Journal of Medicinal and Pharmaceutical Chemistry
VOL. 1, No. 6 (1959)

Review

Biological Activity in Compounds Possessing Thiophen Rings

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The interest in compounds containing thiophen rings as potential biologically active agents stems largely from the ideas inherent in the receptor theory of drug action, the theory of biological antagonism and the concept of bioisosterism. These three concepts can be said to represent the modern approach to the long-standing problem of securing a correlation between chemical structure and biological activity. Because of the large number of variables inherent in biological systems, it is clearly impossible to establish a direct relationship between a single pair of these variables such as chemical structure and a particular biological action without taking into account simultaneous variations in other factors such as solubilities, distribution coefficients, electrical fields, acid and base strengths, detoxification mechanisms in the organism and so on. The advantage of an approach to the problem of structure–action relationships based on the concepts of biological antagonism and bioisosterism is that while not eliminating variation in such factors it does minimize their variation. Thus these concepts provide us with a promising basis for observing changes in biological activity with somewhat limited changes in chemical structure.

Because the reasons behind the preparation and biological testing of the thiophen derivatives to be described can be justified in terms of these postulates, a brief résumé of them will be given in order to provide a perspective of the field.

The idea that drugs exert their effects by interacting with certain receptors in the tissues has been implicity 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,[1] and the concept was used by Clark[2] and others to afford a theoretical basis for the interpretation of experimental dose-response curves. Little is known of the intimate physical nature of these postulated receptors, but 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.[3]

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 the conformation 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, but the results are open to criticism if one accepts the idea inherent in the theory of biological relativity[4] that the receptor is capable of changing its characteristics at the demand of a drug molecule, a phenomenon which has been termed the 'induced fit' theory.[5]

An example of the approach using a rigid molecule is afforded by the work of Beckett *et al.*[6] on the nature of the receptor sites involved in analgesia. These workers made their deductions from considerations of the geometry of the rigid morphine molecule, and they were then able to draw attention to certain similarities, not immediately apparent, which were present in the less rigid molecules of analgesics of other chemical types, including the thiophen derivatives, the thiambutenes.

The value of considering the receptor theory of drug action in attempting to relate biological activity to chemical constitution is that it stresses the importance of three-dimensional molecular geometry including the position and electrical nature of the functional groups. Such considerations are a valuable guide to the synthetic medicinal chemist in his attempts to modify the molecules of compounds of proven therapeutic efficacy in the quest for new agents possessing greater potency, specificity and

duration of action but having lower toxicity. The preparation of many of the thiophen compounds to be discussed can indeed be justified on these grounds.

Actually many biologists have come to regard a receptor as a volume in space which is defined by the surfaces of enzymes, coenzymes and metallic ions, and so they think of drugs as exerting their actions primarily on enzyme systems. While it has been undisputedly established that certain drugs do indeed interfere with specific enzyme systems, it is dangerous to create the generalization that all drugs necessarily interfere with enzyme processes. The intimate mode of action of many drugs is still unknown, and some may act by such mechanisms as merely altering membrane permeabilities by processes that do not involve an enzyme. For this reason the term 'receptor' is used by some workers to express the very general idea that a drug must enter a certain biological environment in order to be able to influence the biological system.

The concept of biological antagonism[7–9] contends that certain compounds which possess similar chemical structure and similar physical properties to an 'essential metabolite' of the organism, will, by virtue of their similarities, possess a degree of affinity for the receptor sites at which the metabolite is believed to initiate a characteristic train of events. The concept can be extended to cover cases where a natural metabolite is not known to be necessarily involved, as for example in the opposing biological effects shown by the compounds morphine and *N*-allylnormorphine which are believed to act at the same site. It is this ability to complex with a receptor normally occupied by another molecular species which confers on such compounds their biological properties. Accordingly, these compounds are usually referred to as antimetabolites in the fields of microbiology and enzymology.

Originally the concept was applied only to the phenomenon of competitive inhibition. In such cases it was assumed that the metabolite analogue was unable to elicit a response on combination with the receptor and, by competing reversibly with the natural metabolite for the available receptors, it was able to prevent the metabolite from fulfilling its normal function. More recently, however, the concept has been extended[10] 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 antimetabolite combines irreversibly with the receptors.

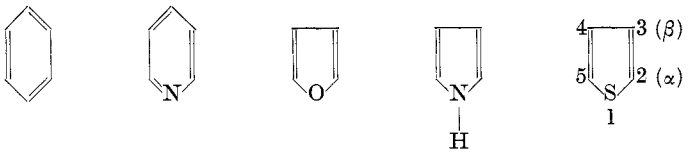
Several compounds containing a thiophen ring have been prepared as antimetabolites, the best known being the isomeric β-thienylalanines* and certain peptides derived from them. Where a thiophen derivative is prepared as an isologue of a known metabolite, we can reasonably expect it to intensify, mimic or oppose the biological effect of its natural analogue depending upon its affinity for the receptor and upon its intrinsic activity. It must always be borne in mind, however, that a completely new biological property may present itself, as the thiophen compound may be capable of acting at a totally different set of receptors in the organism.

Antimetabolites are of great interest to the experimental biochemist as they provide a useful means for studying the metabolic pathways of the substance they antagonize and so contribute to the elucidation of the routes of biosynthesis.[11] They are also of value in elucidating previously unsuspected functions of well recognized metabolites and as specific inhibitors of selected enzymes. Antimetabolites 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 natural metabolite, is always available. The early hopes that potent antibacterial drugs could be prepared by suitable alterations of the chemical structure of an essential growth factor of the organism have in general, however, not been realized, as the antimetabolite must meet the additional requirement of showing a much higher selectivity of action against the micro-organism[9] than against the tissues of the patient. An example of antimetabolites which do meet this additional requirement is provided by the antimalarial pantothenic acid analogues which do not elicit signs of vitamin deficiency in higher animals but do so in micro-organisms.[12]

The physical and chemical properties of benzene, pyridine, furan, pyrrole and thiophen (I–V) have long been recognized as

* The radical formed by abstraction of a hydrogen atom from thiophen is the thienyl radical. The thienylmethyl radical which corresponds to the benzyl radical is known as the thenyl radical.

being very similar, so it would seem logical that thiophen analogues of biologically active compounds containing benzene, pyridine, furan or pyrrole rings should have been well investigated biologically. The similarity in properties of these aromatic rings, each with its six π electrons, have been expressed in the extensions of the concept of isosterism[13] developed by Erlenmeyer,[14] Friedman[15] and others,[16] and which Friedman terms bioisosterism where the two isosteres possess the same type of biological activity. Bioisosterism is thus a specialized case of the more general concept of structural displacement.



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Isosteres will possess similar electronic arrangements and will also usually have similar overall electric fields, similar geometric properties and molecular weights of the same order of magnitude; nevertheless, one can still expect variation in other properties. For example, in the case of thiophen and benzene, the lower resonance energy and the occurrence of a hetero atom in the thiophen ring would perhaps be expected to make the thiophen compound easier to degrade and detoxify in the body. Again, the thiophen ring possesses a dipole moment with a positive charge on the sulphur atom due to the delocalization of one p electron pair and its incorporation in the π electron cloud. Further, the shape and dimensions of the sulphur atom are such as to confer on the thiophen ring different steric properties from those of the benzene ring. Nevertheless it was shown by Erlenmeyer *et al.*[17] that, even in highly specific antigen–antibody reactions, certain isosteric derivatives of benzene and thiophen gave identical precipitin reactions with the antisera to the benzene derivative.

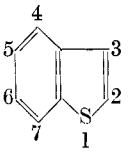
The synthesis and testing of thiophen analogues has been an extremely active field, and thiophen isosteres of compounds

possessing benzene rings belonging to every major group of pharmacological and therapeutic importance are now known. In general, the thiophen compounds are more toxic than their benzene analogues, but there are important exceptions. Only a very small number of such thiophen compounds, however, are employed clinically.

In this review the greatest emphasis will be placed on knowledge gained since 1949 as an excellent summary of the literature up to this year is available.[18] Other reviews less comprehensive in treatment have also appeared,[19] and recently a more complete summary has been published in the French literature.[20] Nevertheless, it is felt that a brief summary of some of the earlier work should be included to give a correct perspective of the field. This is perhaps best accomplished by reviewing work dealing with the biological activity of the parent compounds, thiophen, thionaphthen and dibenzothiophen, and then giving a brief account of the first work concerned with isosteric replacement by the thiophen ring system.

1. Historical Background

Determination of the biological properties of thiophen itself and its higher ring homologues, thionaphthen (VI) and dibenzothiophen (VII) has necessarily been limited by their low solubility



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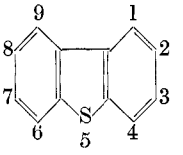
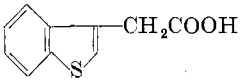


(VII)

in aqueous media, but it would appear that in general they possess activities similar to those of benzene, naphthalene and anthracene, but are more toxic. Determination of the biological properties of these compounds commenced soon after they became available, the metabolism of thiophen in the dog being first studied in 1886.[21] Subsequent studies[22–24] showed that there was an increase of neutral sulphur in the blood but no increase in the

sulphate ion concentration.[23] There was no increase of conjugated sulphate in the urine[21] and some of the thiophen administered was excreted as ethanethiol.[22] Thiophen exerts its toxic action predominantly on the nervous system,[25] and causes the greatest histological injury in the cerebellum, especially in the granulosa elements.[26] It produces convulsions, muscular weakness, fall in blood pressure and death,[27] and has a feeble action similar to that of benzene on the bone marrow. Like benzene, thiophen is claimed to have a slight solvent action on cancer cells.[28] Thiophen has also been claimed as a cure for gonorrhoea[29] and is said to increase the urinary excretion of uric acid in rabbits.[30] Aurousseau[20] mentions the use of thiophen therapeutically as a bacteriostat, insecticide and anthelmintic, and it has been used as an ingredient of an ointment used for treating skin infections.[31]

Thionaphthen is excreted in the urine as thionaphthen-α-glucuronic acid by rabbits.[32] It has been shown to have no formative effect on the tomato,[33] although 3-thionaphthyl acetic acid (VIII) like its isostere, indoleacetic acid, is a plant growth



(VIII)

promoter, albeit a much weaker one.[34] Thionaphthen is claimed to be especially active as a gaseous insecticide in enclosed spaces[35] but to have poor fungistatic properties as measured against rubber-tree mouldy rot fungus mycelia.[36]

Dibenzothiophen shows pronounced toxicity for mosquito larvae,[37] codling moth larvae[38] and screw worms.[39] It is also reported to be active against *Fusarium* wilt of tomatoes.[40] The toxicity of dibenzothiophen to male albino rats was studied[41] and it was found to inhibit growth and to produce extensive fatty metamorphosis of the hepatic cells in 0·1 per cent concentration in the diet.

The simpler thiophen derivatives such as thiophen-2-carboxylic acid, thiophen-2-aldehyde, 2-nitrothiophen, 2-chloromercurithiophen, etc., have been investigated to a greater or lesser degree for biological activity. The new work which has appeared on

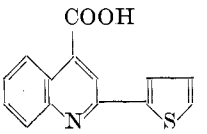
these simpler compounds since the review by Blicke[18] is concerned mainly with the applications of halogenated compounds and sulphones derived from thiophen and thionaphthen as nematocides[42] and as herbicides, and pesticides.[43] Most of the compounds concerned appear in the patent literature. Thiophen-2-carboxylic acid and thiophen-3-carboxylic acid are toxic to mosquito larvae, the 3 isomer being the more active.[44] Thiophen-2-carboxaldehyde lowers the arterial blood pressure of dogs under barbiturate anaesthesia.[45]

The general conclusion to be drawn on surveying the work on the simpler thiophen derivatives as reviewed by Blicke[18] is that these compounds usually possess similar activity to that shown by their benzene isologues, although it is often less pronounced. For example, the thenyl halides and ω-halo acetothienones, like their benzene isosteres, are lachrymators, the thiophen isosteres of p-nitrobenzoic acid and p-aminobenzamide are bacteriostats, thenoylglycine has activity similar to that of hippuric acid, thiophen-2-carboxylic acid has properties similar to those of benzoic acid and the chloromercurithiophens are bacteriostats similar (or weaker in activity) to the corresponding benzene derivatives. The simple thienyl ketones are not hypnotics like acetophenone but convulsants.[46] A study[47] of the simple heterocyclic aromatic ketones of the type $ArCOCH_3$ and $ArCOAr'$ showed that a phenyl or pyrryl radical was necessary for hypnotic activity. There was, therefore, no correlation between the resonance energy of the aromatic ring and the hypnotic activity, the order of resonance energy being benzene > thiophen > pyrrole > furan.[48]

The therapeutic use of ichthyol,[49] which is prepared by sulphonation of the distillate of certain bituminous schists and which contains various thiophen derivatives, appears to be on the decline. At one time ichthyol was greatly favoured as an antiseptic with demulcent and emollient properties in the treatment of skin diseases.

Thiophen isosteres of benzene derivatives of pharmacological importance were prepared quite early in the history of thiophen compounds. Thus in 1917 Steinkopf and Jaffe[50] prepared the thiophen isostere of the hypnotic chloralacetophenoxime, although the compound does not appear to have been tested pharmacologically. Then in 1919 Hartmann and Wybert[51] investigated

the effect on biological activity of replacing the phenyl group in cinchoninic acid by the thienyl group. They claimed that the 2-thienyl compound (IX) possessed greater antiphlogistic and



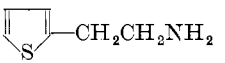
(IX)

analgesic properties than cinchoninic acid, but found that the compound produced a violet coloration of animal tissues and a deeply coloured urine. The biological effects of 2-(5-methyl-2-thienyl) quinoline carboxylic acid and of 2-(2,5-dimethyl-3-thienyl) quinoline carboxylic acid were also similar to those of cinchophen but these compounds produced no coloration. Further investigations with 2-thienylcinchoninic acid and various alkylthienylcinchoninic acids have also been reported.[52] The alkylthienyl compounds are stated to increase the excretion of uric acid, to lower body temperature in rabbits and guinea-pigs and to produce anaesthesia, and the sodium salt of 2-thienylcinchoninic acid potentiates the local anaesthetic activity of cocaine.

The thiophen isosteres of cocaine, atropine, eucaine A, benzoylquinoline and phenacetin were prepared by Steinkopf and co-workers,[53] and found to possess similar activity to the benzene derivatives, although in general they appeared less toxic.

The β-thienylethylamines attracted attention because of their isosteric relationship to both the sympathomimetic β-phenylethylamines and to histamine.

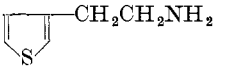
Syntheses of β-2-thienylethylamine (X) have been reported by several schools of workers.[54,55] This compound was found to



(X)

have the same order of pressor activity in cats as β-phenylethylamine.[56] It was also tested by Schulte *et al.*[57] who found that it showed pronounced central nervous system stimulatory

properties, being about as active as β-phenylethylamine but possessing a considerably lower threshold dose. The isomeric compound, β-3-thienylethylamine (XI), was found to be 3 to 4 times as active as the 2-thienyl compound as a pressor agent.[58]

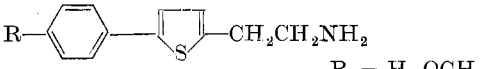


(XI)

The 2-thienyl isostere of amphetamine (β-(2-thienyl)*iso*propylamine[55]) was studied pharmacologically by Alles and Feigen.[59] The threshold dose for pressor activity in anaesthetized dogs was found to be the same as for amphetamine, and the drug had a comparable duration of action. It also had an action similar to that of phenylethylamine when tested on isolated rabbit intestine, but it failed to show CNS stimulation in man. The same compound as well as *dl*-β-methyl-β-(2-thienyl)*iso*propylamine was studied for pressor effect and toxicity by Warren *et al.*[60] The thiophen compounds were found to be less toxic than their benzene isosteres.

The β-ethanolamine derivative 2-amino-1-(2-thienyl)ethan-1-ol was found to have pressor activity *ca.* 60 per cent of that of L-ephedrine hydrochloride.[61]

The compounds β-[5-phenyl-(2-thienyl)]ethylamine and β-(5-*p*-methoxyphenyl-(2-thienyl))ethylamine (XII) prepared by Robin-



(XII)

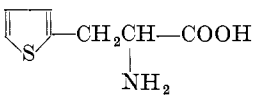
son and Todd[62] were investigated by Graham[63] who found that the first compound stimulated the CNS in mice whilst the second depressed it. Both compounds potentiated the pressor effect of adrenaline in the spinal cat and depressed the carotid blood pressure in the decerebrate cat.

Other 2-thienylaminoalkanes have been prepared and tested for activity[18, 55] and it was found that the pressor activity of the thiophen compounds was strictly parallel to that of the analogous amines in the benzene series.

2. Thiophen Derivatives as Antiamino Acids

The best known of the thiophen antimetabolites are the two isomeric β-thienylalanines which are antimetabolites of the essential amino acid β-phenylalanine. Of the two isomers,[19] the 3-thienyl isomer appears to be a more active antagonist than the 2-thienyl isomer. Although much work has been done with β-2-thienyl-DL-alanine, only the L form is active.[64] The earlier investigations of the β-thienylalanines as antimetabolites are well summarized by Martin.[7] More recently, work has been directed towards the study of the biological activity of simple peptides formed from the β-thienylalanines, and there has been continued interest in the simple amino acids themselves as potential anti-viral and anti-cancer agents. In this work the inhibition of β-phenylalanine has been shown to be reversible, in all cases by the addition of further β-phenylalanine.

Investigations of β-2-thienyl-DL-alanine (XIII) as a potential anti-viral[65] agent have shown that it inhibits the growth of



(XIII)

Theiler's GD VII virus,[66] and Lansing type poliomyelitis virus in monkey testicular cells.[67] The compound has, however, no significant inhibitory effect on mumps and influenza viruses in tissue culture.[68] The growth of chick embryo explants[69] and the maturation of young erythrocytes[70] are reported to be retarded.

In tissue cultures of C–57 black mouse heart and sarcoma T241, β-2-thienyl-DL-alanine acted specifically as a phenylalanine antagonist.[71] In the heart tissue cultures, transamination between the thienyl compound and phenyl pyruvate yielded L-phenylalanine, thus overcoming the inhibition. While β-2-thienyl-DL-alanine inhibits the growth of sarcoma T241 in mice, it does not cause regression of the tumours.[72] β-2-Thienyl-DL-alanine has also been shown to inhibit intracellular multiplication of psittacosis virus (strain 6 BC),[73] and to decrease the survival of *Oniscus asellus*.[74] If fed to rats it causes weight loss, negative

nitrogen balance and a marked decline in antibody formation.[75] A screening for cancer tumour inhibition employing a total of 74 biological systems showed that β-2-thienyl-DL-alanine possessed no significant activity.[76]

In recent years attention has also been paid to peptides containing the β-2- and β-3-thienyl-DL-alanine units. Syntheses are recorded of *N*-(*N*-carbobenzyloxyglycyl)-β-2-thienyl-DL-alanine, *N*-glycyl-β-2-thienyl-DL-alanine, *N*-(*N*-carbobenzyloxyglycyl)-β-3-thienyl-DL-alanine, *N*-glycyl-β-3-thienyl-DL-alanine, *N*-(β-2-thienyl-DL-alanyl) glycine, *N*-carbobenzyloxy-β-2-thienyl-DL-alanylglycine, *N*-carbobenzyloxy-β-3-thienyl-DL-alanine[77] and β-alanyl-β-2-thienyl-DL-alanine.[78] In general, the toxicity for rats[79] and the growth stimulation and inhibition for *Escherichia coli*[77,78,80] are no more pronounced than with the corresponding simple amino acids, and in some cases the thienyl peptides are less effective. Carboxy peptidase has been shown to hydrolyse carboxybenzoxyglycyl-β-2- and carboxybenzoxyglycyl-β-3-thienyl-DL-alanine at two-thirds the rate of hydrolysis of the corresponding phenylalanine derivative.[81] On resolution of glycyl-β-2-thienyl-DL-alanine, only the L-form of the peptide was found to be toxic for *E. coli*, strain 9723.[82]

Amino acids containing a thiophen ring, which can be regarded as being somewhat related in chemical structure to chloramphenicol which appears to produce an irreversible antagonism to β-phenylalanine, have been investigated and β-(2-thienyl)-serine has been found to slightly retard the growth of *E. coli*, while *N*-(dichloroacetyl) thienyl-DL-alanine has little effect.[83] β-2-Thienyl-DL-alanine, which itself retards the growth of *E. coli*, augments the action of chloramphenicol.[84]

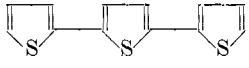
The thiophen isostere of tryptophan, β-3-thionaphthyl-DL-alanine,[85,86] exhibits a significant bacteriostatic action against *Streptococcus pyogenes*, but does not inhibit the growth of *Staphylococcus aureus* and *E. coli*.[85] Inhibition of the root growth of cucumber plants, proportional to the concentration of β-3-thionaphthyl-DL-alanine applied, has been observed.[87] In tests for its ability to act as a displacing agent of tryptophan, the thiophen isostere was shown to antagonize tryptophan in *Lactobacillus arabinosus*.[88] Tryptophan has been shown to overcome the inhibitory effect of β-2-thienyl-DL-alanine in *E. coli*,[89] and in

tubercle bacillus normally resistant to growth inhibitors.[90] This probably indicates that these test organisms possess the ability to interconvert tryptophan and β-phenylalanine, although modern views on the biogenesis of these essential amino acids[91] do not consider that one arises by a direct sequence from the other. It has been shown[92] that the addition of β-2-thienyl-DL-alanine inhibits the biogenetic conversion of phenylalanine to tyrosine, providing a good illustration of the synthetic analogue blocking the normal biochemical reactions. The observation that cell-free extracts[93] of *L. arabinosus* catalysed a wide variety of transamination reactions including L-glutamate formation from β-2-thienyl-DL-alanine may be of significance in connection with studies of the growth inhibition produced.

3. Vitamins and Anti-vitamins

Vitamin A

Although no thiophen analogues of vitamin A appear to have been reported, the interesting blue-fluorescing compound α-terthienyl (XIV) which occurs in marigolds (*Tagetes erecta* L. var.



(XIV)

lemon[94]) has been tested for provitamin A activity in the rat. It showed no such activity and was also devoid of antibiotic potency against *S. aureus*, *Bacillus subtilis*, *E. coli* and *Pseudomonas ovalis*.

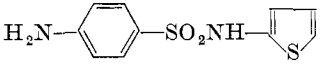
Anti-vitamins B

The classical example which provided the great impetus for the development of the theory of biological antagonism was the discovery of the antagonism between sulphanilamide and *p*-aminobenzoic acid.[95] The fact that sulphanilamide is toxic only to folic acid-requiring bacteria which are unable to use pre-formed folic acid[96] led to the theory that sulphanilamide exerts its antibacterial activity by competing with the *p*-aminobenzoic acid for a site which is concerned with the incorporation of *p*-aminobenzoic acid into folic acid molecules, and in this way it prevents the organism

from synthesizing folic acid. The sulphonamides also possess actions on other enzyme systems and the explanation of their biological effects in higher organisms is to be found in this fact.

In the search for more potent antibacterials, many modifications of the sulphanilamide molecule have been synthesized and amongst these are to be found compounds containing a thiophen ring.[97,98]

Such thiophen isosteres have proved disappointing, possessing either no antibacterial properties or at best only weak activity.[99] Sulphathiophen (XV), the 2-thienyl isologue of sulphapyridine and

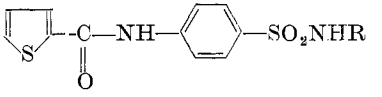


(XV)

sulphathiazole, is reported to have some bacteriostatic and bactericidal activity,[100] but is much weaker than the two heterocycles in clinical use.

4-Amino-2-thiophen sulphonamide and 5-amino-3-thiophen sulphonamide[102] have been prepared. The latter isomer was found to be about as active as sulphanilamide in broth dilution tests against *B. subtilis* and *Pasteurella pestis*. The corresponding nitro compound, 5-nitro-3-thiophen sulphonamide was much more active, having a greater activity than sulphathiazole, but it was also much more toxic when tested in mice.

Compounds of type (XVI), like their isosteres containing 2-furyl



(XVI)

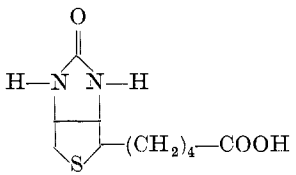
and 3-pyridyl radicals in place of the 2-thienyl radical, showed greatly diminished activity against streptococci and the pneumococcus as compared with the corresponding primary amines.[97] Thiophen-2-sulphonamide, however, has been shown to be much more effective as an inhibitor of carbonic anhydrase than sulphanilamide[103] and so resembles the 1,3,4-thiadiazole derivative, acetazoleamide, in this respect. Like sulphanilamide, thiophen-

2-sulphonamide is reported to slow the decline of potential in frog nerve during anoxia and to reduce its rise during post-anoxic recovery.[104]

Esters of 5-amino-2-thenoic acid, unlike the esters of *p*-aminobenzoic acid, are reported to have no antagonistic effect towards sulphanilamide.[105] 5-Amino-2-thenoic acid itself is an antagonist of *p*-aminobenzoic acid.[106] The thiophen analogue of marfanil, 5-aminomethylthiophen-2-sulphonamide, is reported to be virtually devoid of activity.[107]

Vitamin H

If it is permissible to include compounds possessing a fully reduced thiophen ring (the thiolane or tetrahydrothiophen ring) as thiophen derivatives, then vitamin H or biotin (XVII) and its



(XVII)

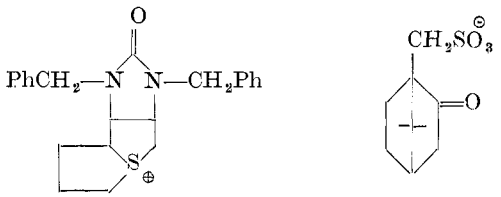
naturally occurring derivative biocytin (ε-*N*-biotinyl-L-lysine)[108] fall within the category of biologically active thiophen compounds. There is an extensive literature on biotin and structurally related compounds such as norbiotin, homobiotin and biotin sulphone which act as antimetabolites of biotin, but this cannot be pursued in detail here. A good review of the earlier work is given by Martin.[7]

It is interesting that homobiotin and norbiotin can replace the need of biotin in certain strains of yeast while functioning as anti-biotins in other strains[109] indicating that the intrinsic activities of these homologues vary with the genetic constitution of the organism.

The true thiophen derivative corresponding to biotin, 2,3,4,5-tetradehydrobiotin or 'aromatic' biotin[110] is reported to be without either biotin-like or anti-biotin activity when tested on *L.*

arabinosus or *Saccharomyces cerevisiae*. Several other thiophen-containing compounds similar in structure to 2,3,4,5-tetradehydrobiotin have also been prepared[111] and these also lack either biotin-like or antibiotin activity when tested on the same two micro-organisms. Aromatization of the thiolane ring would thus appear to change the properties of the biotin molecule to such a degree that the resulting compound is no longer capable of interacting with the receptor involved.

A reversal of the usual approach in which thiophen isologues of compounds containing benzene rings are prepared is afforded by the preparation of isosteres of biotin in which the thiolane ring is replaced by a benzene ring or *cyclo*hexane ring.[112] These com-

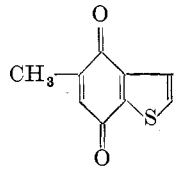


(XVIII)

pounds, especially the *cyclo*hexane derivatives, possess antibiotin activity against *Lactobacillus casei* and yeast. It is interesting that 2,5-thiolane dicarboxylic acid showed biotin-like activity when tested on yeast.[113] A compound somewhat related to biotin in chemical constitution is arfonad, *d*-3,4(1′,3′-dibenzyl-2′-ketoimidazolido)-1,2-trimethylenethiophanium-*d*-camphor sulphonate (XVIII) which has pronounced vasodepressor and ganglion blocking activity,[114] being some 30 times as potent as and having twice the duration of action of tetraethylammonium in the dog, cat and monkey. The *l*-isomer was found to be only one-half as potent as a depressor as the *d*-isomer. The compound was also shown to have hypotensive activity in dogs which is independent of the ganglion blocking action.[115] Large doses are considered to exert their toxic effect by the liberation of heparin and histamine.[116] Other studies including toxicity determinations on this compound have been performed.[117]

Vitamin K

5-Methyl-4,7-thionaphthenquinone (XIX), the thiophen analogue[118] of menadione or vitamin K_4, is reported to have an antihaemorrhagic activity approximately 3 per cent of that of

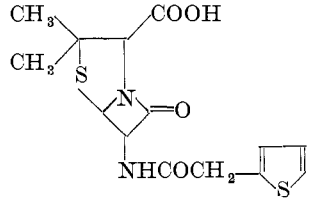


(XIX)

vitamin K_4. It has also been studied as a potential mitotic inhibitor and radiosensitizer to cells in tissue culture,[119] and shown to be active in concentrations of comparable order to those of tetrasodium-2-methyl-1,4-naphthohydroquinone diphosphate. It produced some abnormal mitoses, mainly clumped metaphases, but there were practically no anaphase bridges.

4. Antibiotic Isologues

Considering the medical importance of antibiotics, it is not surprising that several thiophen isosteres have been prepared in this class. Because of the complex chemical structure of many of

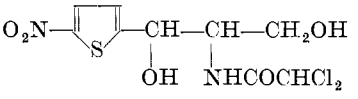


(XX)

the antibiotics, however, the synthesis of antibiotic isosteres has been somewhat limited. In the case of the penicillins, the important discovery that addition of a variety of organic acids or their derivatives to the culture medium resulted in their incorporation into new 'biosynthetic' penicillins[120] provided a route for the easy production of several thiophen-containing penicillins.[121–123]

Although these new biosynthetic penicillins were hydrolysed by penicillinase at a rate not significantly different from that of benzylpenicillin, it was found that the sodium salt of 2-thiophenmethylpenicillin (XX) was the most effective of a series of biosynthetic penicillins against a benzyl penicillin-resistant strain of *S. aureus* 209–P which did not produce demonstrable quantities of penicillinase and, therefore, owed its resistance to some other cause.[124] Ford *et al.*[122] in their paper quote a private communication to the effect that 2-thiophenmethylpenicillin shows a good blood level duration and Behrens *et al.*[121] report the activity of the sodium salt of 2-thiophenmethylpenicillin as tested against *S. aureus* as 1,685 units/mg. The activity of the sodium salt of 3-thiophenmercaptomethylpenicillin is reported as 2,160 units/mg. Neither of these compounds appears to have been on trial clinically.

Several groups of workers have been interested in synthesizing thiophen compounds structurally related to chloramphenicol (D(-)threo-1-(*p* nitrophenyl)-2-dichloroacetamido-1,3-propanediol). Keskin *et al.*[125] prepared the model compound DL-threo-1-(2-thienyl)-2-acetamido-1,3-propanediol, whilst Hermann and Kreuchunas,[126] and Carrara and Weitnauer[127] prepared DL-threo-1-(5-nitro-2-thienyl)-2-dichloroacetamido-1,3-propanediol (XXI). Huebner *et al.*[61] prepared the erythro isomer of (XXI)



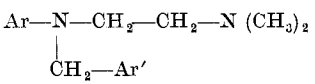
(XXI)

which proved to be less active than chloramphenicol on all the test organisms employed. DL-threo-1-(2-thienyl)-2-acetamido-1,3-propanediol has also been prepared.[128] As DL-threo-1-biphenylyl-2-dichloroacetamido-1,3-propanediol was found to have pronounced antibacterial activity,[129] other 1-biaryl-2-dichloroacetamido-1,3-propanediols including three containing thiophen rings were prepared.[130] These compounds, however, showed only slight activity or were inactive.

5. Antihistamines

The most important thiophen derivatives from the clinical point of view are those which are employed as antihistamines. There is an extensive literature on these compounds which cannot

Table I



	Ar	Ar′	Refs.
Tripelennamine	2-pyridyl	phenyl	
Methapyrilene	2-pyridyl	2-thienyl	134, 135, 136
—	2-pyridyl	3-thienyl	135, 137, 138
Chloropyrilene	2-pyridyl	2-(5-chlorothienyl)	139, 140
—	2-pyridyl	2-(5-bromothienyl)	141
Methaphenilene	phenyl	2-thienyl	142, 143
	2-pyrimidyl	2-thienyl	144
	2-lepidyl	2-thienyl	145
	2-lepidyl	2-(5-chlorothienyl)	145

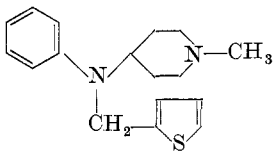
be covered in any detail here, e.g. there are over 100 publications dealing with the 2-thienyl isostere of tripelennamine, which is known as methapyrilene.

A review of antihistamine drugs in general, in which the relationship of the various thiophen derivatives to other drugs of this class is clearly shown, is available.[131] In fact the whole field of antihistamines presents a classical illustration of the problem of 'too many drugs'.[132,133] The summary to be given here must, therefore, be highly selective.

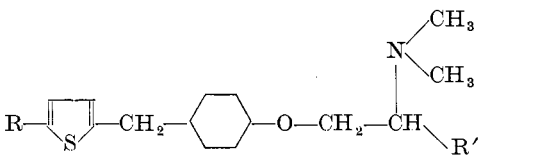
Other antihistamines possessing thiophen rings whose chemical structure is based on that of tripelennamine are well established. The most important are included in Table I but others are known.[141,146] The compound 1-methyl-4-((phenyl-2-thenyl) amino) piperidine (XXII) which has pronounced antihistaminic activity[147] can also be regarded as a derivative of tripelennamine.

Thiophen isosteres of various other well established antihistamine drugs have also been prepared, e.g. isosteres of antazoline and

N-(2-pryidyl)-benzamide[142] have been made. Unsuccessful attempts to prepare the thiophen isostere of doxylamine have been reported[148] although the corresponding nor- compound was synthesized. Its antihistaminic activity was not particularly pronounced. The 2-thienyl analogue[149] of chlorcyclizine, and the 2-thienyl isostere of prophenpyridamine[150] and thiophen derivatives of diphenhydramine[151] have been prepared. Basic phenol ethers of type (XXIII)[152] have also been prepared.



(XXII)



where R = H,Cl, R′ = H,CH_3

(XXIII)

Derivatives of thionaphtheno (3,2-6) indoles were prepared because of their structural similarity to the phenothiazines,[153] and were found to possess antihistaminic activity.

The dialkylaminoethyl esters of phenyl-2-thienyl acetic acid and phenyl-2-thienylglycollic acid as well as showing anticholinergic properties possess the power to antagonize the actions of histamine.[154,155] Certain thiophen derivatives of 1,3-dioxolane like the corresponding phenyl derivatives show a low order of antihistaminic activity in addition to spasmolytic action.[156]

In general, the thiophen compounds have not shown any marked superiority as antihistamines to compounds of other chemical groups. Various theophylline salts have been prepared[157] in order to reduce the toxic- and side-reactions of the thiophen compounds as was done in the case of diphenhydramine. An interesting fact is provided by the variation in the activity of the

thiophen isosteres as compared to the activity of the parent compounds on which they were modelled, giving a good illustration of the difficulty in predicting the exact changes in biological activity to be expected in the modification of the molecules of therapeutic agents. The relative potency of the isosteres also varies according to the biological system employed, that is, according to whether the test for histamine antagonism employs guinea-pig lung, guinea-pig gut, guinea-pig uterus, cat blood pressure, the ability to protect the guinea-pig against histamine-induced shock, the ability to protect guinea-pigs from histamine-induced gastric ulcers or measurement of histamine iontophoresis,[133] as the test system. Thus methapyrilene has an antihistaminic activity 0·8–2·0 times that of its isostere tripelennamine,[134, 135] and the corresponding 3-thienyl compound[137] is reported to have activity greater than tripelennamine, being some three times as active as the 2-thienyl isomer when tested on isolated strips of guinea-pig ileum.[135] The thiophen isostere of antazoline is claimed to be only 5 per cent as active as antazoline itself, and the thiophen isostere of *N*-(2-pyridyl)-benzamide is inactive[142] (test system not given). There seems to be some discrepancy in the literature as to the activity of methaphenilene.[142, 158] Chloropyrilene is claimed to be twice as active as methapyrilene when tested on isolated guinea-pig ileum and to be only half as toxic as methapyrilene.[139] On the other hand, the 3-thienyl isostere of tripelennamine is a more potent antagonist of histamine than are its halogenated derivatives[135] when tested on isolated guinea-pig ileum and against histamine asthma in guinea-pigs.

Despite the considerable difference in its chemical structure from that of histamine, methapyrilene is concluded to exert a competitive antagonism to histamine when tested on guinea-pig ileum.[159] Chloropyrilene, the corresponding bromo derivative, and the 2-thienyl isostere of chlorcyclizine probably act in the same way.[159]

The histamine depressor effect on cat's blood pressure requires large doses of antihistaminic agent before adequate antagonism is achieved,[155] whereas one mole proportions of certain antihistamines can antagonize histamine on isolated or intact guinea-pig lung and less than one mole proportions can antagonize histamine on the isolated guinea-pig ileum.[160] These observations could be

interpreted as meaning that the affinities of the antihistamines for different histamine receptors show a wide variation. The intrinsic activities also vary as some of the antihistamines including some of the thiophen derivatives show broncho-constrictor action.[161]

In common with other antihistamines, the thiophen derivatives show local anaesthetic activity,[162] possess antifungal action,[163] prolong the blood clotting time,[164] exert cardiodepressant activity,[165] possess antipyretic activity in some species,[166] possess some oxytocic activity and show to a greater or lesser degree atropine-like activity. Methapyrilene is reported to possses hypnotic activity approximately equal to that of phenobarbital[167] and to potentiate the effects of other hypnotic drugs.[168] It has also been employed in ophthalmology.[169]

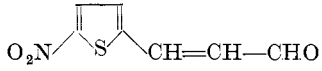
It is to be noted that the 3,3-dithienylalkenylamines, in addition to their analgesic properties, show antihistaminic activity.[170]

6. Antibacterial and Antifungal Agents

In this section will be included compounds containing thiophen rings which have been tested as bacteriocides, bacteriostats, fungicides, fungistats and anti-viral agents, or which show toxicity to protozoa. Because the volume of work warrants it, compounds designed and tested specifically as antitubercular agents will be given a separate sub-section.

General Antibacterial Agents

The marked antibacterial activity of the nitrofurans naturally encouraged investigations of the corresponding thiophen com-



(XXIV)

pounds as potential antiseptics. The preparation of many of these thiophen compounds can also be justified in terms of their structural relationship to *p*-nitrocinnamic acid, itself a potent antibacterial and which in turn possesses a chemical structure related to chloramphenicol. Although the earlier work was not encouraging,[171] nitrothiophen derivatives continued to be synthe-

sized and tested. Thus 3-(5-nitro-2-thienyl)acrolein (XXIV) and 2-bromo-3-(5-nitro-2-thienyl)acrolein have been reported to be very active against *S. aureus* and *E. coli*,[172] and to have a low toxicity to the tissues of the host.

The presence of the double bond as in these acrolein derivatives appears necessary for pronounced antibacterial activity as methyl-2-(5-nitro)-thienyl ketone, synthesized by Bellengi *et al.*, was much less potent.[173] These workers also concluded that the optimum position for the nitro group in the thiophen ring was the 5-position. Replacement of the nitro group in the acrolein series by a cyanide group led to a reduction in bactericidal properties.[174] 5-Nitrothiophen-2-carboxylic acid, the ethyl ester and the amide, as well as bis-5-nitro-2-thienyl sulphide inhibit the *in vitro* growth[175] of *S. aureus* and *albus* and *L. plantarum*.

Of many heterocyclic nitro compounds tested for antibiotic activity against *Shigella dysenteriae*,[176] the most active was 1-(5-nitro-2-thienyl)ethylamine hydrochloride.

Other nitrothiophen compounds reported include 1-(2-thienyl)-2-nitroethene and 1-(2-thienyl)-2-nitropropene which inhibit the growth of *S. aureus* and *E. coli*.[177] Many chalcone derivatives of nitrothiophen carboxaldehydes[178] as well as hydantoin, thiohydantoin and piperidine derivatives[179] have been tested but these compounds exhibit little or no activity as bactericides.

For a series of simple derivatives, Ward and Dodd[180] reported that the nitrofurans were more active *in vitro* than the nitrothiophens. The corresponding pyrrole derivatives were practically devoid of activity.

The presence of a nitro group in the molecule is not essential for effective antibacterial activity in the thiophen series and γ-(2,5-dimethyl-1-pyrryl)propyl-2-thenoate is reported[181] to have considerable activity against certain Streptococcus, Staphylococcus and Escherichia strains. In addition, certain 5-chloro-2-thienyl-β-dialkylaminoethyl ketones exhibit antibacterial activity.[182] Many other thiophen derivatives[183] have been tested for antibacterial activity but none are so active as those already mentioned. In addition, there is an extensive patent literature in which thiophen compounds are claimed as antibacterial agents. A review of the acryl, and nitrovinyl benzene, thiophen and furan antibacterials has recently appeared.[184]

The triphenylmethane dyes have been employed therapeutically because of their effective germicidal action against Gram-positive organisms, and isosteres of these compounds containing thiophen rings have been prepared.[185] The efficiency of these compounds as germicides does not appear to have been investigated. Little or no attention has been paid to preparing thiophen analogues of the halogenated bis(2,2′)phenols. A few quaternary nitrogen derivatives containing the thiophen ring have been described.[186]

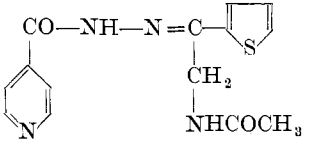
Antitubercular Compounds

It is only recently that drugs capable of overcoming infections caused by acid fast organisms such as *Mycobacterium tuberculosis* have been developed, but among the organic compounds synthesized and tested for antitubercular activity there are many thiophen derivatives. The main chemical classes of drugs showing high antitubercular activity are the sulphones, thiosemicarbazones and certain acid hydrazides. Thiophen derivatives of each of these groups have been prepared and tested. Thus, 4-aminophenyl-2-nitro-5-thienyl sulphone is reported to possess slight antitubercular and antistreptococcal activity,[187] and the thiosemicarbazones of many thiophen compounds have been tested, despite the fact that thiosemicarbazones as a class are very toxic. These include the thiosemicarbazones of thiophen-2-carboxaldehyde,[188,189] 5-acetamido-thiophen-2-carboxaldehyde,[190] ethyl-2-thienylketone,[189,191] 2,5-dimethyl-(methyl-3-thienyl ketone),[192] and 5-substituted thiophen-2-carboxaldehydes where the 5-substituent is an alkyl, arylalkyl or *cyclo*hexylalkyl radical.[193] All of these compounds are reported to be active against *M. tuberculosis*. Moreover, the thiosemicarbazone of 4-(2-thienyl)-3-buten-2-one has been reported to be capable of completely inhibiting the *in vitro* growth of *M. tuberculosis* in relatively low concentrations.[194] Preliminary experiments with the corresponding 3-isomer have indicated that it has even higher activity.

The hydrazide of *iso*nicotinic acid and various substituted derivatives are among the most effective drugs known in the treatment of experimental tuberculosis, and accordingly the hydrazides of many heterocyclic acids have been prepared and tested. The hydrazide of thiophen-2-carboxylic acid[195] interferes

with bacterial growth,[196] but not to the same extent as the hydrazide of *iso*nicotinic acid. The hydrazides of many substituted thiophen carboxylic acids including 5-alkylthiophen-2-carboxylic acids where the alkyl group is long chain,[197] 5-bromothiophen-2-carboxylic acid, 5-chlorothiophen-2-carboxylic acid,[195] thiophen-2-acetic acid, 5-chlorothiophen-2-acetic acid[198] and 2-methyl-4-hydroxy-thiophen-3-carboxylic acid,[199] have been found to have an order of activity somewhat less than that of *iso*nicotinylhydrazide. The condensation products of these hydrazides with a large number of aldehydes and ketones have been investigated in view of the possibility of their being less toxic than the parent hydrazide as a result of the blocking of the free amino group.[197, 199]

Also prepared for testing as potential tuberculostatic compounds were the condensation products of *iso*nicotinylhydrazide and various aldehydes and ketones of the thiophen series. Where the carbonyl compound was thiophen-2-carboxaldehyde, the product was inactive against *M. tuberculosis*,[200] but the condensation products of *iso*nicotinylhydrazide with methyl-2-thienyl ketone and 2-acetamidoacetylthiophen[201] (XXV) showed a high degree of



(XXV)

activity when tested against the H37 Rv strain of human *M. tuberculosis*.

The inhibition of growth of *M. tuberculosis* by *iso*nicotinylhydrazide has been shown to be counteracted by the addition of 2-thiophen-carboxylic acid hydrazide.[202] This fact could be interpreted as an example of a compound with high intrinsic activity competing with a compound of lower intrinsic activity already present in the biological system.[10] It has been suggested that the actual mechanism by which growth inhibition by hydrazides occurs involves cupric ions.[199]

Other compounds found to have some antitubercular action were 1-*p*-thenoylphenyl-3-methyl-2-thiourea[203] which was reported

to be very active against tuberculosis in mice, and 6-(2-thienyl) 3-mercapto-1,2,4,-triazin-5-one.[204]

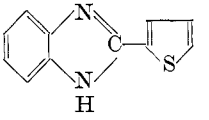
Antifungal Agents

Compounds of a similar constitution to those known to possess antibacterial activity have been reported as possessing fungicidal activity. Of such compounds, α-bromo-β-(5-cyano-2-thienyl-acrolein), 1-(5-nitro-2-thienyl)-2-nitroethylene, and 1-(5-nitro-2-thienyl)-2-bromo-2-nitroethylene have outstanding activity.[205]

The growth-arresting properties of many other nitro thiophen derivatives including bis(5-nitro-2-thienyl) sulphide, 2-iodo-5-nitrothiophen, and 5-nitro-2-thienylmethyl ketone have been tested on yeast.[206]

Antifungal activity has also been reported in many other types of thiophen derivative especially those containing mercury. Thiophen mercurichloride was effective against spores of *Piricularia oryzae, Ophiobolus graminis,* and *Macrosporium bataticola,*[207] and acetoxymercuri derivatives of thienylsubstituted thiazoles are stated to show promise as fungicides.[208] Actually thiophen itself, as well as thiophen-2-carboxyaldehyde, 5-chlorothiophen, and 5-bromothiophen, is reported to induce germination in ascospores of *N. tetrasperma,*[209] but substituted thionaphthen-2-carboxamides have a definite antifungal activity against *Trichophyton rubrum.*[210]

Several 3-thienylrhodanines showed fungistatic activity against *Aspergillus niger,*[211] and the thienyl benzimidazole derivative (XXVI) completely inhibits the growth of the fungi *Trichophyton*



(XXVI)

granulosum and *Microsporum gypseum.*[212] In addition, there are many reports of diverse thiophen derivatives possessing antifungal activity in the patent literature.

Anti-viral Agents

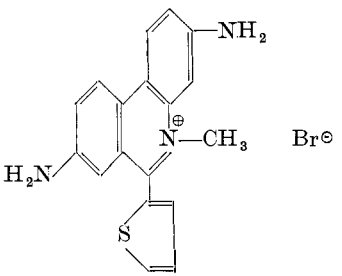
Arising from the observation[213] that *p*-aminobenzaldehyde thiosemicarbazone caused a significant delay in death of chick

embryos and mice infected with vaccinia virus, thiosemicarbazones of many substituted thiophen carboxaldehydes were synthesized as potential anti-viral agents.[214] These compounds, when fed to mice, were found to protect them against intracerebral vaccinia virus,[215] and against Williamsport virus.[216] The corresponding semicarbazones were inactive. The effectiveness of the thiosemicarbazones of 2-acetylthiophen and 2-benzoylthiophen as virus inhibitors[217] was shown by a half-leaf technique with *Nicotiana glutinosa* and tobacco-mosaic virus, and the inhibition was thought to be due to interference with the metabolism of the host, as the oxygen uptake of the leaves was affected.

Several thiophen compounds have been reported to inhibit the multiplication of poliomyelitis virus in monkey testicular explant cultures, and to cause a marked delay of virus appearance.[218] In some cases, the effect is reversed by addition of hydroxyproline, cysteine, phenylalanine, tyrosine and histidine.

Drugs Used against Protozoan Parasites

Relatively few compounds containing thiophen rings have been prepared and tested for their toxicity to protozoan parasites, and it would appear that further work in this field could profitably be undertaken.



(XXVII)

The powerful trypanocidal activity of certain phenanthridinium compounds as demonstrated by Browning *et al.*,[219] and of 2,7-diamino-9-phenyl-10-methylphenanthridinium bromide (dimidium biomide) in particular,[220] led to the synthesis of the 9-(2-thienyl)isostere (XXVII) of dimidium bromide.[221] This compound was found to be 1·3 times as active as dimidium bromide

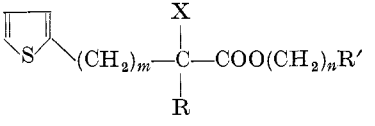
in mice, and to cure *Trypanosoma vivax* infections in Nigerian cattle at 1 mg/kg.

Although phenanthridinium derivatives with a 3-amino substituent are reported to be less active than those with a 2-amino substituent,[220] nevertheless, 3,8-diamino-6-(2-thienyl)-5-methylphenanthridinium bromide has been prepared and tested,[222] and its efficacy was found to exceed that of the corresponding 6-phenyl derivative against *Trypanosoma congolense*. It was also less toxic. Replacement of the methyl group in the 5-position of this compound by an ethyl radical is claimed to increase the activity against infections of *T. congolense*.[223]

Very few attempts appear to have been made to prepare and test thiophen-containing compounds as potential antimalarials. 2-(2-Thenyl)- and 2-(5-methyl-2-thenyl)-4,5-dihydroimidazole are reported to exhibit antimalarial activity and also to act on the circulatory system of warm-blooded animals.[224] A thiophen isostere of the antimalarial alkaloid febrifugine has been synthesized, and was about one-tenth as active as the parent dl-alkaloid.[225] Several α-diethylaminopropylaminodibenzothiophens have been found to be inactive in experimental avian malaria.[226]

7. Anticholinergic Compounds

Powerful antispasmodic activity occurs in various basic esters of α-substituted thienylglycolic acids, thienylacetic acids and thienylpropionic acids as well as in other more complex compounds which can be considered to be derived from these fundamental structures.[227] A generalized formula to represent the majority of the compounds of this type is given in (XXVIII).



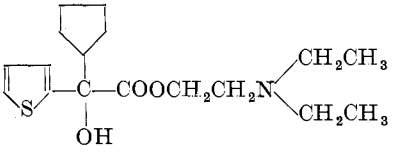
(XXVIII)

General formula of the thienyl anticholinergic drugs where

R = alkyl, *cyclo*alkyl, aryl, aralkyl
R′ = dimethylamino, diethylamino, piperidino
X = H or OH
m = 0 to 5
n = 1, 2, 3

These thiophen compounds were prepared in the course of systematic modifications of the structure of the atropine molecule in attempts to produce effective antispasmodic substances that would be relatively free of the undesirable side-actions of atropine, and represent but a small fraction of the large number of compounds so prepared. Some of these thiophen compounds indeed show anticholinergic properties equal to or exceeding those of atropine.

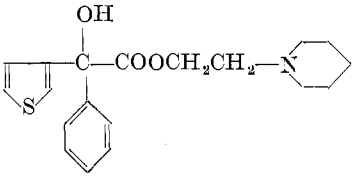
The structural modifications of the atropine molecule can be traced from the earlier minor modifications as exemplified by the production of atropine methylnitrate and homatropine, through the modifications represented by eucatropine and the dialkylaminoalkanol esters of tropic, mandelic and atrolactic acids, to the preparation of the highly active diphenylacetic acid esters, e.g. adiphenine, the esters of benzilic acid and the esters of the *cyclo*alkyl mandelic acids. Finally the replacement of benzene rings by thiophen rings in the mandelic and benzilic acid derivatives gave rise to the series of compounds at present under consideration. One such compound, the 2-diethylaminoethyl ester of *cyclo*pentyl(2-thienyl)glycolic acid (XXIX) is employed clinically



(XXIX)

in the form of its salts. This compound, when administered as the methobromide (penthienate), has been shown to be more active than atropine methylnitrate as an inhibitor of the effects of carbachol in barbitone anaesthetized dogs, and to possess mydriatic activity.[228] It was twice as active as atropine when measured on the isolated rabbit intestine stimulated with acetylcholine. Penthienate has been shown to have a rapid initial adsorption from the intestine, and continues to be absorbed for up to five hours.[229] It has a marked suppressive effect on gastric secretion and intestinal motility.[230] When tested for its ability to increase the survival time in x-ray irradiated mice,[231] it was found to have no significant effect on total mortality.

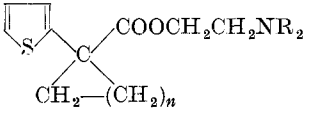
Other compounds closely related to the 2-diethylaminoethyl ester of *cyclo*pentyl-(2-thienyl)glycolic acid have also seen extensive investigation and several members of the group have been shown to antagonize the effect of veratrine given intravenously to cats anaesthetized with chloralose and urethane.[232] The *cyclo*hexyl compound has pronounced mydriatic activity and its nitrate salt is claimed to be non-irritating.[233] The diethylaminoethyl ester of phenyl-(2-thienyl)acetic acid has seen clinical trial.[234] Another spasmolytic agent of the series is β-piperidinoethyl-phenyl-(3-thienyl) glycolate (P.P.T.)[235, 236] (XXX).



(XXX)

The two isomeric thienyl compounds β-diethylaminoethyl-phenyl-(2-thienyl)glycolate and β-diethylaminoethylphenyl-(3-thienyl)glycolate have been prepared and tested. In this case, the 2-isomer is more active than the 3-isomer, being 85 per cent as active as atropine whereas the 3-isomer shows only 65 per cent of the activity of atropine.[236]

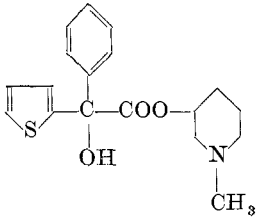
The amino esters of certain 1-substituted alicyclic carboxylic acids of general formula (XXXI) where n = 3,4 and R = CH_3,



(XXXI)

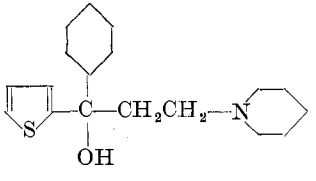
CH_2CH_3, also possess spasmolytic activity which is of the same order as that shown by their phenyl isosteres.[237] Other variants on the general formula (XXVIII) are reported by Biel *et al.*[238] and one of the enantiomorphs of compound (XXXII) was found to be twice as active as atropine and three times as active as the corresponding diphenyl isostere.[238, 239]

Thiophen derivatives somewhat removed from the general formula of (XXVIII) are also known to possess anticholinergic activity. Among these are the 3-tertiaryamino-1,1-di-(2-thienyl)-butan-1-ols,[240] which yield on dehydration the thiambutene series of analgesics, and the 3-tertiary amino-1,1-di-(2-thienyl)propan-1-ols and their anhydro derivatives.[241] 1-*Cyclo*hexyl-1(2-thienyl)-

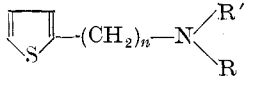


(XXXII)

3-piperidinopropanol (XXXIII) has been resolved into its optical isomers and the L form was found to be more active as an anticholinergic agent than the D form on all the test systems used.[242] The workers discussed the results in terms of a model of the acetylcholine receptors. Deductions about the geometry of these receptors, taking into account the activity to be found in various thiophen compounds, were made earlier by the same school.[243] Because of the antispasmodic activity shown by certain simple secondary and tertiary amines, a series of secondary and tertiary amines containing a ω-(2-thienyl) group (XXXIV) were prepared



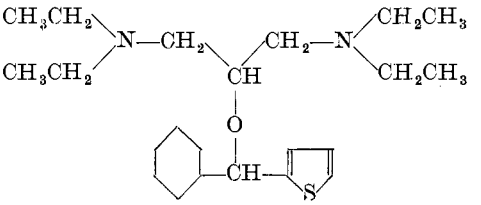
(XXXIII)



(XXXIV)

and these were found to possess antispasmodic activity against intestinal strips treated with barium chloride.[244] β-Piperidinoethyl-(2-thienyl) ketone and 1-(piperidyl)-3-(2-thienyl)-3-pentanol also show antispasmodic action.[245] Certain derivatives of

1,3-bis(dialkylamino) propanes were found to possess antispasmodic activity, and the thiophen compound (XXXV) was reported to be ten times as active as papaverine.[246]



(XXXV)

Included in a series of 1,3-dioxolones and 1,3-dioxones originally prepared as potential hypnotics because of their structural relationship to paraldehyde, but which in fact turned out to possess spasmolytic and antihistaminic activity instead, were two thiophen derivatives.[156, 247] Also certain basic ethers of aralkyl phenols containing thiophen rings are claimed to overcome smooth muscle spasm.[248]

8. Oestrogens

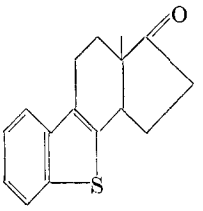
Compounds exhibiting oestrogenic activity can be divided for convenience into three main groups:

(1) Steroid derivatives, both natural and synthetic.
(2) Derivatives of stilbene.
(3) Osetrogens which are *iso*flavones or coumarin derivatives.

Thiophen isosteres of the first two groups have been prepared, but little attention appears to have been paid to the third group in the way of preparing thiophen analogues, apart from one paper on the preparation of some 3-(2-thenoyl) coumarins as potential hypnotics, antimitotics and oestrogen antagonists.[249]

Due to the inherent difficulties in steroid synthesis, only a few thiophen-containing steroid derivatives, namely the thiophen analogues of 3-deoxyequilenin (XXXVI),[250] 3-deoxy*iso*equilenin,[251]

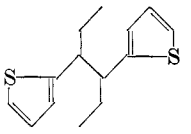
and 3-deoxyestradiol,[252] have so far been prepared. Because of the interest in these compounds from the point of view of the antimetabolite concept, a detailed study of their activity would



(XXXVI)

seem desirable. The absence of the 3-hydroxyl group present in the natural hormones may, however, be a great disadvantage in this respect, and it will be interesting to see whether the corresponding hydroxylated compounds will be prepared.

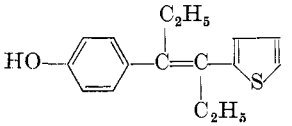
Dodds and his co-workers[253] studied the structure–activity relationship in the stilbene series, and found that 4-4′-dihydroxystilbene was more effective as an oestrogen than the simple hydrocarbon derivatives. Indeed, it has been proposed that oestrogenic activity is associated with strong hydrogen bond-forming groups such as hydroxyl groups separated by an optimum distance of 8·55 Å.[254] Despite this hypothesis many thiophen derivatives of the non-hydroxylated stilbene type have been prepared and tested, including 1-phenyl-2-(2′-thienyl)ethylene,[255] α-2-thienylstilbene and 1,2-diethyl-1-phenyl-2(2′-thienyl)ethylene,[256] 1-phenyl-1-(2′-thienyl)-2-(α-naphthyl)ethylene,[251] *meso*-3,4-



(XXXVII)

di(2′-thienyl)hexane (XXXVII)[258] as well as some 1,2-diaryl-1-(2′-thienyl)ethylenes.[259] No significant activity was observed in any of these compounds. That this could indeed be due to the absence of hydroxyl functions is indicated by the fact that the

introduction of this group into 1,2-diethyl-1-phenyl-2-(2′-thienyl)-ethylene to give 1,2-diethyl-1-(*p*-hydroxyphenyl)-2-(2′-thienyl)-ethylene (XXXVIII),[260] leads to a considerable increase in oestrogenic activity.



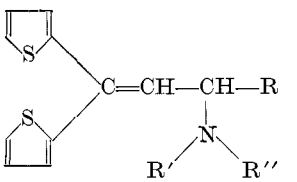
(XXXVIII)

5-Acetyl, 5-propionyl and 5-benzoyl-2-(α-stilbenyl)thiophen are reported to have a weak oestrogenic activity, and to show no antagonism towards the action of true oestrogens.[261]

Of the many other stilbene-like thiophen compounds reported,[262] the only one possessing activity worthy of mention is 1-bromo-1,2-diphenyl-2-(5-bromo-2-thienyl)ethylene, which was found to inhibit body growth and produce extensive testicular atrophy in male rats.[263] It has been suggested that this compound deserves clinical trial in mammary cancer.

9. Analgesics

In the course of an investigation of the biological properties of a series of 3-tertiaryamino-1,1-di-(2-thienyl)but-1-enes prepared as analogues of the 3,3-diphenylallylamines which were known to have atropine-like, antihistaminic and local anaesthetic

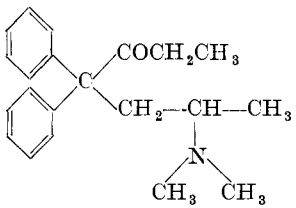


(XXXIX)

properties,[264] the important discovery was made that the thiophen compounds, in addition to having similar activity to the compounds on which they were modelled, also possessed pronounced analgesic activity.[265] This created a new interest in thiophen derivatives as biologically active compounds. Unfortunately the

goal of the synthetic analgesic chemist of divorcing analgesic potency from addiction liability was not attained and compounds of this series are addictive—like other analgesics.[266]

This new class of analgesics has been termed the thiambutenes. They can be represented by the general formula (XXXIX), and can thus be regarded as cogeners of methadone (XL) in which the ketone side-chain has been omitted, with the introduction of a



(XL)

double bond and the benzene rings replaced by thiophen rings. The double bond is not necessary for analgesic activity and the corresponding saturated 1,1-di(2-thienyl)-3-tertiaryaminobutanes are also potent analgesics, although somewhat weaker than the unsaturated compounds.[267] The structural similarity to methadone is further emphasized by the fact that, in the case of both methadone and the thiambutanes, it is the enantiomorph related to D-alanine which is the analgesically active optical isomer,[268] although it so happens that these active enantiomorphs have opposite rotations, positive in the case of the thiambutenes and negative in the case of methadone and its sulphone analogue.

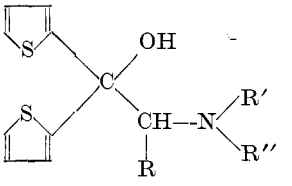
The geometry of the thiambutenes as well as other analgesic molecules has been treated in detail [6, 269] in terms of a specific receptor model, and an attempt has been made to relate the activities and the dissociation constants in the thiambutene series.[270] The activity has also been shown to decrease with an increase in the 'effective width' of the basic group. In addition to possessing addiction liability the thiambutenes produce muscle twitching and so are not used clinically, although 3-diethylamino-1,1-di(2-thienyl)but-1-ene is available as a veterinary analgesic.[271]

Various other compounds of general formula (XXXIX) and their hydrogenated derivatives have been investigated experimentally both in animals and man.[272] All had a high order of analgesic

effectiveness. In man it is stated that drowsiness and sleep occur more frequently than with morphine or pethidine, but nausea and vomiting are less than with morphine.[273]

The compound, 3-diethylamino-1,1-di(2-thienyl)but-1-ene, in addition to its analgesic properties possesses marked sedative and hypnotic action, and pre-medication of dogs with it enhances and prolongs the action of barbiturates,[274] an action which is readily reversed by nalorphine.

The thiambutene analgesics have attracted considerable attention in Japan where modified syntheses have appeared,[275] many of them as patents. The Japanese workers have also investigated antitussive activity in the thiambutene series. It is claimed that 3-piperidyl-1,1-di(2-thienyl)but-1-ene is a potent antitussive as measured on the dog.[276] The same compound was later said to be



(XLI)

very effective by oral administration to adult humans.[277] These later workers also prepared compounds of the type (XLI) for testing as antitussives.

The di(2-thienyl) isosteres of both methadone and isomethadone in which both the benzene rings have been replaced by thiophen rings have been prepared,[278] and in addition other compounds closely related in structure to methadone but which have only one of the benzene rings replaced by a thiophen ring have been tested and shown to be active analgesics.[279] Thiophen derivatives modelled on the meperidine structure have also been prepared and tested.[280]

A large series of complex piperidine derivatives containing thiophen substituents have been prepared as potential analgesics by Sugimoto and co-workers in Japan,[281] and a group of polysubstituted 1-(2-thienyl)*iso*quinoline compounds are reported to possess analgesic activity.[282]

A weak analgesic action is exhibited by dibenzothiophen amino alcohols but it is less than that of the related phenanthrene, carbazole and dibenzofuran compounds.[283]

10. Carcinogenic and Carcinolytic Activity in the Thiophen Series

The discovery that certain polynuclear hydrocarbons can evoke malignant tumours in animal tissues opened a new field for investigation as to the cause of cancer. In an effort to correlate carcinogenic activity with chemical structure, many polynuclear aromatic compounds were synthesized, including some possessing thiophen rings. Of these, 4,9-dimethyl-2,3,5,6-dibenzothiophanthren[284] and 4,9-dimethyl-5,6-benzothiophanthren[285] are highly carcinogenic. In addition, the syntheses of other thiophen isosteres of carcinogenic hydrocarbons have been reported.[286]

Thiophen isosteres of carcinogenic derivatives of carbazole have also been prepared[287] for testing.[288] These had no significant activity against the growth of sarcoma in mice. Such carbazole derivatives include some bearing ethyl groups,[289] the introduction of which is said to increase carcinogenic activity,[290] and others bearing halogen substituents.[291]

Certain furan derivatives of malononitrile were found to be active against the growth of transplanted tumours such as sarcoma, carcinoma and myeloid leukemia in mice, but the thiophen isosteres proved to be inactive.[292] Other compounds studied were various thionaphthindoles and preliminary experiments suggested that some might possess growth inhibitory action on experimental tumours.[293] Two thiophen aminopyridine derivatives were tested for their ability to retard the growth of sarcoma in mice but were completely inactive.[294] Thiophen derivatives of various boronic acids have been prepared in connection with brain tumour studies.[295]

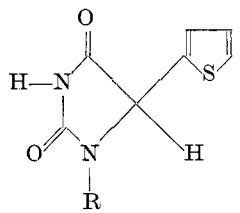
11. Central Nervous System Depressants

Included in this section are the thiophen isosteres of drugs which are well established as therapeutically useful central nervous system depressants without regard as to whether such drugs exert their action at specific centres or not. As has already been mentioned, the simple thiophen ketones unlike acetophenone have no CNS depressant activity.[46]

The chemical group on which the greatest amount of work has been done would appear to be the hydantoins. The three thiophen derivatives 5-methyl-5-(2,5-dimethyl-3-thienyl)hydantoin, 5-ethyl-5-(2,5-dimethyl-3-thienyl)hydantoin and 5-methyl-5-(5-methyl-2-thienyl)hydantoin were prepared in 1945 but no report of their biological activity was given.[296]

The anticonvulsant properties of 5-phenyl-5-(2-thienyl) hydantoin have been well investigated and directly compared with those of 5,5-diphenylhydantoin and 3-methyl-5-ethyl-5-phenylhydantoin.[297] Its spectrum of activity was found to be similar to that of the isosteric 5,5-diphenyl compound, the compound being most effective against grand mal epilepsy. It was used clinically for a time[298] on account of its favourable therapeutic ratio, since although less active than 5,5-diphenylhydantoin it is also less toxic.

A large series of 5-(2-thienyl) substituted hydantoins including some bearing 3-alkyl substituents and 1,3-dialkyl substituents was prepared and tested,[299] and some were found to possess the same order of activity as 5,5-diphenylhydantoin. In all cases *N*-alkylation reduced the anticonvulsant activity. Another series of thiophen derivatives of hydantoin of general formula (XLII)



(XLII)

where R is an alkyl, alkenyl, *cyclo*alkyl or aralkyl radical have been prepared and tested.[300] None of these compounds, however, was as active as 5,5-diphenylhydantoin when tested for ability to inhibit electrically induced convulsions in cats or metrazol-induced convulsions in rats. 5,5-Di-(2-thienyl)hydantoin is also claimed to be active as an anticonvulsant.[301] 5-Phenyl-5(3-thienyl) hydantoin is reported to have higher anticonvulsant activity and lower toxicity than the 2-thienyl isomer.[302] Methylation of

N(3) in the 3-thienylhydantoin series increased the toxicity with little alteration in activity.

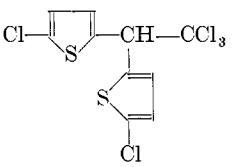
Several substituted barbituric acids containing thiophen rings have been prepared.[303–306] 5-Ethyl-5-(2-thienyl)barbituric acid was stated to be as active as its analogue, phenobarbital, when injected intraperitoneally into rats.[303] Similarly, 5-ethyl-5-(2-thenyl)barbituric acid and the corresponding thiobarbituric acid showed behaviour strictly analogous to their isostere, 5-ethyl-5-benzylbarbituric acid, by producing convulsions.[304] 5-Ethyl-5-(3-thienyl)barbituric acid surprisingly showed different properties from the corresponding 2-thienyl isomer and produced sedation without hypnosis[306] or analgesia.

Unlike phenylacetylurea, 2-thienylacetylurea is practically devoid of anticonvulsant properties.[307]

The preparation of 2-thienyl-3-methyl-4-thiazolidone has been reported[308] but its activity is not recorded. Its furyl isostere, like the parent phenyl derivative, is reported to give complete protection against metrazol - induced convulsions. Certain 3-mercapto-1,2,3-triazine derivatives show CNS depressant activity and the thiophen derivative, 3-mercapto-5-(2-thienyl)-1,2,4-triazine, on testing, produced paralysis followed by convulsions.[309]

12. Insecticides

The discovery of the potent insecticidal activity of 2,2-bis-(*p*-chlorophenyl)-1,1,1-trichloroethane (DDT) in 1939[310] led to the synthesis of many related compounds in an effort to improve upon



(XLIII)

the insecticidal properties, and to obtain information concerning the mode of action of these compounds.

The first synthesis of a thiophen analogue was reported by Prill *et al.*[311] who discovered that 2,2-bis-(2′-thienyl)-1,1,1-trichloroethane was inactive against the house fly. Subsequently, other workers tested this compound as well as various halogenated and

alkylated derivatives,[312] finding that it had no appreciable activity towards the insects *Heliothrips haemorrhoidalis* and *Drosophila melanogaster*.[313]

However, 2,2-bis-(2′-chloro-5-thienyl)-1,1,1-trichloroethane (XLIII) has been reported to be effective against cockroaches,[314] *Blatella germanica* and *Pogonomyrmex barbatus*.[315] The preparation of more complicated thiophen-containing compounds of the trichloromethyl type has been reported.[316] These were found to possess insecticidal activity against *D. melanogaster* M. and *Calandra granaria* L. Keine and citrus red mite (*Paratetranychus citri*) and greenhouse thrips (*H. haemorrhoidalis*).[317] In general, the mode of action and the activity were similar to that of DDT.[315, 318]

2,2,2-Trichloro-1-(2′-thienyl)ethanol and 2,2,2-trichloro-1-(2′-chloro-5′-thienyl)ethanol were prepared and tested for insecticidal activity. Neither was reported to be effective against house flies, but against mosquito larvae they were as active as the corresponding phenyl compounds.[319] The addition of (1, 2-dichloro-2-phenyl) ethyl-2′-thienyl ketone to DDT appears to enhance the insecticidal activity,[320] and there are many other reports in the literature of various thiophen analogues of DDT being used in insecticidal mixtures.

In view of the conclusion of Frear and Seiferle[321] that thienyl substitution does not destroy toxicity towards insects, it would seem reasonable to continue the preparation of thiophen isosteres of other classes of insecticides. Already, a thiophen analogue of allethrin showing about half the activity of allethrin itself,[322] and thienyl substituted pyrrolidines analogous in structure to nicotine but showing less activity against *Thermobia domestica*[323] have been reported.

Numerous halogenated thiophen derivatives and various sulphones are claimed as insecticides in the patent literature.

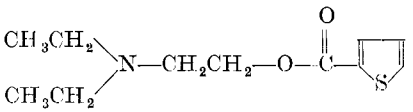
2-Thenylbenzoate, and 2-thenylsalicylate have been reported to give adequate protection against chigger mites,[324] but Cross found 2-thenylsalicylate to be inferior to benzil in field tests.[325]

13. Local Anaesthetics

The pharmacological activity of a large number of the local anaesthetics appears to reside in the dialkylamino ester linkage.

Although the effect of varying the alkyl group has been thoroughly investigated, rather less attention has been paid to the effect of changing the carboxylic acid. Nevertheless, included in those studies that have been performed on the alteration of the carboxylic acid moiety, are several involving thiophen derivatives.

The earliest work was that of Steinkopf and Ohse[53] mentioned previously, who prepared the thiophen analogues of cocaine and eucaine. Gilman and Pickens[326] reported that the local anaesthetic potency of β-diethylaminoethyl-2-thiophenecarboxylate (XLIV) was superior to that of the corresponding furan derivative,



(XLIV)

but inferior to the pyrrole and especially the phenyl isosteres. Preparation of the furan and thiophen isosteres of anethesine and procaine has also been reported, but in this case the thienyl compounds had similar local anaesthetic activity to the parent compounds.[327] In addition, a relatively simple series of dialkylaminoalkyl esters of 3-thenoic acid were compared with the 2-isomers[328] and the only compound found to have significant local anaesthetic activity was γ-di-*n*-butylaminopropyl-3-thenoate, whose activity was slightly less than that of the corresponding 2-isomer.

The use of 2- and 4-dibenzothiophen-carboxylic acids in the preparation of amino esters has also been studied,[329] but the local anaesthetic activity, although significant, is less than that of the corresponding carbazole isosteres.

2-Thienyl-β-piperidinoethyl ketone[330] has been reported to show considerable local anaesthetic activity, although less than that of cocaine,[331] and, accordingly, a series of such compounds containing alkyl substituents in the thiophen ring has been tested.[332] The compounds all show local anaesthetic activity, the most effective being those possessing a butyl or amyl radical.

Several ω-(*N*,*N*-dialkylamino)alkyl-3-thienyl sulphide hydrochlorides were prepared[333] as a consequence of an observation[334] that analogous phenyl compounds showed local anaesthetic

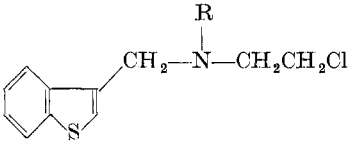
activity, and their activity was found to equal or exceed that of procaine in the guinea-pig wheal test.

14. Miscellaneous

In this section are included compounds containing thiophen rings which are isosteres of the less important biologically active compounds, or else which have had very little work done on them.

The discovery that certain β-haloethylamines possessed powerful adrenergic blocking action inspired a mild interest in thiophen compounds of this type.[335] Several such derivatives were studied by Nickerson and Gump.[336] Of the thiophen derivatives studied, *N*-thenyl-*N*-benzyl-2-chloroethylamine was the most active. The compounds *N*-thenyl-*N*-ethyl-2-chloroethylamine and *N*,*N*-dithenyl-2-chloroethylamine were also active but *N*-thenyl-2-chloroethylamine was inactive. Various *N*-(phenoxy*iso*propyl)-*N*-thenyl-2-haloethylamines are claimed to be adrenergic blockers.[337]

The effects of two compounds belonging to the thionaphthen series (XLVa and XLVb) on the peripheral vascular system have



(XLV)

(a) R = CH_3
(b) R = CH_2CH_3

been studied.[338] They were found to produce vasoconstriction by direct action on the precapillary sphincters and the terminal arterioles. In addition, these compounds possessed antihistaminic activity. The ethyl compound was found to be weakly active in its ability to reduce adrenaline-induced hyperglycaemia,[339] but it is claimed to completely reverse the pressor effect of adrenaline, in relatively high doses.[340]

3-Succinoylthionaphthen is reported to have about one-third the choleretic potency of dehydrocholic acid[341]. In a study of various choline derivatives, Bell and Carr[342] discovered that the

perchlorate salt of 2-thenoylcholine was one-tenth as active as acetylcholine chloride on smooth muscle.

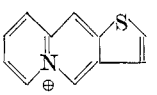
The C-mitotic activity of some thiophen compounds has received attention,[343] and 6-(2-thenyl)-2-thiouracil is stated to be three times as active as 2-thiouracil as an antithyroid agent.[344]

The two isomeric 8-thenyltheophyllines have been prepared and both the 2-thenyl and 3-thenyl compounds have similar vasopressor activity to 8-benzyltheophylline and 8-benzhydryltheophylline which were investigated on account of their structural similarity to tolazoline (2-benzyl-2-imidazoline).[345]

The chalcone derivative 2-(3-hydroxycinnamoyl)thiophen is claimed to inhibit dihyrdoxyphenylalanine decarboxylase,[346] and various 3-acyl coumarins including thiophen derivatives have been prepared in order to study their sedative and antimitotic properties.[249] The ester of 2-(ω-hydroxyethyl)1,2,3,4-tetra-hydro-*iso*quinoline and thiophen-2-carboxylic acid is claimed to have a regulatory action on the heart and to be a peripheral vasodilator[347] and various 4-thenylaminopyrimidines are claimed to be plant growth regulators.[348] Various thiophen amidines have been prepared as potential chemotherapeutic agents.[349]

The hydrochloride salt of 2-thienylmethyl-*iso*thiourea was found to produce a fall in blood pressure and heart rate and to depress respiratory movements in chloralosed cats,[350] and several substituted 2-methylpiperidines including two thienyl derivatives were found to possess a stimulating effect on the CNS.[351]

Some thiophen compounds related to 1-phenylindan proved to be without significant analgesic activity.[352]



(XLVI)

Herz's group has been actively engaged in the preparation of thiophen analogues of various *iso*quinolines,[353] and some of the compounds of this series may well have interesting biological properties.

Thieno-(2,3-6)quinolizinium bromide (XLVI) was found to be without curariform activity but to potentiate the muscle relaxant effects of suxamethonium chloride in male cats.[354] A series

of substituted polymethylene bis quaternary ammonium salts, including some thiophen derivatives, have been reported to be powerful ganglion blocking agents.[355]

Certain 2-aryl-3-alkyl-4-metathiazanones including 3-methyl-2-(2-thienyl)-4-metathiazanone have been shown to possess anti-convulsant and skeletal muscle relaxant properties[356] although the pharmacological activity of the thienyl derivative itself was not reported.

Work concerned with the odours of various thiophen compounds is well summarized by Blicke.[18] The more recent work, especially that dealing with thiophen derivatives of ionone, is covered in articles by Sy.[357]

Conclusions

It is readily seen from this account of the biologically active compounds which possess thiophen rings, that a large amount of time and attention has been paid to compounds of this type. If we were to measure success solely in terms of the number of new drugs of clearly superior clinical desirability which have been produced, it must be admitted that all this work has shown but small reward. Taking a broader criterion, however, we can see that the work has made valuable contributions to the study of antimetabolites and that it has shown in general the biological similarity of the phenyl and thienyl groups. Further, it has shown that the position of substitution of the thiophen ring is important, 3-thienyl derivatives usually being more active and less toxic than their 2-thienyl isomeres. There has thus been accumulated a large amount of factual data which, it is to be anticipated, will make a valuable contribution to the development of newer theories, giving greater understanding of the intimate mode of action of drugs.

Now that the relationship of the thiophen ring to the benzene ring with respect to biological activity has been clearly shown in so many diverse systems, work could profitably be concentrated on the comparison of other ring systems. For example, the indole nucleus plays an important role in biological activity and much work could be done in studying activity in compounds where the indole nucleus has been replaced by the thionaphthen ring system.

(*Received 3 July, 1959*)

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