists of carbinolamine formation from a ketone, a reaction which should be readily reversible. The product **lortalamine (44)** is described as an antidepressant agent [9].



(37) (38) (39)



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

8. PYRROLOISOQUINOLINES

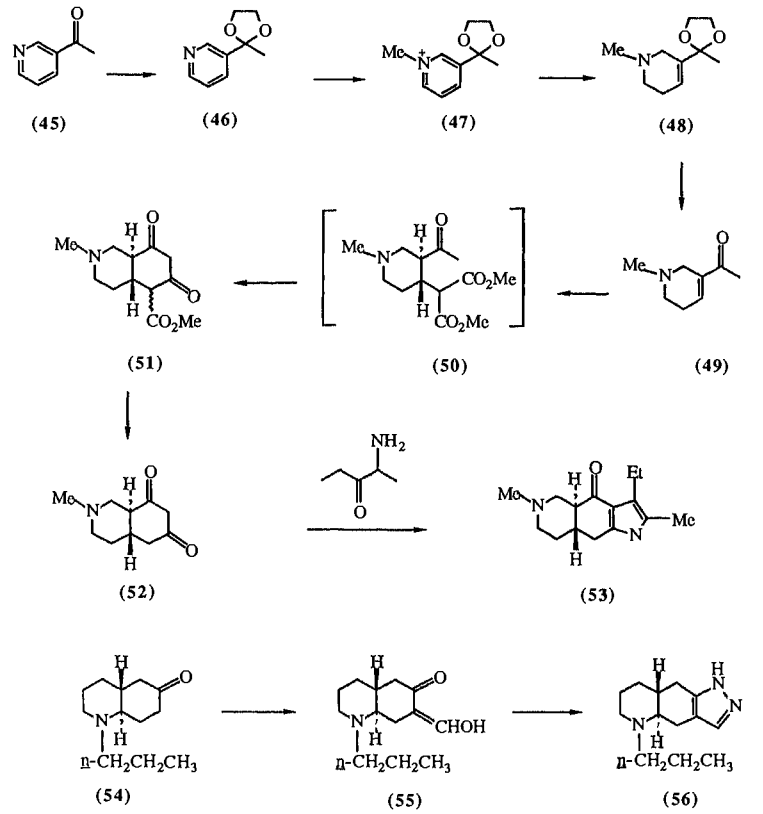
Synthesis of the dopamine antagonist antipsychotic agent **piquindone** (**53**) starts by conversion of nicotinyl methyl ketone **45** to its acetal **46**; alkylation with methyl iodide followed by reduction of the thus formed ternary iminium salt **47** by means of borohydride results in the tetrahydropyridine **48**. Hydrolysis of the acetal group reveals the newly formed unsaturated ketone in **49**. Conjugate addition of dimethyl malonate no doubt proceeds initially to the adduct **50**; the reversible nature of the reaction as well as the ready enolization of the acetyl ring proton will result in formation of the more stable *trans* diequatorial isomer. The product cyclizes under the reaction conditions to perhydroisoquinolone **51**. Hydrolysis of the ester in **51** is followed by decarboxylation to afford **52**. Reaction of this last intermediate with 2-amino-3-pentanone under conditions for the Knorr reaction leads to formation of a pyrrole ring. The reaction sequence may be visualized by assuming initial imine formation between the quinolone and the aminoketone; cyclodehydration would complete the formation of the new ring. It is of note that a small amount of the isomeric angularly annulated product is formed as well. There is thus obtained **piquindone** (**53**) as the major reaction product [10].

9. PYRAZOLOQUINOLINES

Reaction of ethyl formate with perhydroisoquinolone **54**, in the presence of strong base leads to the β-formylketone **55**; condensation of that product with hydrazine leads to the formation of a new pyrazole ring. This product, **quinpirole** (**56**), is an antihypertensive agent [11].

10. NAPHTHOPYRANS

The discovery of the utility of the bis-chromone carboxylic acid derivative **cromolyn sodium** in the treatment of asthma and related allergies has led to an intensive, and thus far not very fruitful, effort to discover analogues which would show oral activity in contrast to the lead which must be administered by inhalation. Preparation of a typical analogue, **proxicromil** (63), starts with the O-allylated phenol **57**. Claisen rearrangement leads to the corresponding C-allylated product **58**. The double bond is then reduced by catalytic hydrogenation (**59**). Base-catalyzed condensation

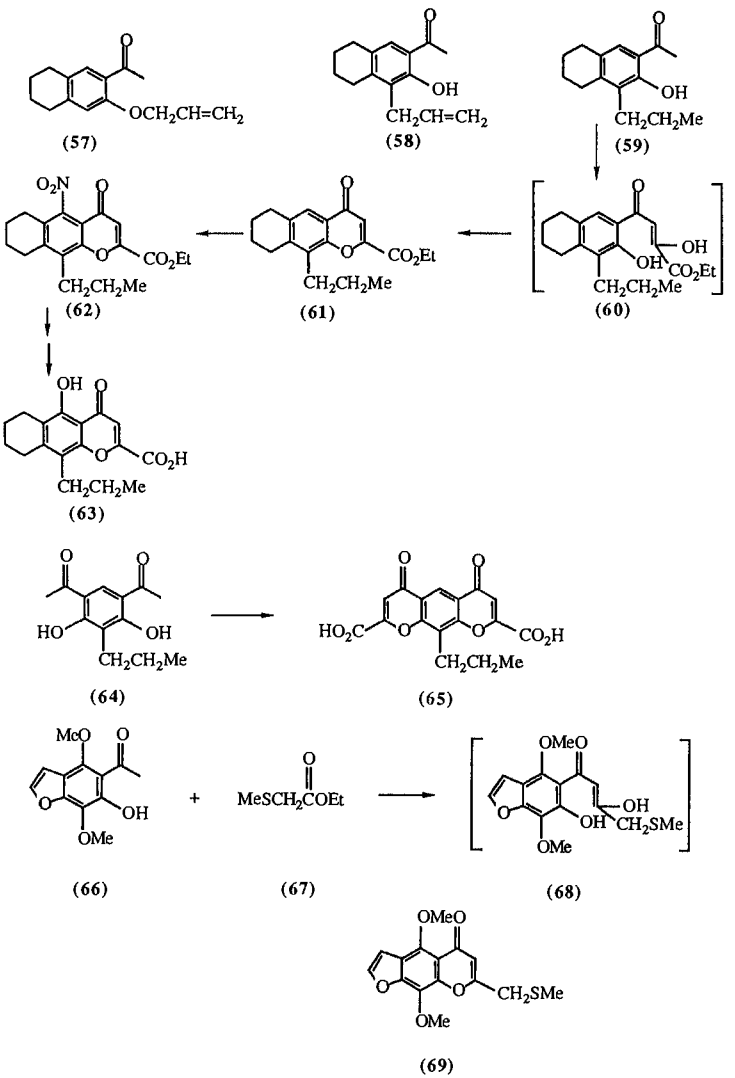


with diethyl oxalate can be envisaged as proceeding initially to the product from acylation of the ketone methyl group (**60**). Cyclodehydration of that product, shown in the enol form, will result in the formation of a pyran ring. There is thus obtained the chromone **61**. Nitration of **61** produces nitro-pyran **62**. The nitro group in **62** serves as a tool to introduce the phenolic hydroxyl group in **63** via reduction of the nitro group, diazotization of the resulting amino group, and treatment of the diazonium salt with aqueous sulfuric acid. During that treatment the ester functionality is hydrolyzed as well. There is thus obtained **proxicromil (63)** [12].

11. BENZODIPYRANS

In much the same vein, condensation of the difunctional o-hydroxyacetophenone **64** with diethyl

oxalate leads to the formation of two pyran rings on the same benzene ring. Workup under aqueous basic conditions leads to *in situ* saponification of the ester groups. There is thus obtained in a single step the mediator release inhibitor, **probicromil** (65) [13].

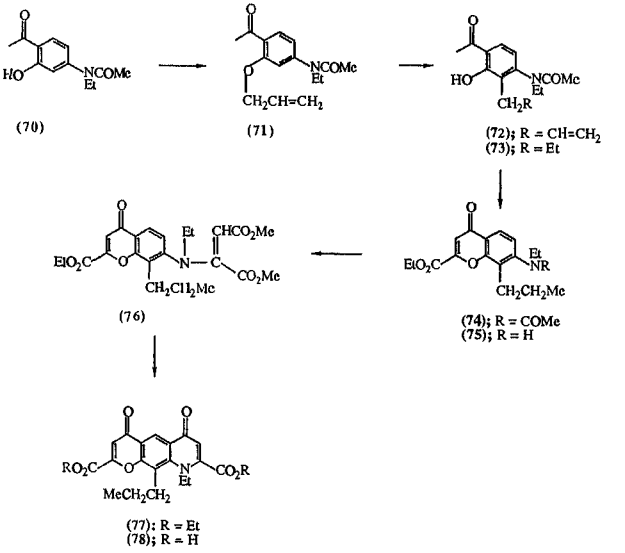


12. FUROBENZOPYRANS

A closely related oxygenated heterocyclic system devoid of acidic groups interestingly shows quite different biological activity. Thus, condensation of the benzofuran hydroxyketone 66 with ethyl thiomethyl acetate (67) probably proceeds initially by formation of the acylation product 68. Intramolecular dehydration leads to formation of a pyran ring. There is thus obtained the hypocholesterolemic agent **timefurone** (69) [14].

13. PYRANOQUINOLINES

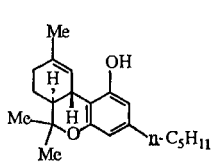
Mediator release inhibiting activity is, interestingly, retained when of one of the pyran rings in a molecule such as **probicromil** is replaced by a pyridine ring. The synthesis of such an agent starts with the allylation of hydroxyacetophenone 70 to give the ether 71. Rearrangement (72) followed by reduction gives the intermediate 73. The chromone ring is then added by base- catalyzed acylation with ethyl oxalate (74). Removal of the acetyl group on nitrogen gives the intermediate, 75, required for construction of the pyridine ring. Thus, conjugate addition of the amino group in 75 to diethyl acetylene dicarboxylate gives the maleic ester 76. The ester function cyclizes onto the benzene ring on heating to form the pyridone 77. Saponification of the esters affords **nedocromil** (78) [15].



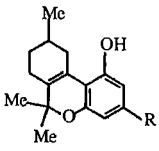
14. DIBENZOPYRANS

Natural products have played an important role in the process of drug discovery. Several important medicinal agents were first identified as a result of the adventitious discovery of their biological activity. Familiar examples include the opioid analgesics, digitalis cardiotonic agents, and antihypertensive agents related to reserpine. The host of biological activities exhibited by marijuana suggested that this natural product should act as a lead to significant new classes of drugs. The identification and structural elucidation of the compound responsible for the biological activities, tetrahydrocannabinol (**79**), spurred interest in this compound. The development, in short order, of facile routes to this compound led to the synthesis of many new analogues.

Acylation of the THC analogue **80**, in which both the position of the double bond and the length of the side chain have been changed, with 4-(homopiperidino)butyric acid gives the ester **nabazenil** (**82**) which is described as an anticonvulsant agent. Esterification of the phenol in the isomeric THC-like compound **81** with 4-(diethylamino)butyric acid gives the ester **83**, **naboctate**, in which antinauseant and antiglaucoma activity predominate [16].

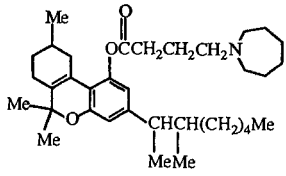


(79)

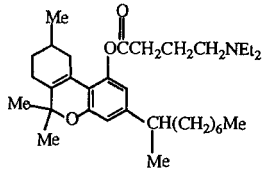


(80); R = CHCH(CH2)4Me
MeMe

(81); R = CH(CH2)6Me
Me



(82)



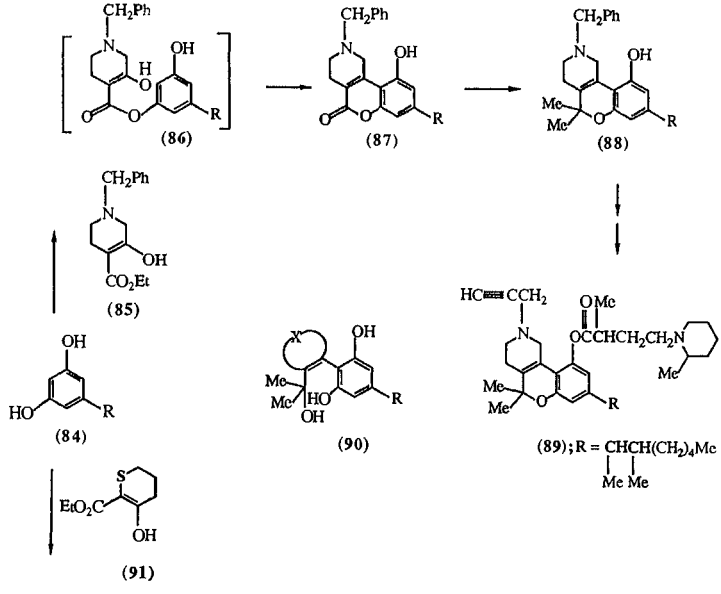
(83)

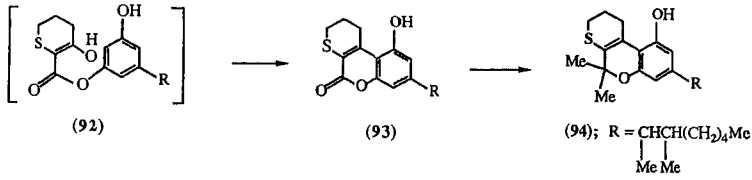
15. BENZOPYRANOPYRIDINES

The synthesis of THC analogues in which the carbocyclic ring is replaced by a heterocycle involves as a key step condensation of the resorcinol **84** with the appropriate β-keto ester. Thus, condensation of that intermediate with piperidone **85**, leads to the lactone **87**. The reaction can be rationalized by assuming initial formation of the ester **86**; the required carbon-carbon bond will then result from a cyclodehydration step. Reaction of the lactone with an excess of methyl Grignard reagent leads to the isolation of the THC analogue **88**. This last reaction may in fact proceed initially to a tertiary carbinol of the general formula shown in **90**. The tertiary carbocation formed under the acidic condition of the workup can in principle cyclize with the phenol to give the pyran ring of the product, **88**, which is finally isolated. Debenzylation of **88** is followed by N-alkylation with propargyl bromide and acylation with 4,N-(1-methylpiperidino)-2-methylbutyric to afford the analgesic agent **menabitan (89)** [17].

16. THIOPYRANOBENZOPYRANS

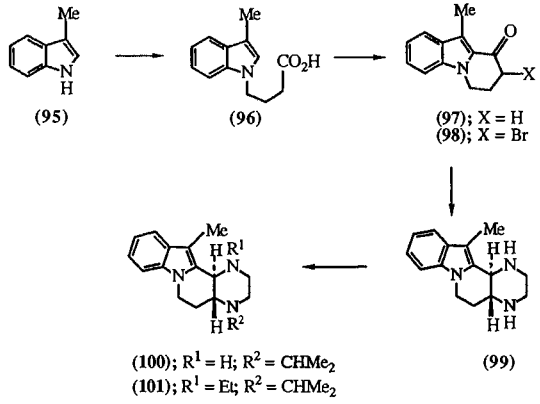
The same sequence starting with the thiapyrone **91** affords via initially **92** the lactone **93**. This intermediate gives the antihypertensive agent **tinabinol (94)** on reaction with excess methylmagnesium bromide (18).





17. PYRAZINOPYRIDOINDOLES

Piperazine rings are a common structural feature in many compounds which act as antagonists at α-adrenergic receptors; it is of interest that a compound which incorporates a fused piperazine acts as an antihypertensive agent by virtue of α-blocking activity. Reaction of the indole **95** with γ-butyrolactone leads to acid **96**. Friedel-Crafts type cyclization affords the tricyclic ketone **97**. Treatment of that intermediate with bromine gives the product from α-bromination (**98**). Reaction of the bromoketone with ethylene diamine in the presence of borohydride leads to formation the fused piperazine ring(**99**). The sequence probably involves formation of the initial carbon-nitrogen bond by displacement of bromine; the second bond is then formed by reductive alkylation of the ketone. The steric environment around each of the two secondary amino groups is sufficiently different so that they show markedly different reactivities toward alkylation reactions. Thus, treatment with isopropyl bromide leads to the monoalkylation product **100**. The remaining amino group is alkylated by reaction with ethyl bromide under more forcing conditions. There is thus produced **atiprosin (101)** [19].

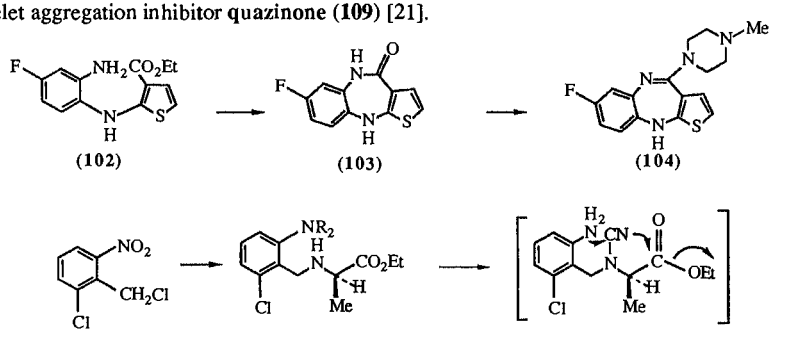


18. THIENOBENZODIAZEPINES

Many examples of retention of activity in the face of replacement of benzene by thiophene have been noted so far. Application of this stratagem to a clozapine-like antipsychotic constitutes yet another example where activity is retained. The seven-membered ring of the compound in question is established by intramolecular amide formation on intermediate **102**. Treatment of amide **103** with N-methylpiperazine in the presence of titanium tetrachloride affords **flumezapine (104)** [20].

19. IMIDAZOQUINAZOLINONES

The growing awareness of the importance of chirality in biological activity has led to a trend to prepare new drugs in enantiomerically pure form. It is hoped by this means to spare the metabolic system the task of handling the inactive or even potentially toxic enantiomer. The more elegant solution to preparation of such enantiomers involves the use of chiral synthons. Thus, alkylation of benzyl chloride **105** with ethyl D-alanine gives the chiral alkylation product **106**, which is hydrogenated to produce the amine **107**. Treatment with cyanogen bromide leads to the N-cyano intermediate **108**. This undergoes a double ring closure under the reaction conditions to form the platelet aggregation inhibitor **quazinone (109)** [21].



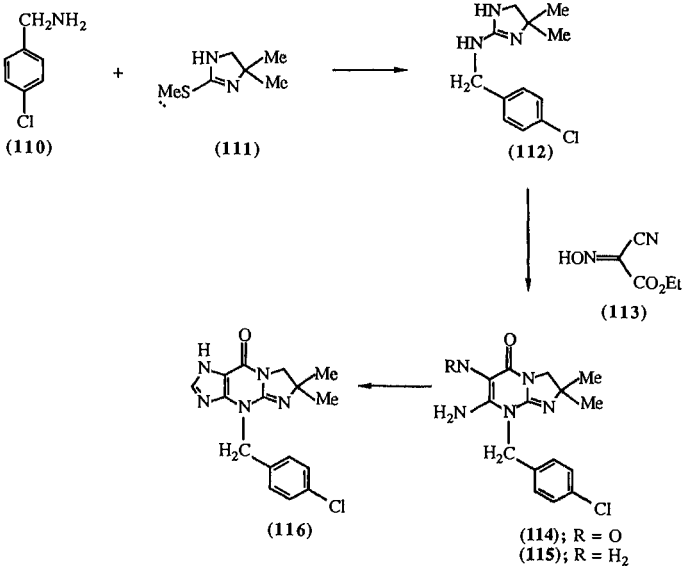
(102) (103) (104)

(105) (106); R = O (107); R = H (108)

(109)

20. IMIDAZOPURINES

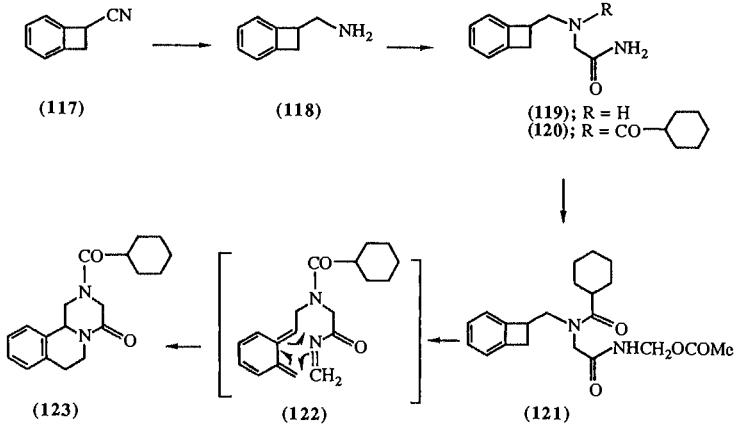
Imidazopyrimidines related to theophylline have been investigated extensively as a source for bronchodilating agents. Alkylation on nitrogen and fusion of an additional heterocyclic ring gives a bronchodilator which also displays some mediator release inhibiting activity. An addition-elimination reaction of benzylamine **110** on imidazoline **111** leads to replacement of the thiomethyl group by the amino group (**112**). This intermediate is then treated in the same pot with nitroso cyanoacetamide (**113**). The reaction can be envisaged as involving addition of the benzylamine nitrogen to the cyano group and amide interchange between **113** and the imidazole nitrogen. The nitroso group is then reduced catalytically and the resulting diamine **115** cyclized by means of ethyl orthoformate and acetic anhydride to afford **fenprinast (116)** [22].



21. PYRAZINOISOQUINOLINES

One of the more interesting syntheses for the anthelmintic agent **praziquantel (123)** involves an Oppolzer type electrocyclization reaction. Reduction of the nitrile in benzocyclobutane **117** by means of LAH gives the corresponding amine **118**. This is alkylated with chloroacet-

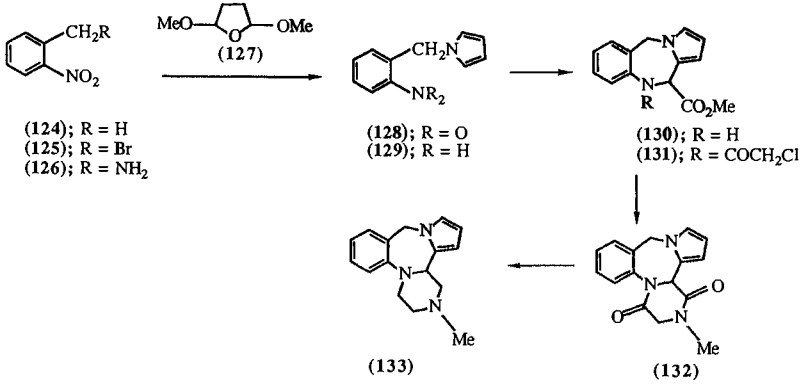
amide, and the product **119** is acylated with cyclohexylcarbonyl chloride. Reaction of the amide with formaldehyde in the presence of acetic anhydride leads to the carbinolamine acetate **121**. Pyrolysis of this intermediate leads to ring opening of the benzocyclobutene to a bis-exomethylene cyclohexadiene and simultaneous loss of acetic acid from the carbinolamine acetate to form a methylene amine **122**. Electrocyclic addition of the latter to the diene forms the required two rings at one time. There is thus obtained **praziquantel (123)** [23].



22. PYRAZINOPYRROLOBENZODIAZEPINES

Antidepressant activity is retained in a mianserin analogue in which a fused benzene ring is replaced by pyrrole even though the two moieties differ in stereoelectronic properties. The starting nitrotoluene **124** is converted to the corresponding benzylamine **126** via bromide **125**. Condensation of the amine with the dimethoxy tetrahydrofuran **127** leads to formation of pyrrole **128**; reduction of the nitro group then affords aniline **129**. Reaction of that intermediate with the methyl hemiacetal from methyl glyoxylate leads to the tricyclic compound **130**. This transformation may involve initial reaction of the aldehyde with the amino group; attack of the iminium derivative on the pyrrole will serve to close the ring. Acylation of the secondary amine with chloroacetyl chloride gives the amide **131**. The transient amine which results from displacement of chlorine by methylamine reacts with the adjacent ester under the reaction conditions to form the remaining

ring of **132**. Reduction of the amide functions by means of LAH leads to **aptazapine (133)** [24].



23. IMIDAZOQUINOLINES

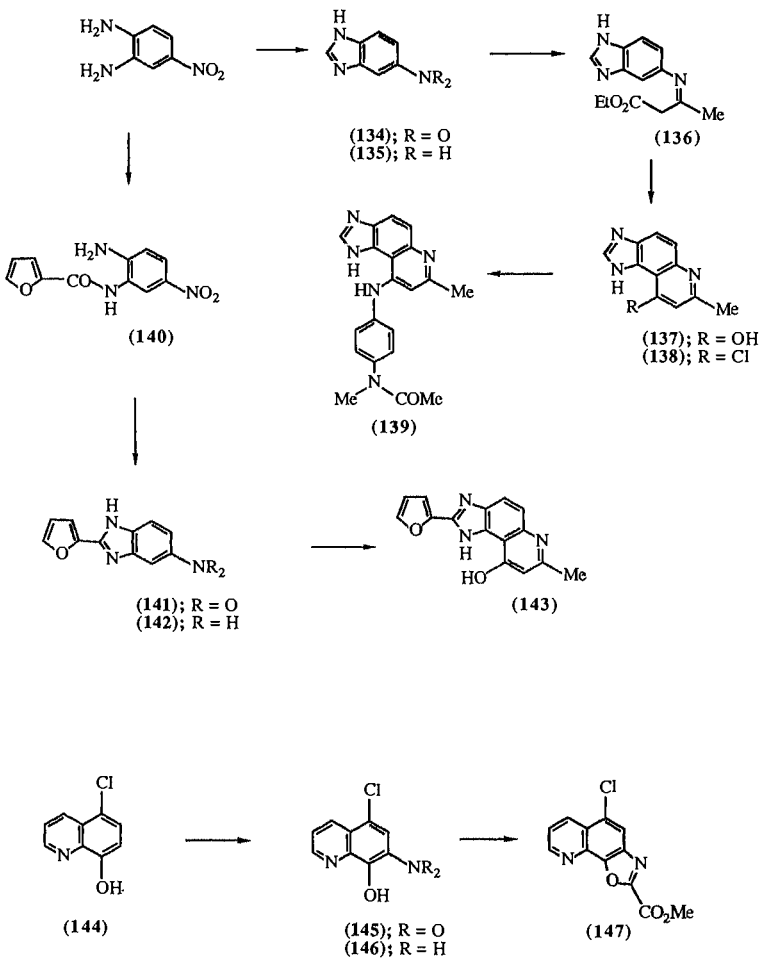
A pair of imidazoquinolines which differ only in substitution patterns differ markedly in biological activities. One of these agents, **acodazole (139)**, shows antineoplastic activity while its seemingly close analogue, **furodazole (143)**, is an anthelmintic agent. Synthesis of the former starts by reaction of 3,4-diaminonitrobenzene with formic acid. Reduction of the nitro group in the product **134** leads to the corresponding amine **135**. Condensation of this last intermediate with ethyl acetoacetate proceeds initially to the imine **136**; this cyclizes to quinoline **137** on heating. The hydroxyl group is then replaced by chlorine with phosphorus oxychloride (**138**). Displacement of halogen by means of N-methyl-N-acetyl-p- phenylenediamine affords **acodazole (139)** [25].

Acylation of the common starting 3,4-diaminonitrobenzene with furoyl chloride proceeds on the more basic amino group *meta* to the nitro group to give **140**. This is then cyclized to imidazole **141** by means of acetic anhydride. Reduction of the nitro group (**142**), followed by condensation with ethyl acetoacetate affords **furodazole (143)** [26].

24. OXAZOLOQUINOLINES

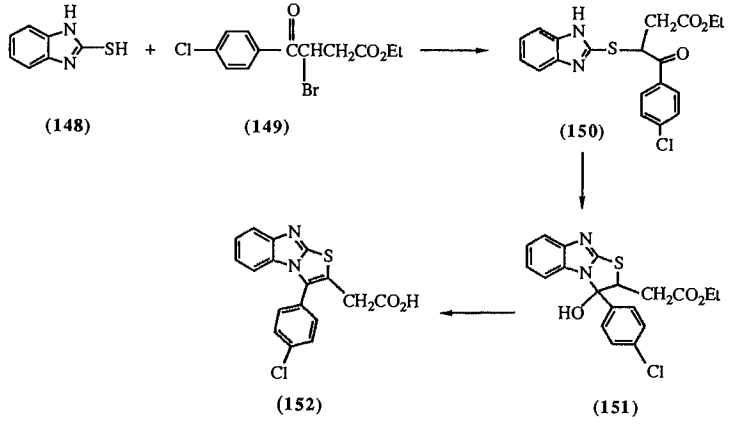
Nitration of quinoline **144** leads to the nitro derivative **145**. Reduction of the nitro group leads to

the *ortho*-aminophenol **146**. Reaction of that intermediate with methyl trimethoxyacetate leads to formation of a benzoxazole ring. There is thus obtained the mediator release inhibitor agent **quazolast (147)** [27].



25. THIAZOLOBENZIMIDAZOLES

The finding that the anthelmintic thiazoloimidazole **levamisole** showed immunoregulatory activity spurred further investigation of this heterocyclic system. Synthesis of a highly modified analogue starts by displacement of bromine in keto ester **149** by sulfur in substituted benzimidazole **148**. Cyclization of the product (**150**), leads initially to the carbinol **151**. Removal of the ester group by saponification in base followed by acid-catalyzed dehydration of the carbinol affords the immune regulator **tilomisole** (**152**) [28].

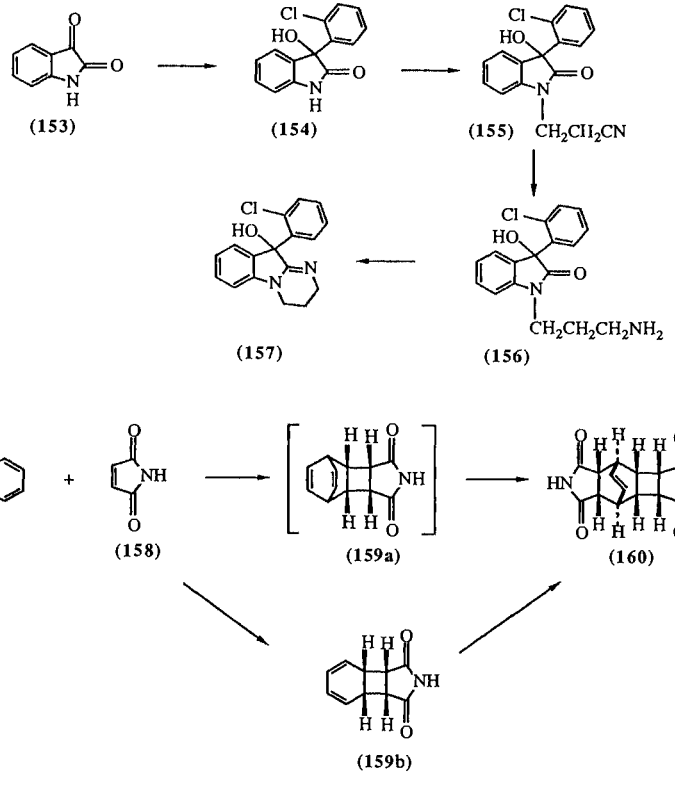


26. PYRIMIDOINDOLES

The two carbonyl groups in isatin (**153**) show quite different reactivities since one is a ketone and the other an amide. Condensation of that compound with the Grignard reagent from o- chlorobromobenzene thus gives **154**. Conjugate addition of the anion from that product to acrylonitrile affords the proprionitrile **155**. The cyano group is then reduced to the primary amine by means of LAH. Internal imine formation leads to cyclization. There is thus obtained the antidepressant agent **ciclazindol** (**157**) [29].

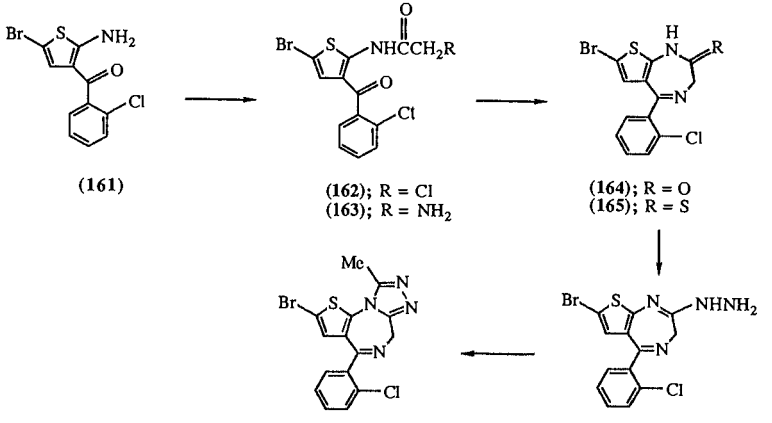
27. ETHENOPYRROLOCYCLOBUTISOINDOLES

The antineoplastic agent mitindomide (**160**) in fact represents the well-known product from irradiation of maleimide in benzene [30]. The activity of this old compound was uncovered by one of the large antitumor screens maintained by the National Cancer Institute. The structure is sufficiently complex and the starting materials sufficiently available to lead one to suspect that the product is still produced photochemically. The product can be rationalized by assuming successive 1,4 and 1,2 additions to benzene. Intermediate **159a** involves the 1,4 followed by 1,2 addition; intermediate **159b** presupposes the steps occur in the reverse order.



28. THIENOTRIAZOLODIAZEPINES

Fusion of an additional heterocyclic ring onto a benzodiazepine is well known to considerably increase potency. This increase in potency is apparently maintained when the benzene ring is replaced by thiophene. Thiophene aminoketone **161** is converted to the benzodiazepine analogue **164** via chloroacetamide **162** and then glycine derivative **163** by the same sequence as that used in the benzene series. Treatment of the product **164** with phosphorus pentasulfide gives the thioamide **165**; reaction of that intermediate with hydrazine leads to the amino amidine **166**. Condensation of this with ethyl orthoacetate gives the anxiolytic agent **brotizolam (167)** [31].



(161)

(162); R = Cl
(163); R = NH_2

(164); R = O
(165); R = S

(166)

(167)

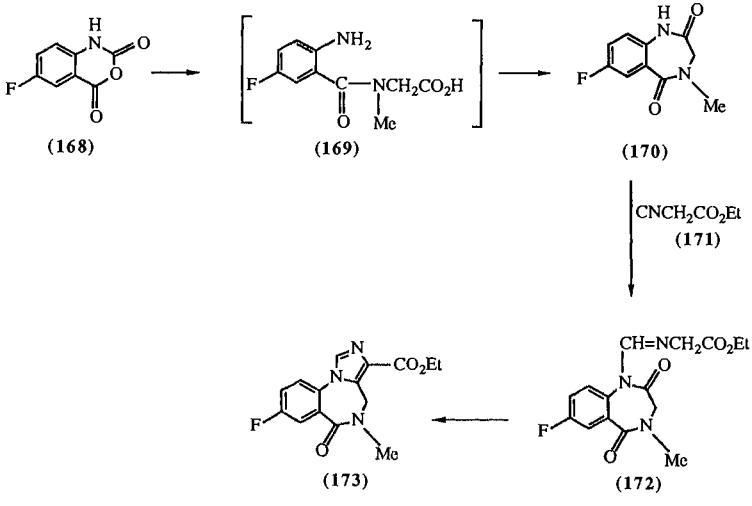
29. IMIDAZOBENZODIAZEPINES

Omission of the pendant aromatic ring from the benzodiazepine structure affords an agent which antagonizes the action of the more classical benzodiazepines at both receptor and whole animal levels. This agent thus finds some use in treatment of tranquilizer overdoses. Reaction of the substituted isatoic anhydride **168** with sarcosine may be envisaged as proceeding initially to the diamide **169** by ring opening by nucleophilic nitrogen. Amide interchange will give the observed product, benzodiazepinone **170**. This intermediate is then condensed with the isonitrile **171**. Addition of nitrogen from the secondary amide to the highly electrophilic isonitrile function will afford the intermediate amidine **172**. This undergoes Claisen type condensation under the reaction

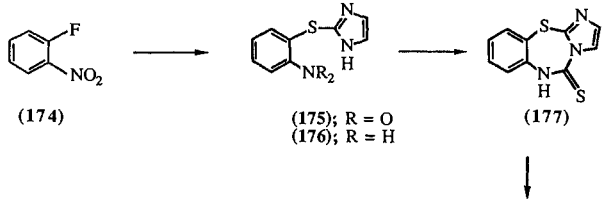
conditions to form an imidazole ring. There is thus obtained **flumazenil (173)** [32].

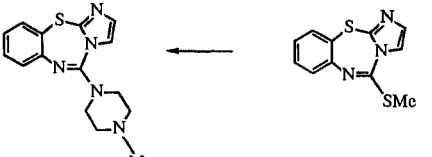
30. IMIDAZOBENZOTHIADIAZEPINES

The breadth of the SAR in the **clozapine** series is demonstrated by the fact that antipsychotic activity is retained when the dibenzdiazepine nucleus of the parent molecule is replaced by an imidazobenzothiadiazepine ring system which contains twice as many hetero atoms. Preparation



of that agent starts with nucleophilic aromatic substitution on 2-fluoronitrobenzene (**174**) by means of imidazole-2-thiol to give sulfide **175**. The nitro group is then reduced to an amine (**176**), and this intermediate cyclized by means of thiophosgene (**177**). Alkylation of the thioamide proceeds on sulfur to give the methyl thioether **178**. Treatment of this last with N-methylpiperazine results in replacement of the thiomethyl group by the piperazine and formation of the antipsychotic agent **pentiapine (179)** [33].





(179) (178)

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