THIONAPHTHEN ISOSTERES OF BIOLOGICALLY ACTIVE INDOLE DERIVATIVES.

A Thesis submitted to the University of Glasgow for the degree of Doctor of Philosophy in the Faculty of Science by

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Summary.

This Thesis is a report of an investigation into the preparation of thionaphthen isosteres of biologically active indole compounds.

The introduction deals with the theoretical implications of the various approaches to the syntheses of biologically active compounds, and in particular those with an indole nucleus present in the molecule. A review on "Biological Activity in Compounds Possessing Thiophen Rings" is included, and justification is provided for the preparation of thionaphthen isosteres of such compounds as 5-hydroxytryptamine.

In section 1, the position of electrophilic substitution in 5-substituted thionaphthens was investigated with a view to employing the various protecting groups in a synthesis of the thionaphthen analogue of 5-hydroxytryptamine. Other interesting orientation effects are also reported.

Section 2 deals with the preparation of various thionaphthen derivatives containing a gramine side-chain as possible antagonists of adrenaline and of 5-hydroxytryptamine.

In section 3, attempts to prepare 3-(2'-aminoethyl)-5-hydroxythionaphthen, the thionaphthen analogue of 5-hydroxytryptamine, are reported. Various other isosteres of 5-hydroxytryptamine-like compounds including 3-(2'-aminoethyl)-6-hydroxythionaphthen are reported. Section 3 also deals with the syntheses of thionaphthen analogues of harmine and harmaline.

Contents.

I Theoretical Considerations.

The major difficulty confronting attempts to design new compounds possessing specifically desired medicinal properties is the lack of a simple correlation between chemical structure and biological activity. In part this may be due to the extensive gaps which exist in our knowledge of the exact manner in which drugs affect the delicately balanced processes that together constitute the normal functioning of tissues. Again, much of the data which is available may not be fully utilised because of our frequent inability to integrate information gained in the different biological disciplines or to weld together the concepts of other scientific endeavours into applicable theories. But even if these handicaps were to be overcome, there are two main reasons why comprehensive structure-action relationships are virtually impossible to establish.

In the first place, the same overall biological effect may be elicited by a variety of mechanisms, and it cannot reasonably be expected that drugs acting by different mechanisms should necessarily show any chemical or physical similarities. A detailed study of

the intimate mechanism by which a drug acts usually necessitates work at the biochemical level, and the issue is then often complicated by the uncertainty of applying results obtained *in vitro* to *in vivo* systems. Moreover, so many facts are often obtained from the *in vitro* system that the basic mechanism involved is not clear because one cannot unambiguously establish the relationship between the primary cause and the resultant effects.

In the second place, numerous factors are simultaneously involved in conferring upon a drug its characteristic mode of action, of which chemical structure is but one, and this cannot be considered out of the context of the other variables. Also, the great sensitivity and delicacy of the animal organism seriously limits intentional variation of such factors as pH, temperature, and osmotic pressure. Thus, the large number of variable factors and the restricted range of intentional variation tolerated *in vivo* hinder the establishment in pharmacology of fundamental quantitative laws capable of mathematical expression such as those characteristic of the more exact sciences of chemistry and physics.

Some of the more important variables known to influence drug action are genetic constitution (comprising species, strain, individual, and sexual differences), tissue constitution, and the weight, age, and condition of health of the test subject. These factors can be collectively grouped as variables inherent in the biological system. By selecting for homogeneity in the biological system, be it whole animal or tissue, one can minimise these variables. There is, however, a residual variation which in practice cannot be eliminated, necessitating analysis of the experimental data by statistical methods before valid conclusions can be drawn. This residual variation may be due to a variety of factors not the least important of which are differences in the rates of absorption, penetration, biotransformation, and elimination of the drug.

Another group of variables which affect drug action are those pertaining to the experimental conditions. These include such factors as the dose and physical state of the drug, the route, frequency, speed and timing of its administration, the dietary history of the experimental animal, the temperature, the

simultaneous presence of other drugs in the system and the pH. Such variables are usually subject to a considerable degree of control.

Finally, there is a third group of factors known to influence drug action - the physico-chemical variables. Although these are uniquely defined for any given substance, they do not necessarily vary in like manner with change in chemical structure, so they must be considered separately when comparison is made between the biological actions of more than one drug. Such variables which include solubilities, distribution coefficients, electrical fields, inductive effects, pK_a's, and steric effects, play an important role in determining the ease with which a drug can penetrate the various permeability barriers in the body (for example, the blood-brain barrier) before reaching its potential site of action.

Despite the non-existence of an overall theory relating drug action to chemical structure, there are, nevertheless, a number of theories of limited application which can be invoked to aid in the design of new biologically active compounds. Among these are the receptor theory of drug action, the theory of metabolite

displacement, and the concept of bioisosterism. Because these three concepts together represent theoretical justification for the present work, they will be briefly summarised.

A. The Receptor Theory of Drug Action.

In general, biologically active compounds can be conveniently considered as belonging to one of two groups - the structurally specific and the structurally non-specific,[1] although as is the case with all biological classifications, there are no hard and fast lines of demarcation between the two groups, one merging into the other by way of compounds possessing intermediate properties. Truly structurally non-specific drugs exhibit biological activity solely by virtue of their favourable physical properties in accordance with the principle so elegantly established by Ferguson,[2] and this activity is quite independent of their functional groups. Examples of such structurally non-specific compounds are to be found in the general anaesthetics such as ether, chloroform, cyclopropane, ethylene dichloride, nitrous oxide, and the inert gases.

Structurally specific drugs on the other hand are thought to exert their effects by interacting with

specific receptors in the tissues which impose restrictions on the size, shape, and electrical properties of molecules capable of complexing with them. The receptor theory has been implicitly accepted by many workers in pharmacology and chemotherapy and related fields for a number of years. It was inherent in the lock and key analogy of Fischer[3] and the concept was used by Clark[4] and others to afford a theoretical basis for the interpretation of experimental dose-response curves. The binding forces of the drug receptor complex are in the majority of cases of such a nature as to be readily reversible at room temperature, and involve energy values of the same order as those of heterogeneous catalysis. The fact that virtually every class of drug can be removed quickly and completely from animal tissue by dialysis or simple solvent extraction supports the contention that electrostatic bonds, multiple van der Waal's bonds, or hydrogen bonds and not covalent bonds are involved in the formation of the receptor complex, although covalent bond formation has been shown to occur in some rather rare instances. Examples of such cases are the interaction of the organic phosphate esters with cholinesterase,[5] the irreversible blockade produced

by the β-haloethylamines,[6] the alkylation of cell constituents by ethyleneimines and the nitrogen and sulphur mustards,[7] and the interaction of arsenoxides, heavy metals, iodoacetic acid and alloxan with sulphydryl groups to form covalent linkages.

Although little is known of the intimate physical nature of drug receptors, attempts have been made to deduce their shape and electric charge distribution from considerations of the charge characteristics and molecular geometry of certain biologically active molecules, based on the assumption that the receptor will have shape and charges complementary to those of the most active species.[8]

Where such an approach is made using non-rigid molecules which are capable of existing in an infinite number of conformations, the conclusions are at best only rough approximations, as there is no reason to suppose that the thermodynamically most stable conformation of the isolated molecule is that actually adopted during complex formation with the receptor. Where rigid molecules have been employed, a more accurate picture of the receptor is to be anticipated. An example of the approach using a rigid molecule is afforded by

the work of Beckett on the nature of the receptor sites involved in analgesia.[9]

Many biologists have now come to regard a receptor as a volume in space defined by the surfaces of enzymes, co-enzymes, and metallic ions, and so think of drugs as exerting their actions primarily on enzyme systems. While it has been undisputedly established that certain drugs do interfere with specific enzymes, it is dangerous to create the generalisation that all drugs necessarily do so. The intimate mode of action of many drugs is still unknown and some may act by merely altering membrane permeabilities by processes that do not involve enzymes. For instance, the mode of action of neuromuscular-blocking agents is thought to involve changes in the electrical potential and the permeability properties of the end-plate region of the muscle membrane by a non-enzymatic process.[10]

B. Metabolite Displacement Theory.

The concept of metabolite displacement[11] contends that certain compounds which possess chemical structure and physical properties similar to those of an "essential metabolite" of the organism, will, by virtue of these similarities, possess a degree of affinity for the

receptor sites at which the metabolite is believed to initiate certain fundamental processes. Originally, the concept was applied only to the phenomenon of competitive inhibition, where the analogue was itself without positive biological activity, but by competing reversibly with the natural metabolite for the available receptors, it was able to prevent this metabolite from fulfilling its normal function. The phenomenon was accordingly termed "biological antagonism".

More recently, however, the concept has been extended[12] to include cases where the analogue is itself able to elicit a response, a measure of its ability to do so being termed its intrinsic activity. It has also been extended to cases where the anti-metabolite combines irreversibly with the receptors.

Antimetabolites are of great interest to the experimental biochemist as they provide a useful means of studying the metabolic pathways of the substance they antagonise, and so contribute to the elucidation of the routes of biosynthesis.[13] They are also of value in demonstrating previously unsuspected functions of well recognised metabolites, and are useful as specific inhibitors of selected enzymes. Again, they are of

interest to the chemotherapist as they offer a possible means of controlling certain pathological processes with the additional advantage that a ready antidote, the metabolite itself, is always available. The early hopes that potent antibacterial drugs could be prepared by suitable alterations in the chemical structure of an essential growth factor of the organism have in general, however, not been realised as the antimetabolite must meet the additional requirement of showing a much higher selectivity of action against the micro-organism than against the tissues of the patient.[14] An example of a series of antimetabolites which do meet this additional requirement is provided by the pantothenic acid analogues used as antimalarials which do not elicit signs of vitamin deficiency in higher animals but do so in micro-organisms.[15]

The intentional design of compounds capable of acting as metabolite-displacing agents is now a well established procedure. The molecules of such compounds must necessarily bear considerable resemblance to those of the compounds which they are designed to displace and are usually related to them by such processes as substitution, homologation, and isomerisation.

Such analogues can be reasonably expected to intensify, mimic, or oppose the biological action of the natural metabolite depending upon their affinities for the receptor and upon their intrinsic activities.

The situation is, however, complicated by the fact that at least three sites may be involved in the biological history of the natural metabolite, and the analogue could conceivably act as a displacing agent at any one of these sites or at any combination of them. The physical and geometrical properties of each of these sites are probably very similar since all are normally concerned in complex-formation with the same molecular species. Firstly there is the binding site which may also be involved in the synthesis of the natural metabolite, and the analogue could act by releasing the metabolite from its bound inactive form. Indeed, certain drugs are known which release such compounds as 5-hydroxytryptamine, adrenaline, and histamine from their binding sites. Secondly there is the receptor site proper at which the metabolite initiates its characteristic train of events and which has already been discussed. Thirdly there is the site at which the metabolite is destroyed. In some cases, this may be

the receptor site itself, but in other cases it would appear to be physically distinct from it - as, for example, in the destruction of acetylcholine at the neuromuscular junction where the enzyme acetylcholinesterase hydrolyses the neurohormone so that its effect is not exerted indefinitely. Anti-cholinesterase drugs act by preventing the degradation of acetylcholine, and it is conceivable that certain metabolite analogues could also act by inhibiting the inactivation of the natural metabolite.

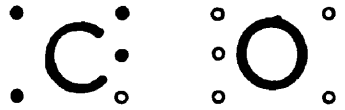
Where a physiologically active substance has more than one site of action, it is possible that the receptors involved in each case may be somewhat different in character. For instance, it has been postulated that there are two types of receptor for adrenaline, and these have been designated the α and β adrenotrophic receptors.[16] There are also indications that the receptors for 5-hydroxytryptamine in the central nervous system are of a somewhat different nature from those involved in the stimulation of smooth muscle.[17] Such variations in the nature of the receptors could create different values for the intrinsic activity and the affinity of the antimetabolite

at each site. The antimetabolite could then reasonably be expected to show quite different actions at the various sites. For example, it might mimic its natural analogue at one site, inhibit it at another, and be totally without effect at a third.

It must always be borne in mind that a new compound, designed as an analogue of a specific metabolite, might exert a completely unexpected biological action due to its ability to act at a totally different set of receptors in the organism. Such a situation arose in the case of the thiambutenes. These compounds which possess marked analgesic properties were originally prepared as potential atropinic, antihistaminic, and local anaesthetic agents on account of their close relationship to the 3,3-diphenylallylamines.

C. Bioisosterism.

One particularly successful approach used to prepare new metabolite-displacing agents is the synthesis of compounds bearing an isosteric relationship to an essential metabolite. The original concept of isosterism, first introduced by Langmuir[18] to express the similarity of physical properties of simple molecules such as carbon monoxide and nitrogen which have identical



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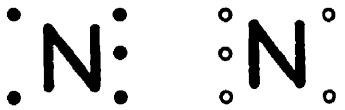

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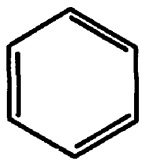

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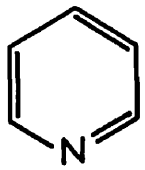

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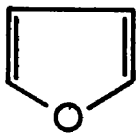

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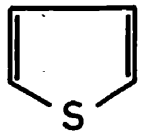


VII

electronic arrangements in the outer or valency shell (as portrayed in the classical manner in figures I and II respectively), has been extended by other workers[19] to include larger molecules whose peripheral layers of electrons are identical. Thus, benzene (III), pyridine (IV), furan (V), pyrrole (VI), and thiophen (VII), each with its 6 π electrons, are considered as being isosteric.

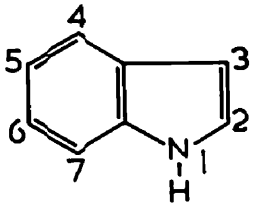
The physical and chemical properties of these five isosteres have long been recognised as being very similar, and it is therefore not surprising that in the case of biologically active compounds possessing one of these rings, considerable attention has been paid to the preparation of isosteres in which this ring has been replaced by one of the others.

Not only will isosteres possess similar electronic arrangements but they will also usually have similar overall electric fields, similar geometric properties, and molecular weights of the same order of magnitude. Hence it is to be expected that variations in physico-chemical properties will be minimised, although not eliminated, enabling a somewhat limited comparison of changes in biological activity with changes in chemical

structure to be made. The idea that isosteres should possess similar biological properties to those of their natural analogues is inherent in the term "bioisosterism" introduced by Friedman.[20] This term covers the case where an isostere opposes the action of the natural metabolite as well as that where it mimics or intensifies it, for as has already been mentioned these different actions depend solely upon the intrinsic activity and the affinity of the isostere for the receptors.

Many thiophen isosteres of biologically active molecules possessing benzene rings have been prepared and tested, and several reviews[21] are available including one[22] prepared especially as background material for this work and which is included in this thesis as appendix I.

Scant attention has been paid, however, to the isosteric replacement of pyrrole rings by thiophen rings in molecules of biologically active compounds. In particular, little work has been done on the study of isosteres of indole derivatives which as a class represent a group of considerable biological interest. It was therefore deemed worthwhile to prepare thionaphthen



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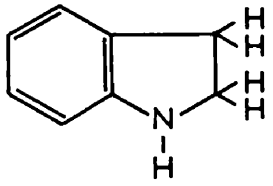

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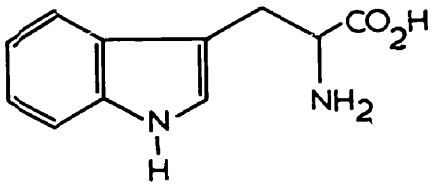

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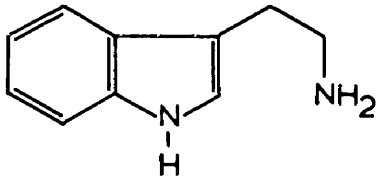

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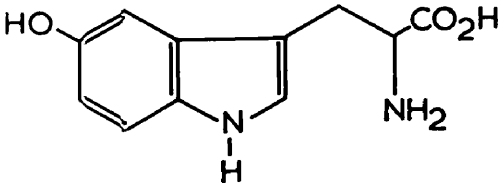

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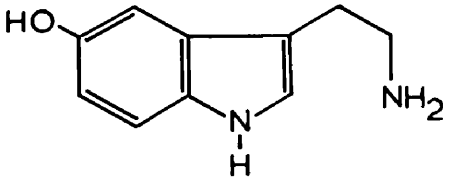


XIII

isosteres of some of the simpler indole compounds. In order that this work may be seen in its correct perspective, a brief summary of the biological importance of indole derivatives is given followed by an account of the thionaphthen isosteres already reported.

II Biological Activity in Compounds Possessing the Indole Nucleus.

The indole nucleus (VIII) and the related indoline or 2,3-dihydroindole nucleus (IX) occur in the molecules of a large number of natural products[23] many of which are of pharmacological importance. These indole and indoline derivatives exhibit a wide range of chemical complexity from the simple alkaloid gramine and the essential amino-acid tryptophan on the one hand to the extremely complex alkaloids of calabash curare on the other.

The parent compound indole is itself without great biological significance but it has been reported[24] to affect the motor elements of the spinal cord in rabbits and mice.

Like all other essential amino-acids, tryptophan (X)

which is regarded as the biogenetic precursor of the naturally occurring indole derivatives, is without pharmacological action, but the related decarboxylation product tryptamine (XI), in common with other proteinogenic amines such as histamine, dopamine, and tyramine possesses pharmacological activity. Tryptamine is a weak pressor agent, exerting its effect by a nicotine-like mode of action.[25] It has also been shown to exert a stimulant action on the mammalian heart and respiratory receptors,[26] but the latter finding is complicated by the fact that tryptamine is known to procure the release of histamine.[27]

5-Hydroxytryptophan (XII) is of considerable interest as it can readily cross the blood-brain barrier, and undergo *in vivo* decarboxylation into 5-hydroxytryptamine (XIII) in the central nervous system,[28] whereas 5-hydroxytryptamine is itself virtually unable to penetrate this barrier.

5-Hydroxytryptamine (*syn.* serotonin or enteramine) is of considerable interest to the animal physiologist. It occurs predominantly in the central and peripheral nervous systems,[29] the blood platelets,[30] and in the enterochromaffin cells of the gastro-intestinal tract.[31]

5-Hydroxytryptamine has a stimulant action on smooth muscle[26] and it exhibits both hyper- and hypotensive actions in the cat, dog, and man. It has been claimed to produce constriction of the renal vascular beds with consequent antidiuresis, and this action has been suggested as a physiological role of the compound.[32] It has also been suggested that it may function as a local hormone involved in gastro-intestinal motility.[31] 5-Hydroxytryptamine has been postulated to be involved in stress,[33] and it has been shown to be a potent pain-producing agent in the blister test.[34]

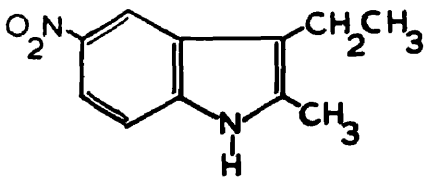
The greatest interest in 5-hydroxytryptamine, however, is in its role in the central nervous system, and it is of extreme importance from the psychopharmacological point of view. It is known to be released from its bound form in the brain under the influence of the tranquillising alkaloids of Rauwolfia,[35] and by the analeptic drug amphetamine.[36] The exact function of 5-hydroxytryptamine in the brain is, however, by no means clear. Direct injection of the compound into the lateral ventricles of the cat has been shown to produce lethargy, anxiety, and muscular weakness together with an ability to maintain strange body

postures reminiscent of those maintained by catatonic schizophrenics.[28] Intraventricular injection of 5-hydroxytryptamine also prolongs barbiturate sleeping time.[37]

Free 5-hydroxytryptamine is destroyed in the organism by monoamine oxidase, 5-hydroxy-3-indole acetic acid being one of the end products. As Woolley and Shaw have produced evidence[38] to show that some mental disorders may arise from a deficiency of 5-hydroxytryptamine, attempts have been made to increase the concentration of free 5-hydroxytryptamine in the brain by inhibiting its destruction by monoamine oxidase with iproniazid.[39]

The accumulated facts and theories concerning 5-hydroxytryptamine have been the subject of several reviews,[40] and an excellent account of its biochemistry and biogenesis has recently appeared.[41] It is interesting to note too that recently there have been speculations that related ortho-dihydroxyindolalkylamines have physiological functions in insects[42] and crustacea.[43]

Many simple synthetic indole derivatives have been prepared as potential antimetabolites of 5-hydroxy-tryptamine.[17,44,45,46] These compounds have usually been



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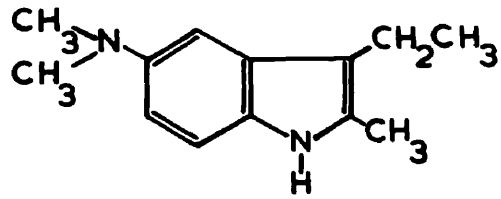

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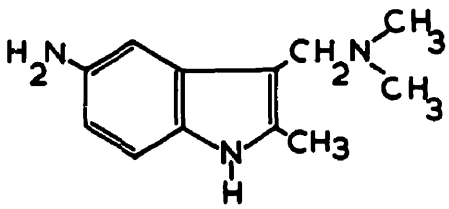

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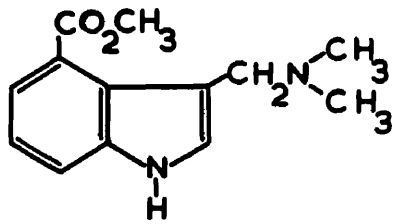

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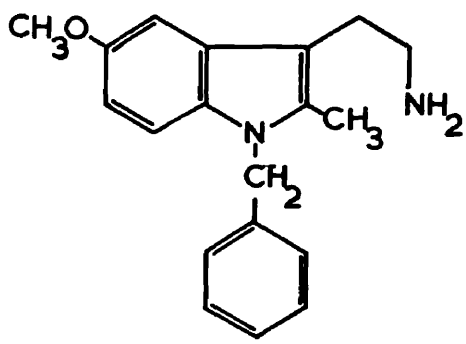


XVIII

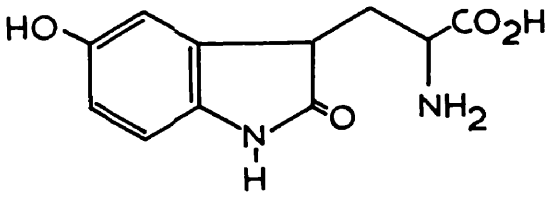
derivatives of tryptamine or gramine, and a number do indeed effectively antagonise the action of 5-hydroxytryptamine on smooth muscle. Some of the compounds also have psychotomimetic action. It is of considerable theoretical interest that these synthetic derivatives may show different activities on different preparations or on the same preparation when administered in different concentrations. Thus, 3-ethyl-2-methyl-5-nitroindole (XIV) opposes the pressor action of 5-hydroxytryptamine in the dog, but mimics the action of 5-hydroxytryptamine on the clam heart,[47] and 5-dimethylamino-3-ethyl-2-methylindole (XV) inhibits the action of 5-hydroxytryptamine on the rat uterus, but will itself produce contractions at slightly higher concentrations. These examples can be interpreted as showing that the nature of the 5-hydroxytryptamine receptor site varies in the different tissues and this is reflected in differences in the affinities and intrinsic activities of the pharmacon. Indeed, Gaddum has postulated[17] that at least two distinct types of 5-hydroxytryptamine receptor exist.

Other simple synthetic antagonists of 5-hydroxytryptamine worthy of mention are 5-amino-2-methylgramine

(XVI),[46] 4-carbomethoxygramine (XVII),[48] and 1-benzyl-2-methyl-5-methoxytryptamine (XVIII) which is a potent peripheral antagonist of 5-hydroxytryptamine and has been used as an antihypertensive agent.[47,49] It appears to have no central effects unless given intraventricularly.

Certain more complex indole derivatives also appear to be able to antagonise 5-hydroxytryptamine. Of these, lysergic acid diethylamide and 2-bromolysergic acid diethylamide are the most important. Lysergic acid diethylamide is a potent hallucinogen[50] and is also a potent antagonist of the action of 5-hydroxytryptamine on smooth muscle.[51] 2-Bromolysergic acid diethylamide on the other hand does not readily produce mental changes in man, but it is even more potent than lysergic acid diethylamide as an antagonist of the peripheral actions of 5-hydroxytryptamine.[52] These facts would seem to be adequately explained on the basis of the different receptors involved being such as to create different affinities and intrinsic activities in the bromo derivative with respect to the two sites of action.

The role of lysergic acid diethylamide in the



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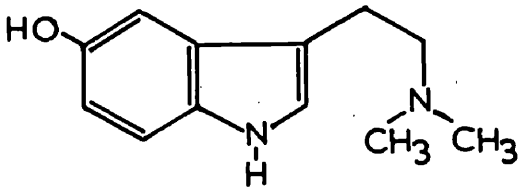

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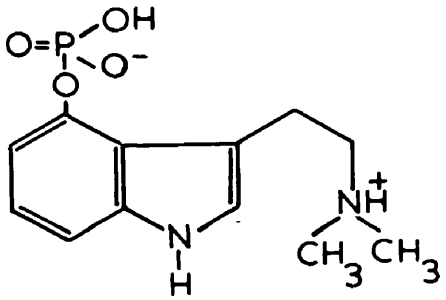
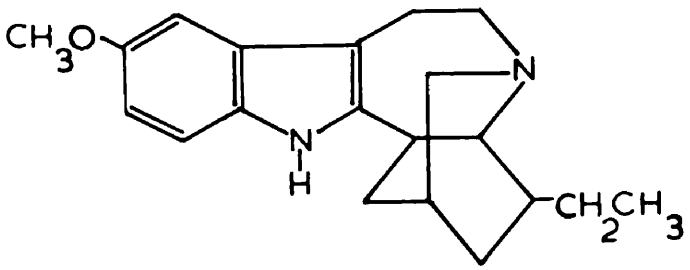


XXI



XXII

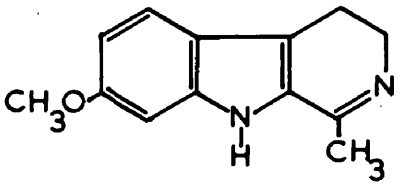
production of mental disturbances has been well reviewed by Rothlin.[53] Many other lysergic acid derivatives also antagonise 5-hydroxytryptamine.[54] Recent work, however, would tend to show that the psychological effects of lysergic acid diethylamide do not result from a simple antagonism to 5-hydroxytryptamine.[55]

Yet other indole derivatives have been synthesised and tested, not for their ability to antagonise the actions of 5-hydroxytryptamine, but for their ability to inhibit the biogenesis and degradation of 5-hydroxytryptamine in the body. Prominant amongst these are various oxindole derivatives[56] which proved to inhibit the action of monoamine oxidase. 5-Hydroxyoxindole-3-DL-alanine (XIX) is noteworthy in that it produces an *in vitro* inhibition of 5-hydroxytryptamine decarboxylase.

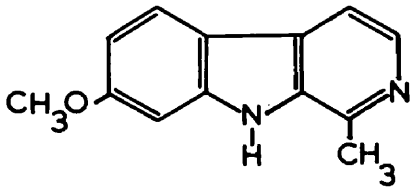
Ability to mimic the actions of 5-hydroxytryptamine or to interfere with its normal metabolism is not confined to synthetic indole derivatives. Many naturally occurring indole derivatives also appear to share these properties. For instance, bufotenine (XX) which occurs both in *Piptadinia perigrina* (long used in

the form of Cohoba snuff in religious rites by some American Indian cults) and in the skin glands and venom of toads, produces bronchoconstriction similar to that produced by 5-hydroxytryptamine.[57] It also produces central nervous system effects in monkeys,[58] and on intravenous injection into man it produces hallucinogenic effects similar to those brought about by mescaline and lysergic acid diethyl-amide although the onset of activity is more rapid and the duration of action shorter.[57]

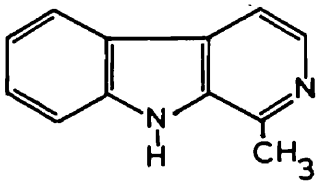
Another psychotomimetic indole alkaloid is psilocybin (XXI) which is obtained from the Mexican mushroom Psilocybe mexicana[59] and which is also stated to possess slight sympathomimetic activity.[60] In this connection it may be noted that there are several observations pointing to a similarity in the nature of the receptor sites for 5-hydroxytryptamine and adrenaline. For example, yohimbine is both an adrenergic blocking agent and a potent 5-hydroxytryptamine antagonist,[61] and the structurally related alkaloid reserpine is known to displace 5-hydroxytryptamine from its binding sites.[62] Similarly, the polypeptide ergot alkaloids are antagonists of both adrenaline



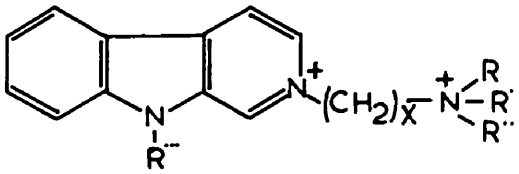
XXIII



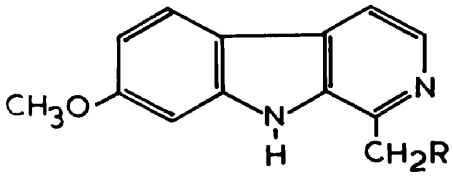
XXIV



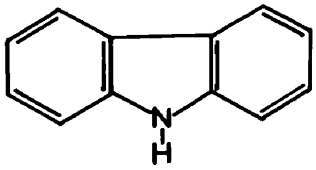
XXV



XXVI



XXVII

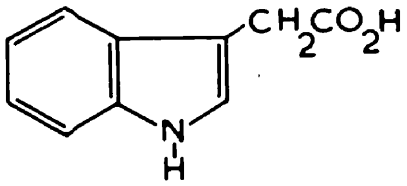


XXVIII

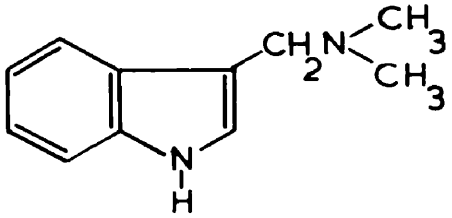
pressor activity and of the peripheral actions of 5-hydroxytryptamine, whilst the simple amide ergonovine shows greater potency against 5-hydroxytryptamine than against adrenaline.[63] The related lysergic acid diethylamide, as well as being a potent inhibitor of 5-hydroxytryptamine, possesses adrenergic blocking activity[64] in addition to some sympathomimetic properties.[65,66]

Ibogaine (XXII), the principal alkaloid of Tabernanthe iboga Baillon,[67] is a central nervous system stimulant[68] and a mild hallucinogen,[69] and so this compound too may interfere with the normal metabolism of 5-hydroxytryptamine. A more general study of its pharmacological actions was made by Raymond-Hamet and Rothlin.[70]

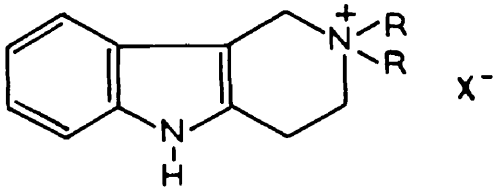
The alkaloids harmaline (XXIII) and harmine (XXIV), which have been isolated from the seeds[71] and roots[72] of Peganum harmala L., also antagonise 5-hydroxytryptamine.[47] Other investigations[73] of the pharmacological actions of these alkaloids have shown that they possess coronary-dilator, cardiotoxic, oxytocic, convulsant and muscle relaxant properties which are qualitatively similar in the case of harmine, harmaline, and tetrahydronorharman. Harman (XXV) potentiates the hypertensive



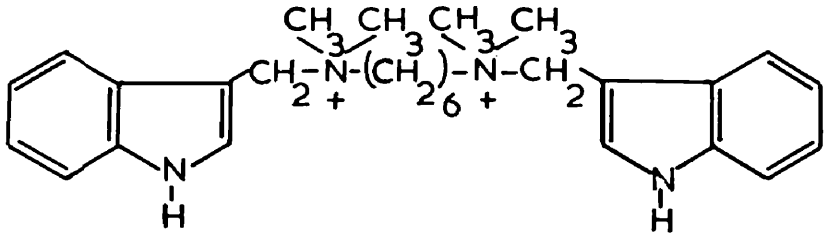
XXIX



XXX



XXXI



XXXII

effects of adrenaline,[74] while harman methosulphate in combination with adrenaline produces ventricular fibrillation in cats and dogs under pentobarbitone anaesthesia.[75] Harmine and harmaline produce tremor in experimental animals.[76]

It has been suggested that the harmala alkaloids act by uncoupling oxidative phosphorylation.[77]

A series of synthetic harmol ethers were found to possess amoebicidal activity.[78] Compounds of type XXVI have been shown to possess hypotensive properties,[79] and in the patent literature there is a claim that compounds of type XXVII possess tranquillising activity.[80]

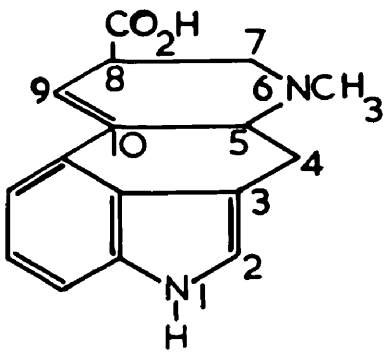
A structure closely allied to harman is carbazole (XXVIII), and various carbazole derivatives are claimed to possess powerful local anaesthetic activity.[81]

Pharmacological interest in the naturally occurring indole compounds is by no means confined to those which have the ability to interfere with the normal functioning of 5-hydroxytryptamine.

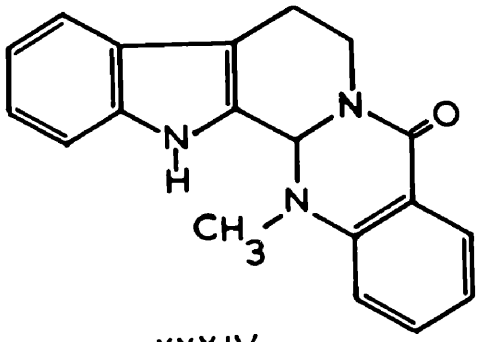
One particularly interesting simple indole derivative is 3-indole acetic acid (XXIX) which is an auxin or plant growth hormone.

The simplest true indole alkaloid is gramine (XXX) which occurs in sprouting barley[82] and in the leaves of Arundo donax.[83] Gramine has a pressor action but it would not appear to be truly sympathomimetic as it exerts no action on the pupil of the rabbit's eye.[84] In general, it stimulates smooth muscle, but the tonus and movements of the rabbit intestine are inhibited.[84] Large doses of gramine produce clonic convulsions and stimulation of the respiratory centre.[26,85] Gramine is also claimed to have a feeble parasympathomimetic action.[85]

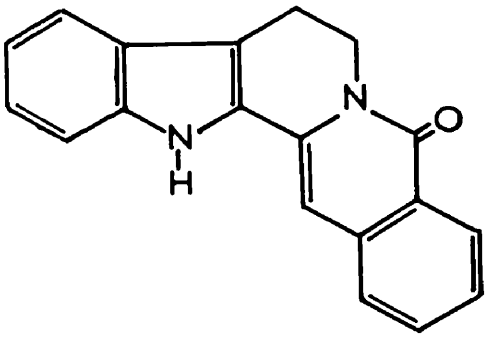
Apart from the synthetic derivatives of gramine which behave as 5-hydroxytryptamine antagonists, others have proved to be oxytocics[86] and local anaesthetics.[87] A series of quaternary ammonium salts derived from gramine have been prepared for testing as neuromuscular blocking agents[88] on account of their relationship as model compounds to the then postulated structure of the calabash curare alkaloid, C-curarine I chloride. Various quaternary β and γ-carboline derivatives (XXXI) of gramine have also been prepared and tested for neuromuscular blocking activity.[89] Other quaternary salts have been reported including the gramine derivative of



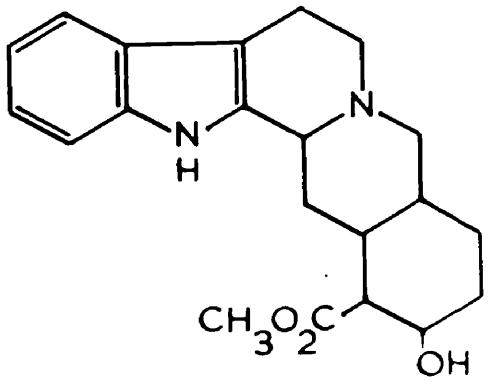
XXXIII



XXXIV



XXXV



XXXVI

hexamethonium (XXXII).[90]

An important group of indole alkaloids occurs in ergot, the sclerotium of the fungus Claviceps purpurea which grows parasitically on the pistils of many grasses and cereals, especially rye. The extremely poisonous nature of ergot has long been recognised and the ergot alkaloids have been the subject of several reviews.[65,66,91] Actually, two series of indole alkaloids occur in ergot. The pharmacologically active alkaloids are all laevorotatory and are derivatives of lysergic acid (XXXIII), several synthetic derivatives of which have already been mentioned. The dextrorotatory alkaloids are derivatives of isolysergic acid which is the C-8 epimer of lysergic acid.

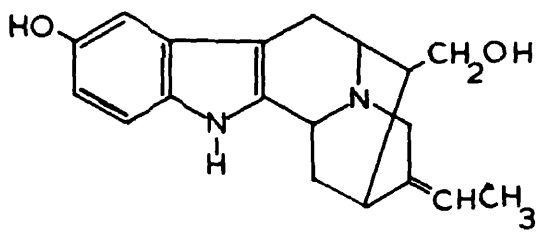
The most important ergot alkaloids from the biological point of view are ergotamine, ergocornine, ergocristine, ergokryptine, and ergonovine (syn. ergometrine). The first four, which are all complex polypeptide derivatives of lysergic acid, possess adrenergic blocking activity, an action even more pronounced in their 9,10-dihydro derivatives.[92]

In addition to their adrenergic blocking properties, the polypeptide alkaloids also show similarities to adrenaline at certain receptors and

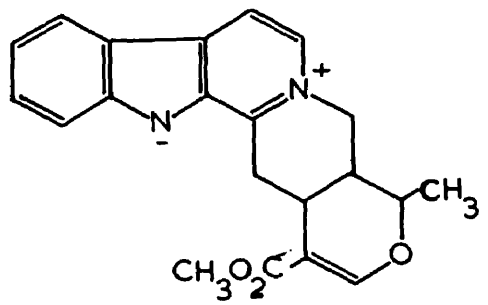
produce an intense peripheral vasoconstriction which is responsible for the gangrene characteristic of severe ergot poisoning. They also stimulate smooth muscle[65] and exert a complex action on the central nervous system. Ergotamine can be effective in relieving migraine, but the mechanism of action is obscure.

Ergonovine, the simplest of the ergot alkaloids, is the amide of lysergic acid and 2-aminopropanol. It has pronounced oxytocic activity and was at one time used to quicken child-birth. This use however led to many still-births and to-day ergonovine is employed only to control post-partum haemorrhage.

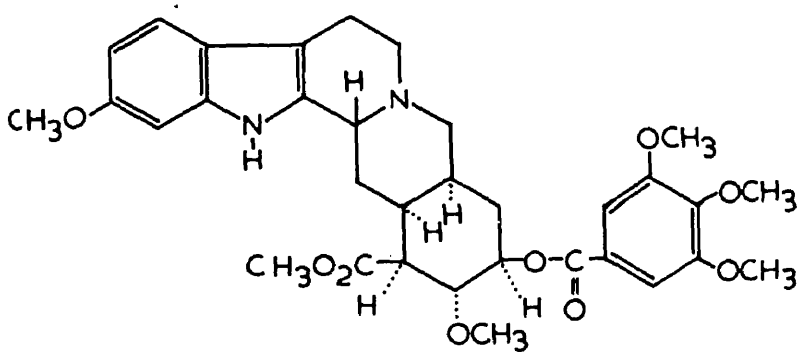
The Chinese drug Wu Chu Yu, formerly used as a stimulant, carminative, deobstruent, stomachic, astringent, and anthelmintic remedy,[93] consists of the dried fruit of Evodia rutaecarpa Hook f. and Thoms, and has been shown to contain the indole alkaloids evodiamine (XXXIV) and rutaecarpine (XXXV).[94] Because of the structural similarity, the pharmacological properties of evodiamine and rutaecarpine were compared with those of yohimbine, and they were shown to increase the arterial blood pressure. They do not, however, have the adrenergic blocking action of yohimbine.



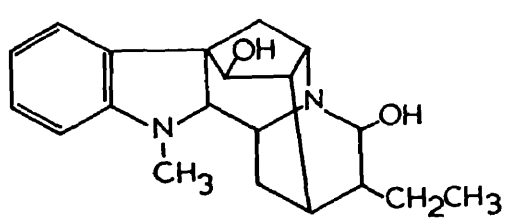
XXXVII



XXXVIII



XXXIX



XL

The alkaloid yohimbine (XXXVI), obtained from the bark of Pausinystalia yohimba Pierre, (syn. Corynanthe yohimbe K.Schum) a tree indigenous to the Cameroons and the French Congo, possesses a variety of pharmacological actions including in addition to its anti-5-hydroxytryptamine activity already mentioned, anaesthetic activity. It opposes the action of adrenaline and its vasodilator activity is particularly pronounced in the genital organs, the resulting stimulation leading to its use as an aphrodisiac in veterinary practice.

The related alkaloid sarpagine (XXXVII)[95] is also an adrenergic blocking agent,[96] and ajmalicine (XXXVIII) has adrenergic blocking properties equal in potency to those of the dihydroergot alkaloids.

Several 17-alkylaminoyohimbans have been prepared as potential hypotensives.[97]

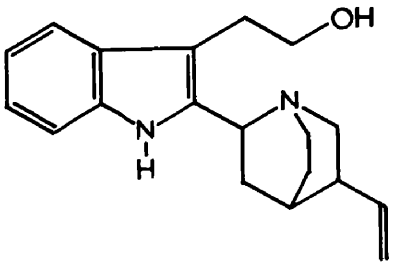
Other complex indole alkaloids are found in various species of Rauwolfia. Reserpine (XXXIX) and rescinnamine are of interest on account of their tranquillising properties and hypotensive action. As previously mentioned, these alkaloids also possess the ability to release 5-hydroxytryptamine both in the

brain and from the blood platelets.

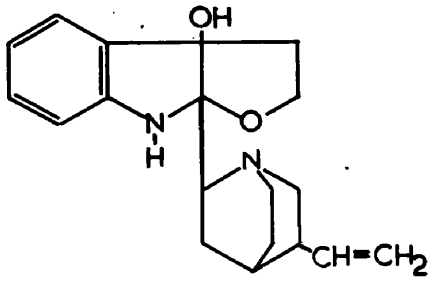
The hypotensive effects are mediated by the action of the alkaloids on the autonomic nervous system. They produce an increase in tonic parasympathetic activity and a decrease in tonic sympathetic activity of the cardiovascular and gastro-intestinal systems, giving a fall in blood pressure and increased gastro-intestinal motility.[96,98] Various simple gramine and tryptamine models of the Rauwolfia alkaloids have been prepared,[99] and various reserpine analogues including 18-O-(3,4,5-trimethoxybenzoyl)-reserpic acid have also been prepared in the search for enhanced sedative or hypotensive activity.[100]

The indoline derivative ajmaline (XL) which occurs with reserpine and rescinnamine in nature is without sedative[35] or hypotensive[101] action, and in large doses actually has a pressor action.

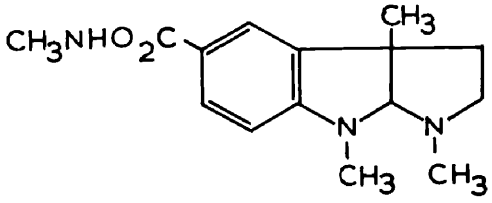
Although the majority of the Cinchona alkaloids are quinoline derivatives, they are postulated to arise in nature from indolic precursors,[102] and several are themselves indole derivatives. One such alkaloid is cinchonamine (XLI) which like quinine is a general protoplasmic poison, has antimalarial activity, and



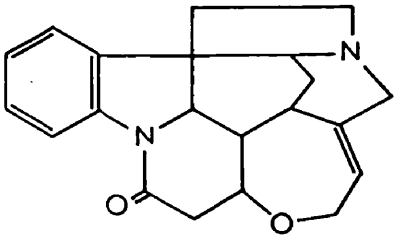
XLI



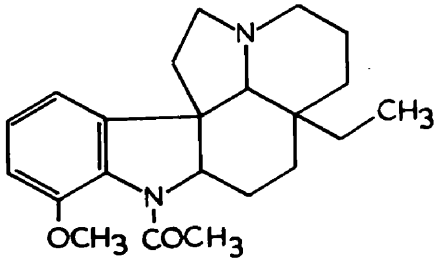
XLII



XLIII



XLIV



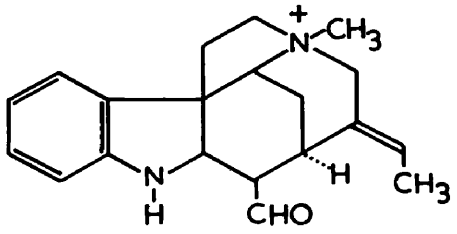
XLV

exerts a powerful action on the heart.[103] It is some six times as toxic as quinine and possesses pronounced central convulsant properties. The indoline derivative quinamine (XLII) has similar biological properties.

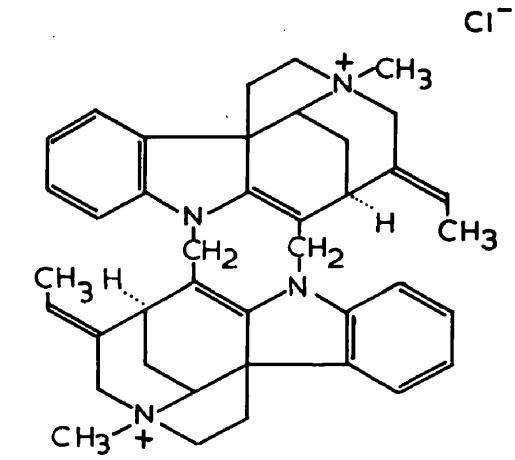
Several other indoline alkaloids are of considerable pharmacological importance. These include the anticholinesterase physostigmine (XLIII), first isolated in 1864 from the calabar bean (Physostigma venenosum),[104] and strychnine which together with brucine and related alkaloids occurs in the seeds of the Indian tree Strychnos nux vomica and whose structure (XLIV) was finally established by Woodward.[105] The predominant action of strychnine is to produce marked stimulation of the spinal cord. Its pharmacology is well summarised by Bogdanski et al.[106]

The structure of the indoline alkaloid aspidospermine (XLV) has recently been elucidated.[107] This compound occurs in the bark of Aspidosperma quebracho blanco and has been shown to reverse the constrictor responses of the perfused blood vessels of the rabbit's ear and the rat hind quarters to adrenaline.[108]

The alkaloids of Calabash curare are powerful

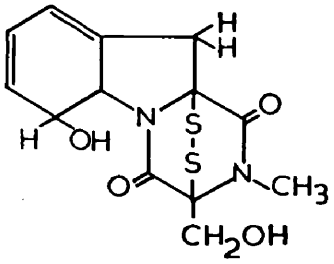


XLVI

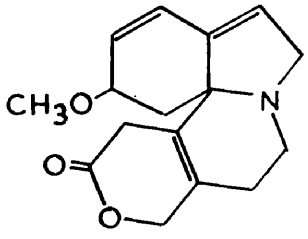


Cl^- Cl^-

XLVII



XLVIII



IL

poisons with potent neuromuscular blocking activity,[109] and nearly all appear to be indoline derivatives.[110] Examples are C-fluorocurarine (XLVI) also known as C-curarine III,[111] and the dimeric toxiferine I (XLVII).[112] Toxiferine I has been shown to be active in the mouse head-drop test at dosage levels of 9 μg. per Kg.,[113] and so is one of the most potent pharmacologically active alkaloids known.

Two alkaloids also worthy of mention although not strictly true indoline derivatives are gliotoxin and β-erythroidine. Gliotoxin, first isolated from the culture fluid of an organism believed to be Gliocladium fimbriatum but more probably Trichoderma viride, has been shown to possess the modified indoline structure XLVIII.[114] It is highly bacteriostatic towards Gram positive bacetria and remarkably effective against fungi, although too toxic to be of therapeutic value.[115] It has, however, seen application against certain plant pathogens.[116] β-Erythroidine (IL) and its dihydro-derivative are of interest as the tertiary bases are more potent as neuromuscular blocking agents than are their derived quaternary salts. The mechanism of action of the dihydro compounds has recently been shown to be similar to that of d-tubocurarine.[117]

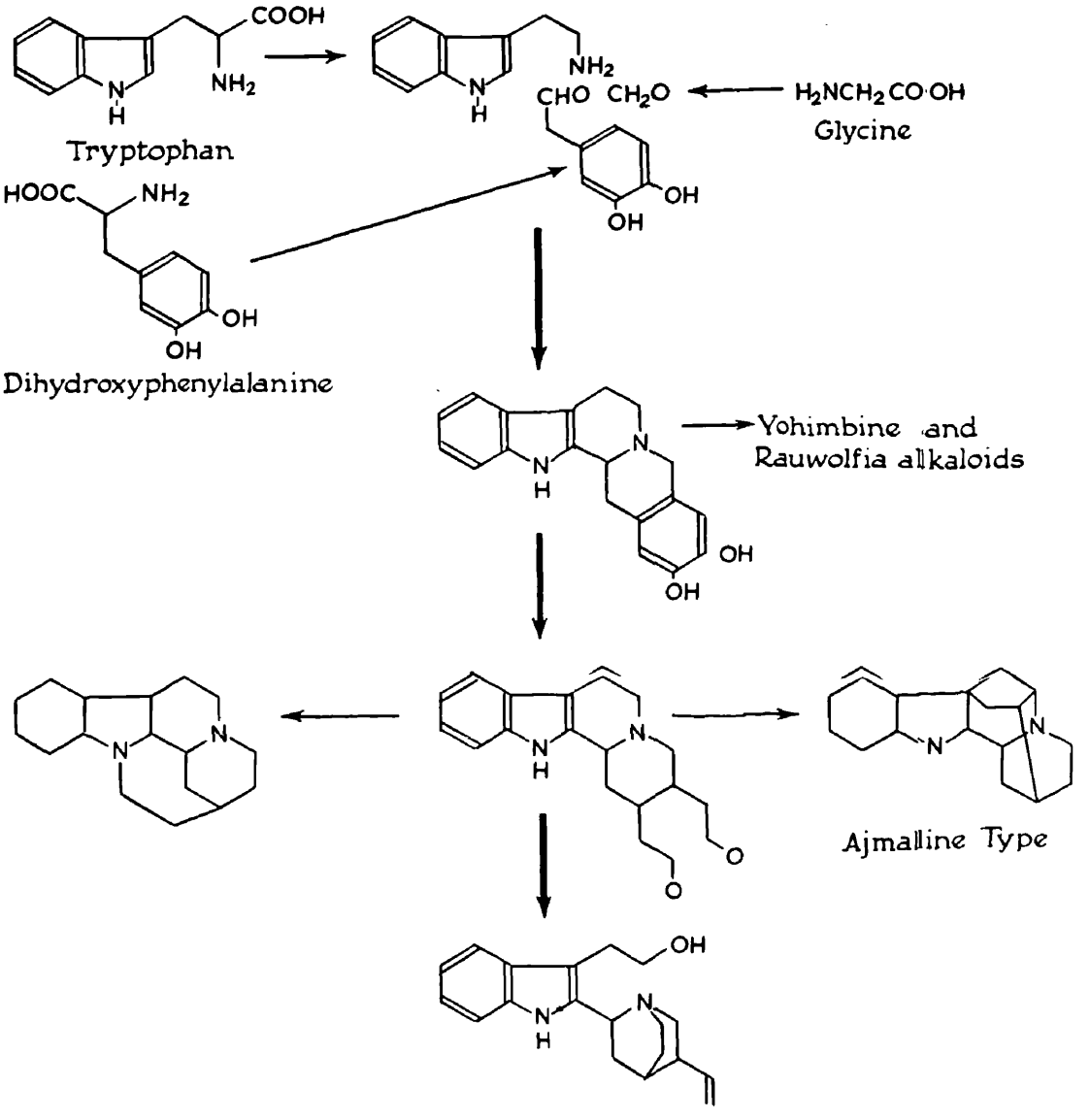

COOH
NH2
N
H
Tryptophan
NH2
CHO CH2O
H2NCH2CO·OH
Glycine
HOOC
NH2
OH
OH
Dihydroxyphenylalanine
OH
OH
Yohimbine and
Rauwolfia alkaloids
O
O
OH
Ajmalline Type

Table 1

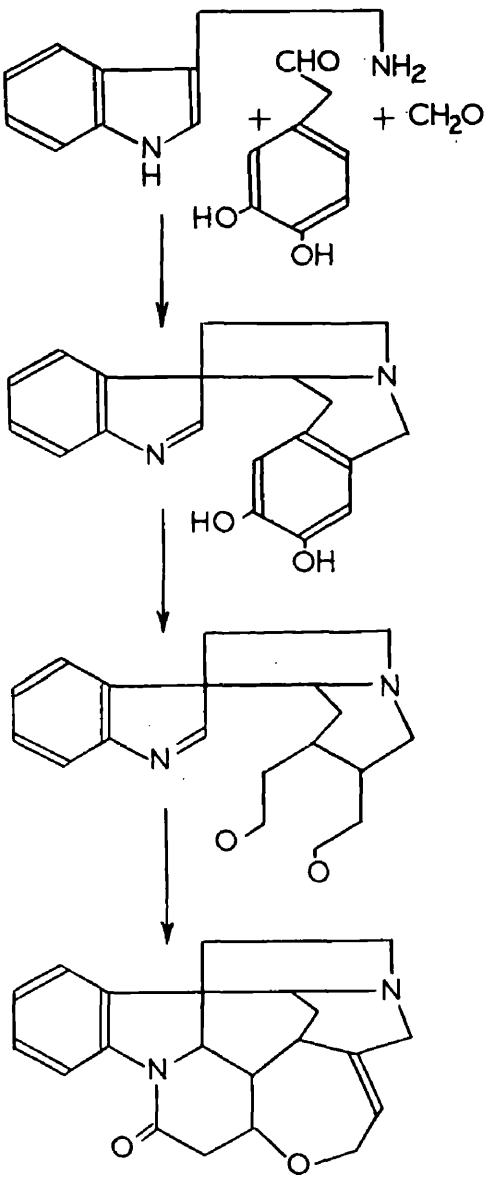
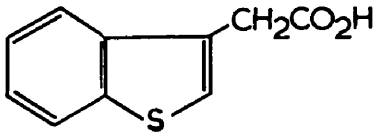


Table 2

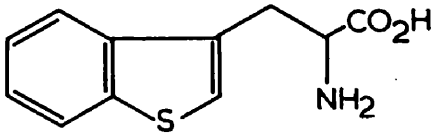
As mentioned previously, all the indole alkaloids are considered to arise biogenetically from tryptophan,[102,118] and in the case of gramine, this relationship was conclusively proved several years ago by means of the radioactive tracer technique.[119] More recently, it has been shown[120] also by radioactive tracer technique that tryptophan is a direct precursor of the reduced β-carboline nucleus of ajmaline. This observation is of the utmost importance as it is the first experimental verification of the hypothesis that tryptophan is involved in the biosynthesis of the complex indole alkaloids.

Tables I and II show the classical schemes by which biogenesis is assumed to occur in the case of the more complex alkaloids such as cinchonamine and strychnine, and the ajmaline and rauwolfia types.

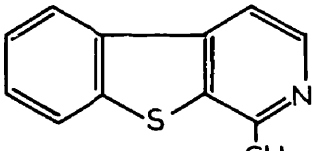
However, certain shortcomings in these biogenetic schemes have been pointed out by Wenkert and Bringi,[121] who feel that the state of oxidation in ring E, the absolute configuration of C-15, and the origin of the carbomethoxy group in the yohimbine nucleus, are not fully explained by the classical hypothesis, and they have suggested that shikimic acid



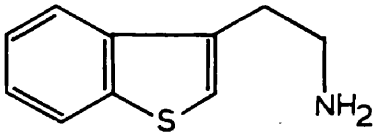
L



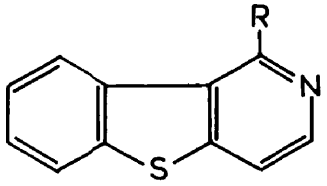
LI



LII

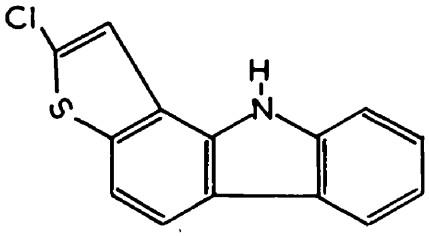


LIII



R = H, CH_3, Ph

LIV



LV

might well replace dihydroxyphenylalanine in the biogenetic scheme. Support for this view comes from the report that shikimic acid is a natural progenitor of the aromatic amino-acids.[122]

III Thionaphthen Isosteres of Indole Derivatives.

As previously stated, relatively little work towards the preparation of thionaphthen isosteres of indole compounds appears to have been recorded so far.

3-Thionaphthen-acetic acid (L) was synthesised from thionaphthen by Crook and Davies,[123] and was found to have much smaller growth-promoting activity than the naturally occurring plant growth hormone, 3-indole acetic acid.[124] Further work by Kefford and Kelso[125] resulted in the syntheses of 2, 3, 5, 6, and 7-thionaphthen acetic acids. They reported the 3- and 7-substituted acids to be somewhat similar in plant-growth regulating activity to 3-indole acetic acid, while the 2, 5, and 6-isomers had the same order of activity as 2,4-dichlorophenoxyacetic acid.

The thionaphthen isostere of tryptophan, β-3-thionaphthenyl-DL-alanine (LI),[126,127] was shown to

be an effective antagonist to tryptophan in the micro-organism Lactobacillus arabinosus.[128] It was also found to have a significant bacteriostatic action against S. haemolyticus, but not to inhibit the growth of S. Aureus or E. Coli.[126] Inhibition of the root growth of cucumber plants, proportional to the concentration of β-3-thionaphthenyl-DL-alanine, has also been reported.[129]

The presence of the β-carboline nucleus in a number of alkaloids inspired Herz to investigate related thionaphthen compounds as potentially active agents.[130] Thus, he prepared the harman analogue (LII) via 3-(2'-aminoethyl)-thionaphthen (LIII), the thionaphthen isostere of tryptamine. The syntheses of thionaphtheno-(2,3-C)pyridine (LIV) and certain derivatives have also been reported.[131]

5-Aminothionaphthen, like 2-naphthylamine, is reported[132] to inhibit the growth of the tubercle bacillus.

Certain thionaphthen isosteres of carcinogenic indole derivatives have been prepared.[133] Preliminary experiments suggest that some of these thionaphthindoles may possess growth-inhibitory action on experimental tumours. Halogen substituted thiophen-carbazoles, for

example 5'-chloro-3',2':1,2-thiophen-carbazole (LV), have also been reported as potential carcinogens.

Apart from these derivatives bearing an isosteric relationship to biologically active indole derivatives, other thionaphthen compounds have been prepared and tested in their own right. These include thionaphthen[134] and dibenzothiophen[135] which are pesticides, 5-methyl-4,7-thionaphthenquinone - the isostere of menadione,[136] the thiophen analogue of 3-deoxyequilenin,[137] and certain β-haloethylamine derivatives of thionaphthen of the dibenamine type.[138]

IV Object of Research.

The object of this thesis, therefore, was to continue the syntheses of thionaphthen isosteres of biologically active indole compounds, and in particular those which might be expected to complex with the receptors for 5-hydroxytryptamine, as these compounds might well shed more light on the physiological significance of this compound. Particular attention was paid to thionaphthen derivatives possessing substituents in the 5- and 6-positions as the presence

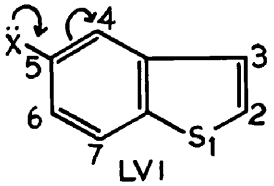
of an oxygenated function in either or both of these positions in the natural indoles is common, and would seem to play an important biological role.

The introduction of substituents into the 5-position of the thionaphthen ring system necessitated an investigation of orientation effects. These are discussed in section 1.

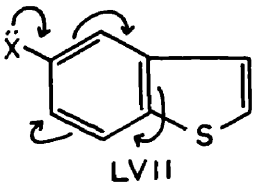
Section 2 is concerned with the preparation of isosteres of gramine derivatives as potential antagonists of both 5-hydroxytryptamine and adrenaline, and section 3 deals with the attempted synthesis of 3-(2'-aminoethyl)-5-hydroxythionaphthen and the syntheses of related compounds.

Section 1.

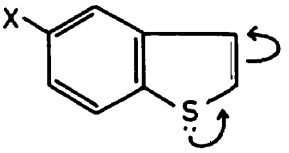
Orientation Studies in 5-Substituted Thionaphthen Derivatives.



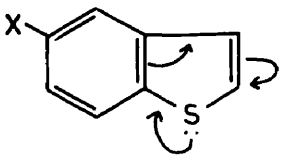
LVI



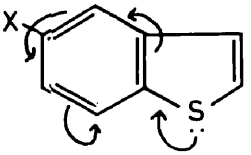
LVII



LVIII



LIX



LX

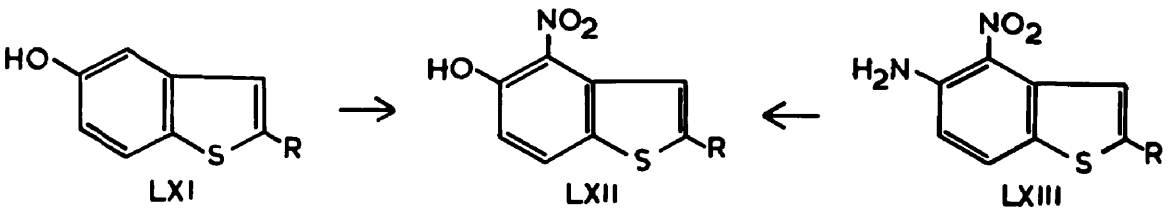
Because all five of the unsubstituted positions in 5-substituted thionaphthens, where the substituent is a group capable of electron donation, are theoretically activated in varying degrees towards electrophilic attack (LVI to LX), a study was made of the influence of variation in the 5-substituent upon the position taken by the entering group. The feasibility of using various protecting groups in the proposed syntheses of the compounds described in sections 2 and 3 could then be evaluated.

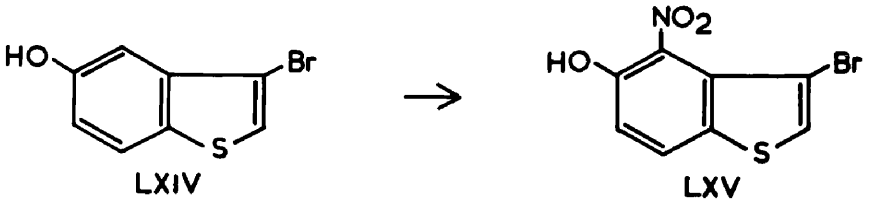
Previous investigations have shown that for a strongly electron-donating group in the 5-position, the order of importance of the activating influences is LVI > LVII > LVIII > LIX > LX. Thus, 5-amino- and 5-hydroxythionaphthen[139] and the corresponding 2-carboxy derivatives[140] are known to undergo monobromination in the 4-position. Although 5-acetamidothionaphthen and 5-acetamidothionaphthen-2-carboxylic acid also suffer electrophilic attack in the 4-position, bromination of 5-acetoxythionaphthen is known to take place in the 3-position.[139] It is thus apparent that the difference in the ability of the acetamido and acetoxy groups to release electrons is sufficient to allow a chahge from

the predominance of activating influence LVI to that of activating influence LVIII. Influence LVIII is the most powerful influence in thionaphthen itself,[141] and in 5-nitrothionaphthen[142] where the 5-substituent is an electron-withdrawing group.

That activating influence LVII is stronger than activating influence LVIII where there is a strongly electron-donating 5-substituent, despite the fact that the transition state involves disruption of the resonance stabilisation of the thiophen ring, is indicated by the formation of 4,6-dibromo derivatives on further bromination of 4-bromo-5-hydroxythionaphthen and of the corresponding 2-carboxylic acid.[143] Additional evidence for activation at the 6-position is to be found in the rearrangement of 4-allyl-5-allyloxythionaphthen to 4,6-diallyl-5-hydroxythionaphthen.[139]

The evidence for concluding that the remaining influences are in the order LVIII > LIX > LX for 5-substituted thionaphthens where the substituent is strongly electron-donating rested solely on the results of bromination experiments with 4,6-dibromo-5-hydroxythionaphthen.[143] On further bromination in acetic acid in the absence of acetate ion, 4,6-dibromo-5-hydroxythionaphthen affords


HO
S
R
LXI
NO2
HO
S
R
LXII
H2N
NO2
S
R
LXIII


HO
Br
S
LXIV
NO2
HO
Br
S
LXV

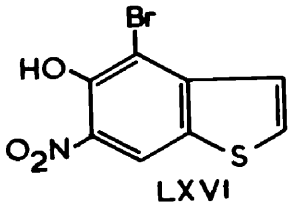
first the 3,4,6-tribromo derivative and then the 2,3,4,6-tetrabromo derivative. In the presence of acetate ion, bromination in acetic acid takes a different course to afford derivatives of 4,5-dihydro-5-keto-thionaphthen.[143]

In extending the knowledge of the substitution reactions of 5-substituted thionaphthens, attention was first directed towards the nitration of certain 5-hydroxythionaphthens. Under the mild conditions employed, the orientation was found to be similar to that encountered in the bromination studies. 5-Hydroxy-thionaphthen (LXI, R = H) itself underwent mononitration in cold acetic acid to form 5-hydroxy-4-nitrothionaphthen (LXII, R = H), identical with a specimen prepared by an alternative synthesis from the known 5-amino-4-nitrothionaphthen (LXIII, R = H),[139] by nucleophilic displacement of the amino group by an hydroxyl group. 5-Hydroxythionaphthen-2-carboxylic acid (LXI, R = CO_2H) was also found to undergo mononitration directly in the 4-position, the product being identical with an authentic sample of 5-hydroxy-4-nitrothionaphthen-2-carboxylic acid (LXII, R = CO_2H) prepared from the 5-amino-4-nitro acid (LXIII, R = CO_2H).[140]

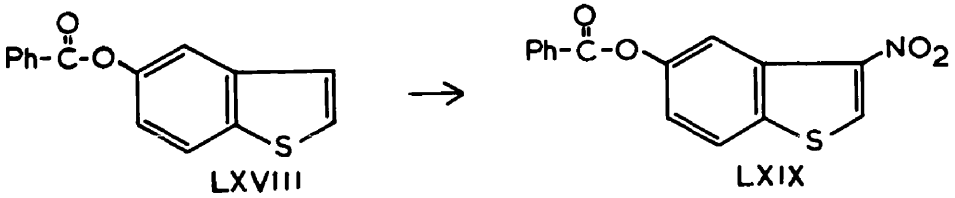
Similarly, 3-bromo-5-hydroxy-4-nitrothionaphthen (LXV) was obtained by mononitration of 3-bromo-5-hydroxythionaphthen (LXIV) in acetic acid. The structure of the product LXV was readily apparent from a study of the infrared spectrum in carbon tetrachloride solution at a dilution sufficient to ensure absence of intermolecular hydrogen bonding (0.5 mg./ml.). The OH stretching frequency at 3290 $cm.^{-1}$ showed chelation of the nitro and hydroxyl groups, thus proving their ortho relationship. Reduction of this compound, followed by oxidation, gave the 4,5-quinone characterised by the Craven test.[144]

With excess of nitric acid, 3-bromo-5-hydroxy-thionaphthen formed a dinitro derivative, the structure of which has not been established.

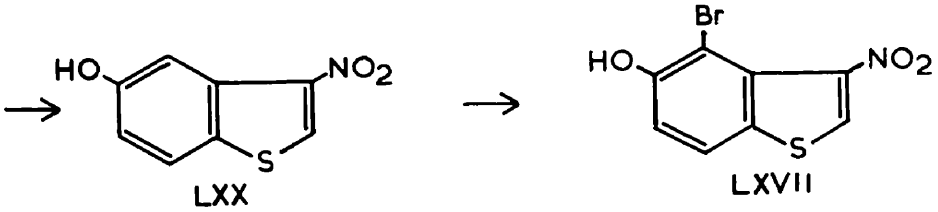
As nitration proved to be strictly analogous to bromination in the above cases, it was felt necessary to reinvestigate the compound previously assigned the structure 4-bromo-5-hydroxy-3-nitrothionaphthen,[145] and formed by the action of nitric acid on 4-bromo-5-hydroxythionaphthen. In view of the fact that the latter compound affords the 4,6-dibromo derivative on further bromination, it seemed probable that the nitration product was in reality 4-bromo-5-hydroxy-6-nitro-



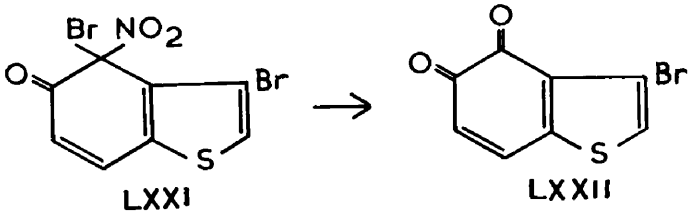
LXVI



LXVIII LXIX



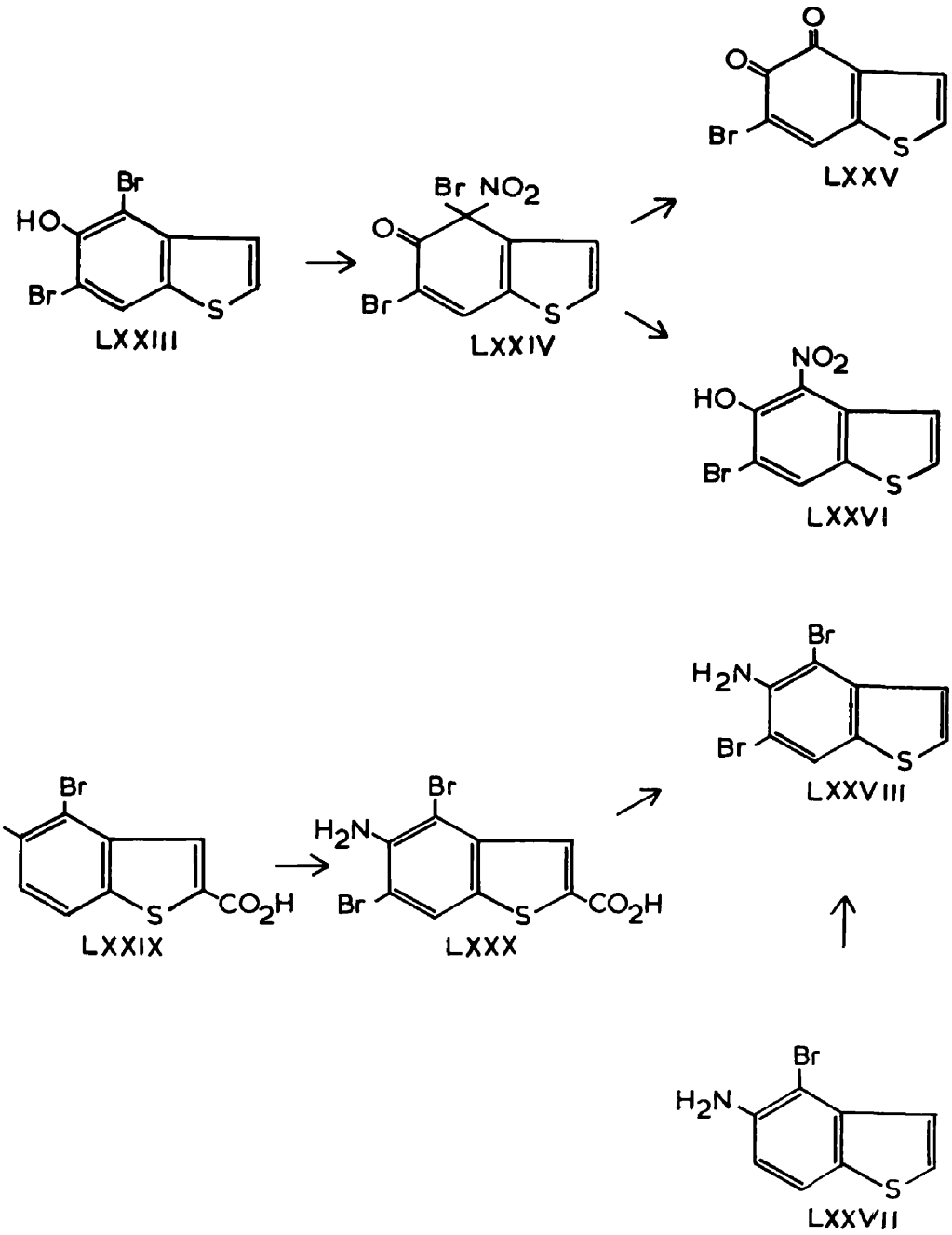
LXX LXVII



LXXI LXXII

thionaphthen (LXVI). That this was indeed the case was readily apparent from a study of its infrared spectrum in carbon tetrachloride solution (1.1 mg./ml.). The position of the fundamental OH stretching frequency at 3211 cm.$^{-1}$ showed that there was complete chelation proving the ortho relationship of the hydroxyl and nitro groups. The true 4-bromo-5-hydroxy-3-nitro-thionaphthen (LXVII) was prepared from 5-benzoyloxy-thionaphthen (LXVIII) by nitration (LXIX) followed by hydrolysis to the free phenol (LXX), and monobromination in acetic acid. The position of the OH stretching frequency of the nitrophenol (LXX) at 3580 cm.$^{-1}$ in carbon tetrachloride solution (1.1 mg./ml.) showed, as was to be expected, complete absence of intramolecular hydrogen bonding between the nitro and hydroxyl groups. The OH stretching frequency of 4-bromo-5-hydroxy-3-nitro-thionaphthen (LXVII) at 3506 cm.$^{-1}$ (1.37 mg./ml.) showed weak intramolecular hydrogen bonding consistant with the ortho relationship of the hydroxyl and bromo functions.

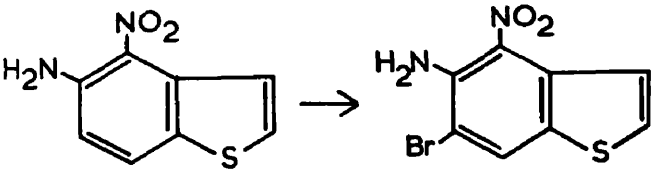
That electrophilic substitution occurs in the 3-position in 5-benzoyloxythionaphthen as in 5-acetoxy-thionaphthen by activation LVIII was confirmed by


Br
HO
Br
S
LXXIII
Br NO2
O
Br
S
LXXIV
O
O
Br
S
LXXV
NO2
HO
Br
S
LXXVI
Br
H2N
Br
S
LXXVIII
Br
H2N
S
CO2H
LXXIX
Br
H2N
Br
S
CO2H
LXXX
Br
H2N
S
LXXVII

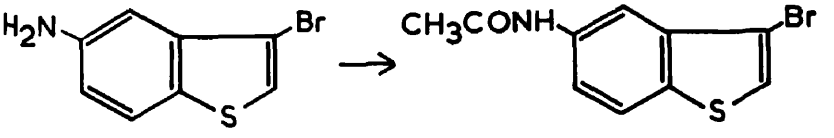
monobromination and hydrolysis to give 3-bromo-5-hydroxy-thionaphthen.

The course of the nitration of 4-bromo-5-hydroxy-thionaphthen was nevertheless interesting as under the same experimental conditions 3,4-dibromo-5-hydroxy-thionaphthen is known to give the keto compound (LXXI) which can be converted to the quinone (LXXII) by boiling in benzene.[140] The formation of LXXI may be favoured by steric considerations as the 3-and 4-positions of thionaphthen are analogous to the peri positions in naphthalene, and removal of the 4-substituent from the plane of the ring system would afford a method of relieving the steric interaction with the 3-substituent.

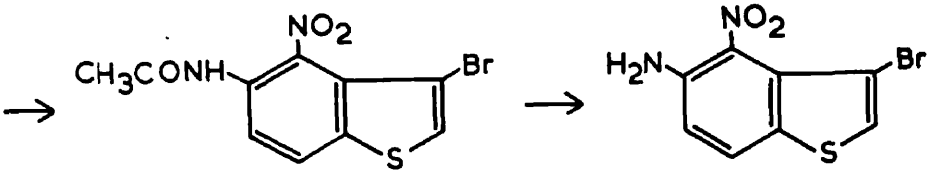
The action of nitric acid on 4,6-dibromo-5-hydroxythionaphthen (LXXIII) has also been postulated[143] to give rise to a keto compound of type LXXIV as initial product in order to afford an explanation for the formation of 6-bromothionaphthen-4,5-quinone (LXXV) when the nitration is carried out in chloroform, and of 6-bromo-5-hydroxy-4-nitrothionaphthen (LXXVI) when the reaction is carried out in acetic acid. This assumption has now been proved correct by the successful isolation of this relatively unstable keto compound,



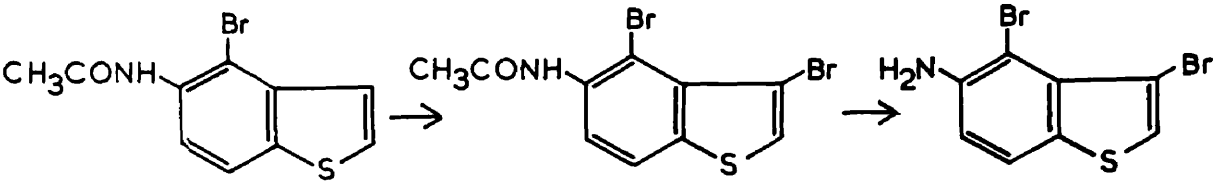
LXXXI LXXXII



LXXXIV LXXXV



LXXXIII



LXXXVI LXXXVII LXXXVIII

and its conversion to the 4,5-quinone by boiling in benzene as indicated by application of the Craven test.

The bromination studies already made on 5-aminothionaphthen[139] were extended in order to discover if 4,6-disubstitution occurred analogously to that with 5-hydroxythionaphthen. On bromination in acetic acid in the presence of sodium acetate, 5-amino-4-bromothionaphthen (LXXVII) gave a crystalline dibromo compound which was shown to be 5-amino-4,6-dibromothionaphthen (LXXVIII) by an alternative synthesis from 5-amino-4-bromothionaphthen-2-carboxylic acid (LXXIX) in which the 3-position is deactivated towards electrophilic attack by the presence of the acid function in the 2-position. Bromination of this acid to give the dibromo derivative (LXXX), followed by decarboxylation via the barium salt gave 5-amino-4,6-dibromothionaphthen (LXXVIII) unambiguously.

The monobromo derivative obtained from 5-amino-4-nitrothionaphthen (LXXXI) must be either the 6-bromo- (LXXXII) or the 3-bromo-derivative (LXXXIII), depending on how greatly the resonance interaction between the nitro group and the p electrons of the amino nitrogen atom counteracts activating influence LVII, thus

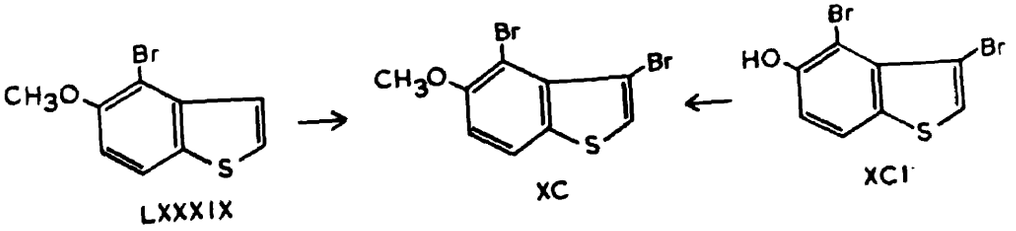
affecting the relative importance of activating influence LVIII. Comparison of the product with authentic 5-amino-3-bromo-4-nitrothionaphthen (LXXXIII), synthesised from the known 5-amino-3-bromothionaphthen (LXXXIV) by nitration of the derived acetamido compound (LXXXV) followed by hydrolysis, showed the non-identity of the two compounds. Thus the product of bromination of 5-amino-4-nitrothionaphthen must be 5-amino-6-bromo-4-nitrothionaphthen (LXXXII).

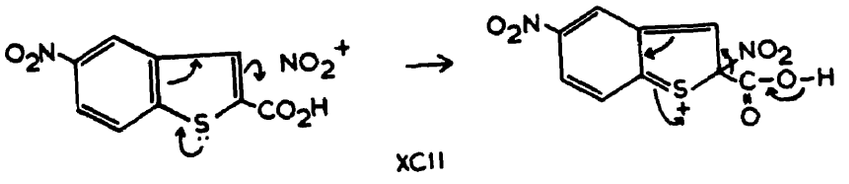
When 5-acetamido-3-bromothionaphthen was dissolved in a minimum amount of acetic acid and warmed with excess nitric acid, an orange crystalline solid separated. It exploded violently at 180° and was relatively insoluble in water and most organic solvents. A strong peak at 2143 cm.$^{-1}$ was present in the infrared spectrum, but there was no evidence for the presence of NH, OH, or carbonyl functional groups. The absence of any acetyl group was confirmed by a negative acetyl analysis. Due to the explosive nature of the compound, microanalytical figures for bromine and nitrogen only were obtained (Br, 21.8; N, 15.1%), and these are consistent with the molecular formula containing the unit (N_4Br). Two molecular formulas are possible, viz.

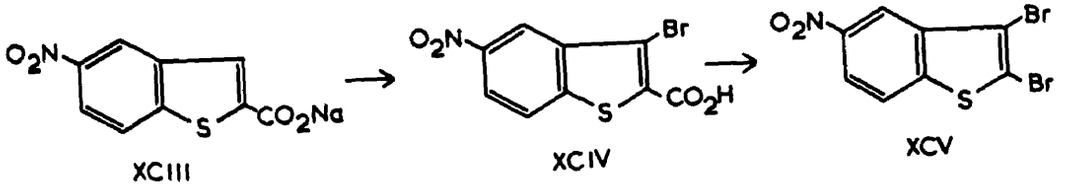
$C_8H_3O_6BrN_4S$ (Br, 22.0; N, 15.4%) and $C_9H_2O_6BrN_4S$ (Br, 21.4; N, 15.0%). Further experimental evidence is obviously required before any conclusions can be drawn regarding the structure of this interesting compound. Preliminary attempts to hydrolyse or reduce it under a variety of experimental conditions gave only intractable material.

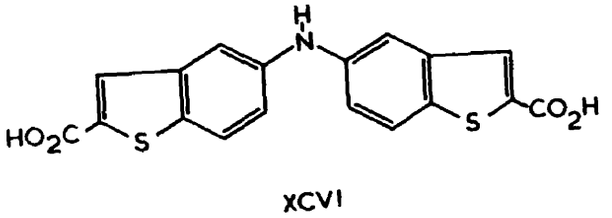
Acetylation of the amino group in 5-amino-4-bromothionaphthen (LXXXVI) was found to change the orientation from the predominant 6-substitution occurring in 5-amino-4-bromothionaphthen to predominant 3-substitution. The reduction in the electron-donating power of the nitrogen atom probably combined with steric effects is such that activation LVIII now predominates over LVII. That the product obtained on bromination was indeed 5-acetamido-3,4-dibromothionaphthen (LXXXVII) was proved by hydrolysis of this compound to the corresponding amine (LXXXVIII) which was prepared unambiguously by direct monobromination of 5-amino-3-bromothionaphthen.

3-Substitution in preference to 6-substitution was also found to occur on bromination of 4-bromo-5-methoxythionaphthen (LXXXIX) which is itself obtained


Br
CH3O
S
LXXXIX
Br
CH3O
Br
S
XC
Br
HO
Br
S
XCI


O2N
NO2+
CO2H
S
XCII
O2N
NO2
C-O-H
O
S+


O2N
CO2Na
S
XCIII
O2N
Br
CO2H
S
XCIV
O2N
Br
Br
S
XCV


H
N
HO2C
S
S
CO2H
XCVI

both by monobromination of 5-methoxythionaphthen and by methylation of 4-bromo-5-hydroxythionaphthen. The bromination product of 4-bromo-5-hydroxythionaphthen proved to be identical with authentic 3,4-dibromo-5-methoxythionaphthen (XC) prepared by methylation of 3,4-dibromo-5-hydroxythionaphthen (XCI).

It is of interest to note that bromination of 5-hydroxy-4-nitrothionaphthen both in the presence and in the absence of sodium acetate gave quinonoid material.

With an electron withdrawing group present in each ring, the thionaphthen nucleus appears so deactivated as to preclude electrophilic attack under the conditions employed. Thus, attempted bromination of 5-nitrothionaphthen-2-carboxylic acid was unsuccessful as were attempts to brominate and nitrate methyl 5-acetoxythionaphthen-2-carboxylate in hot acetic acid. Nitration of 5-nitrothionaphthen-2-carboxylic acid in hot acetic acid in the presence of concentrated sulphuric acid, however, gave rise to a complex mixture from which two isomeric trinitrothionaphthens containing no carboxyl group were isolated in low yield. Presumably, decarboxylation can be attributed to activation by the sulphur atom as in XCII analogous

to the activation exerted by the hydroxyl group in the conversion of 3,5-dinitro-2-hydroxybenzoic acid into 2,4,6-trinitrophenol.[146]

The sodium salt of 5-nitrothionaphthen-2-carboxylic acid (XCIII) has been reported to undergo bromination in aqueous solution,[140] the acid obtained being identical with the main product from an attempted Hunsdiecker reaction[147] on 5-nitrothionaphthen-2-carboxylic acid.[140] This acid has now been shown to be 3-bromo-5-nitrothionaphthen-2-carboxylic acid (XCIV) (and not 7-bromo-5-nitrothionaphthen-2-carboxylic acid as previously suggested[140]) by decarboxylation via the barium salt which gave a product identical with an authentic sample of 3-bromo-5-nitrothionaphthen.[142] The successful bromination of the sodium salt and the failure of the free acid to react with bromine can perhaps be attributed to electronic activation LVIII coupled with the effect of the carboxylic anion. The presence of the anion alone would not seem to be sufficient as sodium benzoate is inert under the same reaction conditions. Application of the Hunsdiecker reaction to 3-bromo-5-nitrothionaphthen-2-carboxylic acid gave 2,3-dibromo-5-nitrothionaphthen (XCV),

identical with the dibromonitro compound obtained in small yield from the Hunsdiecker reaction on 5-nitrothionaphthen-2-carboxylic acid.[140] Thus bromination of silver 5-nitrothionaphthen-2-carboxylate in the 3-position occurs preferentially to the normal Hunsdiecker reaction.

The reduction of nitro compounds to the corresponding amines was accomplished by the Raney-nickel and hydrazine hydrate procedure.[148] When this method was applied to methyl 3-bromo-5-nitrothionaphthen-2-carboxylate, however, debromination occurred and methyl 5-acetamidothionaphthen-2-carboxylate was isolated after acetylation of the crude product. Preliminary experiments indicated that although 9-bromoanthracene was reduced in 55% yield to anthracene, application of the reaction to general aromatic debromination was not satisfactory especially in view of the adequate methods already available.[149] It is to be noted, however, that Raney-nickel in the absence of hydrazine hydrate has been used to remove bromine from o-tert-butyl-p-bromophenol.[150]

The nature of the by-product formed together with 5-hydroxythionaphthen-2-carboxylic acid by

application of the Bucherer reaction[151] to 5-amino-thionaphthen-2-carboxylic acid has now been elucidated. It is di-(2-carboxy-5-thionaphthenyl)amine (XCVI). The formation of this compound by nucleophilic attack of unchanged amine on the intermediate Bucherer complex is readily apparent and is in accord with the well established examples of secondary amine formation in the Bucherer reaction.[152] The reason for the bright yellow colour shown by XCVI is not so apparent. The anion lacks this colour, and the disodium salt and solutions of the acid in pyridine are nearly colourless. In this connection, it is to be noted that 5-amino-4-bromothionaphthen-2-carboxylic acid[140] and 5-amino-4,6-dibromothionaphthen-2-carboxylic acid whose preparation is described above exist in both colourless and yellow forms.

That structure XCVI is correct for the by-product of the Bucherer reaction was established by its decarboxylation to the colourless 5,5'-dithionaphthenyl-amine which was identical with a specimen prepared unambiguously by heating equal quantities of 5-amino-thionaphthen and 5-aminothionaphthen hydrochloride in a sealed tube following the conditions previously

described for the preparation of diphenylamine.[153] Attempts to prepare the compound by way of 5-iodothionaphthen were unsuccessful.

The conclusions drawn regarding the influence of the 5-substituent on the position of further substitution in the thionaphthen nucleus are summarised in table 3. Much of this work has already been published, and a reprint[154] is included as appendix 2.

5-Subst.	4-Subst.	3-Subst.	Predominant position of electrophilic substitution.
OH	H	H	4
OH	Br	H	6
OH	H	Br	4
OH	Br	Br	6
OH	NO_2	Br	undetermined
OH	H	NO_2	4
OCH_3	H	H	4
OCH_3	Br	H	3
$OCOCH_3$	H	H	3
OCOPh	H	H	3
NH_2	H	H	4
NH_2	Br	H	6
NH_2	NO_2	H	6
NH_2	H	Br	4
$NHCOCH_3$	H	H	4
$NHCOCH_3$	Br	H	3
$NHCOCH_3$	H	Br	4

Table 3.

Section 2.

Synthesis of the Thionaphthen Analogue of Gramine and Related Compounds.

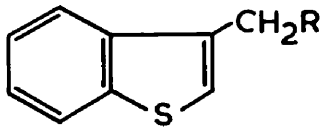
In recent years, cardiovascular disease has come to assume a prominent position as a cause of death in Western Europe and North America, and accordingly considerable time and attention are currently being devoted to the search for drugs capable of lowering high blood pressure. The efforts of the synthetic chemist have fallen into four main categories. The first is the production of agents capable of acting at the level of the central nervous system, the second is the production of agents capable of selectively blocking nerve impulse transmission at the level of the sympathetic ganglionic synapses, the third is the production of drugs capable of antagonising the action of noradrenaline at the sympathetic neuroeffector junction or of antagonising the direct action of adrenaline on the peripheral blood vessels, and the fourth is the production of drugs capable of interfering with the liberation of noradrenaline. Several drugs of the third class (adrenergic blocking agents) are available but none have the ideal properties required by the clinician,[155] and so are not in clinical use today.

A further logical approach to the preparation

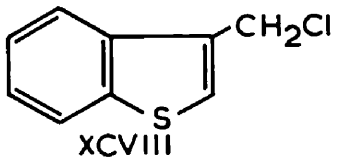
of drugs of the third class is from considerations of the metabolite displacement concept. If a compound with strong specific affinity for the adrenaline or noradrenaline receptors but having zero intrinsic activity could be devised, it might well be a valuable anti-hypertensive drug.

As previously mentioned, gramine has pressor activity[84] so it may conceivably have affinity for the adrenaline receptors and positive intrinsic activity. Again, several gramine derivatives have affinity for 5-hydroxytryptamine receptors, and as has been previously discussed, there appears to be some similarity in the nature of the receptors for 5-hydroxytryptamine and for adrenaline.

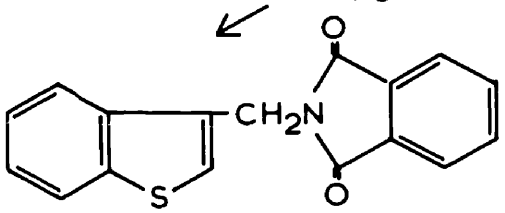
Thus, several aminomethylthionaphthen derivatives including 3-(dimethylaminomethyl)-thionaphthen, the thionaphthen analogue of gramine itself, were synthesised for testing both as antagonists of adrenaline and of 5-hydroxytryptamine. Preliminary results[156] on isolated tissues indicate that some of these agents do indeed antagonise the action of adrenaline. Further work utilising the pA_x technique[157] should show whether these drugs are truly competitive with adrenaline,



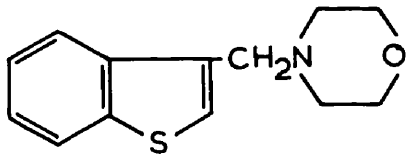
XCVII



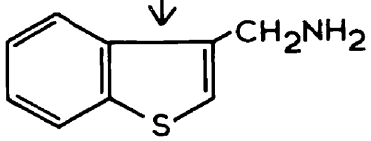
XCVIII



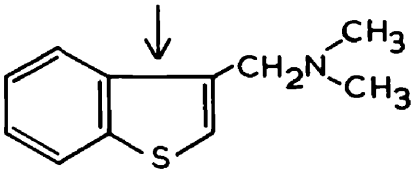
XCIX



CII



C



CI

molecule for molecule, and application of the techniques so elegantly established by Ariens and his school[158] could be used to determine the affinities and the intrinsic activities of these drugs.

Two compounds chemically similar to some of those to be described, viz., 3-(1,2,3,4-tetrahydro-isoquinolinomethyl)-thionaphthen and 3-(isoindolino-methyl)-thionaphthen, have been reported in the patent literature,[159] and do show hypotensive properties.

In view of the fact that certain gramine derivatives are oxytocics,[86] or local anaesthetics,[87] it was planned to have the compounds now to be described tested for these properties as well. In addition, several quaternary salts were prepared from the new compounds for testing as neuromuscular blocking agents as Craig and Tarbell[88] have shown that certain quaternary gramine derivatives possess this activity.

The first group of compounds prepared were of general formula XCVII, where R is dimethylamino, pyrrolidino, piperidino, 2-methylpiperidino, morpholino, and cyclohexylamino.

3-Chloromethylthionaphthen (XCVIII), obtained from thionaphthen by the use of trioxan and dry hydrogen

chloride in acetic acid,[160] was employed as the starting material for the syntheses of these amines. Attempts to react the chloromethyl compound directly with ammonia to give 3-(aminomethyl)-thionaphthen (C) both in the presence and in the absence of solvent were unsuccessful, so this compound was prepared by means of a Gabriel reaction,[161] in which 3-chloromethylthionaphthen was condensed with potassium phthalimide in dimethylformamide,[159] and the resulting N-substituted phthalimide (XCIX) hydrolysed to the amine (C) by the modified procedure of Ing and Manske[162] using hydrazine hydrate and hydrochloric acid.

3-(Dimethylaminomethyl)-thionaphthen (CI) was prepared directly from 3-(aminomethyl)-thionaphthen by the use of formaldehyde solution and formic acid employing the conditions described by Gent and McKenna[163] for the dimethylation of amino steroids.

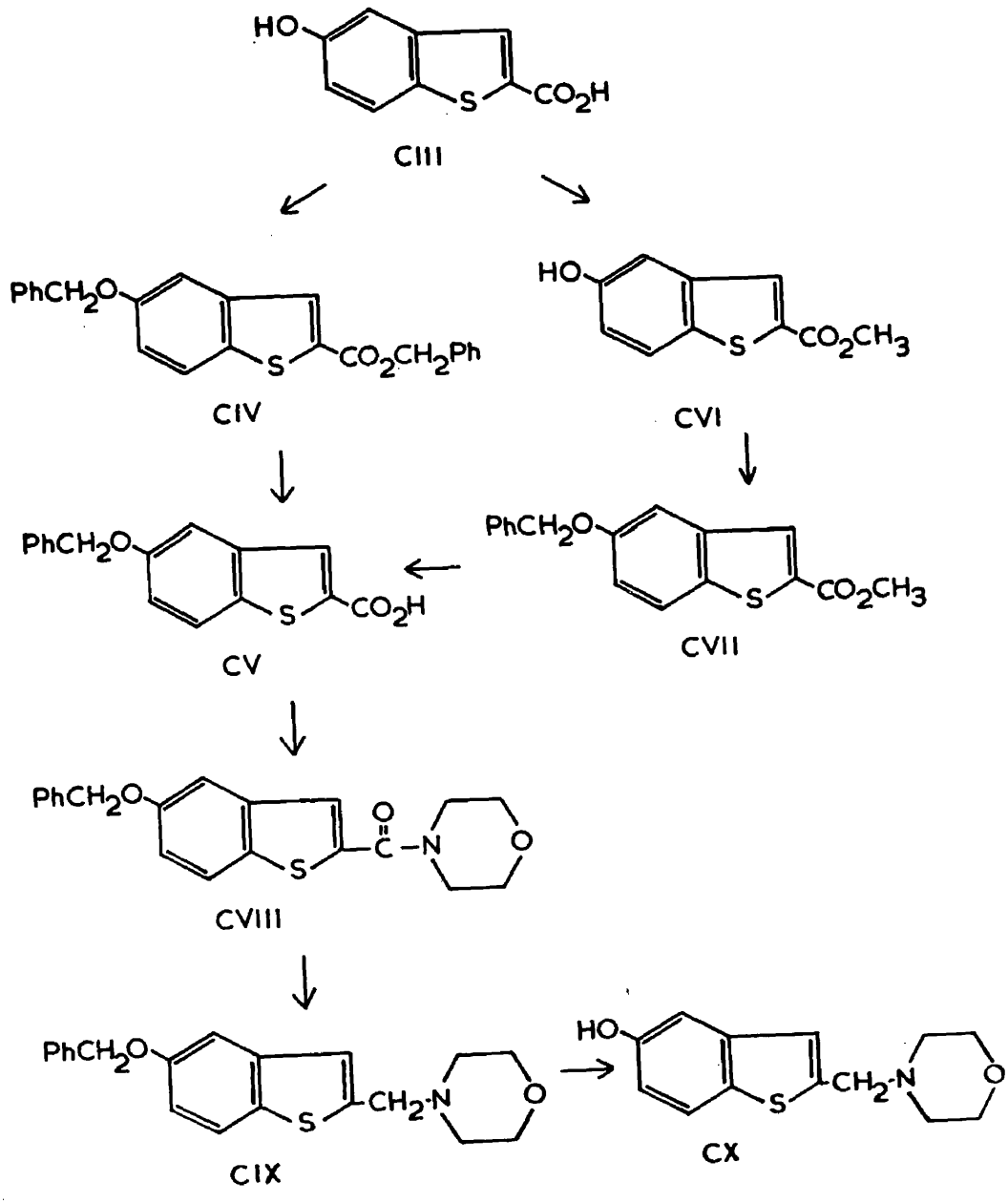
The other amines, for example 3-(morpholinomethyl)-thionaphthen (CII), were prepared directly from 3-chloromethylthionaphthen and the requisite amine in toluene in the presence of excess sodamide by an analogous procedure to that previously described for the condensation of 3-chloromethylthionaphthen with

tetrahydroisoquinoline,[159] the products being isolated and characterised as the water soluble hydrochlorides.

The crystalline methiodides of 3-(dimethylaminomethyl)-thionaphthen, 3-(pyrrolidinomethyl)-thionaphthen, 3-(piperidinomethyl)-thionaphthen, and 3-(morpholinomethyl)-thionaphthen were also prepared.

Because of the ready availability of 5-substituted thionaphthen-2-carboxylic acids,[140] it was decided to prepare several thionaphthen derivatives possessing a 5-substituent and a substituted aminomethyl side chain in the 2-position. As the corresponding compounds lacking the 5-substituent are readily available from a series of amides of thionaphthen-2-carboxylic acid synthesised by Goettsch and Wiese,[164] by way of lithium aluminium hydride reduction,[165] it was decided not to investigate them in this project. 2-(Aminomethyl)-thionaphthen is already known.[166]

In particular, it seemed of interest to prepare a number of N-substituted 2-(aminomethyl)-thionaphthen derivatives possessing a hydroxyl function in the 5-position to ascertain whether such compounds would prove to either mimic or oppose the biological actions of 5-hydroxytryptamine, especially as 5-hydroxygramine


HO
S
CO_2H
CIII
$PhCH_2O$
S
CO_2CH_2Ph
CIV
HO
S
CO_2CH_3
CVI
$PhCH_2O$
S
CO_2H
CV
$PhCH_2O$
S
CO_2CH_3
CVII
$PhCH_2O$
S
C
O
N
O
CVIII
$PhCH_2O$
S
CH_2
N
O
CIX
HO
S
CH_2
N
O
CX

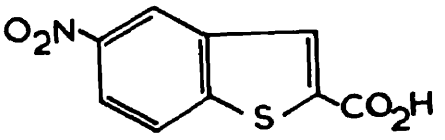
produces contraction of the rat's uterus[45] and so unlike most other gramine derivatives shows a degree of 5-hydroxytryptamine-like activity.

The known 5-hydroxythionaphthen-2-carboxylic acid (CIII)[140] proved to be a convenient starting point for the synthesis of these derivatives. The phenolic group was protected by conversion into the benzyl ether with a view to subsequent removal by hydrogenolysis[167] or acid hydrolysis. This particular protecting group was chosen because both 5-benzyloxygramine and 6-benzyloxygramine have been reported to be 5-hydroxytryptamine antagonists,[45] and so the intermediate benzyl ethers could also be screened biologically. The benzyloxythionaphthen amines, as well as being potential 5-hydroxytryptamine antagonists in vitro, should be able to penetrate the blood-brain barrier more easily than the zwitterionic hydroxylamines, and thus be useful in in vivo studies. Again, certain substituted 5-benzyloxyindoles have been reported to have vasoconstrictor properties,[168] and so there appeared once more the possibility of finding adrenergic blocking agents within the series.

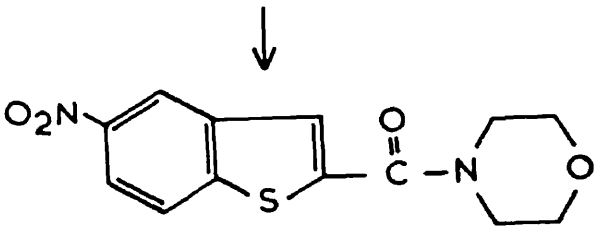
5-Benzyloxythionaphthen-2-carboxylic acid (CV)

was first prepared using the method described[169] for the conversion of 4-hydroxybenzoic acid into 4-benzyloxybenzoic acid by treatment with two equivalents of benzyl chloride and sodium hydroxide in aqueous ethanol to give benzyl 5-benzyloxythionaphthen-2-carboxylate (CIV) followed by basic hydrolysis of the benzyl ester. However, it was later found more convenient to prepare CV via methyl 5-hydroxythionaphthen-2-carboxylate (CVI) by benzylation of the phenolic hydroxyl group with benzyl chloride in the presence of sodium hydroxide using the procedure of Cohen and Dudley.[170] Basic hydrolysis of the resulting product (CVII) afforded 5-benzyloxythionaphthen-2-carboxylic acid in 60% yield.

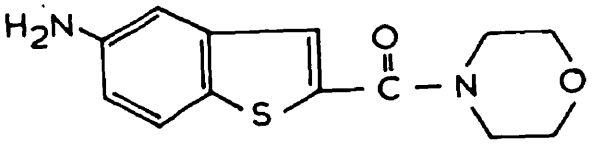
The acid chloride, obtained by warming the acid gently with excess thionylchloride, was condensed with the requisite amine in pyridine to give the amide which in turn was reduced in ether with lithium aluminium hydride[165] to the N-substituted 2-(aminomethyl)-5-benzyloxythionaphthen. Attempts to cleave the benzyl ether by hydrogenation with palladium on charcoal and Adam's catalyst were unsuccessful. This is probably due to poisoning of the catalyst by the sulphur atom in the thiophen ring. The cleavage was effected



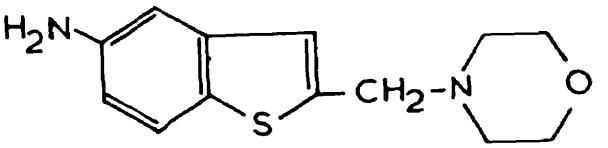
CXI



CXII



CXIII



CXIV

successfully, however, by gently heating the benzyl ether in concentrated hydrochloric acid. The reaction scheme is shown in figures CVIII, CIX, and CX using the preparation of 5-hydroxy-2-(morpholinomethyl)-thionaphthen (CX) as an example.

Other amines prepared by the same procedure were 2-(dimethylaminomethyl)-5-hydroxythionaphthen and 5-hydroxy-2-(pyrrolidinomethyl)-thionaphthen, along with the corresponding 5-benzyloxy intermediates and 5-benzyloxy-2-(piperidinomethyl)-thionaphthen.

As 5-amino-2-methylgramine (XVI) has also been reported to be a 5-hydroxytryptamine antagonist,[46] the present work was extended to include a series of 5-amino-2-aminomethyl thionaphthen derivatives. These were prepared from 5-nitrothionaphthen-2-carboxylic acid (CXI) by treatment of the acid chloride with the requisite amine, for example morpholine, in benzene to give the required amide, in this case 2-(morpholinocarbonyl)-5-nitro-thionaphthen (CXII). Lower yields of amide were obtained when pyridine was employed as solvent.

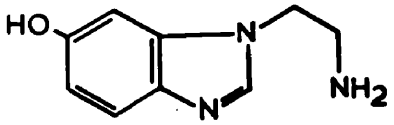
The nitro group in 2-(morpholinocarbonyl)-5-nitrothionaphthen was smoothly reduced by Raney-nickel and hydrazine hydrate[148] in ethanol to give

5-amino-2-(morpholinocarbonyl)-thionaphthen (CXIII). Reduction of the carbonyl function in this compound with lithium aluminium hydride to give 5-amino-2-(morpholinomethyl)-thionaphthen (CXIV) was achieved only after prolonged refluxing in tetrahydrofuran with excess lithium aluminium hydride. The difficulty encountered in the reduction can be attributed to the presence of a primary amino group, and its ability to form insoluble complexes with lithium aluminium hydride.[165]

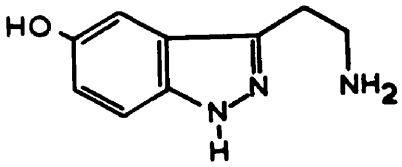
Other amines of this series prepared by the same procedure were 5-amino-2-(dimethylaminomethyl)-thionaphthen, 5-amino-2-(pyrrolidinomethyl)-thionaphthen, and 5-amino-2-(piperidinomethyl)-thionaphthen. These amines could not be obtained crystalline, and proved difficult to characterise either as mono- or di-hydrochlorides and hydrobromides. Accordingly, the N-benzoyl derivatives were prepared for chemical characterisation.

Section 3.

The Preparation of Analogues of 5-Hydroxytryptamine.



CXV



CXVI

The importance of obtaining antagonists of 5-hydroxytryptamine in order to facilitate more detailed studies of its physiological significance was first stressed by Gaddum and Hameed.[171] In the search for such agents, the main effort has been directed towards the preparation of various gramine and tryptamine derivatives, several of which have been mentioned in the introduction to this thesis. Relatively little attention has been paid to the isosteric approach, and it would appear that only two isosteres of 5-hydroxytryptamine are recorded in the literature. These are the benziminazole analogue (CXV),[172] and the indazole analogue (CXVI) which has similar pharmacological properties to 5-hydroxytryptamine although only $\frac{1}{2}$ to $\frac{1}{8}$ as potent.[173]

These two isosteres possess additional centres of electron density at the second ring nitrogen atom, and so differ considerably from 5-hydroxytryptamine itself in electric charge distribution. The benzofuran or thionaphthen isostere would be expected to be more closely akin to 5-hydroxytryptamine in this respect.

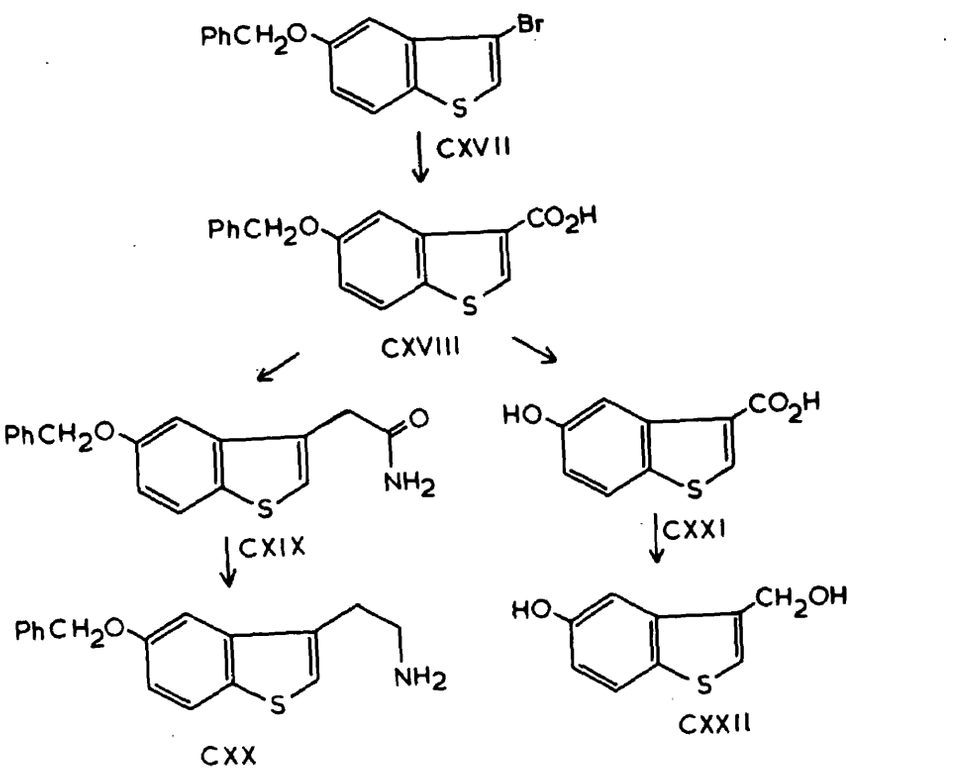
The availability of a further isostere for comparison with those already known as well as for

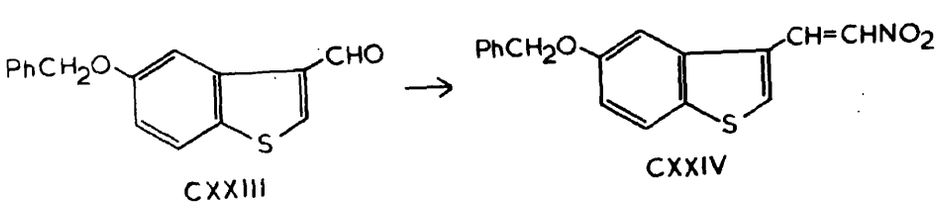
comparison with 5-hydroxytryptamine itself would therefore seem to be of considerable interest.

Apart from its potential ability to mimic or oppose the action of 5-hydroxytryptamine at the receptor site, the thionaphthen analogue - 3-(2'-aminoethyl)-5-hydroxythionaphthen - might perhaps be expected to affect the concentration of 5-hydroxytryptamine by inhibiting either 5-hydroxytryptophan decarboxylase or monoamine oxidase.

Attempts were made to synthesise this analogue, and although the corresponding benzyl ether, 3-(2'-aminoethyl)-5-benzyloxythionaphthen (CXX), was obtained, it resisted all attempts at conversion into 3-(2'-aminoethyl)-5-hydroxythionaphthen either by hydrogenation or hydrolysis.

The route employed for the synthesis of this benzyl ether was via the key intermediate 3-bromo-5-hydroxythionaphthen which was available by an eight stage synthesis from o-chlorobenzaldehyde.[139,140] The initial step in the route taken from 3-bromo-5-hydroxythionaphthen was the protection of the hydroxyl group as the corresponding benzyl ether (CXVII) by treatment with benzyl chloride and aqueous sodium hydroxide.


PhCH2O
Br
S
CXVII
PhCH2O
CO2H
S
CXVIII
PhCH2O
O
NH2
S
CXIX
HO
CO2H
S
CXXI
PhCH2O
NH2
S
CXX
HO
CH2OH
S
CXXII


PhCH2O
CHO
S
CXXIII
PhCH2O
CH=CHNO2
S
CXXIV

The resulting 5-benzyloxy-3-bromothionaphthen (CXVII) was then converted into 5-benzyloxythionaphthen-3-carboxylic acid (CXVIII) by the action of carbon dioxide on the Grignard complex. The technique employed was based on that used for the conversion of 3-bromothionaphthen into thionaphthen-3-carboxylic acid,[123] utilising the method of "entrainment" or continuous activation,[174] which employs methyl iodide and excess magnesium. The yield of 5-benzyloxythionaphthen-3-carboxylic acid varied from 20 to 50% according to the amount of methyl iodide present.

The amide of 5-benzyloxythionaphthen-3-acetic acid (CXIX) was prepared directly from 5-benzyloxythionaphthen-3-carboxylic acid by use of the Arndt-Eistert reaction[175] following the procedure employed in the preparation of the amide of p-homoanisic acid.[176] The acid chloride of 5-benzyloxythionaphthen-3-carboxylic acid, obtained from the acid by the action of thionyl chloride, was converted into the diazoketone with excess of diazomethane, and the product rearranged to the amide of 5-benzyloxythionaphthen-3-acetic acid (CXIX) by the action of ammonia and silver nitrate solution in dioxan.

3-(2'-Aminoethyl)-5-benzyloxythionaphthen (CXX) was then obtained by reduction of the amide in ether with lithium aluminium hydride.[162]

Again, attempts to hydrogenolyse the benzyl ether were unsuccessful, and difficulty was also encountered in attempts to hydrolyse it to the free phenol. Warming with concentrated hydrochloric acid - the method successfully employed in section 2 of this thesis for a similar reaction when there was a tertiary amino group present in the molecule - gave an extremely small yield of crystalline material soluble in sodium hydroxide solution. Although there was insufficient of the product for characterisation, mass numbers of 284 and 375 obtained from mass spectroscopy studies indicated that the compound must have a much higher molecular weight than that of the expected product.

Hydrolysis of the amide of 5-benzyloxy-thionaphthen-3-acetic acid (CXIX) with concentrated hydrochloric acid was of little value as the amide group was also hydrolysed to the acid, the material isolated being soluble in sodium carbonate solution

Another synthetic route to 3-(2'-aminoethyl)-5-benzyloxythionaphthen investigated was via

5-Benzyloxythionaphthen-3-aldehyde (CXXIII). Attempts to prepare this aldehyde by the method of Brown and Subba Rao[177] which involves reduction of the acid chloride with lithium tri-t-butoxyaluminohydride proceeded in low yield, and the aldehyde was not characterised as such but converted into 5-benzyloxy-3-(2'-nitrovinyl)-thionaphthen (CXXIV) by the action of nitromethane in the presence of ammonium acetate following the procedure described by Young.[178]

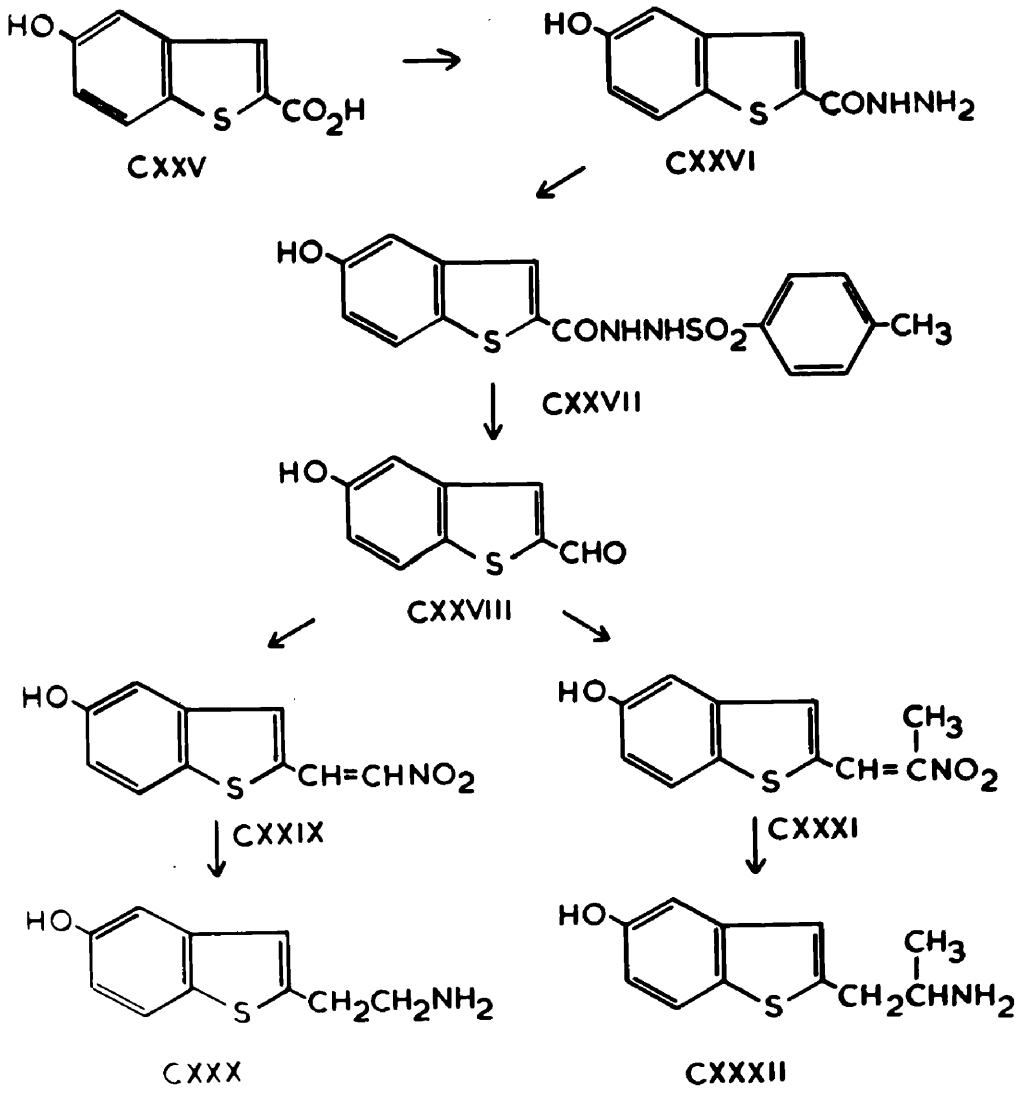
Although this nitrovinyl compound would have served as a suitable intermediate for the preparation of 3-(2'-aminoethyl)-5-benzyloxythionaphthen which could be obtained by lithium aluminium hydride reduction,[165,179] it offered no advantages over the route already reported via the amide of 5-benzyloxythionaphthen-3-acetic acid (CXIX).

Because of the difficulty associated with hydrolysis of the benzyl ether in the presence of a primary amino group, other routes in which the phenolic hydroxyl group was not protected were investigated. 5-Hydroxythionaphthen-3-carboxylic acid (CXXI) was obtained by acid hydrolysis of 5-benzyloxythionaphthen-3-carboxylic acid, and gave 5-hydroxy-3-hydroxymethyl-

thionaphthen (CXXII) on lithium aluminium hydride reduction. Although primary allylic alcohols are reported[180] to be easily oxidised to the corresponding aldehydes by manganese dioxide, attempts to oxidise 5-hydroxy-3-hydroxymethylthionaphthen and 5-hydroxy-2-hydroxymethylthionaphthen, prepared by lithium aluminium hydride reduction of methyl 5-hydroxythionaphthen-2-carboxylate, in this way were unsuccessful. The product which had a weak peak at 1670 cm.$^{-1}$ in the infrared indicative of carbonyl absorption was contaminated by a considerable amount of high melting material from which it could not be readily separated. When the reaction was repeated in nitromethane and in the presence of ammonium acetate, a considerable darkening in colour associated with the formation of a nitrovinyl compound was observed, but no crystalline material could be isolated.

A final attempt to utilise N-bromosuccinimide in the preparation of 5-hydroxythionaphthen-3-aldehyde followed the procedure reported[181] for the conversion of 4,5-dimethoxyphthyl alcohol to 4,5-dimethoxyphthal-aldehyde. This was also unsuccessful.

Attempts were made to employ 3-cyano-5-nitro-


HO
S
CO2H
CXXV
CONHNH2
CXXVI
CONHNHSO2
CH3
CXXVII
CHO
CXXVIII
CH=CHNO2
CXXIX
CH=CNO2
CXXXI
CH2CH2NH2
CXXX
CH2CHNH2
CXXXII

thionaphthen, prepared from 3-bromo-5-nitrothionaphthen by means of a Rosenmund-von Braun nitrile synthesis,[182] as an intermediate in a synthesis of the thionaphthen analogue of 5-hydroxytryptamine, but the extreme resistance of the nitrile to hydrolysis and the difficulty encountered in attempts to selectively reduce the nitrile led to an early rejection of this approach.

Although it has not been possible to obtain 3-(2'-aminoethyl)-5-hydroxythionaphthen itself, the 5-benzyloxy derivative is worthy of extensive pharmacological investigation especially on account of the interesting results obtained with benzyloxy derivatives of certain indole compounds and mentioned in the introduction and in section 2.

In many cases, biologically active thiophen compounds substituted in the 3-position have been found to be slightly more active than the corresponding 2-isomers,[21,22] but, as there are several exceptions to this rule, it was decided to synthesise 2-(2'-aminoethyl)-5-hydroxythionaphthen as a possible antagonist of 5-hydroxytryptamine. 2-(2'-Aminoethyl)-5-hydroxy-thionaphthen (CXXX) was synthesised from 5-hydroxy-thionaphthen-2-carboxylic acid (CXXV) via 5-hydroxy-

thionaphthen-2-aldehyde (CXXVIII), obtained from the acid by the method of McFadyen and Stevens which involves the alkaline decomposition of a 1-acyl-2-arylsulphonyl-hydrazine.[183] The use of this method avoided any necessity to protect the phenolic hydroxyl group.

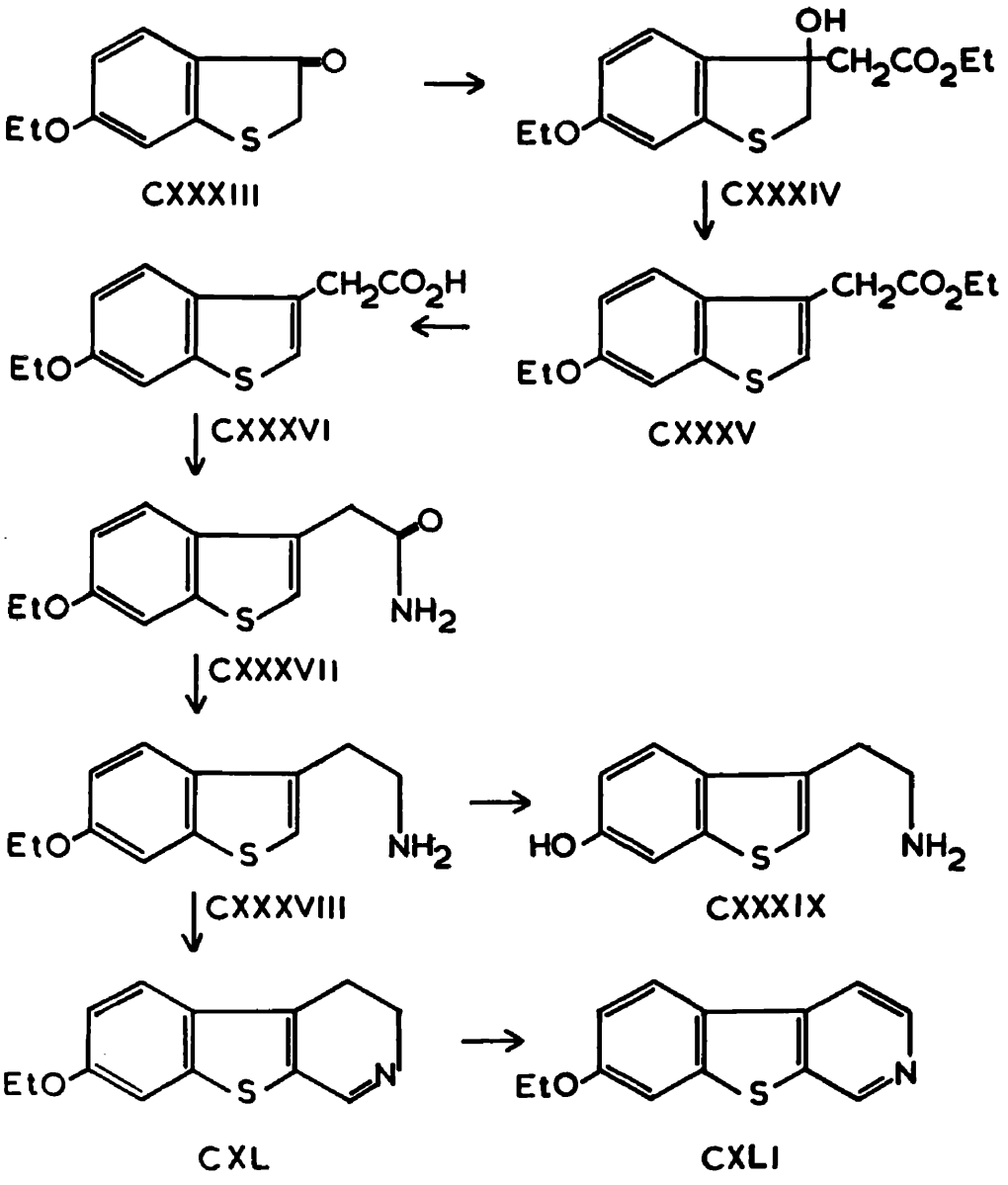
Methyl 5-hydroxythionaphthen-2-carboxylate was obtained in 79% yield by heating the acid under reflux in methanol in the presence of concentrated hydrochloric acid, and in quantitative yield by treating the acid with an excess of diazomethane. The ester was converted into the acid hydrazide (CXXVI) by refluxing with hydrazine hydrate in methanol. Treatment of the acid hydrazide with one equivalent of p-toluenesulphonyl chloride in pyridine gave 1-(5'-hydroxythionaphthen-2'-yl-carbonyl)-2-p-toluenesulphonyl hydrazine (CXXVII), a p-toluenesulphonyl derivative of the substituted hydrazine being formed in preference to a derivative of the hydroxyl function. 5-Hydroxythionaphthen-2-aldehyde (CXXVIII) was then obtained by the addition of solid potassium carbonate to a solution of the p-toluenesulphonyl derivative in ethylene glycol at 160°.

The aldehyde was condensed with nitromethane in the presence of ammonium acetate[178] to give

5-hydroxy-2-(2'-nitrovinyl)-thionaphthen (CXXIX), and on reduction of this compound with lithium aluminium hydride,[165,179] 2-(2'-aminoethyl)-5-hydroxythionaphthen (CXXX) was isolated and crystallised as the hydrochloride.

As various β-substituted α-methylethylamines including 5-hydroxy-α-methyltryptamine are claimed[184,185] to inhibit monoamine oxidase, it seemed worthwhile to prepare 2-(2'-aminopropyl)-5-hydroxythionaphthen (CXXXII) to discover whether it would exert a more prolonged action than 2-(2'-aminoethyl)-5-hydroxythionaphthen. Another justification for preparing this compound lies in the fact that α-methyltryptamine has been shown to inhibit the formation of 5-hydroxytryptamine from 5-hydroxytryptophan by blocking the action of 5-hydroxytryptophan decarboxylase,[184] and so there was considered to be a strong possibility that this compound might possess similar activity.

Accordingly, 2-(2'-aminopropyl)-5-hydroxythionaphthen (CXXXII) was prepared by lithium aluminium hydride reduction of 5-hydroxy-2-(2'-methyl-2'-nitrovinyl)-thionaphthen (CXXXI), the condensation product from the reaction of 5-hydroxythionaphthen-2-aldehyde with nitroethane.[178]


EtO
S
O
CXXXIII
OH
CH2CO2Et
CXXXIV
CH2CO2Et
CXXXV
CH2CO2H
CXXXVI
NH2
CXXXVII
HO
CXXXVIII
CXXXIX
N
CXL
CXLI

It was also decided to synthesise 3-(2'-amino-ethyl)-6-hydroxythionaphthen (CXXXIX) as this would form the starting material for a synthesis of thionaphthen isosteres of the indole alkaloids harmine and harmaline as well as certain more complicated 6-methoxyindole alkaloids such as reserpine. Moreover, as 3-(2'-amino-ethyl)-6-hydroxythionaphthen is the thionaphthen analogue of 6-hydroxytryptamine, it seemed interesting to have it available for pharmacological investigation. 6-Hydroxytryptamine, synthesised by Stoll,[186] is only feebly active when compared with 5-hydroxytryptamine.[45] Another interest in having 6-hydroxythionaphthen derivatives available lies in the fact that the 6-position of indole alkaloids is subject to hydroxylation in nature.[187]

6-Ethoxythioindoxyl (6-ethoxy-3-oxo-2,3-dihydro-thionaphthen) (CXXXIII) was employed as starting material for the synthesis. Thioindoxyls generally react both as ketones and as phenols, forming oximes, semicarbazones, ethers and sodium salts, but as attempts to condense the keto function, present in thioindoxyl, with malonic acid under a variety of conditions have been reported to be unsuccessful,[123] it was decided to ascertain

whether application of the Reformatski reaction with ethylbromacetate was feasible. Accordingly, 6-ethoxy-thioindoxyl was heated under reflux for 4 hours in a mixture of benzene and toluene with two equivalents of ethylbromacetate and zinc 'wool', and the product hydrolysed with ethanolic sodium hydroxide solution. The fraction soluble in sodium carbonate solution was separated, and from this a 20% yield of crystalline material was isolated.

The analytical figures for the product were consistant with the molecular formula $C_{12}H_{12}O_3S$ showing that dehydration of the intermediate β-hydroxy-ester (CXXXIV) had taken place. This dehydration would be expected to take place in such a way as to regenerate the fully aromatic thionaphthen nucleus (CXXXV). That this was indeed the case and that the product was 6-ethoxythionaphthen-3-acetic acid (CXXXVI) was indicated by the compound showing an absorption maximum at 234 mμ (ϵ = 27,100) in the ultraviolet spectrum similar to that of 5-methoxythionaphthen at 235 mμ (ϵ = 19,200). Conformation of this structure was provided by repeating the reaction with thioindoxyl itself which was prepared from anthranilic acid by the known procedure.[188] The

product of the Reformatski reaction on this compound had identical physical constants to those of 3-thionaphthenylacetic acid.[123]

The success of the Reformatski reaction thus provides a route to other thionaphthen analogues of substituted tryptamines, particularly as many thioindoxyls are readily available as dyestuff intermediates.

As attempts to prepare the acid chloride of 6-ethoxythionaphthen-3-acetic acid by the action of thionyl chloride were unsuccessful, the acid chloride was obtained by warming the acid gently with oxalyl chloride in dry benzene.[189] The addition of excess ammonia solution to the acid chloride gave a good yield of the corresponding amide (CXXXVII), and on reduction of the product with lithium aluminium hydride in ether, 3-(2'-aminoethyl)-6-ethoxythionaphthen (CXXXVIII) was obtained.

Finally, hydrolysis of the ethyl ether function with hydrobromic acid in acetic acid gave 3-(2'-aminoethyl)-6-hydroxythionaphthen (CXXXIX), the thionaphthen analogue of 6-hydroxytryptamine.

The thionaphthen analogue of harmaline, containing a 7-ethoxy group in place of the 7-methoxy group present

in the natural alkaloid, was prepared by ring closure of the N-acetyl derivative of 3-(2'-aminoethyl)-6-ethoxythionaphthen using the method described by Herz[130] in his synthesis of the thionaphthen analogue of harman. On heating the acetyl derivative under reflux for 4 hours in toluene with phosphorus pentachloride and phosphorus oxychloride, 7-ethoxy-1-methyl-3,4-dihydrothionaphtheno-(2,3-C)pyridine (CXL) was isolated as a crystalline solid after chromatography on grade 3 alumina. The tricyclic product was characterised as the water soluble amine hydrochloride.

The corresponding analogue of harmine itself, 7-ethoxy-1-methylthionaphtheno(2,3-C)pyridine (CXLI) was obtained from this compound by dehydrogenation with Adam's catalyst at 200°.

Experimental.

5-Hydroxy-4-nitrothionaphthen (LXII, R = H).- 5-Acetamido-4-nitrothionaphthen (2.29 g., 9.7 mmoles)[139] was dissolved in Claisen's alkali[190] (35 g. of potassium hydroxide in 25 ml. of water and 100 ml. of methanol) and heated under reflux for 5 hr. Ammonia was liberated and, on cooling, a potassium salt crystallised. 5-Hydroxy-4-nitrothionaphthen was obtained as light yellow needles by acidifying an aqueous solution of the potassium salt, and after recrystallisation from ethanol (1.61 g., 85%) had m.p. 119-121° (Found: C, 49.2; H, 2.3. $C_8H_5NO_3S$ requires C, 49.2; H, 2.6%).

5-Hydroxy-4-nitrothionaphthen was also obtained by direct nitration of 5-hydroxythionaphthen.[145] To 5-hydroxythionaphthen (0.114 g., 0.76 mmole) dissolved in acetic acid (5 ml.) at 10°, concentrated nitric acid (0.048 ml., 0.76 mmole) in acetic acid (5 ml.) was gradually added. A red colour was immediately apparent, and on addition of water orange crystals were obtained. These formed yellow needles (0.070 g., 47%), m.p. 119° and mixed m.p. 119°, from ethanol; infrared spectra of the two samples in Nujol were identical.

5-Hydroxy-4-nitrothionaphthen-2-carboxylic acid

(LXII, R = CO_2H).- 5-Hydroxythionaphthen-2-carboxylic acid[140] (0.73 g., 3.8 mmole) was dissolved in acetic acid (20 ml.), and concentrated nitric acid (0.24 ml., 3.8 mmole) gradually added at 10°. Overnight the nitro-compound crystallised. Light yellow needles (0.54 g., 61%) were obtained from ethanol, having m.p. 273° and mixed m.p. with an authentic sample[140] 274°.

3-Bromo-5-hydroxy-4-nitrothionaphthen (LXV).- To a solution of 3-bromo-5-hydroxythionaphthen[139] (0.177 g., 0.77 mmole) in acetic acid (20 ml.) at 10°, concentrated nitric acid (0.05 ml., 0.77 mmole) in acetic acid (2.4 ml.) was added. Addition of water precipitated the nitro-compound which crystallised as needles (from ethanol)(0.124 g., 59%) with m.p. 160° (Found: C. 35.6; H, 1.7. $C_8H_4BrNO_3S$ requires C, 35.1; H, 1.5%). On reduction in ethanol with Raney-nickel and hydrazine hydrate, followed by oxidation with potassium ferricyanide, a green colour was obtained with triethylamine and ethyl cyanoacetate, indicating the formation of a 7-(cyanoethoxycarbonyl)-thionaphthen-4,5-quinone.

With excess of concentrated nitric acid, a

dinitro-compound was formed. 3-Bromo-5-hydroxythionaphthen (34 mg.) was dissolved in acetic acid (1 ml.), and 2 drops of concentrated nitric acid were added. Orange needles crystallised; recrystallisation from ethanol gave a product, m.p. 211-213° (36 mg., 76%) (Found: C, 30.2; H, 1.3. $C_8H_3BrN_2O_5S$ requires C, 30.1; H, 1.0%).

4-Bromo-5-hydroxy-6-nitrothionaphthen (LXVI).- To 4-bromo-5-hydroxythionaphthen[145] (2.0 g., 8.7 mmole) in acetic acid (20 ml.), concentrated nitric acid (0.55 ml., 8.7 mmole) was added at room temperature. Immediately, 4-bromo-5-hydroxy-6-nitrothionaphthen crystallised; it formed orange needles, m.p. 175-176° (1.4 g., 58%) from ethanol (Found: C, 35.5; H, 2.0; N, 5.4. $C_8H_4BrNO_3S$ requires C, 35.1; H, 1.5; N, 5.1%).

The methyl ether, prepared by reaction with an excess of ethereal-ethanolic diazomethane, formed pale yellow needles (95%), m.p. 114.5°, from ethanol (Found: C, 37.6; H, 1.9. $C_9H_6BrNO_3S$ requires C, 37.6; H, 2.1%).

5-Benzoyloxythionaphthen (LXVIII).- With benzoyl chloride (3.09 g., 0.022 mole) in ice-cold pyridine for 30 min., 5-hydroxythionaphthen (3.33 g., 0.022 mole) gave

the benzoyl derivative, forming cubic crystals (4.97 g., 88%), m.p. 111.5-113°, from light petroleum (b.p. 60-80°) (Found: C, 71.0; H, 4.1. $C_{15}H_{10}O_2S$ requires C, 70.9; H, 4.0%).

5-Benzoyloxy-3-bromothionaphthen.- 5-Benzoyloxythionaphthen (0.529 g., 2.0 mmole), sodium acetate (0.35 g., 5.0 mmole), and bromine (0.333 g., 2.0 mmole) were heated in acetic acid (10 ml.) on the steam bath for 30 min. Addition of water precipitated the crude bromo-compound, m.p. 130.5° (0.65 g., 69%) from light petroleum (b.p. 60-80°) (Found: C, 54.0; H, 2.7. $C_{15}H_9BrO_2S$ requires C, 54.1; H, 2.7%).

Hydrolysis in 5% sodium hydroxide solution at 90° gave 3-bromo-5-hydroxythionaphthen in quantitative yield, m.p. 135° and mixed m.p. 135-136°.

5-Benzoyloxy-3-nitrothionaphthen (LXIX).- To 5-benzoyloxythionaphthen (0.80 g., 3.15 mmole) in acetic acid (10 ml.) containing concentrated sulphuric acid (1 ml.), fuming nitric acid (0.22 ml., 3.5 mmole) was added. Within 2 hr., yellow needles of 5-benzoyloxy-3-nitrothionaphthen appeared. After crystallisation from ethyl

acetate, this had m.p. 180° (0.65 g., 69%) (Found: C, 60.3; H, 3.0. $C_{15}H_9NO_4S$ requires C, 60.2; H, 3.0%).

5-Hydroxy-3-nitrothionaphthen. (LXX).- Preliminary attempts to hydrolyse the benzoyl compound with dilute sodium hydroxide solution were unsuccessful. 5-Benzoyloxy-3-nitrothionaphthen (0.70 g., 2.3 mmole) was refluxed in absolute ethanol (200 ml.) containing concentrated hydrochloric acid (3 ml.) for 12 hours. The ethanol was removed under reduced pressure and the product extracted with 2N-sodium hydroxide solution. On acidification of this solution, the hydroxy-compound was precipitated. Fine yellow needles (0.060 g.), m.p. 164.5-166°, were obtained from water (Found: C, 49.2; H, 2.6. $C_8H_5NO_3S$ requires C, 49.2; H, 2.6%). Starting material (0.47 g.) was recovered.

4-Bromo-5-hydroxy-3-nitrothionaphthen (LXVII).- To 5-hydroxy-3-nitrothionaphthen (0.043 g., 0.22 mmole) and sodium acetate (0.05 g.) in acetic acid (4 ml.), bromine (0.0353 g., 0.22 mmole) in acetic acid was added at 10°. On addition of water, a pale yellow precipitate of 4-bromo-5-hydroxy-3-nitrothionaphthen separated;

fine yellow needles (0.051 g., 84.5%), m.p. 129-131°, were formed from light petroleum (b.p. 60-80°) (Found: C, 34.8; H, 1.8. $C_3H_4BrNO_3S$ requires C, 35.1; H, 1.5%).

4,6-Dibromo-4,5-dihydro-4-nitro-5-oxothionaphthen (LXXIV).- To 4,6-dibromo-5-hydroxythionaphthen (0.81 g., 2.6 mmole) in acetic acid (5 ml.), concentrated nitric acid (0.40 ml.) was added at 10°. Orange crystals of the keto-compound formed. Dilution of an acetic acid solution of the keto-compound with water gave 6-bromo-5-hydroxy-4-nitrothionaphthen, m.p. 124° and mixed m.p. 127°. A positive Craven's test with ethyl cyanoacetate and triethylamine was obtained after boiling in benzene.

5-Amino-4,6-dibromothionaphthen-2-carboxylic acid (LXXX).- Bromine (6.64 g., 0.0415 mole) was added to 5-aminothionaphthen-2-carboxylic acid (4.0 g., 0.0207 mole) and sodium acetate (3.1 g.) in hot acetic acid (800 ml.), and the resulting solution heated at 80° for 10 min. On cooling, prisms of the dibromo-compound crystallised; pale yellow needles (4.7 g., 65%) from ethanol had m.p. 314° (Found: C, 30.6; H, 1.7. $C_9H_5Br_2NO_2S$ requires C, 30.8; H, 1.4%).

5-Amino-4,6-dibromothionaphthen (LXXVIII).- The barium salt (0.158 g.) of 5-amino-4,6-dibromothionaphthen-2-carboxylic acid was prepared and heated *in vacuo* with barium hydroxide (0.50 g.). At 330°, decarboxylation took place, and 5-amino-4,6-dibromothionaphthen sublimed onto a cold finger. Colourless crystals (0.038 g., 33%) from ethanol had m.p. 119° (Found: C, 31.4; H, 1.5. $C_8H_5Br_2NS$ requires C, 31.3; H, 1.5%).

5-Amino-4,6-dibromothionaphthen was also obtained from 5-amino-4-bromothionaphthen. To a solution of this compound (0.50 g., 2.2 mmole) in acetic acid (5 ml.) was added bromine (0.35 g., 2.2 mmole) in acetic acid at room temperature, and the crude product was precipitated with water. After recrystallisation from ethanol it had m.p. 119° and mixed m.p. 119° (0.52 g., 77%); infrared spectra of the two samples in Nujol were identical.

5-Amino-6-bromo-4-nitrothionaphthen (LXXXII).- Bromine (0.163 g., 1.0 mmole) in acetic acid (5 ml.) was gradually added to a solution of 5-amino-4-nitrothionaphthen (0.175 g., 0.90 mmole) and sodium acetate (0.2 g.) in acetic acid (10 ml.), and the resulting

solution heated on the steam bath for 30 min. The bromo-compound was isolated by the addition of water, and crystallised from ethanol as orange needles (0.176 g., 71%) with m.p. 144-145° (Found: C, 35.1; H, 1.7. $C_8H_5BrN_2O_2S$ requires C, 35.2; H, 1.8%).

3-Bromo-5-nitrothionaphthen.- 5-Nitrothionaphthen (5.0 g., 0.0279 mole), bromine (4.47 g., 0.0279 mole), and sodium acetate (2.3 g.) were heated under reflux for 1 hr. in acetic acid (200 ml.) and, on cooling, red needles of the crude bromo-compound separated. Purification in hot ethanol (charcoal) gave pale yellow needles (5.9 g., 82%), m.p. 171°(Lit.,[142] 170-171°).

5-Amino-3-bromothionaphthen (LXXXIV).- 3-Bromo-5-nitrothionaphthen (4.59 g., 0.0178 mole) was hydrogenated with shaking in ethanol (250 ml.) at room temperature. Platinum oxide (200 mg.) was used as catalyst. After 2½ hr., 1200 ml. of hydrogen (0.05 mole, 94%) had been taken up. The solution was reduced to 50 ml. and dilute hydrochloric acid added. The amine hydrochloride thus precipitated was extracted with hot benzene to remove any unchanged nitro-compound and recrystallised from water as colourless

needles (2.64 g., 60%), m.p. 262° (Found: C, 36.2; H, 2.4. $C_8H_7BrClNS$ requires C, 36.3; H, 2.7%).

The free amine had m.p. 80-82°. With acetyl chloride in pyridine at 5° (2 hr.), it gave the acetyl derivative (LXXXV), forming plates (80%) with m.p. 164° from benzene (Found: C, 44.8; H, 3.2. $C_{10}H_8BrNOS$ requires C, 44.4; H, 3.0%).

5-Acetamido-3-bromo-4-nitrothionaphthen.- To 5-acetamido-3-bromothionaphthen (1.90 g., 7.04 mmole) in acetic acid (4 ml.), concentrated nitric acid (0.46 ml., 7.2 mmole) was added, and the solution heated on the steam bath for 15 min. On cooling, crystals of 5-acetamido-3-bromo-4-nitrothionaphthen separated; pale yellow needles (1.29 g., 58%) from ethanol had m.p. 197° (Found: N, 9.2. $C_{10}H_7BrN_2O_3S$ requires N, 8.9%).

The addition of excess nitric acid (0.5 ml.) to a solution of 5-acetamido-3-bromothionaphthen (0.50 g.) in acetic acid (1 ml.) gave, on heating on the steam bath for 15 min., yellow crystals (0.40 g.) of undertermined structure.

5-Amino-3-bromo-4-nitrothionaphthen (LXXXIII).-

Hydrolysis of 5-acetamido-3-bromo-4-nitrothionaphthen (1.25 g., 3.97 mmole) in ethanol and 2N sodium hydroxide solution (1:1) on the steam bath gave, on extraction with ether, 5-amino-3-bromo-4-nitrothionaphthen, which formed orange prisms (0.87 g., 80%), m.p. 150°, from ethanol (Found: N, 10.2. $C_8H_5BrN_2O_2S$ requires N, 10.3%).

When 5-amino-3-bromo-4-nitrothionaphthen (0.80 g.) was heated under reflux with Claisen's alkali[190] (25 ml.) for 3 hr., ammonia was liberated. Unreacted amine was recovered (0.29 g.) by dilution of the reaction mixture with water, and isolated by ether extraction. Acidification of the basic solution remaining gave pale yellow needles (0.31 g.) of 3-bromo-5-hydroxy-4-nitrothionaphthen (from benzene), m.p. 159° and mixed m.p. 159°. The infrared spectrum in nujol was identical with that of authentic 3-bromo-5-hydroxy-4-nitrothionaphthen.

5-Amino-3,4-dibromothionaphthen (LXXXVIII).- Bromine (0.152 g., 0.95 mmole) in acetic acid (1.2 ml.) was added gradually to a solution of 5-amino-3-bromothionaphthen (0.216 g., 0.95 mmole) in acetic acid (10 ml.). After 5 min. heating on the steam bath, 5-amino-3,4-dibromothionaphthen hydrobromide was precipitated. It

was shaken with ether and sodium hydroxide solution, and the dibromo-amine obtained from the ethereal solution by removal of the solvent under reduced pressure. White needles (0.21 g., 72%) were formed from light petroleum (b.p. 60-80°) and had m.p. 143° (Found: C, 31.7; H, 1.6. $C_8H_5Br_2NS$ requires C, 31.3; H, 1.6%).

5-Acetamido-3,4-dibromothionaphthen (LXXXVII).- 5-Acetamidothionaphthen (0.82 g., 4.3 mmole), bromine (1.36 g., 8.6 mmole), and sodium acetate (0.8 g.) were heated under reflux in acetic acid (40 ml.) for 1 hr. Addition of water precipitated a dibromo-compound which formed needles (0.87 g., 58%), m.p. 172°, from benzene (Found: C,34.5; H, 2.0. $C_{10}H_7Br_2NOS$ requires C, 34.4; H, 2.0%).

Hydrolysis of this compound (0.105 g.) in ethanol and 2N-sodium hydroxide solution (1:1) on the steam bath gave 5-amino-3,4-dibromothionaphthen (0.081 g., 90%), m.p. 143° and mixed m.p. 143°. The infrared spectrum in nujol was identical with that of authentic 5-amino-3,4-dibromothionaphthen.

5-Methoxythionaphthen.- Dimethyl sulphate

(0.189 g., 1.5 mmole) was added to 5-hydroxythionaphthen (0.217 g., 1.5 mmole) dissolved in 0.1N-sodium hydroxide (14.5 ml.), and the resulting mixture shaken for 1 hr. The methoxy compound was isolated as an oil by extraction with ether. White needles (0.12 g., 51%), m.p. 42° (lit.,[145] 44°), were obtained by sublimation at 150° under reduced pressure.

4-Bromo-5-methoxythionaphthen (LXXXIX).- 5-Methoxythionaphthen (0.079 g., 0.48 mmole), bromine (0.077 g., 0.48 mmole), and sodium acetate (0.08 g.) were warmed in acetic acid (4 ml.) on the steam bath for 30 min. The bromo-compound was precipitated by the addition of water; crystallisation from light petroleum (b.p. 60-80°) gave needles (0.093 g., 80%) with m.p. 90° (Found: C, 44.2; H, 2.8. C_9H_7BrOS requires C, 44.5; H, 3.0%)

4-Bromo-5-methoxythionaphthen was also prepared from 4-bromo-5-hydroxythionaphthen by methylation with dimethyl sulphate, then having m.p. 88-89° and mixed m.p. 89°.

3,4-Dibromo-5-methoxythionaphthen (XC).- (a) 4-Bromo-5-methoxythionaphthen (0.028 g., 0.115 mmole)

was heated in acetic acid with bromine (0.019 g., 0.118 mmole) on the steam bath for 30 min., and 3,4-dibromo-5-methoxythionaphthen was precipitated by water. White crystals (0.027 g., 73%) were obtained from light petroleum (b.p. 40-60°), m.p. 119° (Found: C, 33.9; H, 2.1. $C_9H_6Br_2OS$ requires C, 33.6; H, 1.9%).

(b) 3,4-Dibromo-5-hydroxythionaphthen[139] (0.37 g., 1.2 mmole) was shaken with 0.1N-sodium hydroxide (12 ml.) and dimethyl sulphate (0.164 g., 1.3 mmole) for 1 hr. The methoxy-compound, obtained by extraction with ether, had m.p. and mixed m.p. 122° (0.15 g., 70%) (from light petroleum (b.p.40-60°)). Starting material (0.18 g.) was recovered.

5-Methoxy-4-nitrothionaphthen.- 5-Hydroxy-4-nitrothionaphthen with an excess of diazomethane in ether gave 5-methoxy-4-nitrothionaphthen as pale yellow needles (82%) (from ethanol), m.p. 108° (Found: C, 51.6; H, 3.3. $C_9H_7NO_3S$ requires C, 51.9; H, 2.9%).

Trinitrothionaphthens.- Attempts to nitrate 5-nitrothionaphthen-2-carboxylic acid at room temperature led to recovery of unchanged starting material.

Concentrated nitric acid (1.2 ml., 0.019 mole) and concentrated sulphuric acid (9.0 ml.) were added to a solution of 5-nitrothionaphthen-2-carboxylic acid (2.1 g., 9.4 mmole) in acetic acid (30 ml.), and the solution was heated on the steam bath for 20 minutes. The addition of water precipitated an orange solid partially soluble in a small amount of benzene and forming light brown crystals (1.0 g., 29%) with m.p. 163°. The residue formed pale yellow needles (0.4 g., 12%), m.p. 193°, from ethanol. The infrared spectrum (Nujol) of neither compound showed carboxyl absorption; analyses were consistant with trinitrothionaphthens (Found: (a) C, 35.7; H, 1.3; N, 15.4 (b) C, 35.2; H, 1.0. $C_9H_3N_3O_6S$ requires C, 35.7; H, 1.1; N, 15.6%).

Methyl 5-hydroxythionaphthen-2-carboxylate.- (a) Excess of diazomethane (0.1 mole) in ether was added to a solution of 5-hydroxythionaphthen-2-carboxylic acid (3.51 g., 0.018 mole) in ethanol. After 24 hr., the solvent was removed under reduced pressure. The ester formed plates (3.60 g., 96%) from benzene with m.p. 162-163° (Found: C, 57.9; H, 3.9. $C_{10}H_8O_3S$ requires C, 57.7; H, 3.9%).

(b) A solution of 5-hydroxythionaphthen-2-carboxylic acid (14.2 g., 0.073 mole) in methanol (250 ml.) containing concentrated hydrochloric acid (10 ml.) was heated under reflux for 4 hr. The solvent was removed under reduced pressure. The white residue obtained in this way was dissolved in ether, and extracted with sodium carbonate solution to remove unreacted hydroxy-acid. The ester (12.0 g., 79%) was obtained by distillation of the ether, and had m.p. 163°, and mixed m.p. 163° with sample prepared by method (a). 5-Hydroxythionaphthen-2-carboxylic acid (2.4 g.) was recovered.

With acetyl chloride in pyridine at 5° (2 hr.), the ester gave the acetyl derivative which formed feathery needles (83%) with m.p. 130° from ethanol (Found: C, 57.4; H, 4.0. $C_{12}H_{10}O_4S$ requires C, 57.6; H, 4.0%).

3-Bromo-5-nitrothionaphthen-2-carboxylic acid (XCIV).- When bromine (8.0 g., 0.050 mole) was gradually added to a solution of sodium 5-nitrothionaphthen-2-carboxylate (12.0 g., 0.049 mole) in water (1 l.), a bromo-compound was precipitated (11.0 g., 73%). Efficient stirring was required to prevent the product

from being contaminated by unbrominated acid. Crystallisation from ethanol gave material of m.p. 307-309° (lit.,[140] 310°) (9.6 g., 63%). (When 5-nitrothionaphthen-2-carboxylic acid was heated under reflux with bromine and sodium acetate in acetic acid it was all recovered unchanged).

Barium 3-bromo-5-nitrothionaphthen-2-carboxylate was precipitated from a solution of the sodium salt by addition of aqueous barium chloride solution. After thorough drying, the barium salt (0.50 g.) was heated with barium hydroxide (0.50 g.) at 0.5 mm. At 300° vigorous decarboxylation took place and the product obtained by ether extraction crystallised from ethanol as pale yellow needles (0.12 g., 32%), m.p. 173° and mixed m.p. with 3-bromo-5-nitrothionaphthen 172°; infrared spectra in Nujol of the two samples were identical (Found: C, 37.3; H, 1.5. Calc. for $C_8H_4BrNO_2S$: C, 37.2; H, 1.5%).

Methyl-5-acetamidothionaphthen-2-carboxylate.- To 5-aminothionaphthen-2-carboxylic acid (1.1 g., 5.7 mmole) in methanol (20 ml.), an excess of ethereal diazomethane (0.01 mole) was added. The solvent was

allowed to evaporate overnight, and the product dissolved in pyridine (10 ml.). Acetyl chloride (0.46 g., 5.8 mmole) was added at 5°, and the acetyl compound precipitated by addition of water. White crystals (0.77 g., 54%) obtained from benzene-light petroleum (b.p. 60-80°) had m.p. 151° (Found: C, 57.8; H, 4.3. $C_{12}H_{11}NO_3S$ requires C, 57.8; H, 4.5%).

Methyl 3-bromo-5-nitrothionaphthen-2-carboxylate.- 3-Bromo-5-nitrothionaphthen-2-carboxylic acid (1.9 g., 6.3 mmole) in methanol (100 ml.) with ethereal diazomethane (0.01 mole) (12 hr.) gave the ester (1.8 g., 91%), m.p. 211-212° (from ethanol) (Found: C, 38.3; H, 2.0. $C_{10}H_6BrNO_4S$ requires C, 38.0; H, 1.9%).

Reduction with Raney Nickel and Hydrazine Hydrate.- The preceding ester (1.2 g., 3.8 mmole) was heated in ethanol with Raney-nickel (2 g.) and hydrazine hydrate (5 ml.) on the steam bath for 30 min. The product obtained by the removal of solvent under reduced pressure was immediately dissolved in pyridine (15 ml.), and acetyl chloride (0.30 g., 3.8 mmole) was added dropwise at 5°. Addition of water precipitated methyl 5-acetamido-

thionaphthen-2-carboxylate (0.65 g., 69%) m.p. 151° and mixed m.p. 150-151° (from benzene-light petroleum).

2,3-Dibromo-5-nitrothionaphthen (XCV).- Sodium 3-bromo-5-nitrothionaphthen-2-carboxylate (2.4 g., 7.4 mmole) was treated in distilled water (50 ml.) with excess of silver nitrate solution. The precipitated silver salt was dried and suspended in dry carbon tetrachloride (40 ml.) containing bromine (1.18 g., 7.5 mmole), and the mixture was heated under reflux for 2 hr. The precipitated silver bromide was removed from the hot solution. 2,3-Dibromo-5-nitrothionaphthen (1.75 g., 70%) crystallised in yellow needles with m.p. 216° (lit.,[140] 217-218°).

5-Iodothionaphthen.- 5-Aminothionaphthen sulphate (11.3 g., 0.057 mole) was suspended in water (1 l.) containing concentrated sulphuric acid (19.5 ml.). Sodium nitrite (4.5 g., 0.057 mole) in water (50 ml.) was added dropwise at 5° and the mixture stirred for 2 hr. The cold solution was filtered directly into one of potassium iodide (83 g., 0.5 mole) in water (500 ml.) and heated for 20 min. at 90°. Extraction with ether

followed by washing of this extract with potassium iodide solution and sodium hydroxide solution yielded, on removal of ether, 5-iodothionaphthen. Colourless crystals (6.3 g., 49%) from ethanol had m.p. 54° (Found: C, 37.1; H, 1.9. C_8H_5IS requires C, 36.9; H, 1.9%).

5,5'-Dithionaphthenylamine-2,2'-dicarboxylic acid (XCVI).- The yellow material obtained as by-product in the Bucherer reaction[140] was taken up in a minimum amount of dry pyridine, and the solution filtered through hardened filter paper. The solution was then diluted with water and acetic acid to give the acid with m.p. > 360°. Peaks at 1670 and 1284 cm.$^{-1}$ with broad absorption below 2800 cm.$^{-1}$ in the infrared spectrum in Nujol showed the presence of carboxylic acid functions whilst the peak at 3360 cm.$^{-1}$ indicated the secondary amine (Found: C, 58.5; H, 3.0; N, 3.8; S, 17.4. $C_{18}H_{11}NO_4S_2$ requires C, 58.6; H, 3.5; N, 3.8; S, 17.0%).

5,5'-Dithionaphthenylamine.- The foregoing acid (4.5 g.), copper bronze (8.0 g.), and quinoline (60 ml.) were heated under nitrogen at 180° for 45 min. Vigorous evolution of carbon dioxide was observed. The mixture

was allowed to cool under nitrogen and diluted with ether. After removal of the copper bronze and ether, the quinoline solution was poured into 6N-sulphuric acid (600 ml.). A brown solid was precipitated; from ethanol it formed feathery needles (2.2 g., 65%), m.p. 157-158° and mixed m.p. with an authentic sample 156° (infrared spectra of the two samples in nujol were identical) (Found: C, 67.9; H, 3.8; N, 5.2; S, 22.7. $C_{16}H_{11}NS_2$ requires C, 68.3; H, 3.9; N, 5.0; S, 22.8%).

5-5'-Dithionaphthenylamine was prepared unambiguously by an adaption of the method used for preparing diphenylamine[153]. 5-Aminothionaphthen (0.30 g.) and 5-aminothionaphthen hydrochloride (0.35 g.) were heated together in a sealed tube at 240° for 30 hr. The secondary amine was extracted with hot ethanol and formed needles (0.25 g., 43%) from ethanol with m.p. 156°.

3-Aminomethylthionaphthen hydrochloride (C).- 3-Chloromethylthionaphthen[160] (4.53 g., 0.025 mole) was dissolved in dimethylformamide (70 ml.) and heated under reflux with potassium phthalimide (4.59 g., 0.025 mole) for 3 hr. The condensation product was precipitated

by the addition of water, and formed white crystals (5.30 g., 73%) with m.p. 162° (lit.,[159] 163°) from ethyl acetate.

A slight excess of hydrazine hydrate (5 ml. 98-100%) was added to the substituted phthalimide (5.0 g.) in ethanol (250 ml.), and the solution heated under reflux for 20 min. A white solid crystallised from the hot solution, and after further refluxing in the presence of dilute hydrochloric acid (50 ml.) for 30 min., the solution obtained by filtration was made basic with dilute sodium hydroxide solution and extracted with ether to give 3-aminomethylthionaphthen (2.47 g., 89%) as a pale yellow liquid. The amine was characterised as the hydrochloride which formed colourless cubic crystals with m.p. 259-260° from ethanol (Found: C, 54.1; H, 5.2. $C_9H_{10}ClNS$ requires C, 54.1; H, 5.1%).

3-(Dimethylaminomethyl)-thionaphthen hydrochloride (CI).- 3-Aminomethylthionaphthen (1.0 g.), 36% formaldehyde solution (4 ml.), formic acid (4 ml.), and water (8 ml.) were gently warmed under reflux on the steam bath for 4 hr. Excess dilute hydrochloric acid was added and the solvent removed by distillation under reduced pressure

leaving 3-(dimethylaminomethyl)-thionaphthen hydrochloride as a white solid; colourless prisms (0.99 g., 71%) from ethanol had m.p. 218-222° (Found: C, 57.5; H, 6.0. $C_{11}H_{14}ClNS$ requires C, 58.0; H, 6.2%).

3-(Morpholinomethyl)-thionaphthen hydrochloride (CII).- Sodamide (3.7 g., 0.095 mole) was added to 3-chloromethyl thionaphthen (6.0 g., 0.033 mole) and morpholine (2.86 g., 0.033 mole) in dry toluene (70 ml.), and the mixture heated vigorously under reflux for 24 hr. A considerable darkening in colour was observed. Water was added to decompose the excess sodamide, and the organic layer separated. Distillation of the toluene under reduced pressure afforded the amine as a faintly coloured liquid, b.p. 208-210°/18 mm. 3-(Morpholinomethyl)-thionaphthen hydrochloride was obtained when dry hydrogen chloride was passed into an ethereal solution of the amine, and formed white needles (4.66 g., 52%) with m.p. 225° from chloroform (Found: C, 57.8; H, 5.8. $C_{13}H_{16}ClNOS$ requires C, 57.9; H, 6.0%).

A series of amines (table 4) were prepared and characterised by this procedure.

Table 4

Amine	b.p.(18 mm.)	m.p.(HCl)	Yield	Analyses Found	Analyses Required
3-(pyrrolidinomethyl)-thionaphthen	142-146°	190-191°	60%	C, 61.0; H, 6.4	C, 61.5; H, 6.4%
3-(piperidinomethyl)-thionaphthen*	152-156°	194-195°	59%	C, 50.6; H, 5.5	C, 50.7; H, 5.5%
3-(2'-methylpiperidinomethyl)-thionaphthen	146-150°	212°	53%	C, 63.4; H, 7.0	C, 63.9; H, 7.2%
3-(cyclohexylaminomethyl)-thionaphthen	195-205°	198°	35%	C, 64.2; H, 7.0	C, 63.9; H, 7.2%

* characterised as the amine perchlorate

Acid chloride of 5-nitrothionaphthen-2-carboxylic acid.- 5-Nitrothionaphthen-2-carboxylic acid (5.0 g.) was dissolved in thionyl chloride (60 ml.) and heated under reflux for 2 hr. The acid chloride, obtained as a brown crystalline solid by distillation of the excess thionyl chloride, formed pale yellow needles (5.1 g., 95%) with m.p. 160° from ethyl acetate (Found: C, 45.0; H, 1.7. $C_9H_4ClNO_3S$ requires C, 44.7; H, 1.7%).

2-(Morpholinocarbonyl)-5-nitrothionaphthen (CXII).- To the crude acid chloride obtained from 5-nitrothionaphthen-2-carboxylic acid (5.0 g., 0.022 mole) dissolved in 'analar' benzene (120 ml.), morpholine (3.2 ml., 0.044 mole) was added gradually with shaking at 10°, and the mixture heated under reflux for 1 hr. On cooling, the morpholine hydrochloride was filtered off. 2-(Morpholinocarbonyl)-5-nitrothionaphthen, obtained on removal of the benzene by distillation, formed pale yellow plates (4.55 g., 75%) with m.p. 189-190° from ethanol (Found: C, 53.6; H, 4.4. $C_{13}H_{12}N_2O_4S$ requires C, 53.4; H, 4.1%).

A 60% yield was obtained when the reaction was carried out in ice-cold pyridine.

Other substituted amides prepared from the acid chloride of 5-nitrothionaphthen-2-carboxylic acid by the same procedure are listed in table 5.

Table 5

Amide	m.p.
2-(dimethylaminocarbonyl)-5-nitrothionaphthen	141-142°
2-(pyrrolidinocarbonyl)-5-nitrothionaphthen	194-195°
2-(piperidinocarbonyl)-5-nitrothionaphthen	132°

Analyses	
Found	Required
C, 52.7; H, 3.8	C, 52.8; H, 4.0%
C, 56.5; H, 4.5	C, 56.5; H, 4.4%
C, 57.9; H, 5.0	C, 57.9; H, 4.9%

5-Amino-2-(morpholinomethyl)-thionaphthen (CXIV).- To 2-(morpholinocarbonyl)-5-nitrothionaphthen (4.50 g.) suspended in ethanol (150 ml.), 98% hydrazine hydrate solution (5 ml.) and Raney-nickel (2 g.) were added, and the mixture heated gently on the steam bath for 1 hr. The hot solution was filtered to remove the Raney-nickel, and on cooling, 5-amino-2-(morpholinocarbonyl)-thionaphthen (CXIII) (3.63 g., 90%) crystallised; fine needles from methanol had m.p. 189°.

The amine (1.00 g.) together with lithium aluminium hydride (3.0 g.) was dissolved in tetrahydrofuran (90 ml.), and heated under reflux for 48 hr; water was added gradually to decompose the excess lithium aluminium hydride, and the solution made basic with aqueous sodium hydroxide. The tetrahydrofuran was removed by distillation, and 5-amino-2-(morpholinomethyl)-thionaphthen isolated by ether extraction. Yellow crystalline plates (0.59 g., 65%) from ethyl acetate

had m.p. 147° (Found: C, 62.5; H, 6.3. $C_{13}H_{16}N_2OS$ requires C, 62.9; H, 6.5%).

The other nitro-amides were converted into diamines (Table 6) by the same procedure. These amines could not be obtained crystalline, and are characterised chemically as the N-benzoyl derivatives.

Table 6

Diamine	m.p.(amino-amide	m.p.(N-benzoyl derv.)	Analyses Found	Analyses Required
5-amino-2-(dimethylaminomethyl)-thionaphthen	148°	210-211°	C, 69.6; H, 5.9	C, 69.6; H, 5.9%
5-amino-2-(pyrrolidinomethyl)-thionaphthen	152-154°	207.5°	C, 71.1; H, 6.3	C, 71.4; H, 6.0%
5-amino-2-(piperidinomethyl)-thionaphthen	163°	200°	C, 71.9; H, 5.9	C, 72.0; H, 6.3%

5-Benzyloxythionaphthen-2-carboxylic acid (CV).- (a) To methyl 5-hydroxythionaphthen-2-carboxylate (4.40 g., 0.022 mole) dissolved in ethanol (25 ml.), sodium hydroxide solution (7.0 ml. of 2.98 N, 0.023 mole) and benzyl chloride (2.7 ml., 0.023 mole) were added

dropwise. After heating gently under reflux for 3 hr., water was added to the mixture followed by extraction with ether. The ethereal solution was washed with dilute sodium hydroxide solution to remove unreacted phenolic material, and on distillation of the ether, methyl 5-benzyloxythionaphthen-2-carboxylate was isolated as an oil.

Hydrolysis of the ester with 2N-sodium hydroxide solution (100 ml.) in ethanol (100 ml.) by heating on the steam bath for 45 min. gave, on acidification of the basic solution with dilute hydrochloric acid, 5-benzyloxythionaphthen-2-carboxylic acid. Prisms (3.10 g., 52%) from methanol had m.p. 220-221° (Found: C, 67.6; H, 4.3. $C_{16}H_{12}O_3S$ requires C, 67.6; H, 4.3%).

(b) To 5-hydroxythionaphthen-2-carboxylic acid (2.58 g., 0.013 mole) dissolved in sodium hydroxide solution (27.0 ml. of N, 0.027 mole) and ethanol (25 ml.), benzyl chloride (3.2 ml., 0.027 mole) was added dropwise and the solution heated under reflux for 3 hr. On cooling, benzyl 5-benzyloxythionaphthen-2-carboxylate separated, and was filtered and washed thoroughly with water to remove sodium chloride and unreacted sodium salt. Fine needles with m.p. 118-119° were obtained from

methanol (Found: C, 73.9; H, 4.8. $C_{23}H_{18}O_3S$ requires C, 73.8; H, 4.8%).

Hydrolysis of the benzyl ester was accomplished by heating for 1 hr. with 2N-sodium hydroxide solution in ethanol (1:1). 5-Benzyloxythionaphthen-2-carboxylic acid (2.0 g., 53%) separated on acidification with dilute hydrochloric acid, and formed cubic crystals with m.p. 220° from methanol. No depression was observed in a mixed m.p. with sample prepared by method (a).

5-Benzyloxy-2-(morpholinocarbonyl)-thionaphthen (CVIII).- 5-Benzyloxythionaphthen-2-carboxylic acid (1.0 g., 3.5 mmole) was dissolved in thionyl chloride (10 ml.), and heated gently under reflux for 2 hr. The crystalline acid chloride obtained on distillation of the excess thionyl chloride *in vacuo* was dissolved in a minimum amount of ice-cold pyridine (5 ml.). Morpholine (0.61 ml., 7.0 mmole) was added dropwise, and the solution allowed to stand at room temperature for 30 min. 5-Benzyloxy-2-(morpholinocarbonyl)-thionaphthen separated on the addition of water (200 ml.), and formed white plates (0.70 g., 57%) with m.p. 120° from methanol (Found: C, 68.5; H, 5.5. $C_{20}H_{19}NO_3S$ requires

C, 68.0; H, 5.4%).

5-Benzyloxy-2-(morpholinomethyl)-thionaphthen (CIX).- 5-Benzyloxy-2-(morpholinocarbonyl)-thionaphthen (0.50 g.) and lithium aluminium hydride (1.0 g.) in dry ether (150 ml.) were heated gently under reflux for 4 hr. Water was added dropwise to decompose the excess of lithium aluminium hydride, and the mixture shaken with sodium hydroxide solution. The ether layer was seperated, and on distillation of the ether 5-benzyloxy-2-(morpholinomethyl)-thionaphthen was obtained. The crystalline amine hydrochloride (0.32 g., 60%) had m.p. 223-224° (from ethanol).

Other related benzyloxy-amides and benzyloxy-amines were prepared and are listed in table 7.

Table 7

Benzyloxy-amine	m.p.(amide)
5-benzyloxy-2-(dimethylaminomethyl)-thionaphthen	118°
5-benzyloxy-2-(pyrrolidinomethyl)-thionaphthen*	152-154°
5-benzyloxy-2-(piperidinomethyl)-thionaphthen	145°

	Analyses	
m.p.(amine)	Found	Required
86-87.5°	C, 72.1; H, 6.3	C, 72.6; H, 6.4%
73-75°	C, 71.3; H, 5.6	C, 71.2; H, 5.7%
108°	C, 74.7; H, 6.5	C, 75.1; H, 6.9%

* analysed as the benzyloxy-amide.

5-Hydroxy-2-(morpholinomethyl)-thionaphthen (CX).- 5-Benzyloxy-2-(morpholinomethyl)-thionaphthen hydrochloride (0.25 g.) was warmed on the steam bath with concentrated hydrochloric acid (10 ml.) for 1 hr. The solution was made basic with sodium hydroxide solution, filtered, and the filtrate saturated with carbon dioxide (pH 8.3). 5-Hydroxy-2-(morpholinomethyl)-thionaphthen was obtained on ether extraction and formed white prisms (0.092 g., 55%) with m.p. 178° from ethyl acetate (Found: C, 62.7; H, 5.7. $C_{13}H_{15}NO_2S$ requires C, 62.6; H, 6.1%).

Other hydroxy-amines prepared by the same procedure were 2-(dimethylaminomethyl)-5-hydroxy-thionaphthen m.p. 158° (Found: C, 63.6; H, 5.8. $C_{11}H_{13}NOS$ requires C, 63.7; H, 6.3%), and 5-hydroxy-2-(pyrrolidinomethyl)-thionaphthen m.p. 125° (Found: C, 66.9; H, 5.9. $C_{13}H_{15}NOS$ requires C, 66.9; H, 6.5%).

Methiodides.- The following methiodides were also prepared from the corresponding amines and iodomethane in ethanol, and crystallised from ethanol - 3-(dimethylaminomethyl)-thionaphthen methiodide m.p. 192-193°, 3-(pyrrolidinomethyl)-thionaphthen methiodide m.p. 153°, 3-(piperidinomethyl)-thionaphthen methiodide m.p. 195-196°, and 3-(morpholinomethyl)-thionaphthen methiodide m.p. 207-209°.

5-Benzyloxy-3-bromothionaphthen (CXVII).- 3-Bromo-5-hydroxythionaphthen (7.26 g., 0.032 mole) was dissolved in N-sodium hydroxide solution (31.6 ml., 0.032 mole), benzyl chloride added (3.64 ml., 0.032 mole), and the mixture heated under reflux for 4 hr. On cooling, the reaction mixture was made basic by the addition of further sodium hydroxide solution, and extracted with ether. 5-Benzyloxy-3-bromothionaphthen was obtained as an oil on removal of the ether by distillation, but crystallised as white needles (4.84 g.) with m.p. 74-75° from diethyl ether or acetic acid (Found: C, 56.7; H, 3.7. $C_{15}H_{11}BrOS$ requires C, 56.4; H, 3.5%).

3-Bromo-5-hydroxythionaphthen (1.4 g.) with m.p. 136° was recovered by acidification of the basic

solution with dilute hydrochloric acid, and crystallisation from light petroleum (b.p. 60-80°).

5-Benzyloxythionaphthen-3-carboxylic acid (CXVIII).- Clean dry magnesium turnings (5.0 g.) were suspended in a solution of 5-benzyloxy-3-bromothionaphthen (5.20 g., 0.016 mole) and methyl iodide (10.1 ml., 0.16 mole) in dry ether (400 ml.), and the resulting mixture warmed gently under reflux for 5 hr. It was found necessary to initiate the reaction by scratching the magnesium turnings with a glass rod. Small pieces of solid carbon dioxide were added to the cooled reaction mixture for 15 minutes, and the Grignard complex decomposed by the addition of dilute hydrochloric acid. The ethereal layer was separated and extracted with dilute sodium hydroxide solution. 5-Benzyloxy-thionaphthen-3-carboxylic acid was obtained on acidification of this basic solution, and formed white prisms (2.22 g., 48%) with m.p. 224° from ethyl acetate (Found: C, 67.2; H, 4.6. $C_{16}H_{12}O_3S$ requires C, 67.6; H, 4.3%).

5-Benzyloxy-3-bromothionaphthen was recovered from the ethereal solution.

When only 2 equivalents of methyl iodide were

employed, the yield of acid was 20%.

5-Benzyloxy-3-thionaphthen-acetamide (CXIX).- A solution of 5-benzyloxythionaphthen-3-carboxylic acid (0.48 g.) in 'analar' benzene (20 ml.) and thionyl chloride (4 ml.) was heated under reflux for 45 min. The benzene and excess thionyl chloride were removed by distillation under reduced pressure, and the acid chloride dissolved in ether. Excess of an ethereal solution of diazomethane was added, and the solution allowed to stand for 24 hr. On removal of the ether by distillation at room temperature under reduced pressure, the diazoketone was obtained as yellow cubic crystals.

To a solution of the diazoketone in dioxan (6 ml.) at 60°, concentrated ammonium hydroxide solution (4.5 ml.) and 10% silver nitrate solution (0.9 ml.) were added, and after heating for 2 hr. under reflux, 5-benzyloxy-3-thionaphthen-acetamide was isolated by the addition of water. It formed white plates (0.20 g., 40%) with m.p. 171° from ethyl acetate (Found: C, 69.2; H, 5.1. $C_{17}H_{15}NO_2S$ requires C, 68.7; H, 5.1%).

3-(2'-Aminoethyl)-5-benzyloxythionaphthen hydrochloride (CXX).- 5-Benzyloxy-3-thionaphthen-acetamide (0.12 g.) was dissolved in dry ether (100 ml.) containing lithium aluminium hydride (1.0 g.), and the solution heated gently under reflux for 6 hr. Water was added gradually to decompose the excess lithium aluminium hydride, the ether solution shaken with dilute sodium hydroxide solution, and the ether layer separated. The amine was obtained as an oil (0.10 g.) on distillation of the ether.

The amine hydrochloride was prepared, and formed crystals (0.090 g., 70%) with m.p. 278-281° from ethanol (Found: C, 63.9; H, 5.3. $C_{17}H_{18}ClNOS$ requires C, 63.9; H, 5.7%).

5-Benzyloxy-3-(2'-nitrovinyl)-thionaphthen (CXXIV).- The acid chloride, obtained from 5-benzyloxythionaphthen-3-carboxylic acid (0.50 g.) by gently heating under reflux for 30 min. in thionyl chloride (10 ml.), was dried thoroughly under vacumn and dissolved in ethylene glycol dimethyl ether (2 ml.). To the solution cooled by a methylated spirit - solid carbon dioxide mixture, lithium tri-t-butoxyaluminohydride[177] (0.46 g.) dissolved

in ethylene glycol dimethyl ether (3 ml.) was added slowly. The reaction mixture was allowed to come to room temperature over a period of 30 min., and poured into water.

The oil obtained on ether extraction was immediately dissolved in nitromethane (3 ml.), and heated gently on the steam bath in the presence of ammonium acetate (0.20 g.) for 30 min. The product obtained on distillation of the nitromethane at reduced pressure was dissolved in benzene and chromatographed on grade 3 alumina. Yellow crystals of 5-benzyloxy-3-(2'-nitrovinyl)-thionaphthen with m.p. 149° were obtained from ethyl acetate (Found: C, 66.0; H, 4.1. $C_{17}H_{13}NO_3S$ requires C, 65.6; H, 4.2%).

5-Hydroxythionaphthen-3-carboxylic acid (CXXI).- 5-Benzyloxythionaphthen-3-carboxylic acid (0.55 g.) was dissolved in acetic acid (25 ml.) and concentrated hydrochloric acid (25 ml.), and heated on the steam bath for 3 hr. The reaction mixture was evaporated to dryness under reduced pressure, and the crude solid sublimed at 180°/0.5 mm. Fine white crystals (0.32 g., 84%) of 5-hydroxythionaphthen-3-carboxylic acid were

obtained, and had m.p. 260° (Found: C, 56.4; H, 3.3. $C_9H_6O_3S$ requires C, 55.8; H, 3.1%).

5-Hydroxy-3-hydroxymethylthionaphthen (CXXII).- 5-Hydroxythionaphthen-3-carboxylic acid (0.226 g.) and lithium aluminium hydride (0.5 g.) were dissolved in dry ether (250 ml.) and heated under reflux for 24 hr. The excess lithium aluminium hydride was decomposed by the careful addition of water, followed by the addition of dilute hydrochloric acid. The ether layer was separated and on distillation of the ether, 5-hydroxy-3-hydroxymethylthionaphthen was obtained. White crystals (0.15 g., 72%) from ethyl acetate had m.p. 176-178° (Found: C, 60.0; H, 4.0. $C_9H_8O_2S$ requires C, 60.0; H, 4.5%).

5-Hydroxy-2-hydroxymethylthionaphthen.- A solution of methyl 5-hydroxythionaphthen-2-carboxylate (2.53 g.) and lithium aluminium hydride (0.50 g.) in tetrahydrofuran (80 ml.) was heated under reflux for 3 hr. The excess lithium aluminium hydride was decomposed by the careful addition of water. Dilute sulphuric acid was added to dissolve the inorganic material, and the tetrahydrofuran removed by distillation. The alcohol

was isolated by ether extraction and formed white plates (1.60 g., 73%) with m.p. 199° from ethyl acetate (Found: C, 60.1: H, 4.3. $C_9H_8O_2S$ requires C, 60.0; H, 4.5%).

3-Cyano-5-nitrothionaphthen.- 3-Bromo-5-nitrothionaphthen (5.0 g., 0.019 mole) and cuprous cyanide (1.7 g., 0.019 mole) were heated under reflux for 4½ hr. in quinoline (40 ml.) and the hot solution poured into 2N-hydrochloric acid (200 ml.). After filtration, the solid product was extracted with hot ethanol from which 3-cyano-5-nitrothionaphthen crystallised as pale yellow plates (2.7 g., 68%) with m.p. 180° (Found: C, 53.3; H, 2.2. $C_9H_4N_2O_2S$ requires C, 53.0; H, 2.0%).

1-(5'-Hydroxythionaphthen-2'-yl-carbonyl)-2-p-toluenesulphonyl hydrazine (CXXVII).- Methyl 5-hydroxythionaphthen-2-carboxylate (4.0 g.) was dissolved in methanol (80 ml.), hydrazine hydrate (10 ml.) added, and the solution heated under reflux for 4 hr. The acid hydrazide crystallised out of the hot solution and formed pale yellow needles (3.64 g., 91%) with m.p. 282-284° from acetic acid.

p-Toluenesulphonyl chloride (2.58 g., 0.014 mole)

in dry pyridine (30 ml.) was added dropwise to an ice-cold solution of the hydrazide (2.84 g., 0.014 mole) in dry pyridine (50 ml.) over a period of 30 min. The solution was allowed to stand for a further 30 min. at room temperature, and poured into water (1500 ml.). 1-(5'-hydroxy-thionaphthen-2'-yl-carbonyl)-2-p-toluenesulphonyl hydrazine was obtained by filtration, and formed pale yellow prisms (3.39 g., 69%) with m.p. 215° from ethyl acetate (Found: C, 53.0; H, 4.3. $C_{16}H_{14}N_2O_4S_2$ requires C, 53.0; H, 3.9%).

5-Hydroxythionaphthen-2-aldehyde (CXXVIII).- 1-(5'-Hydroxythionaphthen-2'-yl-carbonyl)-2-p-toluene-sulphonyl hydrazine (1.86 g., 5.15 mmole) in ethylene glycol (8 ml.) was heated with an oil bath, and at 160° anhydrous sodium carbonate (1.36 g., 12.8 mmole) added. Vigorous effervesence took place, and after 90 sec., the reaction mixture was poured into water. The aldehyde was extracted with ether, and formed pale yellow needles (0.43 g., 47%) with m.p. 193-196° from ethyl acetate (Found: C, 60.7; H, 3.6. $C_9H_6O_2S$ requires C, 60.7; H, 3.4%).

5-Hydroxy-2-(2'-nitrovinyl)-thionaphthen (CXXIX).- To a solution of 5-hydroxythionaphthen-2-aldehyde (0.79 g.)

in nitromethane (6 ml.), ammonium acetate (0.25 g.) was added, and the mixture heated gently on the steam bath for 30 min. On cooling, crystals of 5-hydroxy-2-(2'-nitrovinyl)-thionaphthen separated, and were filtered and washed with hot water. Red cubes (0.60 g., 61%) from ethyl acetate had m.p. 220° (Found: C, 54.7; H, 3.3. $C_{10}H_7NO_3S$ requires C, 54.3; H, 3.2%).

5-Hydroxy-2-(2'-methyl-2'-nitrovinyl)-thionaphthen (CXXXI).- To a solution of 5-hydroxythionaphthen-2-aldehyde (1.46 g.) in nitroethane (10 ml.), ammonium acetate (0.40 g.) was added, and the mixture heated gently on the steam bath for 30 min. On cooling, 5-hydroxy-2-(2'-methyl-2'-nitrovinyl)-thionaphthen separated; yellow cubes (1.20 g., 62%) from ethyl acetate had m.p. 223.5-224° (Found: C, 56.1; H, 3.5. $C_{11}H_9NO_3S$ requires C, 56.2; H, 3.8%).

2-(2'-Aminoethyl)-5-hydroxythionaphthen hydrochloride (CXXX).- Lithium aluminium hydride (0.5 g.) was added to dry tetrahydrofuran (150 ml.) in the flask of a Soxhlet extractor, and 5-hydroxy-2-(2'-nitrovinyl)-thionaphthen (0.23 g.) extracted from the thimble for 3 hr. The

solution developed a green colouration. After the excess lithium aluminium hydride had been decomposed by the careful addition of water, 2N-sodium hydroxide solution (100 ml.) was added, and the tetrahydrofuran removed by distillation. The basic solution was filtered, saturated with carbon dioxide (pH 8.3), and extracted continuously with ether for 24 hr. Dry hydrogen chloride was passed into the ether solution, and 2-(2'-aminoethyl)-5-hydroxythionaphthen hydrochloride was precipitated. It formed white plates (0.123 g., 52%) with m.p. 296° from methanol (Found: C, 52.8; H, 5.5. $C_{10}H_{12}ClNOS$ requires C, 52.3; H, 5.3%).

2-(2'-Aminopropyl)-5-hydroxythionaphthen hydrochloride (CXXXII).- 5-Hydroxy-2-(2'-methyl-2'-nitrovinyl)-thionaphthen was reduced with lithium aluminium hydride in tetrahydrofuran by the same procedure as was employed in the case of 5-hydroxy-2-(2'-nitrovinyl)-thionaphthen. White needles of 2-(2'-aminopropyl)-5-hydroxythionaphthen hydrochloride were obtained from methanol, and had m.p. 267-270° (Found: C, 54.2; H, 5.8. $C_{11}H_{14}ClNOS$ requires C, 54.2; H, 5.6%).

6-Ethoxythioindoxyl; 6-ethoxy-3-oxo-2,3-dihydrothionaphthen (CXXXIII).- Fine white needles of 6-ethoxythioindoxyl with m.p. 126° (lit.,[191] 124-125°) were obtained by crystallisation (from ethyl acetate) of the crude compound supplied by ICI Dyestuffs Division.

6-Ethoxythionaphthen-3-acetic acid (CXXXVI).- Ethylbromacetate (34.4 g., 0.206 mole) and small pieces of zinc wool (13.5 g., 0.206 mole) were added to a solution of 6-ethoxythioindoxyl (20.0 g., 0.103 mole) in dry benzene (100 ml.) and dry toluene (100 ml.). The mixture was heatly gently to initiate the reaction, allowed to stand for 30 min., and then heated under reflux for 4 hr. The reaction mixture was diluted with benzene (400 ml.), shaken with dilute sulphuric acid, and the organic layer separated and filtered. The dark viscous oil obtained on distillation of the benzene and toluene was hydrolysed by heating with 2N-sodium hydroxide solution (200 ml.) in ethanol (250 ml.) on the steam bath for 2 hr. The hot solution was filtered after treatment with charcoal. Acidification with dilute hydrochloric acid gave an oily precipitate which was dissolved in ether and extracted with sodium carbonate solution. 6-Ethoxythionaphthen-3-

acetic acid was obtained by acidification of the carbonate solution, and separated by ether extraction. It formed white needles (4.8 g., 20%) with m.p. 105° from benzene (Found: C, 61.4; H, 5.2. $C_{12}H_{12}O_3S$ requires C, 61.0; H, 5.1%).

Thionaphthen-3-acetic acid.- Thioindoxyl[188] (5.0 g., 0.033 mole), purified by steam distillation, was dissolved in dry toluene (100 ml.), and ethylbromacetate (5.57 g., 0.033 mole) and zinc (2.18 g., 0.033 mole) added. The mixture was warmed gently to initiate the reaction, and then heated under reflux for 2 hr. with stirring. Thionaphthen-3-acetic acid was isolated by the technique employed for the separation of 6-ethoxythionaphthen-3-acetic acid. White needles from benzene had m.p. 108-109° (lit.,[123] 109°).

6-Ethoxythionaphthen-3-acetamide (CXXXVII).- 6-Ethoxythionaphthen-3-acetic acid (2.0 g.) was dissolved in benzene (40 ml.), oxalyl chloride (2.0 ml.) added, and the solution heated gently under reflux for 30 min. The acid chloride remained as a light coloured oil on distillation of the benzene and excess oxalyl chloride at reduced pressure. Concentrated ammonia solution was

added, and the amide separated as a white solid; plates (1.73 g., 87%) from methanol had m.p. 197-200° (Found: C, 61.8; H, 5.4. $C_{12}H_{13}NO_2S$ requires C, 61.3; H, 5.6%).

3-(2'-Aminoethyl)-6-ethoxythionaphthen (CXXXVIII).- 6-Ethoxythionaphthen-3-acetamide (1.00 g.) was added to a solution of lithium aluminium hydride (3.0 g.) in dry ether (80 ml.), and the solution heated gently under reflux for 4 hr. The excess of lithium aluminium hydride was decomposed by the careful addition of water. Dilute sodium hydroxide solution was added, and the ether layer separated. The amine (0.78 g., 83%) was obtained as an oil on distillation of the ether, and formed a solid water-soluble hydrobromide.

With benzoyl chloride in pyridine at 5° (30 min.), this gave the N-benzoyl derivative; white needles from diethyl ether had m.p. 100.5-101.5° (Found: C, 70.2; H, 6.1. $C_{19}H_{19}NO_2S$ requires C, 70.1; H, 5.9%).

3-(2'-Aminoethyl)-6-hydroxythionaphthen hydrochloride (CXXXIX).- 3-(2'-Aminoethyl)-6-ethoxythionaphthen (0.50 g.) was heated under reflux with hydrobromic acid (10 ml.) in acetic acid (10 ml.) for 16 hr. The solution was

made basic with dilute sodium hydroxide solution, filtered, and the filtrate saturated with carbon dioxide (pH 8.3). Continuous extraction of this solution with ether for 4 hr. gave 3-(2'-aminoethyl)-6-hydroxythionaphthen (0.24 g., 46%) as a glass. The amine hydrochloride was prepared, and formed prisms with m.p. 205° from ethanol (Found: C, 52.6; H, 5.1. $C_{10}H_{12}ClNOS$ requires C, 52.3; H, 5.3%).

N-acetyl-3-(2'-aminoethyl)-6-ethoxythionaphthen.- 3-(2'-Aminoethyl)-6-ethoxythionaphthen (0.77 g., 3.5 mmole) was dissolved in dry pyridine (3 ml.), acetyl chloride (0.25 ml., 3.5 mmole) added dropwise, and the reaction mixture allowed to stand for 10 min. On addition of water, the N-acetyl derivative crystallised. It formed fine white platlets (0.75 g., 82%) with m.p. 128-129° from benzene (Found: C, 63.8; H, 6.3. $C_{14}H_{17}NO_2S$ requires C, 63.8; H, 6.5%).

7-Ethoxy-1-methyl-3,4-dihydrothionaphtheno(2.3-C)-pyridine hydrochloride (CXL).- N-Acetyl-3-(2'-aminoethyl)-6-ethoxythionaphthen (0.50 g.), phosphorus pentoxide (1.0 g.), and phosphorus oxychloride (1.0 g.) were heated under reflux for 4 hr. in dry toluene (40 ml.); water

was added dropwise, and the aqueous layer separated, made basic with sodium hydroxide solution, and extracted (3 times) with benzene. Chromatography on grade 3 alumina in benzene gave the tricyclic product as a crystalline solid (0.23 g., 50%) with m.p. 47-49°. The hydrochloride was prepared and formed colourless plates with m.p. 212-218° from ethanol (Found: C, 60.2; H, 5.9. $C_{14}H_{16}ClNOS$ requires C, 59.7; H, 5.7%).

7-Ethoxy-1-methylthionaphtheno(2,3-C)pyridine (CXLI).- 7-Ethoxy-1-methylthionaphtheno(2,3-C)pyridine was prepared from the corresponding 3,4-dihydro compound by dehydrogenation. The dihydro compound (0.40 g.) and Adam's catalyst (0.40 g.) were heated together for 30 min. at 190-200°. The residue was extracted with hot methanol, treated with activated charcoal, and filtered. White needles (0.175 g., 43%) of 7-ethoxy-1-methylthionaphtheno(2,3-C)pyridine were formed from methanol. On standing in contact with methanol at room temperature for 1 hr., these needles were converted into prisms with m.p. 151° (Found: C, 69.3; H, 5.4. $C_{14}H_{13}NOS$ C, 69.1; H, 5.4%).

References.

1 Ing, Il Farmaco, 1959, 14, 612; Beckett and Casy, J.Pharm.Pharmacol., 1955, 7, 433.

2 Ferguson, Proc.Roy.Soc., 1939, 127B, 387; Ferguson and Pirie, Ann.App.Biol., 1948, 35, 532; Badger, Nature, 1946, 158, 585; Brink and Posternak, J.Cell. Comp.Physiol., 1948, 32, 211.

3 Fischer, Ber., 1894, 27, 2985.

4 Clark, "Mode of Action of Drugs on Cells," Arnold, London, 1933; Clark, in "Hefters Handbuch Exp. Pharm.," Erg.Werk.Bnd.IV, Springer Verlag, Berlin, 1937.

5 Koelle, J.Pharmacol., 1957, 120, 488.

6 Nickerson and Goodman, Fed.Proc., 1948, 7, 397; Chapman, James, Graham, and Lewis, Chem. and Ind., 1952, 805; Chapman and James, J.Chem.Soc., 1953, 1865; Agarwal and Harvey, J.Pharmacol., 1956, 117, 106.

7 Golumbic, Fruton, and Bergmann, J.Org.Chem., 1946, 11, 518.

8 Pfeiffer, Science, 1948, 107, 94; Ing, ibid., 1949, 109, 264; Kimura, Unna, and Pfeiffer, J.Pharmacol., 1949, 95, 149; Nachmansohn and Wilson, Adv.Enzymology, 1951, 12, 259; Schueler, Arch.int.Pharmacodyn., 1953 93, 417.

9 Beckett et al., J.Pharm.Pharmacol., 1956, 8, 848,860,874.

10 Katz, Brit.Med.Bull., 1956, 12, 210.

11 Martin, "Biological Antagonism," Blakiston Co., New York, 1951; Woolley, "A Study of Antimetabolites," Wiley and Sons, New York, 1952; Work and Work, "The Basis of Chemotherapy," Oliver and Boyd, Edinburgh, 1948; Albert, "Selective Toxicity," Methuen, London, 1951.

12 Symposium on Drug Antagonism in Pharmacol.Reviews, 1957, 9, 211; Ariens, van Rossum, and Simonis, Arzneimittel Forschung, 1956, 6, 282; Ariens et al., Arch.int.Pharmacodyn., 1954, 99, 32,174,193.

13 Shive and Roberts, J.Biol.Chem., 1946, 162, 463; Shive, Ann.N.Y.Acad.Sci., 1950, 52, 1212.

14 Albert, "Selective Toxicity," Methuen, London, 1951.

15 Winerbottom, Clapp, Miller, English, and Roblin, J.Amer.Chem.Soc., 1947, 69, 1393; Marshall, Fed. Proc., 1946, 5, 298; Woolley and White, Proc.Soc. Exp.Biol.N.Y., 1943, 52, 106; Unna, ibid., 1943, 54, 55.

16 Ahlquist, Amer.J.Physiol., 1948, 153, 586; McCutcheon and Ahlquist, J.Amer.Pharmaceut.Assoc., 1959, 48, 647.

17 Gaddum and Picarelli, Brit.J.Pharmacol., 1957, 12, 323.

18 Langmuir, J.Amer.Chem.Soc., 1919, 41, 1543.

19 Meunier, Bull.Soc.chim., 1945, 12, 517; Bradlow, Vanderwerf, and Kleinberg, J.Chem.Educ., 1947, 24, 433; Erlenmeyer, Bull.Soc.Chim.biol., 1948, 30, 792; Burger, "Medicinal Chemistry," Interscience, New York, 1951, Vol.I; Burger, J.Chem.Educ., 1956, 33, 362.

20 Friedman, Nat.Res.Counc., Wash., 1951, Pub. 206; Friedman, Data presented at the section on Microbiological Deterioration, Gordon Research Conferences, New Hampton, New Hampshire, 1953.

21 Blicke and Hartough, "Thiophen and its Derivatives," Interscience, New York, 1952, pp. 29-45; Nord, Vaitiekunas, and Owen, Fortschr.Chem.Forsch., 1955, 3, 312; Campaigne, J.Amer.Pharmaceut.Assoc., 1957, 46, 129; Aurousseau, Prod.pharm., 1958, 13, 189.

22 Martin-Smith and Reid, J.Medicin.Pharmaceut.Chem., 1959, 1, 507.

23 Stowe, Fortschr.der.Chem.Organischer Naturstoffe, 1959, 17, 248.

24 Feinberg and McCulloch, Proc.Soc.Exp.Biol.N.Y., 1944, 56, 193.

25 Chen and Chen, J.Amer.Pharmaceut.Assoc., 1933, 22, 813.

26 Erspamer, Pharmacol.Reviews, 1954, 6, 425.

27 Feldberg and Smith, Brit.J.Pharmacol., 1953, 8, 406.

28 Udenfriend, Titus, Weissbach, and Peterson, J.Biol. Chem., 1956, 219, 335

29 Amin, Crawford, and Gaddum, J.Physiol., 1954, 126, 576.

30 Rapport, J.Biol.Chem., 1949, 180, 961; Rapport, Green, and Page, ibid., 1948, 176, 1243.

31 Erspamer, "Ciba Foundation Symposium on Hypertension," Churchill, London, 1954, pp. 78-84.

32 Erspamer and Ottolengi, Arch.int.Pharmacodyn., 1953, 93, 177.

33 Johansson, Acta physiol. Scand., 1960, 48, 126.

34 Armstrong, Dry, Keele, and Markham, J.Physiol., 1952, 117, 70; 1953, 120, 326.

35 Pletscher, Shore, and Brodie, J.Pharmacol., 1956, 116, 84: Pletscher, Shore and Brodie, Science, 1955, 122, 374.

36 Paasonen and Vogt, J.Physiol., 1956, 131, 617.

37 Brodie, Pletscher, and Shore, Science, 1955, 122, 968.

38 Woolley and Shaw, Proc.Nat.Acad.Sci., 1954, 40, 228.

39 Ann.N.Y.Acad.Sci., 1959, 80, pp 551-1045.

40 Lewis, "5-Hydroxytryptamine," Pergamon Press, London, 1958; Page, Physiol.Reviews, 1954, 34, 563; 1958, 38, 277; Crossland, J.Pharm.Pharmacol., 1960, 12, 1

41 Udenfriend, Vitamins and Hormones, 1959, 17, 133.

42 Davey, Canad.J.Zoology, 1960, 38, 39.

43 Knowles and Carlisle, Biol.Reviews, Cambridge Phil. Soc., 1956, 31, 396.

44 See inter alia, Woolley and Shaw, J.Amer.Chem.Soc., 1952, 74, 2948; Shaw and Woolley, J.Biol.Chem., 1953, 203, 69,979; Woolley and Shaw, J.Pharmacol., 1953, 108, 87; Shaw and woolley, ibid., 1954, 111, 43; Quadbeck and Röhm, Z.physiol.Chem., 1954, 297, 229; Sletzinger, Gaines, and Ruyle, Chem. and Ind., 1957, 1215; Swaminathan and Sulochana, J.Org.Chem., 1958, 23, 90; Greig, Walk, and Gibbons, J.Pharmacol., 1959, 127, 110.

45 Gaddum, Hameed, Hathway, and Stevens, Quart.J.Exp. Physiol., 1955, 40, 49.

46 Erspamer, Science, 1955, 121, 369.

47 Woolley and Shaw, Ann.N.Y.Acad.Sci., 1957, 66, 649.

48 Harris and Uhle, J.Pharmacol., 1960, 128, 358.

49 Shaw and Woolley, Proc.Soc.Exp.Biol.N.Y., 1956, 93, 217; Woolley and Shaw, Science, 1956, 124, 34; Woolley and Shaw, J.Pharmacol., 1957, 121, 13.

50 Stoll and Hofmann, Helv.Chim.Acta, 1943, 26, 944; Page, Ann.N.Y.Acad.Sci., 1957, 66, 592; Rothlin,

ibid., 1957, 66, 668.

51 Gaddum, J.Physiol., 1953, 121, 15P.

52 Cerletti and Rothlin, Nature, 1955, 176, 785; Sollero, Page, and Salmoiraghi, J.Pharmacol., 1956, 117, 10.

53 Rothlin, J.Pharm.Pharmacol., 1957, 9, 569.

54 Cerletti and Doepfner, J.Pharmacol., 1958, 122, 124.

55 Zanowiak and Rodman, J.Amer.Pharmaceut.Assoc., 1959, 48, 165.

56 Freter, Weissbach, Redfield, Udenfriend, and Bitkop, J.Amer.Chem.Soc., 1958, 80, 983.

57 Fabing and Hawkins, Science, 1956, 123, 886.

58 Evarts, Arch.Neurol.Psychiat., 1956, 75, 49.

59 Hofmann, Frey, Ott, Petrzilka, and Troxler, Experientia, 1958, 14, 397.

60 Weidmann, Taeschler, and Konzett, Experientia, 1958, 14, 378.

61 Woolley and Shaw, J.Biol.Chem., 1953, 203, 979.

62 Brodie, Tomich, Kuntzman, and Shore, J.Pharmacol., 1957, 119, 461; Brodie and Shore, Ann.N.Y.Acad.Sci., 1957, 66, 631.

63 Fingl and Gaddum, Fed.Proc., 1953, 12, 320; Gaddum, Ann.N.Y.Acad.Sci., 1957, 66, 643.

64 Hoagland, ibid., 1957, 66, 445.

65 Stoll, Experientia, 1945, 1, 250.

66 Nelson and Calvery, Physiol.Reviews, 1938, 18, 297.

67 Dybowski and Landrin, Compt.rend., 1901, 133, 748; Haller and Heckel, ibid., 1901, 133, 850; Bartlett, Diekel, and Taylor, J.Amer.Chem.Soc., 1958, 80, 126.

68 Schneider and Sigg, Ann.N.Y.Acad.Sci., 1957, 66, 765.

69 Salmoiraghi and Page, J.Pharmacol., 1957, 120, 20.

70 Raymond-Hamet and Rothlin, Arch.int.Pharmacodyn., 1939, 63, 27.

71 Hooper, Chem.Zentr., 1888, 1, 725.

72 Rozenfeld, Chem.Abs., 1931, 25, 2811.

73 Gunn, Quart.J.Pharm., 1930, 3, 1; Gunn and Simonart, ibid., 1930, 3, 218; Gunn and Heathcote, ibid., 1931, 4, 549; Gunn, Arch.int.Pharmacodyn., 1935, 50, 379.

74 Raymond-Hamet, Compt.rend.Soc.Biol., 1941, 135, 328; Raymond-Hamet, Compt.rend., 1945, 221, 387.

75 Scriabine and Hutcheon, J.Pharmacol., 1956, 118, 239.

76 Ahmed, Marshall, and Shepherd, J.Pharm.Pharmacol., 1958, 10, 672.

77 Abood and Romanchek, Ann.N.Y.Acad.Sci., 1957, 66, 812.

78 Pyman, Chem. and Ind., 1937, 56, 789.

79 Cavallito, Gray, and O'Dell, Arch.int.Pharmacodyn.,

1955, 101, 38; O'Dell, Luna, and Napoli, J.Pharmacol., 1955, 114, 317.

80 U.S.P. 2,759,000 in Chem.Abs., 1957, 51, 3669.

81 Ray and Sarin, J.Indian Chem.Soc., 1941, 17, 619.

82 von Euler and Hellstrom, Z.physiol.Chem., 1933, 217, 23; Kirkwood and Marion, J.Amer.Chem.Soc., 1950, 72, 2522.

83 Massa and Stolfi, Arch.Sci.biol.(Italy), 1931, 16, 183.

84 Powell and Chen, Proc.Soc.Exp.Biol.N.Y., 1945, 58, 1.

85 Supniewski and Serafinovna, Bull.int.acad.polon., Classe med., 1937, 479 in Chem.Abs., 1939, 33, 8788.

86 DeJongh and van Proosdj-Hartzema, J.Pharmacol., 1952, 105, 130.

87 Erdtman and Löfgren, Svensk kem.Tidskr., 1937, 49, 163.

88 Craig and Tarbell, J.Amer.Chem.Soc., 1949, 71, 462.

89 Boekelheide and Ainsworth, J.Amer.Chem.Soc., 1950, 72, 2132.

90 Gray, J.Amer.Chem.Soc., 1953, 75, 1252.

91 Smith, J.Amer.Med.Assoc., 1938, 111, 2201.

92 Sollmann, "A Manual of Pharmacology," Saunders, Philadelphia, 1957, 8th Ed., p. 535.

93 Chu, Science Record (China), 1951, 4, 279.

94 Asahina and Kashiwaki, J.Pharm.Soc.Japan, 1915, 405, 1293; Ling Chen and Chen, J.Amer.Pharmaceut.Assoc., 1933, 22, 716.

95 Hofmann and Seeback, Helv.Chim.Acta, 1957, 40, 508.

96 Bein, Pharmacol.Reviews, 1956, 8, 435.

97 U.S.P. 2,793,210 in Chem.Abs., 1958, 52, 9230.

98 Bein, Ann.N.Y.Acad.Sci., 1955, 61, 4.

99 Nograd, Monatsh., 1957, 88, 768,1087.

100 Lucas, Kiesel, and Ceglowski, J.Amer.Chem.Soc., 1960, 82, 493; Karim, Linnell, and Sharp, J.Pharm. Pharmacol., 1960, 12, 74, 82.

101 Cronheim. Stipp, and Brown, J.Pharmacol., 1954, 110, 13.

102 Turner and Woodward, "The Alkaloids," Ed. Manske and Holmes, Academic Press, New York, 1953, Vol. 3, P. 54.

103 White and Hale, "Textbook of Pharmacology and Therapeutics," Pentland, Edinburgh, 1901, p. 623.

104 Jobst and Hesse, Annalen, 1864, 129, 115; Hesse, ibid., 1867, 141, 82.

105 Woodward and Brehm, J.Amer.Chem.Soc., 1948, 70, 2107.

106 Pogdanski, Weissbach, and Udenfriend, Fed.Proc., 1956, 15, 402.

107 Mills and Nyburg, Tetrahedron Letters, 1959, 11, 1; Conroy, Brook, and Amiel, ibid., 1959, 11, 4.

108 Banerjee and Lewis, J.Pharm.Pharmacol., 1955, 7, 46.

109 Bovet, Bovet-Nitti, and Marini-Bettolo, "Curare and Curare-like Agents," Elsevier, 1959; Craig, "The Alkaloids," Ed.Manske, Academic Press, New York, 1955, Vol. 5, p. 265.

110 Battersby and Hodson, Quart.Reviews, 1960, 14, 77.

111 Fritz, Besch, and Wieland, Angew.Chem., 1959, 71, 126; von Philipsborn, Bernauer, Schmid, and Karrer, Helv.Chim.Acta, 1959, 42, 461.

112 Bernauer, Berlage, von Philipsborn, Schmid, and Karrer, Helv.Chim.Acta, 1958, 41, 2293.

113 Kebrle, Schmid, Waser, and Karrer, Helv.Chim.Acta, 1953, 36, 102.

114 Johnson, Roger Adams Symposium, Univ.Illinois, 1954, 60-90; Bell, Johnson, Wildi, and Woodward, J.Amer.Chem.Soc., 1958, 80, 1001.

115 Hemming, Ann.Applied Biol., 1945, 32, 214; Robinson, "Antibiotics," Pitman, London, 1953, p. 45.

116 Kenner and Murray, Antibiotics and Chemotherapy, 1951, 1, 509.

117 Hanna, MacMillan, and McHugo, Arch.int.Pharmacodyn., 1960, 124, 445.

118 Robinson, "The Structural Relations of Natural Products," Clarendon Press, Oxford, 1955.

119 Leete and Marion, Canad.J.Chem., 1953, 31, 1195.

120 Leete, Chem. and Ind., 1960, 692.

121 Wenkert and Bringi, J.Amer.Chem.Soc., 1959, 81, 1474.

122 Davis, McElroy, and Glass, "A Symposium on Amino-acid Metabolism," The John Hopkins Press, Baltimore, 1955, p. 799.

123 Crook and Davies, J.Chem.Soc., 1937, 1697.

124 Crook, Davies, and Smith, Nature, 1937, 139, 154.

125 Kefford and Kelso, Austral.J.Biol.Sci., 1957, 10, 80.

126 Elliott and Harington, J.Chem.Soc., 1949, 1374.

127 Avakian and Martin, U.S.P. 2,517.826 in Chem.Abs., 1951, 45, 662.

128 Avakian, Moss, and Martin, J.Amer.Chem.Soc., 1948, 70, 3075.

129 Hammer, Rebstock, and Sell, Science, 1954, 119, 217.

130 Herz, J.Amer.Chem.Soc., 1950, 72, 4999.

131 Capps and Hamilton, J.Amer.Chem.Soc., 1953, 75, 697.

132 Bloch, Lehr, and Erlenmeyer, Helv.Chim.Acta, 1945, 28, 1406.

133 Buu-Hoi, Hoan, Khoi, and Xuong, J.OrgChem., 1949, 14, 802; Buu-Hoi, Hoan, and Khoi, ibid., 1950, 15, 957; Buu-Hoi, Hoan, Khoi, and Xuong, ibid., 1951, 16, 309; Badger, Cook, Hewett, E.L.Kennaway, N.M.

Kennaway, and Martin. Proc.Roy.Soc., 1942, B131, 170; Lacassagne, Buu-Hoi, Zajdela, and Xuong, Bull.Assoc. franc.Cancer, 1955, 42, 1.

134 Dutch P. 79,480 in Chem.Abs., 1956, 50, 11598.

135 Bushland and King, U.S.Dept.Agr., Bur.Entomol.plant quarantine, E-585, 1943, in Chem.Abs., 1943, 37, 2111; Fink and Smith, J.Econ.Entomol., 1936, 29, 804; Campbell, Sullivan, Smith, and Haller, ibid., 1934, 27, 1176; Smith, Siegler, and Munger, ibid., 1938, 31, 322; Smith and Melvin, ibid., 1943, 36, 475.

136 Tarbell, Fukushima, and Dam, J.Amer.Chem.Soc., 1945, 67, 1643; Kitchen and Sandin, ibid., 1945, 67, 1645.

137 Mitra and Tilak, J.Sci.Ind.Res., India, 1955, 14B, 132; 1956, 15B, 497.

138 Haley and Andem, J.Pharmacol., 1951, 102, 50.

139 Bordwell and Stange, J.Amer.Chem.Soc., 1955, 77, 5939.

140 Martin-Smith and Gates, J.Amer.Chem.Soc., 1956, 78, 5351.

141 Weissgerber and Kruber, Ber., 1920, 53, 1551; Fries and Hemmecke, Annalen, 1929, 470, 1; Komppa, J.prakt.Chem., 1929, 122, 319; Buu-Hoi and Cagniant, Ber., 1943, 76, 1269; Flicke and Sheets, J.Amer. Chem.Soc., 1948, 70, 3768.

142 Bordwell and Albisetti, J.Amer.Chem.Soc., 1948, 70, 1955.

143 Martin-Smith and Gates, J.Amer.Chem.Soc., 1956, 78, 6177.

144 Craven, J.Chem.Soc., 1931, 1605.

145 Fries, Heering, Hemmecke, and Siebert, Annalen, 1936, 527, 83.

146 Cahours, Annalen, 1849, 69, 230; Lange, Rec.Trav.chim., 1926, 45, 19.

147 Hunsdiecker and Hunsdiecker, Ber., 1942, 75, 291.

148 Balcom and Furst, J.Amer.Chem.Soc., 1953, 75, 4334.

149 See, for example, Mayo and Hurwitz, J.Amer.Chem.Soc., 1949, 71, 776; Smith, ibid., 1953, 75, 3602; Gilman, ibid., 1951, 73, 470; Blatt et al., J.Org.Chem., 1957, 22, 1046, 1588; Blatt and Tristram, J.Amer.Chem.Soc., 1952, 74, 6273.

150 Hart, J.Amer.Chem.Soc., 1949, 71, 1966.

151 Bucherer, J.prakt.Chem., 1904, 69, 49.

152 Bucherer, J.prakt.Chem., 1905, 71, 433.

153 DeLaire, Girard, and Chapoteaut, Compt.rend., 1866, 63, 92.

154 Martin-Smith and Reid, J.Chem.Soc., 1960, 938.

155 Nickerson, Pharmacol.Reviews, 1949, 1, 27.

156 Lewis and Nanjappa, Private Communication.

157 Schild, Brit.J.Pharmacol., 1947, 2, 189.

158 Ariens, Simonis, and de Groot, Arch.int.Pharmacodyn., 1954, 99, 32,175,193.

159 U.S.P. 2,806,034 in Chem.Abs., 1958, 52, 2931.

160 Avakian, Moss, and Martin, J.Amer.Chem.Soc., 1948, 70, 3075; Blicke and Sheets, ibid., 1948, 70, 3768.

161 Gabriel, Ber., 1887, 20, 2224.

162 Ing and Manske, J.Chem.Soc., 1926, 2348.

163 Gent and McKenna, J.Chem.Soc., 1959, 137.

164 Goettsch and Wiese, J.Amer.Pharmaceut.Assoc., 1958, 47, 319.

165 Nystrom and Brown, J.Amer.Chem.Soc., 1948, 70, 3738; Micovic and Mihailovic, J.Org.Chem., 1953, 18, 1190.

166 Shirley and Cameron, J.Amer.Chem.Soc., 1952, 74, 664.

167 Hartung and Simonoff in "Organic Reactions," Wiley and Sons, New York, 1953, Vol. 7, p. 263.

168 B.P. 744,765 in Chem.Abs., 1956, 50, 16870.

169 Cavallito and Buck, J.Amer.Chem.Soc., 1943, 65, 2140.

170 Cohen and Dudley, J.Chem.Soc., 1910, 1732.

171 Gaddum and Hameed, Brit.J.Pharmacol., 1954, 2, 240.

172 Foster, Ing and Rogers, J.Chem.Soc., 1957, 1671.

173 Ainsworth, J.Amer.Chem.Soc., 1957, 79, 5245.

174 Grignard, Compt.rend., 1934, 198, 625.

175 Bachmann and Struve in "Organic Reactions," Wiley and Sons, New York, 1942, Vol. 1, p. 38.

176 Burger and Avakian, J.Org.Chem., 1940, 5, 606.

177 Brown and Subba Rao, J.Amer.Chem.Soc., 1958, 80, 5377.

178 Young, J.Chem.Soc., 1958, 3493.

179 Hamlin and Weston, J.Amer.Chem.Soc., 1949, 71, 2210; Ramirez and Burger, ibid., 1950, 72, 2781.

180 Ball, Goodwin, and Morton, Biochem.J., 1948, 42, 516.

181 Blair, Logan, and Newbold, J.Chem.Soc., 1956, 2443.

182 Koelsch and Whitney, J.Org.Chem., 1941, 6, 795.

183 McFadyen and Stevens, J.Chem.Soc., 1936, 584.

184 Greig, Walk, and Gibbons, J.Pharmacol., 1959, 127, 110.

185 Hartung, Ind.Eng.Chem., 1945, 37, 126.

186 Stoll, Troxler, Peyer, and Hofmann, Helv.Chim.Acta, 1955, 38, 1452.

187 Robinson, Chem. and Ind., 1952, 358.

188 Hansch and Lindwall, J.Org.Chem., 1945, 10, 381; Allen and Mackay, Org.Synth., 1932, 12, 76.

189 Adams and Ulich, J.Amer.Chem.Soc., 1920, 42, 599.

190 Claisen, Annalen, 1919, 418, 97.

191 Friedländer, Ber., 1916, 49, 955.

Appendix 3.

A list of thionaphthen derivatives, prepared for biological testing, is provided;

3-(Aminomethyl)-thionaphthen (C)

3-(Dimethylaminomethyl)-thionaphthen (CI)

3-(Pyrrolidinomethyl)-thionaphthen

3-(Piperidinomethyl)-thionaphthen

3-(2'-Methylpiperidinomethyl)-thionaphthen

3-(Morpholinomethyl)-thionaphthen (CII)

3-(Cyclohexylaminomethyl)-thionaphthen

3-(Dimethylaminomethyl)-thionaphthen methiodide

3-(pyrrolidinomethyl)-thionaphthen methiodide

3-(Piperidinomethyl)-thionaphthen methiodide

3-(Morpholinomethyl)-thionaphthen methiodide

5-Benzyloxy-2-(dimethylaminomethyl)-thionaphthen

5-Benzyloxy-2-(pyrrolidinomethyl)-thionaphthen

5-Benzyloxy-2-(piperidinomethyl)-thionaphthen

5-Benzyloxy-2-(morpholinomethyl)-thionaphthen (CX)

2-(Dimethylaminomethyl)-5-hydroxythionaphthen

5-Hydroxy-2-(pyrrolidinomethyl)-thionaphthen

5-Hydroxy-2-(morpholinomethyl)-thionaphthen (CX)

5-Amino-2-(dimethylaminomethyl)-thionaphthen

5-Amino-2-(pyrrolidinomethyl)-thionaphthen

5-Amino-2-(piperidinomethyl)-thionaphthen

5-Amino-2-(morpholinomethyl)-thionaphthen (CXIV)

3-(2'-Aminoethyl)-5-benzyloxythionaphthen (CXX)

2-(2'-Aminoethyl)-5-hydroxythionaphthen (CXXX)

2-(2'-Aminopropyl)-5-hydroxythionaphthen (CXXXII)

6-Ethoxythionaphthen-3-acetic acid (CXXXVI)

3-(2'-Aminoethyl)-6-ethoxythionaphthen (CXXXVIII)

3-(2'-Aminoethyl)-6-hydroxythionaphthen (CXXXIX)

7-Ethoxy-1-methyl-3,4-dihydrothionaphtheno(2,3-C)pyridine (CX

7-Ethoxy-1-methylthionaphtheno(2,3-C)pyridine (CXLI)