SOME THIOPHEN AND BENZO[b]THIOPHEN DERIVATIVES OF POTENTIAL BIOLOGICAL INTEREST

BY

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SUMMARY

In an introductory section, the chemotherapeutic activity of thiophens, benzo[b]thiophens, and guanidine and related compounds is briefly surveyed, and the pharmacological activity of alkylamines derived from the first two groups of compounds is considered. Methods for the preparation of arylthiophens and benzo[b]thiophens are then reviewed, and the electronic structure and electrophilic aromatic substitution of these compounds are discussed.

The synthesis of a series of 5-halogenobenzo[b]thien-3-ylalkylguanidines and biguanides from the corresponding 5-halogenobenzo[b]thien-3-ylalkylamines is described, and the preparation of some N-methyl-substituted 5-halogenobenzo[b]thien-3-ylacetamidines is also reported.

Four methods for the preparation of 2-arylthiophens have been investigated and these compounds have been converted to the corresponding 5-arylthiophen-2-carboxylic acids from which a series of primary and tertiary amides has been prepared.

Reduction of certain 5-arylthien-2-ylamides (aryl = phenyl, p-chlorophenyl, p-tolyl) with an excess of lithium aluminium hydride has been found to give the corresponding 5-arylthien-2-ylmethylamines, but reduction of the 5-p-bromophenylthien-2-ylamides under similar conditions is accompanied by hydrogenolysis of the aromatic bromine. The required 5-p-bromophenylthien-2-ylmethylamines have therefore been prepared either by reduction of the amide with the calculated quantity of lithium aluminium hydride, or by treatment of 5-p-bromophenyl-2-chloromethylthiophen with the appropriate secondary amine.

Some preliminary work on the synthesis of a related series of 2-(5-arylthien-2-yl)ethylamines is discussed. The required intermediate 5-arylthien-2-ylacetic acids have been prepared by two methods, and 2-(5-phenylthien-2-yl)ethylamine itself has been prepared by the reduction of 2-cyanomethyl-5-phenylthiophen.

Certain 5-p-halogenophenylthien-2-ylaldehydes and their thiosemicarbazone derivatives have been synthesised, and the preparation of two 5-phenylthien-2-ylmethylamidines has been accomplished.

The i.r. and n.m.r. spectra of many of the new compounds are recorded.

The mass spectra of a selection of 5-halogenobenzo[b]thien-3-ylalkylguanidines, 5-arylthien-2-ylamides, 5-arylthien-2-ylmethylamines, and 5-arylthien-2-yl acid hydrazides have been measured and possible fragmentation pathways for these compounds have been suggested.

The author is indebted to Professor N. B. Chapman for his kindness and encouragement, and to Dr. K. Clarke and Dr. D. G. Wibberley for their constant guidance during the course of this work.

The author also wishes to thank her colleagues, in particular Dr. J. Raines, for their interest and helpful suggestions.

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To My Family

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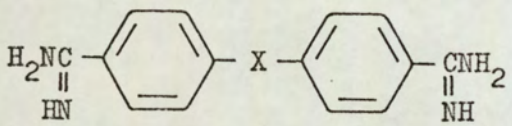
INTRODUCTION

PART I

Chemotherapeutic Activity of Guanidines and Related Compounds.

Guanidine is one of the strongest organic bases known, having a pK_a value of 13.6, and this property is shared by the structurally-related amidines and biguanides. The ions of these bases are thus readily attached to carboxyl or other anionic groups present in macromolecules and will therefore be expected to show some biological activity.

Guanidine hydrochloride itself displays only weak anti-bacterial action,[1] but in 1938, in an extensive survey[2] of the trypanocidal activity of a series of aliphatic and aromatic mono-, and di-guanidines, their related amines, amidines and isothioureas, potent activity was found in all four groups of compounds. The disubstituted derivatives were more active than the monosubstituted derivatives and the most promising compounds were diamidines (1).



(1)

X = -CH=CH- , Stilbamidine.

X = $-O(CH_2)_3O-$, Propamidine.

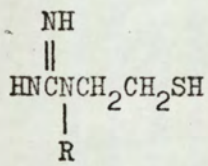
X = $-O(CH_2)_5O-$, Pentamidine.

The mode of action of these diamidines is uncertain, but it may be due to bonding between the amidine groups and the phosphate groups of the nucleic acid of the trypanosome resulting in a disturbance of the cell metabolism.[3] The diamidines show greatest activity against those trypanosomes which are heavily dependent on oxygen and glucose and since

the oxidation of certain amino-acids is known to be impaired in the presence of these drugs, their action may involve the inhibition of the oxidative metabolism of the cell.[4]

This same series of compounds was also found to possess anti-bacterial activity, and again, the disubstituted derivatives were the most active. Optimum results were obtained when the two functional groups were separated by an aliphatic chain of from five to seven carbon atoms. In general, this series exhibited a wide spectrum of anti-bacterial action; the stronger bases showed greatest activity against Gram-negative bacteria while the weaker bases were more active against the Gram-positive strains. Since their anti-bacterial activity was similar to their trypanocidal activity in most cases, it is reasonable to assume that a common mode of action exists. It is interesting to note that, although the primary amines were active, the corresponding N,N-dimethyl derivatives were inactive which suggests that hydrogen bonding to an anionic receptor-site is involved.[2a]

Anti-bacterial activity has since been observed in other guanidines. Thus, 1-alkyl derivatives of 1-(2-mercaptoethyl)guanidine (2) showed high *in vitro* and *in vivo* activity against *S.pyogenes* and *S.aureus*, but their toxicity was rather high.[5]

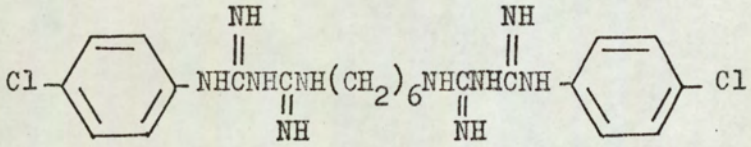


(2)

A series of mono-, di-, and poly-amidines prepared by McKay *et al.*[6] showed anti-bacterial activity, particularly against Gram-positive strains, and a related series of guanidines were also screened as anti-bacterial agents.[7] In both series the difunctional compounds were the most active. The enhanced activity of these

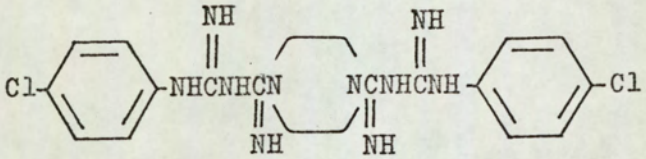
difunctional molecules may be due to their action at a receptor-site having two anionic centres. Once one basic group has occupied one receptor-site, the other basic group is more favourably placed to occupy the second. Optimum activity is obtained when the distance between the basic groups is equal to the distance between the two receptor-sites.

The interest in guanidine derivatives was extended to the biguanides and in a series of bis-biguanides,[8] greatest activity was shown by Hibitane (3) against a wide spectrum of bacteria. Its action is quite unusual, in that, at a concentration of five parts per million it can kill 99.9% of an inoculum within five minutes, but is not completely effective in twice this time unless considerably stronger concentrations are used.



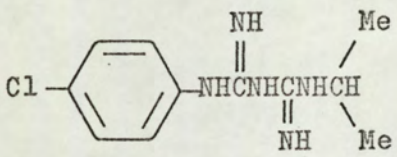
(3)

Incorporation of the terminal nitrogen atoms into a piperazine ring led to Picloxydine (4) which also showed broad spectrum anti-bacterial activity.[9]



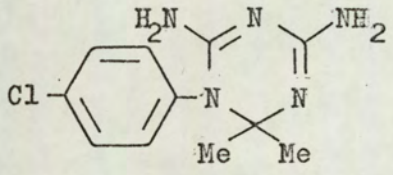
(4)

Guanidine itself shows slight anti-malarial activity,[10] but the biguanide, Paludrine (5), discovered during a systematic search for anti-malarial agents,[11] is of greater importance.

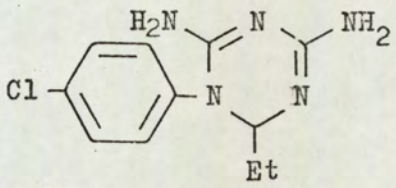


(5)

Although inactive *in vitro*, Paludrine is highly active *in vivo* which suggests that it undergoes some metabolic change. The active metabolite was finally isolated from rabbit urine and shown to be the 1,3,5-triazine(6),[12] which bears a marked structural similarity to the anti-malarial drug Pyrimethamine (7).



(6)



(7)

Paludrine and Pyrimethamine, like the Sulpha-drugs, interfere with the production of tetrahydrofolic acid, which is vital for the synthesis of purines, pyrimidines, and amino-acids, but their activity is retained against strains of plasmodium which are resistant to the sulphonamides. The sulphonamides inhibit the conversion of *p*-aminobenzoic acid into folic acid,[13] and it is thought that Paludrine and Pyrimethamine prevent the metabolism of folic acid by displacing its 2-amino-4-hydroxypyrimidine group from a receptor-site on the enzyme, dihydrofolic reductase.[14] This is supported by the ability of folic acid to reverse the action of these drugs, and morphological changes *in vivo* suggest that chromatin synthesis and nuclear division are inhibited.[15]

The guanidine residue is present in the sulphonamide, Sulphaguanidine, in the streptidine moiety of the natural antibiotic, Streptomycin, and in the anti-fungal agent, Eulicin, and a comprehensive list of over two hundred biguanides, many of which possess significant anti-bacterial action, have been reported.[16]

Although the successes achieved in the conquest of bacterial infections have not been equalled in the field of viral diseases, certain classes of compounds possess some anti-viral activity.

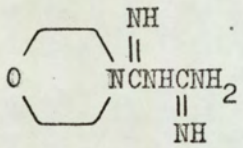
Guanidine itself is active against the polio-virus[17] and its action has been extensively studied.[18] The genetic material of the polio-virus, unlike that of animal cells, is ribonucleic acid (RNA), and in order to reproduce it, an enzyme, RNA replicase, must be synthesised during the latent period of the viral life-cycle. The addition of guanidine hydrochloride at this stage effectively blocks the synthesis, and its action is thought to involve interference with the association of the monomeric units required to form the polymeric enzyme. However, strains of the virus which are resistant to guanidine rapidly develop.

Anti-viral activity has been observed in a variety of related compounds such as the amidines,[19,20] natural amino-acids,[20] and even ammonia.[21] Guanidine-resistant strains of polio-virus are also resistant to these compounds which suggests a common mode of action.

The amidino-group is present in the natural antibiotics, Netropsin and Noformicin, both of which show pronounced anti-viral activity. Netropsin also contains a guanidino-group.

The biguanide (8) has been used effectively against the influenza,[22] and herpes[23] viruses, whose genetic material is desoxyribonucleic acid (DNA). Enzymes capable of replicating DNA are

present in all animal cells and these viruses can utilise the available enzymes in order to reproduce. Thus, the action of the biguanide cannot be similar to that of guanidine on the polio-virus, but must involve direct interference with the replication of the viral DNA.

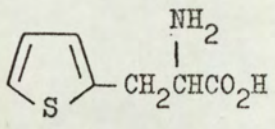


(8)

Following the observation that the thiosemicarbazone of p-aminobenzaldehyde protected mice against neurovaccinia,[24] a wide variety of thiosemicarbazones derived from aromatic, aliphatic, and heterocyclic systems have been synthesised and shown to possess anti-viral activity.[25] In general, the greatest activity is shown by compounds in which the thiosemicarbazone group is separated from the heteroatom by one carbon atom, as in 2-thiophenaldehyde. The production of the viral genetic material is not affected by these compounds, but they are thought to interfere with the maturation of the viral components required to produce an infectious form.[26]

Chemotherapeutic Activity of Thiophen Derivatives.

In the search for chemotherapeutic activity in thiophen derivatives, much of the earlier work was devoted to the sulphur analogues of natural amino-acids. DLβ-Thien-2-ylalanine (9) was found to inhibit the growth of yeast, bacteria,[27] chick blastoderms[28] and rats[29] by its antagonistic action against β-phenylalanine.

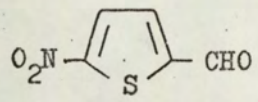


(9)

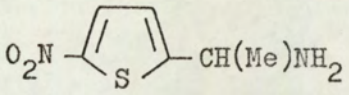
Subsequent studies have shown that in bacterial systems only the L form of the acid is active[30] and it is thought to compete with the natural amino-acid for receptor-sites on the enzyme responsible for the oxidation of β-phenylalanine to tyrosine.[31] β-Thien-3-ylalanine is even more active than the 2-isomer,[32] and radioactive labelling techniques have shown that it prevents the incorporation of β-phenylalanine into proteins.[33] The toxic effects of β-thien-2-ylalanine are increased by incorporating it into synthetic dipeptides, which are thought to compete with the natural analogue for a common receptor-site without prior conversion into the constituent amino-acids.[34]

β-Thien-2-ylalanine also inhibits the growth of Theiler's GD.VII virus.[20] In this case, its action does not involve competitive inhibition since its effect is not reversed by β-phenylalanine, and it is thought that the whole course of the viral cycle is altered.

The high anti-bacterial activity of the nitrofurans stimulated interest in the corresponding nitrothiophens as potential chemotherapeutic agents. 5-Nitrothien-2-ylaldehyde (10) is active against S.aureus, enteric bacteria, and some fungi. Anti-bacterial activity was also found in the amide and methyl ester but thien-2-ylaldehyde itself is completely inactive so the presence of a nitro-group is clearly essential in these compounds.[35] The 5-nitrothien-2-ylalkylamine (11) has been shown to be active against S.dysenteriae.[36]



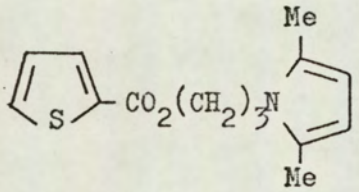
(10)



(11)

In a series of nitrothiophens prepared by Dann,[36] considerable activity was shown against a wide variety of micro-organisms possessing a high redox potential. It is thought that the action of these nitro-compounds may be attributed to their partial reduction by the bacteria into active hydroxylamine derivatives. Bacteria having a low redox potential are resistant to these nitro-compounds, and alkali-producing bacteria rapidly become insensitive by virtue of their ability to catalyse the formation of azo-derivatives which are known to be inactive.

In other thiophen derivatives, the presence of a nitro-group is not essential for anti-bacterial activity. The basic ester (12) shows high activity against a wide spectrum of bacterial strains and has a favorable effect on certain types of human rhinitis.[37] It can be used as an antiseptic and as a mild anaesthetic.[38] Some anti-bacterial activity was observed in a series of secondary amides (13) of thiophen-2-carboxylic acid, and N-then-2-oyl-3-aminobenzoic acid was also shown to be effective against A_2 influenza virus.[39]



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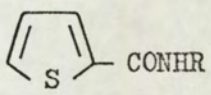
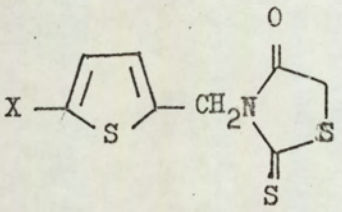


(13)

Some 3-substituted rhodanines (14) were shown to inhibit the growth of E.Coli,[40] and a series of Mannich bases (15) was found to be active against S.aureus, S.pyogenes, and P.vulgaris.[41]



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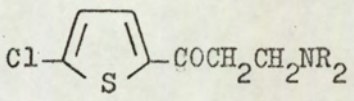
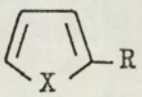


(15)

Activity against influenza and Newcastle disease viruses has been demonstrated in thien-2-yl glyoxal (16).[42] In the furan series, the hydroxy-aldehyde (17) and the keto-alcohol (18) are also active, and since these are readily oxidised to the glyoxal (19) it is thought that the mode of action involves the oxidative metabolism of the virus.



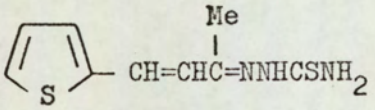
(16) X = S, R = COCHO.

(17) X = O, R = CH(OH)CHO.

(18) X = O, R = $COCH_2OH$.

(19) X = O, R = COCHO.

In vitro[43] and in vivo[44] anti-tubercular activity is shown by the thiosemicarbazones of thiophen-2-aldehyde and its derivatives.[45] M.tuberculosis is completely inhibited by the thiosemicarbazone (20), and preliminary investigations suggest that the 3-isomer has superior activity.[46]



(20)

The thiosemicarbazones of 5-nitro, and 5-bromo-thien-2-ylaldehyde protect mice against Williamsport virus when injected intercerebrally,[47] but the corresponding semicarbazones and the thiosemicarbazones of the

related 5-substituted-thien-2-ylketones are quite devoid of anti-viral activity.

As a group, the thiosemicarbazones have largely been replaced in tuberculosis chemotherapy by Isoniazid. Subsequently, the hydrazides of various thiophen acids, e.g. thiophen-2-carboxylic acid[48] and 4-hydroxy-2-methylthiophen-3-carboxylic acid[49] were shown to possess anti-tubercular activity, but none of these compounds are as effective as Isoniazid. Thien-2-ylacetic acid hydrazide was found to be completely inactive.[48]

Although the mode of action of the hydrazides is uncertain, their ability to chelate copper ions[50] and to reduce the activity of the bacterial enzyme, diamine oxidase,[51] has been demonstrated, and their anti-tubercular activity is thought to be associated with one or both of these properties.

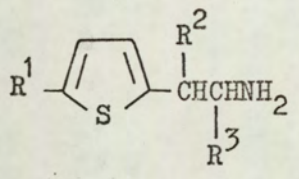
A wide spectrum of anti-bacterial activity has been shown for the sulphur analogue of Chloramphenicol[52] and some closely related derivatives,[53] particularly against actinomyces, yeasts, and fungi. These compounds are essentially bacteriocidal and this action is typical of the 5-nitrothienyl system.

The addition of organic acids to penicillin culture mediums results in their incorporation into the antibiotic, and this discovery led to the production of several thiophen-containing biosynthetic penicillins. 2-Thiophenmethylpenicillin[54] has proved useful against strains of S.aureus which are resistant to benzylpenicillin.

A large number of amidines and amidoximes of thienylcarboxylic acids and thienylacetic acids have been prepared as potential anti-bacterial agents,[55] but their pharmacological evaluation has not been reported.

Pharmacological Activity of Thiophen Alkylamines and Their Derivatives.

The ethylamine side chain is common to many adrenergic amines which act on the Autonomic nervous system, agonising or antagonising the action of adrenaline, and the pressor activity of β-thien-2-ylethylamine (21) is therefore not unexpected.[56] Its ability to stimulate the central nervous system (CNS) is shared by the 5-phenyl derivative (22), but in contrast, the corresponding p-tolyl compound is a CNS depressant.[57] The analogue (23) of Amphetamine has similar activity to that of the parent compound,[58] and the amino-alcohol (24) shows properties akin to those of Ephedrine, to which it is structurally related.[59]



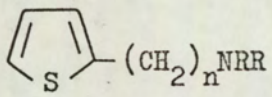
(21) $R^1 = H, R^2 = H, R^3 = H.$

(22) $R^1 = Ph, R^2 = H, R^3 = H.$

(23) $R^1 = H, R^2 = H, R^3 = Me.$

(24) $R^1 = H, R^2 = OH, R^3 = H.$

Anti-cholinergic activity has been shown for a series of simple secondary and tertiary thien-2-ylalkylamines (25) which make them useful as anti-spasmodic agents.[60]

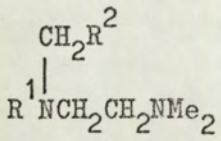


(25)

n = 1,2,3,4.

R = alkyl, cycloalkyl, or hydrogen

The tertiary thienylmethylamines show pronounced anti-histaminic activity and Methaphenilene (26), Methapyrilene (27), Chloromethapyrilene (28), and Thenyldiamine (29), all isosteres of Tripelenamine, are in clinical use.[61]



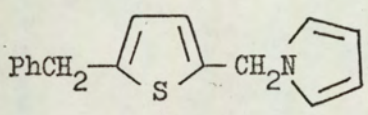
(26) R^1 = phenyl, R^2 = thien-2-yl.

(27) R^1 = pyrid-2-yl, R^2 = thien-2-yl.

(28) R^1 = pyrid-2-yl, R^2 = 5-chlorothien-2-yl.

(29) R^1 = pyrid-2-yl, R^2 = thien-3-yl.

The N-pyrrolidinothien-2-ylmethylamine (30) has been patented as an anti-hypercholesterolemic agent,[62] and anthelmintic properties have been reported for the methiodide of the tertiary thien-2-ylmethylamine (31).[63]



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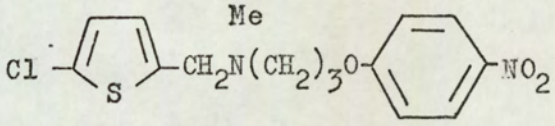
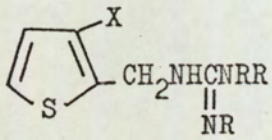


(31)

The Thiambutenes [3-tertiaryamino-1,1-di-(thien-2-yl)-1-butenes] are potent, but addictive analgesics,[64] and are used only in veterinary medicine.[65]

The N-phenylamidine of thiophen-2-carboxylic acid has been shown to protect mice against radiation by X-, and γrays, but the mode of action of this unusual property has not been explained.[66]

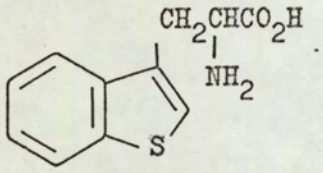
Ability to block the adrenergic neurones has been demonstrated in a series of thenylguanidines (32)[67] and their intrinsic activity is increased by their preferential accumulation in tissue having a high noradrenaline content. Thus, these compounds are potent sympatholytic agents and their structure-activity relationship parallels that of the corresponding benzylguanidines.



(32) X = H, Me; R = alkyl.

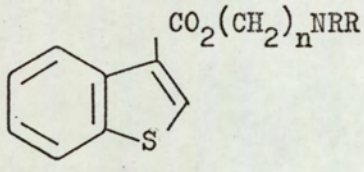
Chemotherapeutic Activity of Benzo[b]thiophen Derivatives.

In common with β-indoleacrylic acid and related compounds, β-(benzo[b]thien-3-yl)alanine (33) displaces tryptophan in microbiological systems and prevents its incorporation into essential proteins. The growth of L.arabinosus[68] and S.haemolyticus[69] is inhibited by the amino acid (33), but S.aureus and E.coli are unaffected by it, and are thought to be capable of by-passing the blocked metabolic pathway.



(33)

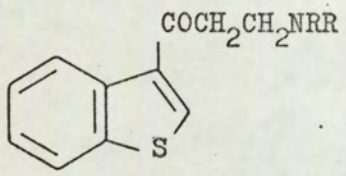
Anti-viral and anti-fungal activity is shown by a series of dialkylaminoalkylbenzo[b]thiophen-2-, and 3-carboxylates (34) which are also reported to be hypotensive agents.[70]



(34)

The Mannich bases (35) exhibit considerable anti-bacterial activity against S.aureus, E.coli, and S.cerevisiae.[71] Optimum results were obtained using the morpholino-derivative (35,NRR=morpholino) which displayed a degree of activity equal to that of penicillin, and subsequent tests showed that it was not germicidal at low concentrations.

All of these Mannich bases suppress the growth of Gram-positive and Gram-negative bacteria, and yeast cells, which suggests that the mode of action does not interfere with cell-wall synthesis.

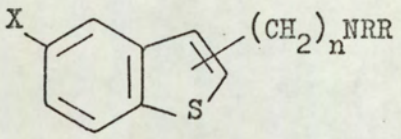


(35)

Anti-microbial activity has been reported for a series of benzo[b]thiophen-2, and 3-carboxamides derived from 6-aminopenicillanic acid, and from 7-aminocephalosporanic acid.[72] Benzo[b]thiophen carboxamides derived from substituted anilines, cyclic aliphatic amines, alkyl-, and arylalkyl-amines have been screened for anti-fungal activity against T.rubrum,[73] and some interesting structure-activity relationships were observed. N-(benzo[b]then-2-oyl)aniline was inactive, but the mono-chlorinated aniline derivatives gave positive results and optimum activity was obtained with the p-chloro-compound. The 2,5-dichloroaniline derivative was also active, in contrast to the 2,4-isomer, and high activity was also shown by the amides derived from cyclohexamine, morpholine, and phenylethylamine, so the presence of a halogen is not essential for anti-fungal action.

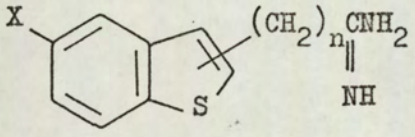
Anti-tubercular activity has been found in the thiosemicarbazone of 3-formylbenzo[b]thiophen and 3-hydroxybenzo[b]thiophen,[74] and this property is shared by a series of primary amines including 5-aminobenzo[b]thiophen.[75]

At the University of Hull, a series of benzo[b]thienylalkylamines (36) was prepared. Many of these compounds showed considerable anti-bacterial activity against a wide variety of micro-organisms, and promising anti-viral activity was shown by 5-bromobenzo[b]thien-3-ylethylamine.

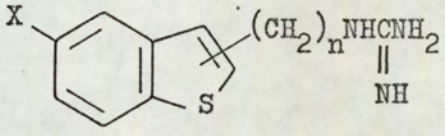


(36) n = 1,2; X = H, Cl, Br, Me.

Preliminary investigations have indicated that the related derivatives of methylamidine (37) and of guanidine (38) also possess anti-microbial activity.



(37) X = Cl, Br.

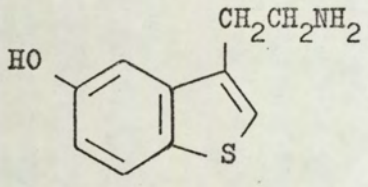


(38) X = Cl, Br.

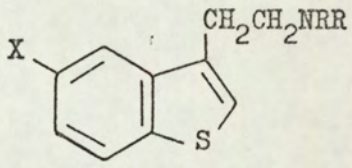
Pharmacological Activity of Benzo[b]thienylalkylamines And Their Derivatives.

In an effort to determine the effect of replacing the indole system by the benzo[b]thiophen nucleus, much work has been devoted to the sulphur isosteres of the important indolealkylamines.

Using amplitude analysis of cortical electro-encephalograms (EEG), 5-hydroxybenzo[b]thien-3-ylethylamine (39)[76,77] was shown to produce a highly stimulated state similar to that produced by the corresponding indole derivative, 5-hydroxytryptamine (5-HT).[76] The dose-response curves for this amine (39) and 5-hydroxytryptophan (the precursor of 5-HT) are also similar, but subsequent studies suggest that some fundamental pharmacological differences exist between 5-HT and its sulphur isostere.[78]



(39)



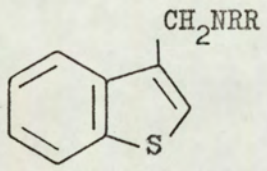
(40)

X = H, Cl, Br, Me.
R = H, Me.

In a series of 5-substituted ethylamines (40), tests on smooth muscle showed that the primary amines potentiated the action of 5-HT, but that the secondary and tertiary amines were effective 5-HT antagonists.[79]

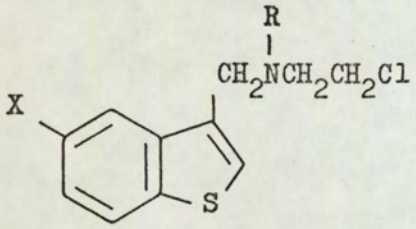
The activity of benzo[b]thien-3-ylethylamine has been compared with tryptamine. EEG measurements of the CNS effects suggest that the replacement of the indolic -NH- by a sulphur atom has little effect on the activity,[80] in fact, Campaigne suggests that the CNS effects are enhanced by this change.[76] Comparison of the contractions produced in smooth muscle also support this conclusion,[81] so it is unlikely that the indolic -NH- plays an important role in bonding to the receptor-sites involved.

The related methylamines have also received some attention. A study of the activity of a series of benzo[b]thien-3-ylmethylamines (41) on smooth muscle gave rather inconclusive results which suggest that, in this case, replacement of the indolic -NH- by sulphur leads to a reduction in pharmacological activity.[82] At low concentrations, these amines antagonise the stimulant response to 5-HT, but they exert a direct stimulatory effect of their own at higher concentrations. These results suggest that the weakly stimulating sulphur isosteres are competing with the powerful stimulant, 5-HT, for the same receptor-sites.



(41) NRR = NH_2, NMe_2, morpholino, piperidino, pyrrolidino

The halogenoethylamines have long been known to inhibit catecholamines at α receptor-sites, and this property is shown by a series of benzo[b]then-3-ylhalogenoethylamines (42) which are adrenergic blocking agents. Highest activity was found for the N-ethyl derivative (43) which was more efficient than Dibenamine in completely reversing the pressor effect of adrenaline.[83]



(42) R = H, alkyl; X = H, Cl, Br, Me.

(43) R = Et; X = H.

In common with many other adrenergic blocking agents, these compounds are also anti-histaminics.[84] The 5-substituted halogenoethylamines (42) display strong antagonism towards 5-HT[85] and this may arise from their anti-adrenaline activity, for Innes[86] has shown that both 5-HT and adrenaline act on the same peripheral nervous system receptors.

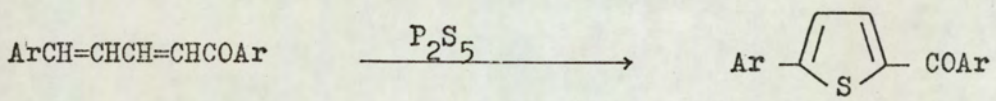
Anti-tumour activity, more usually associated with the N,N-dihalogenoethylamine derivatives, was noticed in the monohalogenoethylamines (42) by Hellman[87] in 1967, and subsequently Chapman et al.[88] have synthesised an extensive series of these compounds as potential anti-cancer agents. Their pharmacological evaluation is now in progress.

PART II

Preparation of 2-Arylthiophens.

The synthesis of the arylthiophens has received considerable attention and a wide variety of methods, mainly based on ring-closure reactions, are now available.

The cyclisation of γ-keto-acids with phosphorus sulphides has been used to prepare 2-phenylthiophen and 2-*p*-tolylthiophen.[88] 2,5-Diphenylthiophen has been prepared from the reaction of 1,2-dibenzoylethane with hydrogen sulphide,[89] and phosphorus pentasulphide has been employed as the cyclising agent to obtain 2-keto-arylthiophens (45) from the corresponding pentadienes (44).[90]

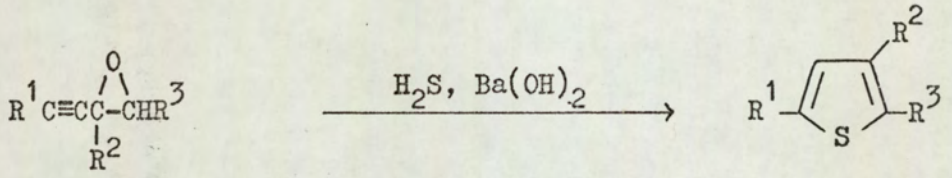


(45)

Arylthiophens have been prepared by the high temperature reaction of sulphur with various hydrocarbons[91] and the most promising results are obtained with substituted butenes. In the presence of sulphur at 200-250°, 1-, and 2-phenylbut-1-ene yield 2-, and 3-phenylthiophen respectively, and in a similar manner, the three isomeric methyl-2-phenylthiophens have been prepared from the appropriately substituted butenes,[92] albeit in moderate yield. Diarylthiophens can be similarly prepared from diarylbutenes.[93] This reaction has been extended to include the arylbutadienes and 1,4-, and 2,3-diarylbuta-1,3-dienes yield 2,5-, and 3,4-diarylthiophens respectively on treatment with sulphur at 200°.[94]

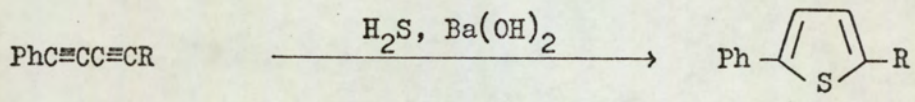
2,5-Diphenylthiophen has been prepared from acetophenone and hydrogen sulphide in the presence of a chromia-alumina catalyst but the yield was poor.[95]

Acetylene and its derivatives have proved to be a fruitful source of thiophens. Hydrogen sulphide in alkaline solution has been used to cyclise a wide variety of acetylenic epoxides (46) to yield thiophens (47) and this reaction has been extended to include the preparation of phenylthiophens.[96]



(46) (47)

The same reagent has been used for the cyclisation of diphenylpoly-ynes to phenylthiophens.[97] 1,4-diphenylbuta-1,3-diyne (48) yields 2,5-diphenylthiophen (51), and the triyne (49) likewise yields the acetylenic derivative (52). However, the tetrayne (50) gives only the dialkyne derivative (53) and not the anticipated bithienyl. This reaction has been extended to include monophenyldiynes e.g. 1-phenylpenta-1,3-diyne may be cyclised to 2-methyl-5-phenyl-thiophen.[98]



(48) R = Ph.

(49) R = PhC≡C

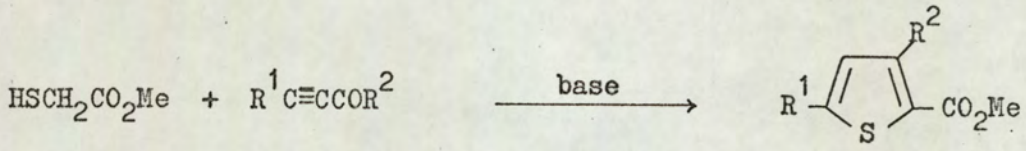
(50) R = PhC≡CC≡C

(51) R = Ph.

(52) R = PhC≡C

(53) R = PhC≡CC≡C

The condensation of methylthioglycollate (54) with acetylenes, their precursors, or β-dicarbonyl compounds yields adducts which are readily cyclised to thiophens in the presence of a base.[99] Thus, the hydroxy-thiophen (57) is prepared from ethyl phenylpropiolate (55), and β-bromobenzalacetone, a precursor of the acetylenic ketone (56) yields the corresponding phenylthiophen (58). α β-Dihalogenonitriles[100] and β-ketoalcohols[101] have also been employed in this reaction.



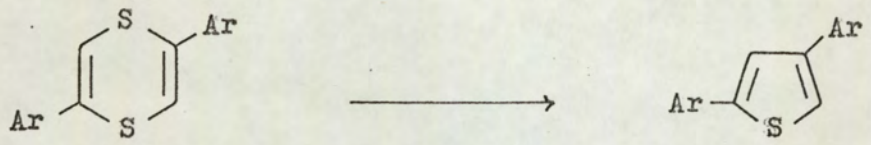
(54) (55) R^1 = Ph, R^2 = OEt. (57) R^1 = Ph, R^2 = OH.

(56) R^1 = Ph, R^2 = Me. (58) R^1 = Ph, R^2 = Me.

Thioamides have been used in the synthesis of thiophen derivatives and the reaction of acetophenone with sulphur and ammonia at 250° yields 2,4-diphenylthiophen.[102] When morpholine is used in this reaction instead of ammonia, morpholino-substituted arylthiophens are produced[103] e.g. 2-morpholino-5-phenylthiophen can be prepared in this way from benzoylacetone.[104]

β-Styryl-α-mercaptoacrylic acid is cyclised by chlorine in carbon tetrachloride to 5-phenylthiophen-2-carboxylic acid, a variation of the method employed in the preparation of benzo[b]thiophen-2-carboxylic acids.[105]

2,4-Diarylthiophens (60) have been obtained from 2,5-diaryl-1,4-dithiadienes (59) by oxidation with hydrogen peroxide in acetic acid, by thermal rearrangement, or by treatment with Raney nickel.[106] The rearrangement of 1,2-dithiadienes also yields thiophens.[107]



(59) (60)

Arylthiophens may be prepared by free-radical substitution of the thiophen nucleus. Treatment of thiophen with an aryl diazonium chloride was first attempted in the presence of aluminium trichloride, and was found to give a mixture of 2-, and 3-arylthiophens.[108] In the presence of a slight excess of sodium hydroxide, 2-arylthiophens, together with small amounts of diaryl derivatives, were obtained[109] and this method is still widely used, although sodium acetate is often employed as base instead of sodium hydroxide.[110]

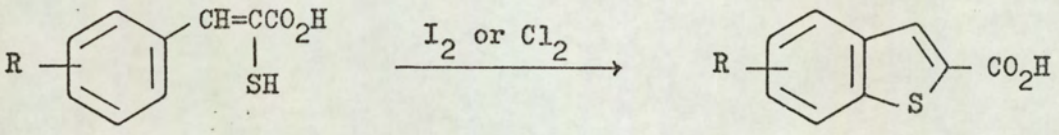
The production of phenylthiophens by the homolytic phenylation of thiophen has been investigated, but the yields were very poor.[111]

Preparation of Benzo[b]thiophens.

An excellent comprehensive review of the synthesis and chemistry of benzo[b]thiophen and its derivatives has recently been published.[112]

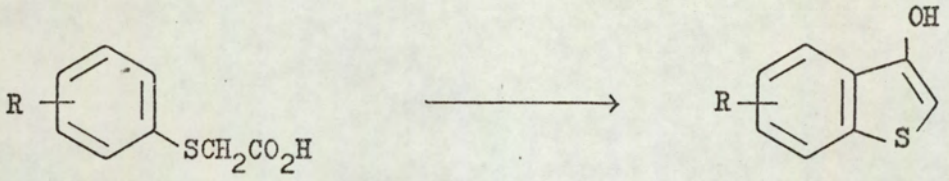
Of the many methods available for the preparation of benzo[b]thiophens, very few employ a thiophen as the starting material. The adduct of 2-vinylthiophen and maleic anhydride may be hydrolysed and dehydrogenated to yield benzo[b]thiophen-4,5-dicarboxylic anhydride.[113] More recently, 4,5,6,7-tetrahydrobenzo[b]thiophen-4-, and 7-ones have been prepared by the cyclisation of γ-(2-,and 3-thienyl)butyric acids and their derivatives.[114]

It is more usual for benzo[b]thiophens to be prepared from benzene derivatives. The oxidative cyclisation of β-aryl-α-mercaptoacrylic acids (61) yields benzo[b]thiophen-2-carboxylic acids (62) which are useful synthetic intermediates. Iodine in dioxan or nitrobenzene was originally used as the cyclising agent,[115] but chlorine in carbon tetrachloride was subsequently shown to be more efficient.[105]

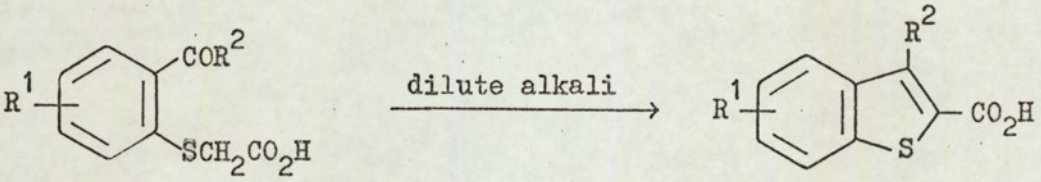


(61) (62)

A wide variety of benzo[b]thiophens have been prepared by the cyclisation of β-carbonyl derivatives of arylthiols and this is the synthetic method most usually employed in the laboratory. S-Arylthioglycollic acids (63) may be cyclised to the corresponding 3-hydroxybenzo[b]thiophen (64) using phosphorus pentoxide,[116] hydrofluoric acid,[117] or chlorosulphonic acid.[118] If the S-arylthioglycollic acid (65) bears an o-acyl substituent, treatment with dilute alkali affords a 3-substituted benzo[b]thiophen-2-carboxylic acid (66), but when acetic anhydride is used, the decarboxylated product is obtained instead.[119]

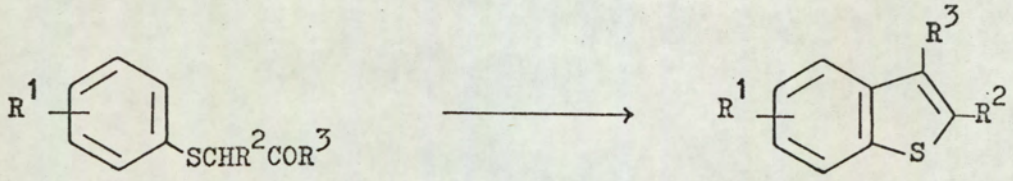


(63) (64)



(65) (66)

The cyclisation of (arylthio) acetaldehydes (67) (as the dialkyl acetals) using polyphosphoric acid (PPA) was introduced in 1950 by Tilak,[120] and its wide application has been reviewed.[121] The cyclisation of o-, and p-substituted starting materials yields 7-, and 5-substituted benzo[b]thiophens respectively, but the m-substituted derivative gives a mixture of 4-, and 6-substituted products,[122] and not exclusively the 6-isomer as originally thought.[120]



(67) R^2 = H, alkyl; R^3 = H.

(68) R^2 = H, alkyl; R^3 = alkyl.

This method has been extended to include the (arylthio) acetones (68) and is now widely used to obtain benzo[b]thiophens bearing a 3-alkyl substituent. PPA is again used as the cyclising agent. However, attempts to prepare 3-phenylbenzo[b]thiophen by this method led to rearrangement, and a mixture of the 2- and 3-isomers was obtained.

Electronic Structure

The simplest concept of the electronic structure of sulphur heterocycles considers the sulphur atom to be an sp^2 hybridised state. Of the three sp^2 orbitals, one is a fully occupied non-bonding atomic orbital and the other two, each containing one electron, overlap with the sp^2 orbitals of the adjacent carbon atoms to form σ-bonds. The remaining two electrons are contained in the $3p_z$ orbital and are available for π-bonding. However, the molecular dimensions of thiophen have been accurately determined from a study of the microwave spectrum, and the CSC bond angle found to be only 92.2° [123] which is not in keeping with this simple concept.

In sulphur, the 3p and 3d orbitals are of comparable energy and it is therefore possible for the 3d orbitals, unlike those of nitrogen and oxygen, to be involved in bonding. d-Orbital participation in the bonding of thiophen was first suggested by Pauling,[124] and using this concept, Longuet-Higgins[125] reported the first quantum-mechanical calculations based on a molecular orbital approach. The $3p_z$ orbital is favourably placed to interact with the $3d_{xz}$ and $3d_{yz}$ orbitals thereby generating three new hybrid orbitals. One of these is a high energy, unoccupied anti-bonding orbital, but the other two, which closely resemble the π-orbitals of carbon, lie along the C-S bonds and each contains one of the two electrons originally held in the $3p_z$ orbital.

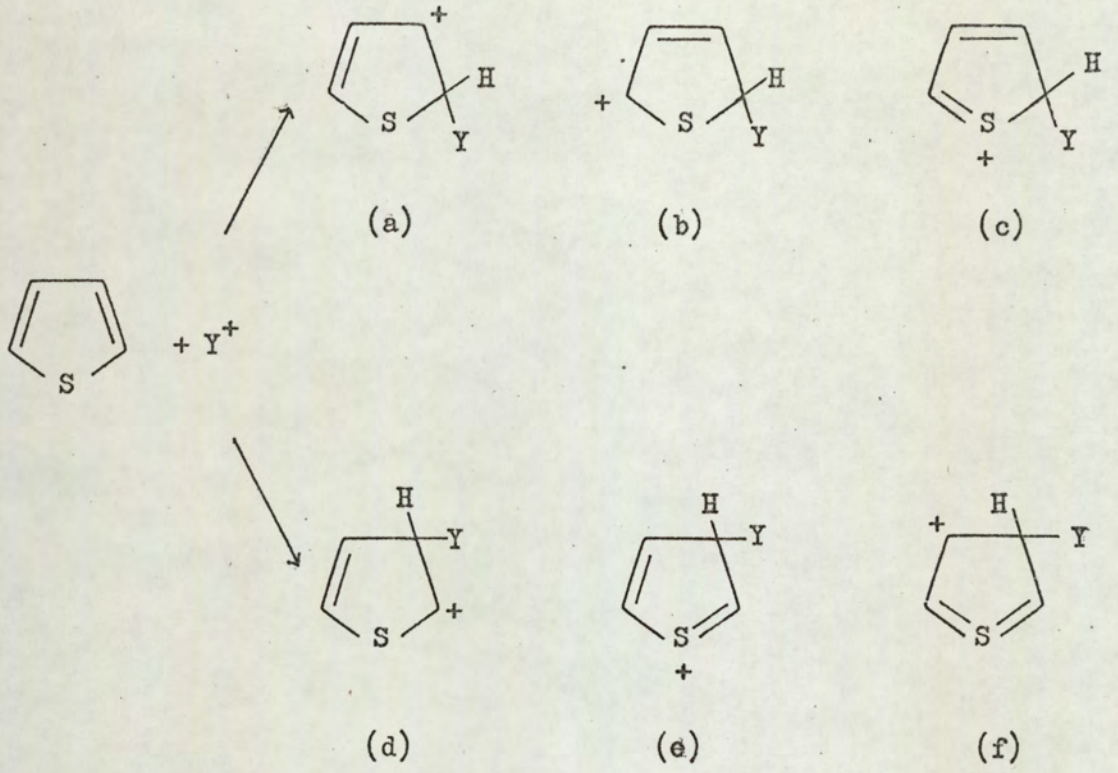
The formal identity between -S-, and -CH=CH- given by this approach is supported by the physical and chemical similarity of benzene and thiophen, and of naphthalene and benzo[b]thiophen.

Subsequently, many calculations have been made on thiophen and its derivatives. Some ignore d-orbital participation,[126] while others include it to a greater or lesser extent,[127] but both "models" have been made to fit the observed properties by the choice of suitable parameters[128] and both can offer a satisfactory interpretation of the course of electrophilic substitution.

Electrophilic Aromatic Substitution

The electron-density at each carbon atom in thiophen is greater than unity because the sulpur atom contributes two electrons to the delocalised π-system, and thiophen is therefore more reactive than benzene towards electrophilic substitution. In the ground state according to the simple approach of Longuet-Higgins, the electron-density is equal at all four carbon atoms. However, calculations of the localisation energy, a measure of the stability of the intermediate transition-state,[129] support the experimentally observed fact that thiophen is preferentially substituted at the 2-, and 5-positions.

The simple resonance structures of the transition states formed by 2-, or 3-position attack show that greater delocalisation of the positive charge is possible following 2-substitution, if the structure (f), which involves a decet of electrons around the sulphur atom, is considered to make only a minor contribution.



The presence of a substituent in the thiophen ring may influence the position of further electrophilic substitution, either aiding or opposing the directive effect of the heteroatom.

A 2-phenyl substituent is capable of exerting either a positive mesomeric (+M) effect which leads to increased activation of position 5, or a negative mesomeric (-M) effect resulting in deactivation of position 5 and activation of position 4.

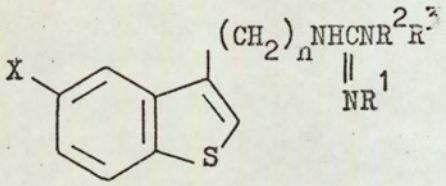
In view of the π-excessive nature of thiophen, it might be expected that the phenyl group would exert a slight -M effect, and this is supported experimentally by the positive Hammett parameter (+0.02), determined from the dissociation of 2-phenylthiophen-5-carboxylic acid.[130] However, the rate of bromination of 2-phenylthiophen by bromine in 15% aqueous acetic acid is greater than that for thiophen, and this suggests that the phenyl group exerts a positive electromeric effect, equivalent to a +M effect, under the influence of the attacking electrophile.[131]

2-Phenylthiophen is mercurated,[132] formylated,[109,110] and acylated[109] at the 5-position. Bromination with elemental bromine yields a mixture of products due to attack on both the thiophen and benzene rings,[88a] but the use of N-bromosuccinimide[111] or cyanogen bromide[133] gives 5-bromo-2-phenylthiophen exclusively. 5-Substituted derivatives are also obtained from 2-p-tolyl, and 2-p-chlorophenyl-thiophen on acylation, or bromination with N-bromosuccinimide.[134] However, the nitration of 2-phenylthiophen using cupric nitrate in acetic anhydride is reported to yield a 3:2 mixture of 5-, and 3-nitro-derivatives.[135]

PART III

The Present Work

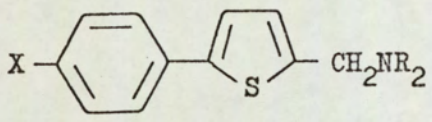
The search for chemotherapeutic agents initiated at the University of Hull has been extended to include a series of 5-halogenobenzo[b]thienylalkyl-guanidines (69), some biguanides (70) and acetamidino-derivatives (37) bearing N-methyl-substituents.



(69) X = Cl, Br; n = 1, 2; R = H, alkyl, aryl.

(70) X = Cl; n = 1; $R^1 = R^2 = H$, $R^3 = -C(NH)NHR$.

A series of 5-arylthien-2-ylalkylamines (71), corresponding to the series of benzo[b]thienylalkylamines previously prepared at Hull, has also been synthesised.



(71) X = H, Cl, Br, Me;

$NR_2 = NH_2$, NMe_2, morpholino, piperidino, pyrrolidino.

The intermediate 5-arylthiophen-2-carboxamides are of potential chemotherapeutic interest too, and in view of the anti-tubercular activity shown by thiosemicarbazones and hydrazides, a few of these derivatives of 2-arylthiophens have been prepared.

The mass spectra of some of these compounds has been recorded. All of the compounds prepared have been submitted for initial anti-bacterial and anti-viral screening.

DISCUSSION

5-Halogenobenzo[b]thien-3-ylalkylguanidines and biguanides.

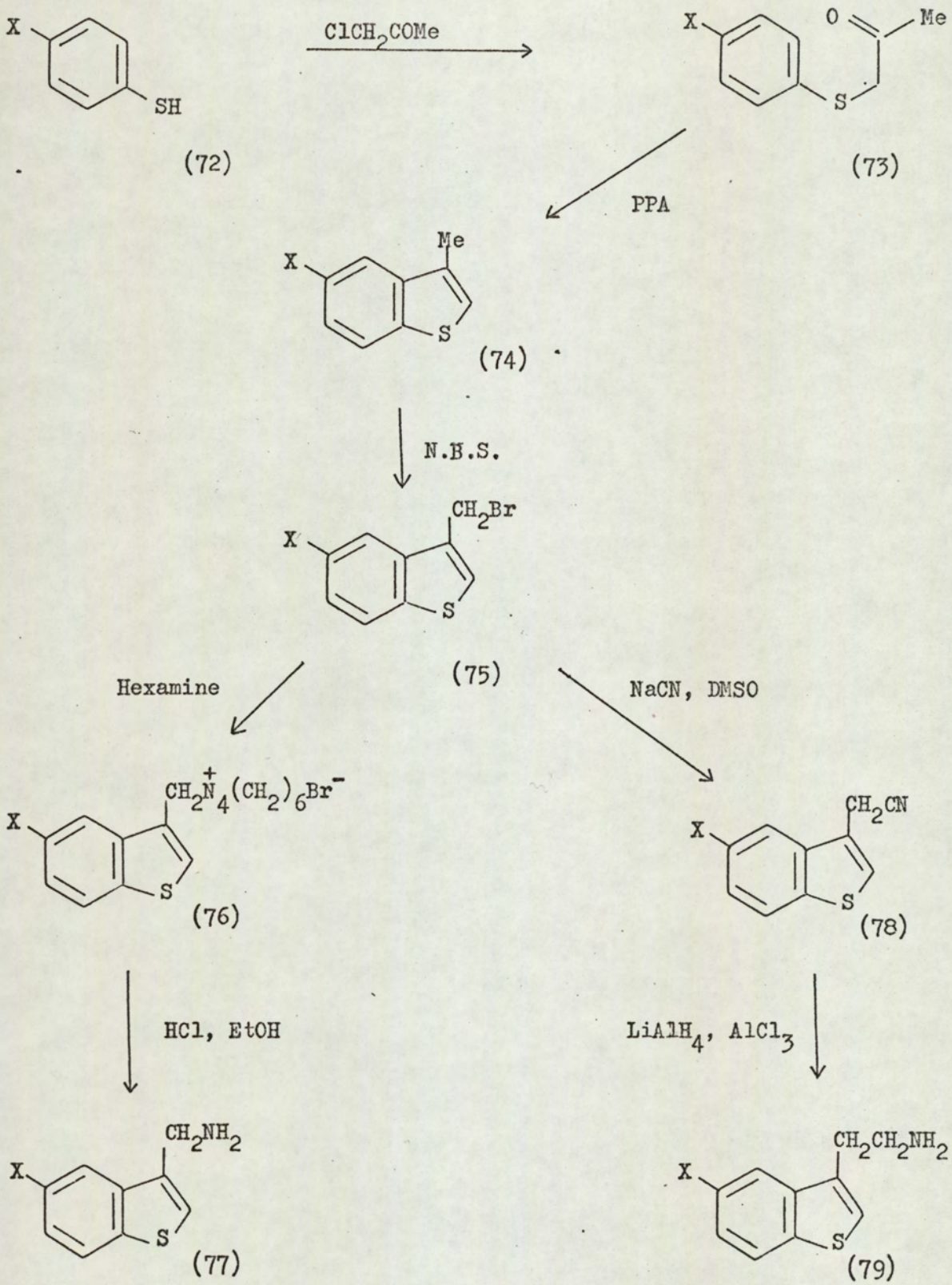
Benzo[b]thien-3-ylalkylamines (77, 79) are suitable intermediates for the synthesis of the guanidines (80, 82) and biguanides (81) (Scheme 2). They were prepared from the same intermediate, 3-bromomethyl-5-halogenobenzo[b]thiophen (75), by the sequence of reactions shown in Scheme 1. The condensation of p-halogenothiophenol (72) with chloroacetone in the presence of sodium hydroxide, followed by cyclisation of the product (73) with polyphosphoric acid[136, 137] gave the 5-halogeno-3-methylbenzo[b]thiophen (74) in good yield. Bromination of this compound with N-bromosuccinimide in the presence of peroxides and light[138] gave the bromomethyl compound (75).

Treatment of the bromomethyl compound with hexamine in chloroform, and subsequent hydrolysis of the hexamine salt (76) with aqueous ethanolic hydrogen chloride by the method of Porter,[139] gave the methylamine (77) in good yield.

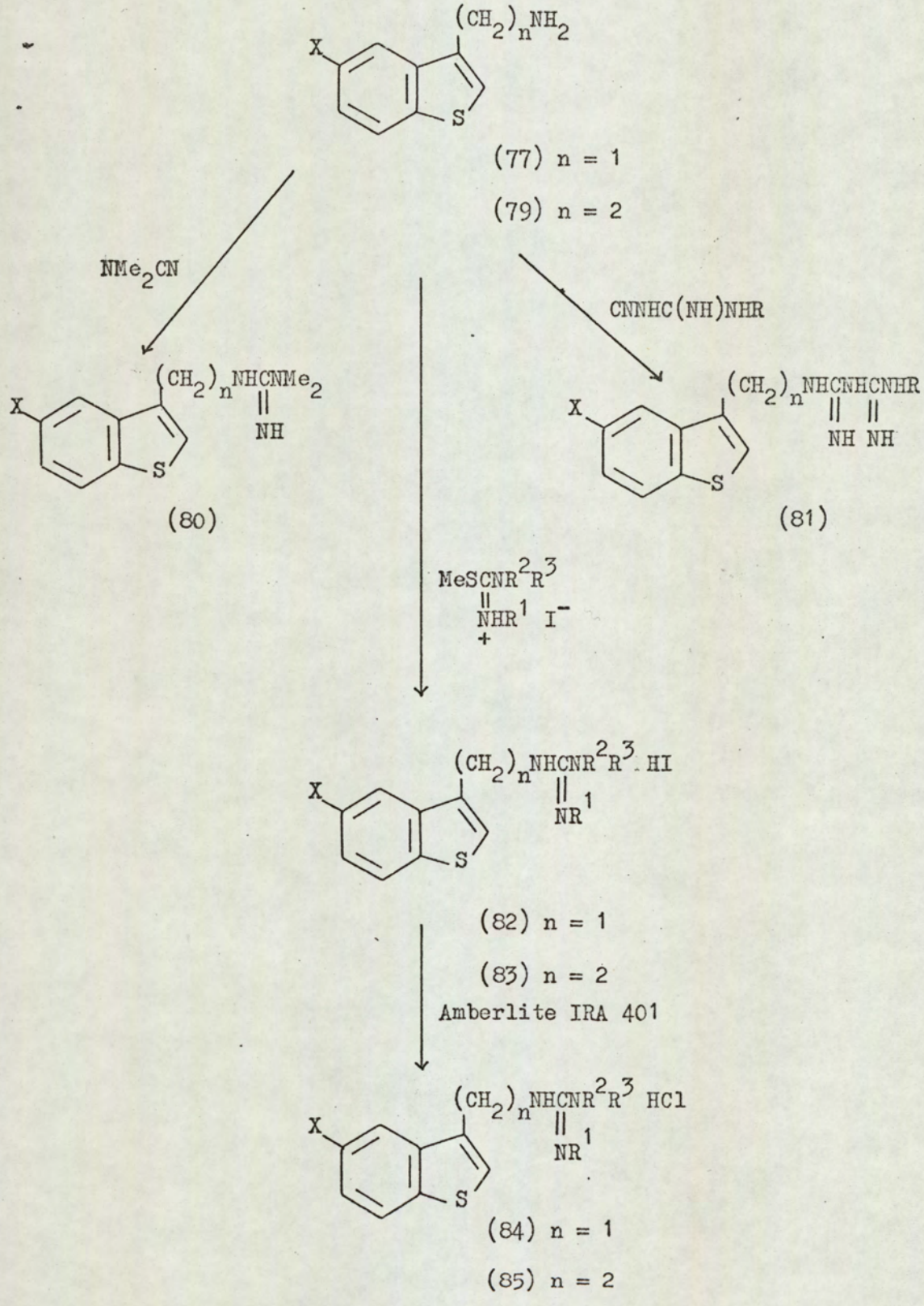
The reaction of the bromomethyl compound with sodium cyanide in dimethyl sulphoxide gave 3-cyanomethyl-5-halogenobenzo[b]thiophen (78),[140] and a preliminary purification was carried out by filtration of a benzene solution of the crude product through a column of alumina. The first fractions contained a small quantity of the 2-cyanomethyl compound and these were discarded. The formation of 2% of the 2-isomer in the reaction of 3-bromomethylbenzo[b]thiophen with sodium cyanide in dimethyl sulphoxide has been reported,[141] but similar rearrangements have not been observed for this reaction in other solvents.

The reduction of a benzene solution of 3-cyanomethyl-5-halogenobenzo[b]thiophen (78) with a 1:1 molar ratio of lithium aluminium hydride and aluminium trichloride in ether gave the ethylamine (79) in excellent yield.[140]

Scheme 1.


X
SH
(72)
ClCH2COMe
X
O
Me
S
(73)
PPA
X
Me
S
(74)
N.B.S.
X
CH2Br
S
(75)
Hexamine
CH2N4(CH2)6Br−
X
S
(76)
NaCN, DMSO
CH2CN
X
S
(78)
HCl, EtOH
CH2NH2
X
S
(77)
LiAlH4, AlCl3
CH2CH2NH2
X
S
(79)

Scheme 2.


(CH2)nNH2
X
S
(77) n = 1
(79) n = 2
NMe2CN
CNNHC(NH)NHR
(CH2)nNHCNMe2
NH
(CH2)nNHCNHCNHR
NH NH
(80)
(81)
MeSCNR2R3
NHR1 I−
+
(CH2)nNHCNR2R3 HI
NR1
(82) n = 1
(83) n = 2
Amberlite IRA 401
(CH2)nNHCNR2R3 HCl
NR1
(84) n = 1
(85) n = 2

Of the methods available for the preparation of guanidines,[142] two procedures which employ amines as the starting materials were used in the present work.

The reaction of primary or secondary amines with S-alkylisothiouronium salts, originally outlined by Rathke,[143] was chosen as the most convenient method, and a wide variety of N-substituted guanidines were obtained from the alkylamines (77, 79) and the appropriate S-methylisothiouronium iodide.

Thiourea, its N-allyl-, N-methyl-, and N-phenyl-derivatives are commercially available. N,N'-dimethyl-,[144] and N,N,N'-trimethyl-thiourea[145] were obtained from the reaction of methylisothiocyanate[146] with the appropriate amine, and N,N-dimethylthiourea[147] was prepared from dimethylamine and silicon tetraisothiocyanate.[148] For the preparation of the guanidines, the methiodide salts of these thioureas were chosen because they are generally well defined crystalline solids, freely soluble in ethanol. They were prepared in excellent yield by treatment of an ethanolic solution of the thiourea at 60° with a 10% excess of methyl iodide. The use of these salts has the additional advantage that the other main reaction product, methyl mercaptan, is volatile and therefore easily removed from the reaction mixture.

The reaction of equimolar amounts of the alkylamine (77, 79) with an S-methylisothiouronium iodide in ethanol gave the required guanidine hydriodide (82, 83) in good yield. Since iodides are unsuitable for pharmacological testing, they were converted to the corresponding hydrochlorides (84, 85). Initially, this was done by basification of an aqueous solution of the hydriodide followed by treatment of the free base in ethanol with hydrogen chloride. However, the instability of the bases, especially the N-allyl-derivatives, made their isolation undesirable and an ion-exchange resin, Amberlite IRA 401, was used instead. Excellent yields of the hydrochloride were obtained when a solution of the hydriodide

in ethanol was stirred with an excess of the resin for 24 hr.

The preparation of the guanidine hydriodide (82, 83) by this method was accompanied by the formation of some insoluble material which was deposited during the course of the reaction. The molecular weight, obtained from the mass spectrum indicated that this was the N,N-dimethyl derivative of the amine (77, 79) and this was supported by the i.r. spectrum which showed a band at 2800-2760 $cm.^{-1}$ (NMe). These N,N-dimethyl-5-halogenobenzo[b]thien-3-ylalkylamine hydriodides were converted to the corresponding hydrochloride salts which were identified by comparison with authentic samples.

It is possible that these N,N-dimethyl-derivatives arise from the original amine by methylation with methyl mercaptan. If the methyl mercaptan is continuously removed from the reaction by a slow stream of dry nitrogen, only negligible quantities of these amines are formed.

Owing to some initial difficulty encountered in the synthesis of N,N-dimethylthiourea, an alternative method,[149] for the preparation of the N,N-dimethylguanidines (80) was investigated. A good yield of these guanidines was obtained by fusion of the amine hydrochloride (77, 79) with dimethyl cyanamide (prepared from cyanogen bromide and dimethylamine), but the crude product was obtained initially as a glass which proved difficult to crystallise.

The biguanides (81) were similarly prepared by fusion of the amine hydrochloride (77) with an equimolar amount of dicyandiamide, or p-chlorophenyldicyandiamide; a reaction which has been used by many workers[150] for the preparation of biguanides from aliphatic amines. Occasionally, the guanidine is obtained, possibly by the decomposition of the initially formed biguanide, and this process is more evident if the reaction is carried out on the amine instead of its salt. In the present work, no guanidine was detected, but some ammonium chloride was formed during the reaction, and this proved difficult to remove.

The i.r. spectrum of all the guanidine and biguanide salts showed one or more strong adsorption bands in the region 1655-1620 cm.$^{-1}$ (C=N stretching).

5-Halogenobenzo[b]thien-3-ylacetamidines.

These amidines are conveniently prepared from the cyanomethyl compound (78) by the method of Pinner (Scheme 3). Saturation of an ice-cold solution of the nitrile (78) and ethanol in benzene with hydrogen chloride[151] gave the ethyl-5-halogenobenzo[b]thien-3-ylacetimidate hydrochloride (86) in good yield, and subsequent treatment with an equimolar amount of methylamine in ethanol gave the required N-methyl-5-halogenobenzo[b]thien-3-ylacetamidine hydrochloride (87).

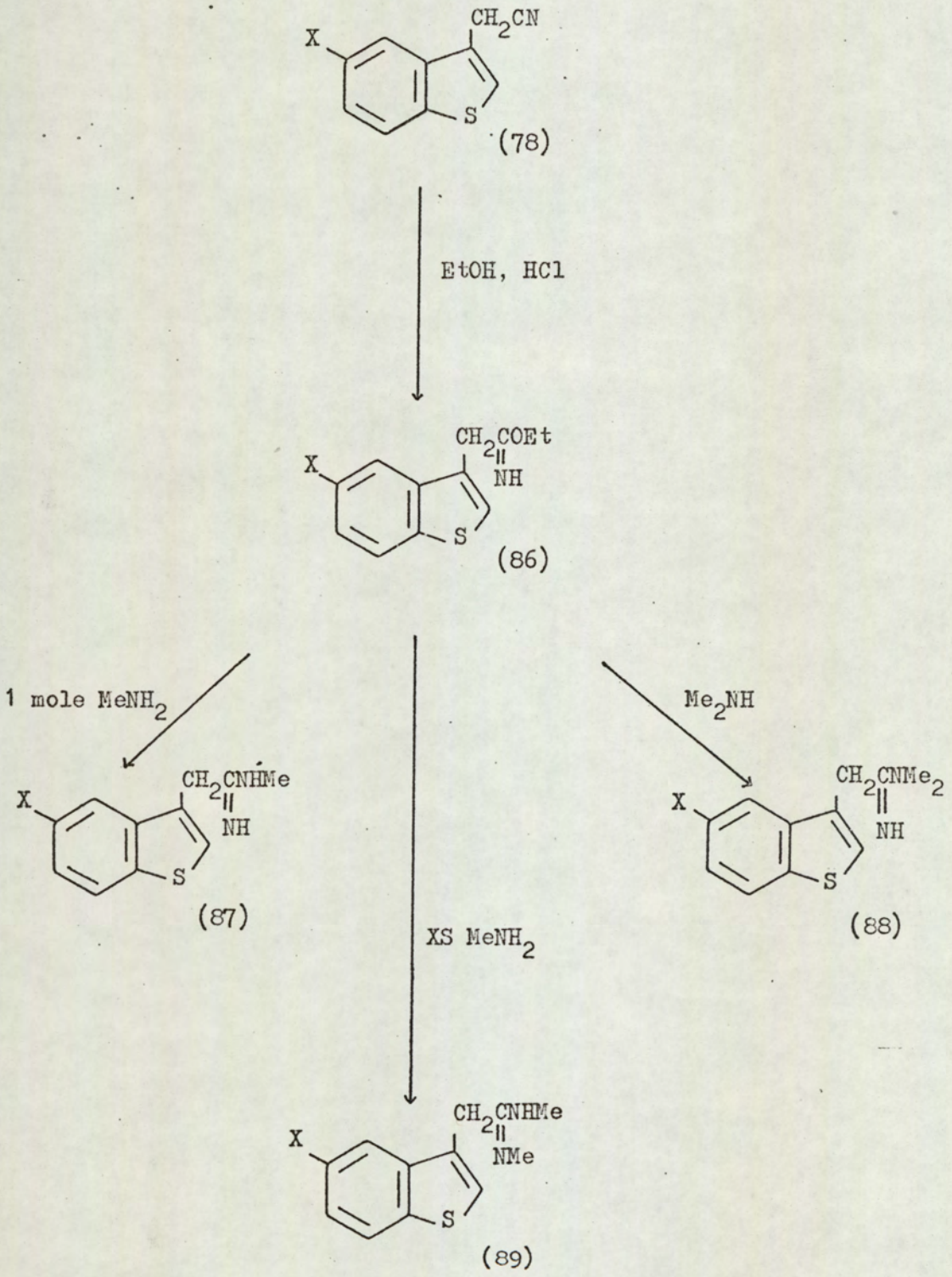
If the imino-ether hydrochloride (86) was added to an excess of methylamine in ethanol, the N,N'-dimethyl-derivative (88) was obtained. The formation of N,N'-disubstituted amidines under similar conditions has been reported by several workers[152] and it may be explained by nucleophilic addition of the amine to the monomethylamidine (87) followed by the elimination of ammonia (Scheme 3a). Amidines react similarly with other nucleophilic reagents, for example, they will react with hydroxylamine to yield amidoximes.[153]

For comparison, the N,N-dimethylamidine hydrochloride (89) was prepared from the imino-ether (86) and dimethylamine. The melting point and i.r. spectra of this compound were different to those of the N,N'-dimethyl-derivative (88).

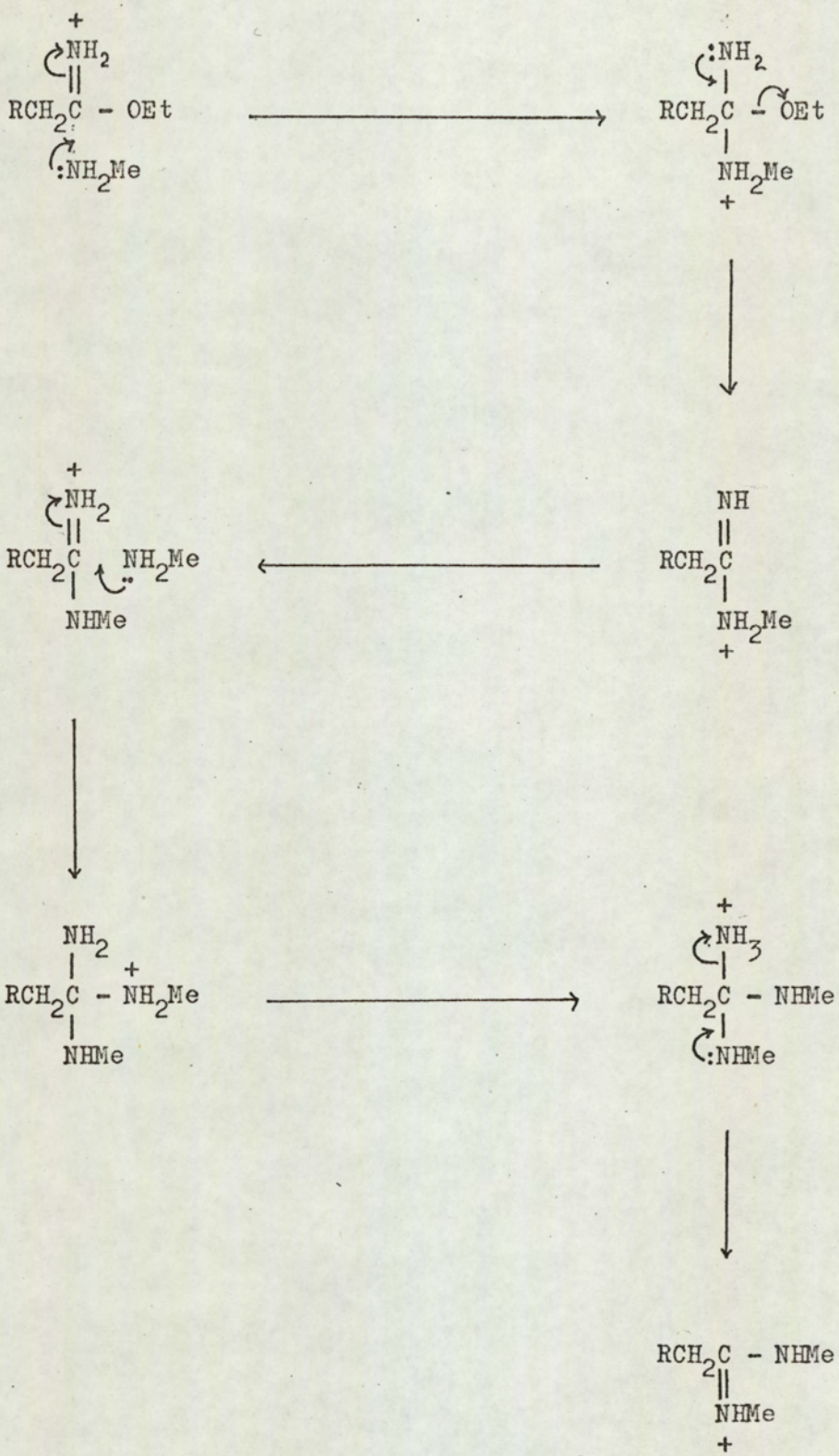
The i.r. spectra of all of the amidines showed bands at 1680-1660 and 1550-1520 cm.$^{-1}$ (C=N stretching), and in addition, the N,N-dimethyl-amidines (89) adsorbed at 1630 cm.$^{-1}$.

In the n.m.r. spectrum of N,N-dimethyl-5-chlorobenzo[b]thien-3-ylacetamidine hydrochloride, the aromatic-6-proton appeared as a quartet

Scheme 3.


CH2CN
X
S
(78)
EtOH, HCl
CH2COEt
NH
(86)
1 mole MeNH2
Me2NH
CH2CNHMe
CH2CNMe2
(87)
(88)
XS MeNH2
CH2CNHMe
NMe
(89)

Scheme 3a.

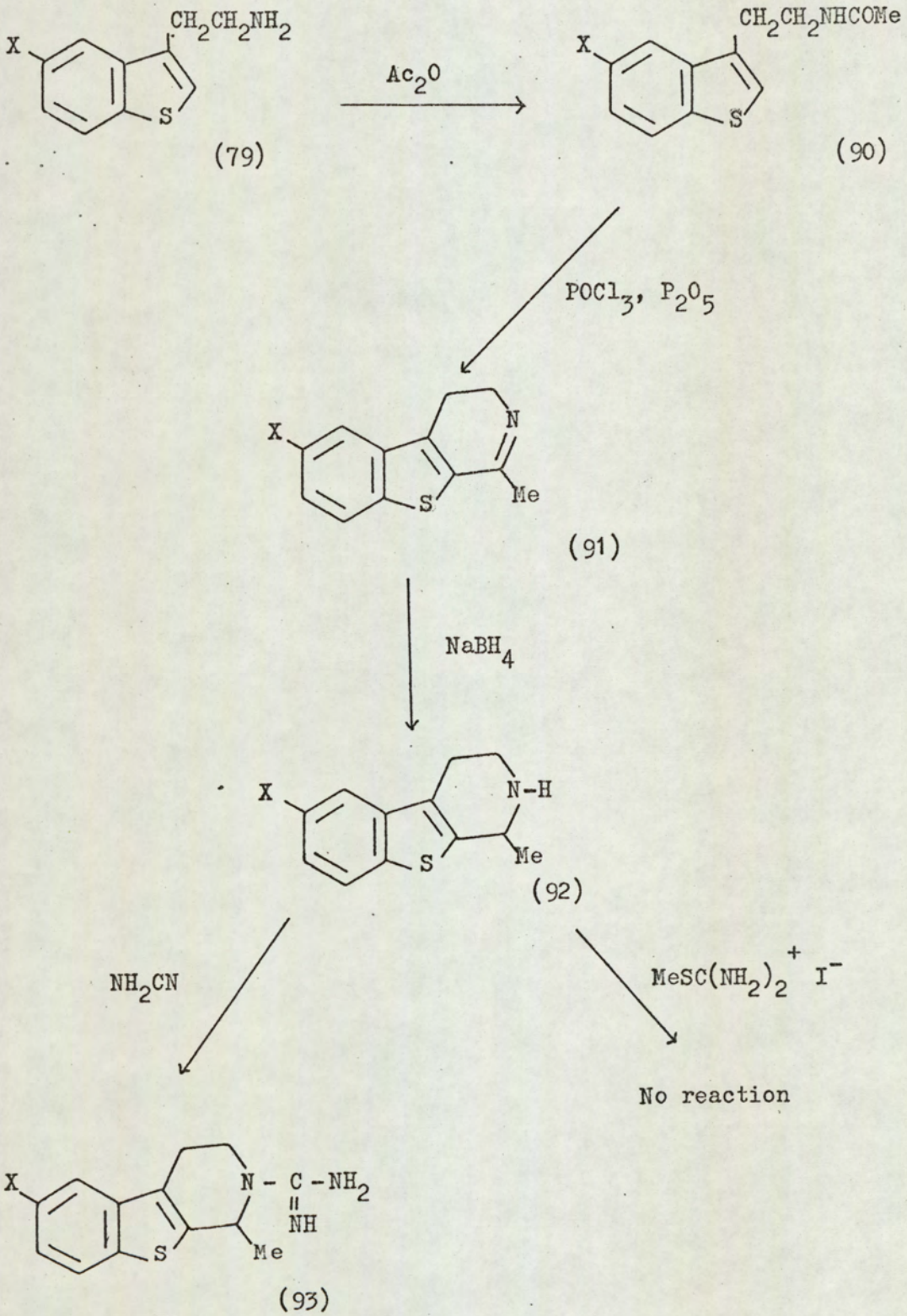


at τ2.97 due to o-, and m-coupling with the protons at the C-7, and C-4 positions respectively. At 40°, the N-methyl protons appeared as a doublet, but at approximately 60°, they were observed as a singlet. This suggests that rotation about the C-N bonds is restricted, leading to the adoption of a preferred configuration at 40° in which the two methyl groups are not equivalent. As the temperature is raised, the molecule is able to overcome the energy barrier to rotation and when free rotation is possible, the two methyl groups, now equivalent, are observed as a singlet in the n.m.r. spectrum. Similar observations on the n.m.r. spectra of amidinium salts have been reported by other workers.[154] No evidence of restricted rotation was indicated by the spectrum of N,N'-dimethyl-5-chlorobenzo[b]thien-3-ylacetamidine hydrochloride and the two methyl groups appeared as a singlet at 40°. Presumably, the energy barrier to rotation about the C-N bonds is lower for this compound.

6-Bromo-1-methyl,1,2,3,4-tetrahydrothianaphtheno-[2,3-c]-pyridine guanidine (93).

The proposed synthetic route to this compound is shown in Scheme 4. Cyclisation of the N-acetyl-derivative of 2-(5-bromobenzo[b]thien-3-yl)ethylamine (79, X = Br) with phosphorus oxychloride and phosphorus pentoxide in dry xylene gave 6-bromo-1-methyl-3,4-dihydrothianaphtheno-[2,3-c]-pyridine (91, X = Br) in good yield. The i.r. spectrum showed adsorption due to the methyl group at 2930 cm.$^{-1}$, and the C=N stretching vibration appeared at 1610 cm.$^{-1}$. Reduction of the dihydro-derivative (91, X = Br) with sodium borohydride in methanol gave the required tetrahydro-derivative (92, X = Br), and as expected, the C=N adsorption in the i.r. spectrum was now absent. 6-Chloro-1-methyl-1,2,3,4-tetrahydrothianaphtheno[2,3-c]pyridine (92, X = Cl) has been prepared by a similar series of reactions.[155]

Scheme 4.


X
CH2CH2NH2
S
(79)
Ac2O
CH2CH2NHCOMe
(90)
POCl3, P2O5
N
Me
(91)
NaBH4
N-H
(92)
NH2CN
MeSC(NH2)2+ I−
No reaction
N - C - NH2
NH
(93)

Difficulty was experienced in the preparation of the guanidine (93, X = Br). No reaction was observed between the amine (92, X = Br) and S-methylisothiouronium iodide in ethanol at reflux for 48 hr., and when the reaction was attempted in dimethylformamide, a black intractable tar was obtained.

The reaction of S-alkylisothiouronium salts with secondary amines is known to proceed less readily than with primary amines,[139] so the more vigorous procedure involving fusion of the amine hydrochloride with cyanamide at 210° for 2 hr. was used. The i.r. spectrum of the solid obtained from this reaction showed the expected adsorptions due to NH_2^+ and NH_3^+, and the C=N stretching vibration at 1620 $cm.^{-1}$, but repeated recrystallisation of this product failed to give an analytically pure specimen. The consistently low figure obtained for the nitrogen analysis was probably due to contamination of the required guanidine hydrochloride by the hydrochloride of the original amine.

2-Arylthiophens.

Four methods were investigated for the synthesis of 2-arylthiophens.

(a) Cyclisation of an epoxyacetylene (Scheme 4a).

2-Phenylthiophen (96) was obtained from the cyclisation of phenylpropargyloxirane (95) with hydrogen sulphide in alkaline solution, a method which has been used to prepare 4-alkyl-2-phenylthiophens.[96]

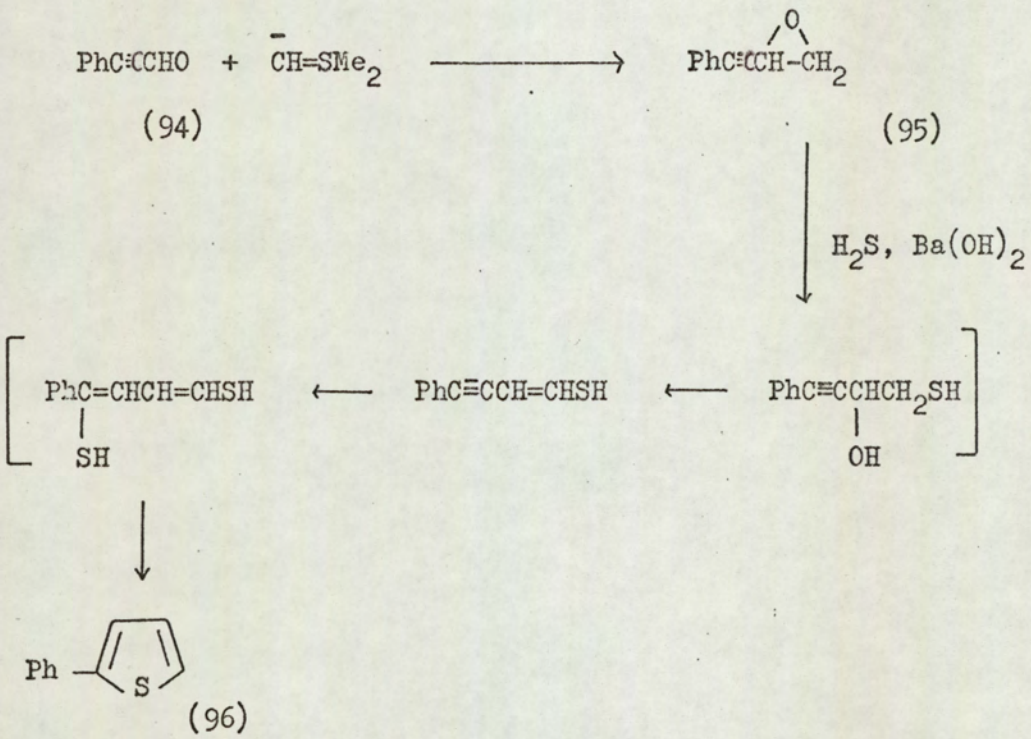
The mechanism of the reaction[156] is thought to involve initial fission of the oxirane ring, nucleophilic addition of hydrogen sulphide, and subsequent dehydration. Addition of hydrogen sulphide across the acetylinic bond then gives a 1,4-dithiol which cyclises to the required 2-phenylthiophen (96).

The value of this reaction was limited by the difficulty encountered in the preparation of the intermediate oxirane (95). Treatment of phenylpropargylaldehyde (94) with dimethylsulphonium methylide[157] at -30° gave the oxirane (95) in only 19% yield, and at room temperature, only an intractable tar was obtained. The low yield could be due to the presence of two sites for nucleophilic attack on the acetylenic aldehyde (94). Attack at the carbonyl carbon with subsequent elimination of dimethyl sulphide leads to the required oxirane, but the triple bond is polarised by the aldehyde function, and thus, attack at the β-carbon atom could also occur, leading to the formation of cyclopropane derivatives and polymers.

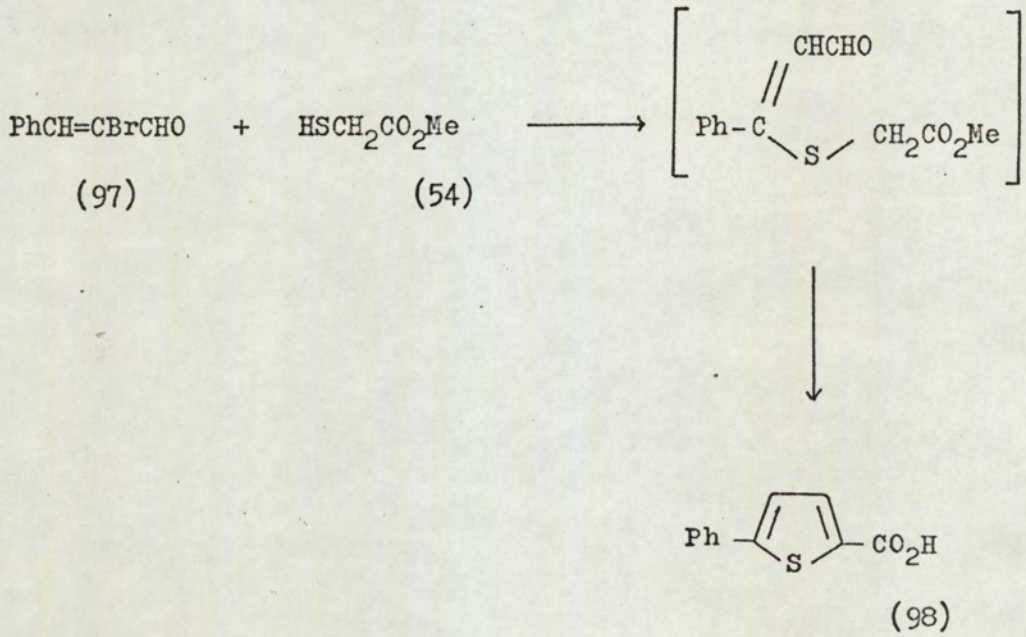
(b) Reaction of α-bromocinnamaldehyde with methyl thioglycollate (Scheme 4b).

The product from the reaction between α-bromocinnamaldehyde (97) and methyl thioglycollate (54) was cyclised with methanolic potassium hydroxide to give 5-phenylthiophen-2-carboxylic acid in 47% yield.

Scheme 4a.



Scheme 4b.



3-Methyl-5-phenylthiophen-2-carboxylic acid has been similarly prepared from α-bromobenzylidene acetone.[99c] A methyl ester is intially formed, but this is hydrolysed to the acid under the reaction conditions. The relative inaccessibility of p-substituted cinnamaldehydes precluded the use of this reaction for the preparation of p-substituted phenylthiophens, and the reaction was not used extensively in the present work.

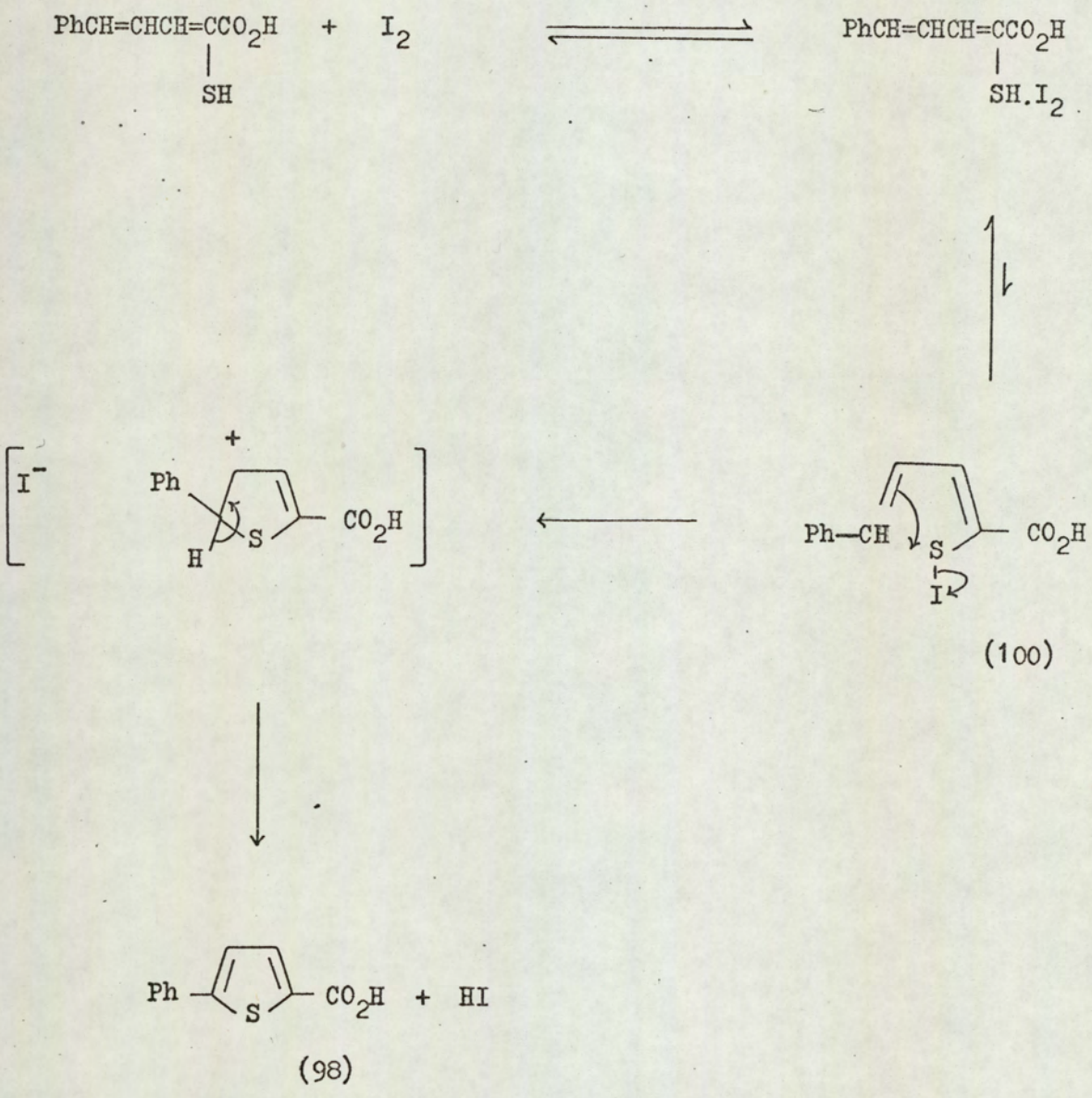
The unsatisfactory yield may have been due to the instability of the unprotected aldehyde group towards methanolic potassium hydroxide, and it seemed likely that the cyclisation, which is essentially an internal Aldol-type condensation, could be effected with dilute aqueous sodium hydroxide solution. However, treatment of a mixture of methyl thioglycollate and phenylpropargylaldehyde (94) (of which α-bromocinnamaldehyde is a precursor) with this reagent gave phenylacetylene in 80% yield. The i.r. spectrum showed characteristic bands due to a monosubstituted acetylene at 3310 and 2160 $cm.^{-1}$, and the acetylenic proton was observed as a singlet at τ6.14 in the n.m.r. spectrum. The formation of phenylacetylene is probably accounted for by initial aerial oxidation of the aldehyde to phenylacetylene carboxylic acid, small quantities of which were also isolated from the reaction mixture, and this is readily decarboxylated in alkaline solution.

(c) The oxidative-cyclisation of mercapto-acids (Scheme 4c).

5-Phenylthiophen-2-carboxylic acid was most conveniently prepared by the oxidative-cyclisation of β-styryl-α-mercaptoacrylic acid (99). Iodine was initially used as the oxidising agent,[115] but chlorine in dry carbon tetrachloride leads to a cleaner product in superior yields.[105]

The mechanism of this reaction, using iodine,[158] has been investigated, and it is suggested that an initial equilibrium is set up between the mercapto-acid (99) and a small concentration of the corresponding sulphenyl iodide (100). In dry, aprotic solvents the

Scheme 4c.


PhCH=CHCH=CCO2H
SH
+ I2
PhCH=CHCH=CCO2H
SH.I2
Ph—CH
S
I
CO2H
(100)
I⁻
Ph
H
S
CO2H
Ph
S
CO2H
+ HI
(98)

sulphenyl iodide undergoes an intramolecular cyclisation to give the required 5-phenylthiophen-2-carboxylic acid (98). A similar mechanism may operate when chlorine is used.

2-Phenylthiophen (96) was obtained from the acid (98) by decarboxylation with copper powder in quinoline.[159]

(d) The Gomberg reaction.

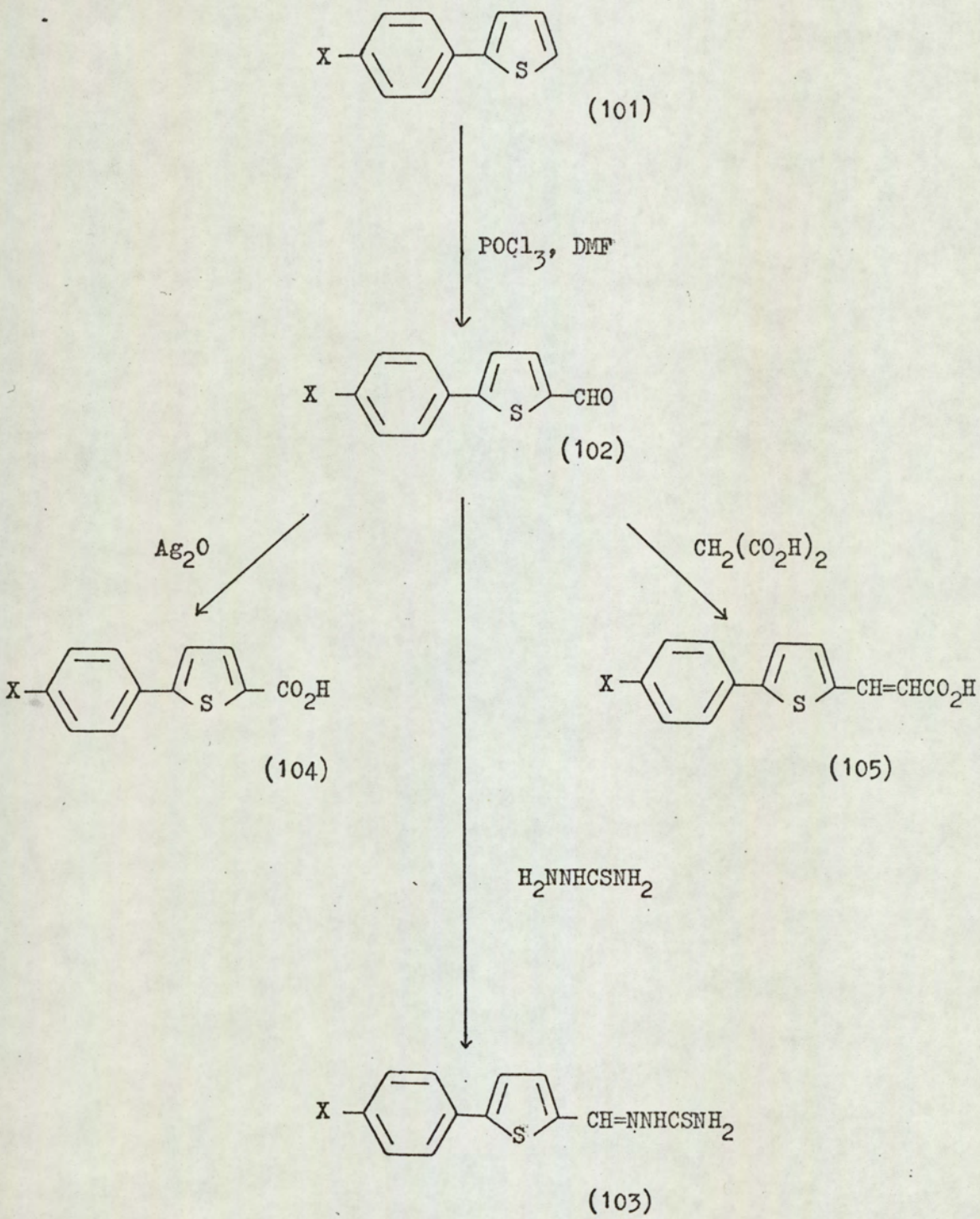
All of the p-substituted 2-phenylthiophens were obtained directly from thiophen by substitution with radicals derived from the decomposition of the appropriate p-substituted phenyldiazonium acetate.[110] In spite of the poor yields, this simple one-stage procedure was the only practicable route to the required arylthiophens.

5-Arylthien-2-ylaldehydes.

The formylation of 2-p-halogenophenylthiophen with phosphorus oxychloride and dimethylformamide gave the 5-p-halogenophenylthien-2-ylaldehydes (102). Optimum yields were obtained when the 2-arylthiophen in dry toluene was added to a cold solution of the pre-formed dimethylformamide-phosphorus oxychloride complex, and the intermediate imine was hydrolysed with sodium acetate. The formylation of 2-phenylthiophen has already been reported.[109]

In the n.m.r. spectrum of 5-p-bromophenylthien-2-ylaldehyde (102, X = Br) the aldehyde proton appeared as a sharp singlet at τ 0.08, and the two thienyl protons were recorded as two doublets. As anticipated, the signal from the thienyl-3-proton was observed at low field due to the electron-withdrawing effect of the aldehyde group. The electronic effect of the thienyl group and the bromine atom on the four phenyl protons must be closely equivalent, for they appear as a singlet.

Scheme 5.


X
S
(101)
POCl3, DMF
X
S
CHO
(102)
Ag2O
CH2(CO2H)2
X
S
CO2H
(104)
X
S
CH=CHCO2H
(105)
H2NNHCSNH2
X
S
CH=NNHCSNH2
(103)

Similar chemical shifts were observed in the n.m.r. spectrum of the p-chloro-derivative (102, X = Cl). Thus, the aldehyde proton appeared at τ 0.12 and the doublet due to the thienyl-3-proton was visible at lower field than the remaining aromatic protons which were recorded as a multiplet.

The thiosemicarbazone derivatives (103) were prepared in excellent yield from the reaction between equimolar amounts of the aldehyde (102) and thiosemicarbazide in aqueous ethanol in the presence of catalytic amounts of acetic acid.

5-p-Bromophenylthien-2-ylaldehyde (102, X = Br) was oxidised to the carboxylic acid (104, X = Br) by freshly prepared silver oxide in aqueous methanol, and condensation of this aldehyde (102, X = Br) with malonic acid in pyridine and piperidine readily gave the acrylic acid (105, X = Br) in 71% yield.

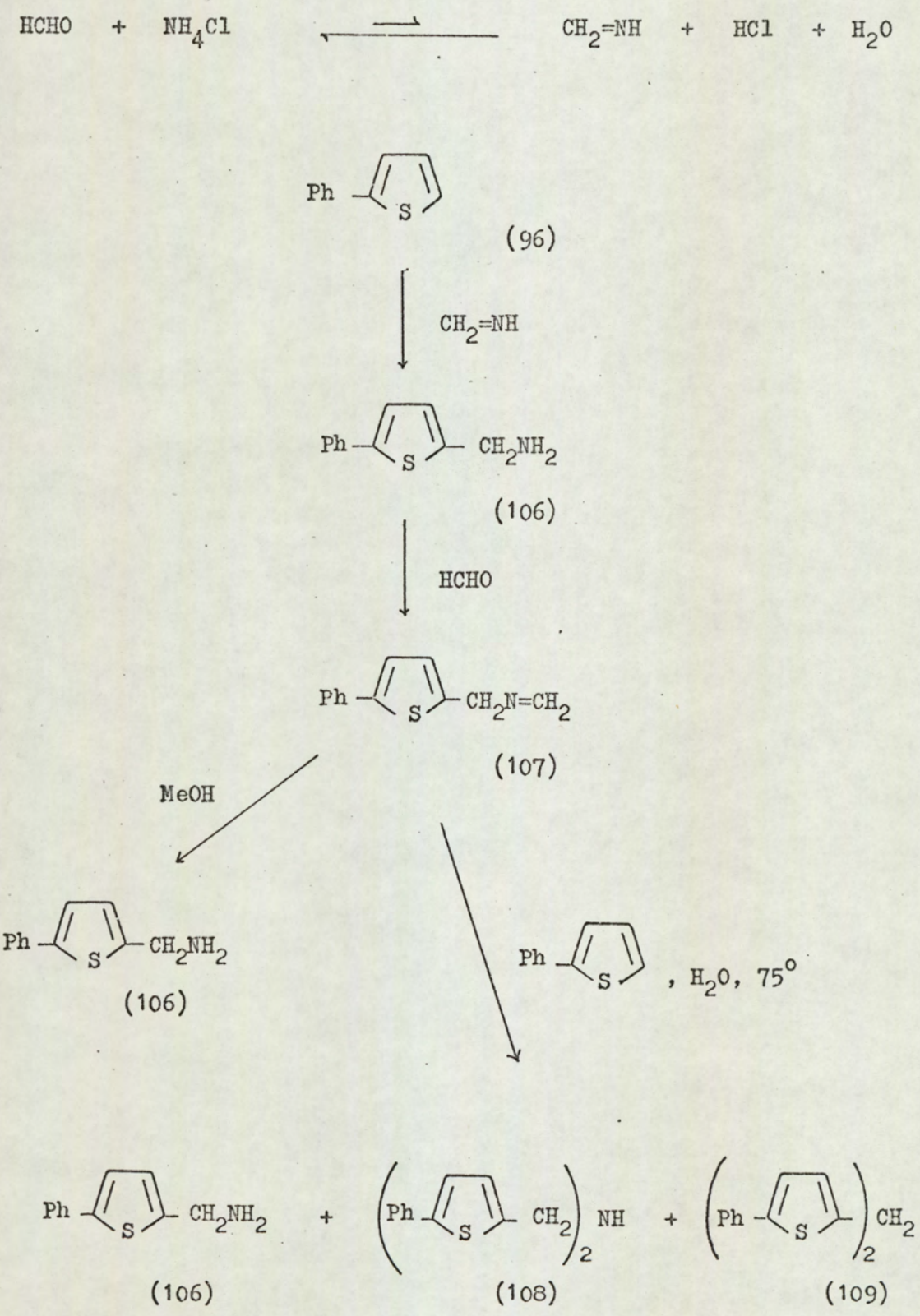
5-Arylthien-2-ylmethylamines.

Three possible routes to these amines were investigated.

Direct aminomethylation of 2-phenylthiophen with formalin and ammonium chloride at 65°, and subsequent treatment of the intermediate N-(5-phenylthien-2-yl) formaldimine (107) with methanol gave 5-phenylthien-2-ylmethylamine (106) in 73% yield (Scheme 6).

The aminomethylation of thiophen has been thoroughly investigated by Hartough.[160] The pronounced acidity of formalin and ammonium chloride mixtures is ascribed to the existence of an equilibrium with formaldimine and hydrochloric acid. Electrophilic substitution of 2-phenylthiophen by the formaldimine yields the methylamine (106) which reacts with the formaldehyde present to give the imine (107). Treatment of this imine with methanol gives the required 5-phenylthien-2-ylmethylamine (106).

Scheme 6.


HCHO + NH4Cl
CH2=NH + HCl + H2O
Ph
S
(96)
CH2=NH
CH2NH2
(106)
HCHO
CH2N=CH2
(107)
MeOH
(106)
, H2O, 75°
(106)
(108)
(109)

At temperatures above 70°, the imine (107), itself an electrophile, may react with thiophen which is present in excess to give the methylamine (106) together with the corresponding secondary amine (108) and bis-(5-phenylthien-2-yl)methane (109). Therefore, careful control of the temperature during the formation of the imine (107) is essential to prevent the occurrence of these side reactions.

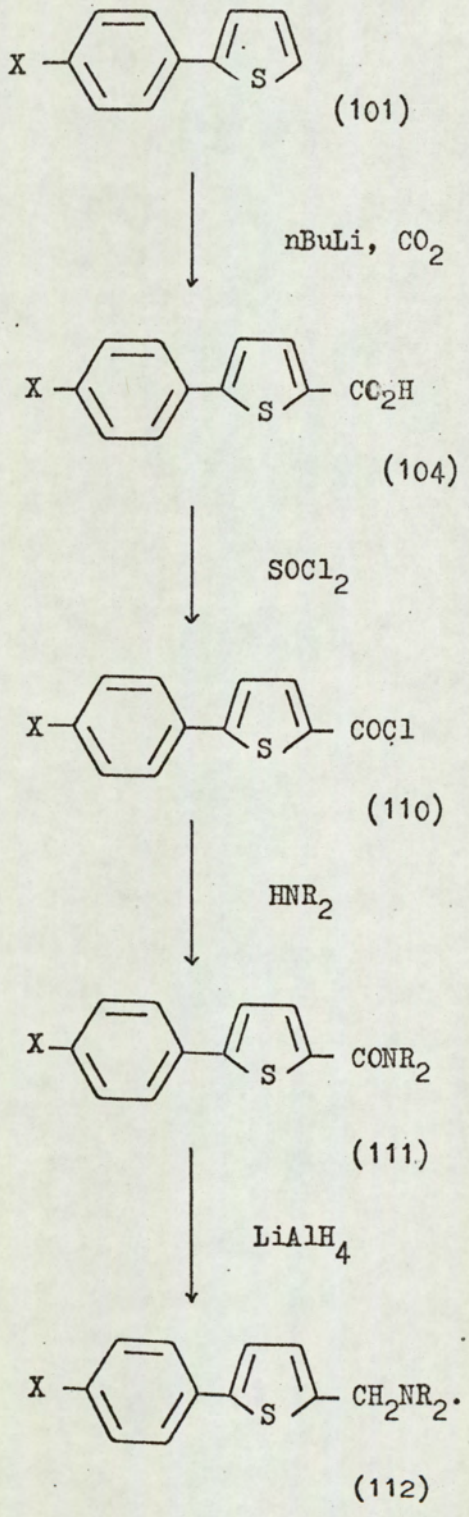
A more versatile synthesis of the required methylamines (113) is shown in Scheme 7. 5-Phenylthiophen-2-carboxylic acid (98) was obtained directly from the oxidative cyclisation of the mercapto-acid (99). The other 5-arylthiophen-2-carboxylic acids (104) were obtained in good yield by direct metalation of the 2-arylthiophens (101) with n-butyl-lithium in ether followed by treatment of the organo-lithium derivative with solid carbon dioxide. This method has been widely used for the preparation of thiophen-2-carboxylic acids and in all cases exclusive α-substitution was reported.[161, 162].

The acids were readily converted to the acid chlorides (110) by treatment with thionyl chloride. In the n.m.r. spectrum of 5-p-bromophenylthien-2-yl acid chloride (110, X = Br), the four phenyl protons appeared as a singlet at τ 2.43, and the two thienyl protons were observed as doublets at τ 2.71 and τ 2.13; the low-field signal was assigned to the thienyl-3-proton. This spectrum is consistent with α-substitution in the formation of the acid (104).

Reaction of the acid chloride (110) in dry benzene, with an excess of a secondary amine gave the corresponding tertiary amide (111) in excellent yield. The primary 5-arylthien-2-ylamides (111, R=H) were obtained by the addition of the acid chloride (110) to an excess of ammonia in methanol.

The i.r. spectra of the tertiary amides (111) (as dilute solutions in chloroform) showed strong absorption at 1620-1600 cm.$^{-1}$. The low

Scheme 7.


X
S
(101)
nBuLi, CO_2
X
S
CO_2H
(104)
$SOCl_2$
X
S
COCl
(110)
HNR_2
X
S
$CONR_2$
(111)
$LiAlH_4$
X
S
CH_2NR_2.
(112)

frequency of the carbonyl absorption is due to hydrogen-bonding between the solvent and the amide. The i.r. spectra of the primary amides showed characteristic adsorption bands at 3410 and 3190 (N-H), and 1650 (C=O) $cm.^{-1}$. The "Amide II" band was observed at 1615 $cm.^{-1}$.

Reduction of the amides (111, X = H, Cl, Me) in benzene with a suspension of lithium aluminium hydride in ether for 12 hr. gave the thienylmethylamines (112, X = H, Cl, Me) in excellent yield. However, reduction of the 5-p-bromophenylthien-2-ylamides (111, X = Br, NR_2 = morpholino, piperidino, pyrrolidino, NMe_2) with an excess of lithium aluminium hydride gave a mixture of the 5-p-bromophenylthien-2-ylmethylamine (112, X = Br, NR_2 = morpholino, piperidino, pyrrolidino, NMe_2) and the corresponding 5-phenylthien-2-ylmethylamine (112, X = H, NR_2 = morpholino, piperidino, pyrrolidino, NMe_2). T.l.c. showed little separation of the two amines and although recrystallisation of the mixed hydrochlorides in all cases yielded crystalline material having a constant melting point, the analytical figures were intermediate between those of the two hydrochlorides.

In the mass spectrum of the reaction product, characteristic peaks due to the fragmentations of both of the amines were observed. In each case, the expected molecular ion peak of the 5-p-bromophenylthien-2-ylmethylamine was recorded at the appropriate m/e value as a characteristic doublet, accompanied by the molecular ion peak of the corresponding 5-phenyl-derivative at 78 and 80 mass units lower. The peaks due to the 2-p-bromophenylthiopyrylium ion, arising from cleavage of the molecular ion at the bond β to the thiophen ring were observed at m/e 251 and 253. These were accompanied in every case by a peak at m/e 173 due to the 2-phenylthiopyrylium ion generated by the parallel fragmentation of the 5-phenylthien-2-ylmethylamine.

From the mass spectrum, the percentage of the 5-p-bromophenylthien-2-ylmethylamine present in the mixture was estimated from the intensity of

the molecular ion peaks, and compared with the percentage calculated from the analysis figures. The former percentage is only approximate, since the calculation assumes that both amines are equally stable to electron impact, but some similarity can be observed in Table 1.

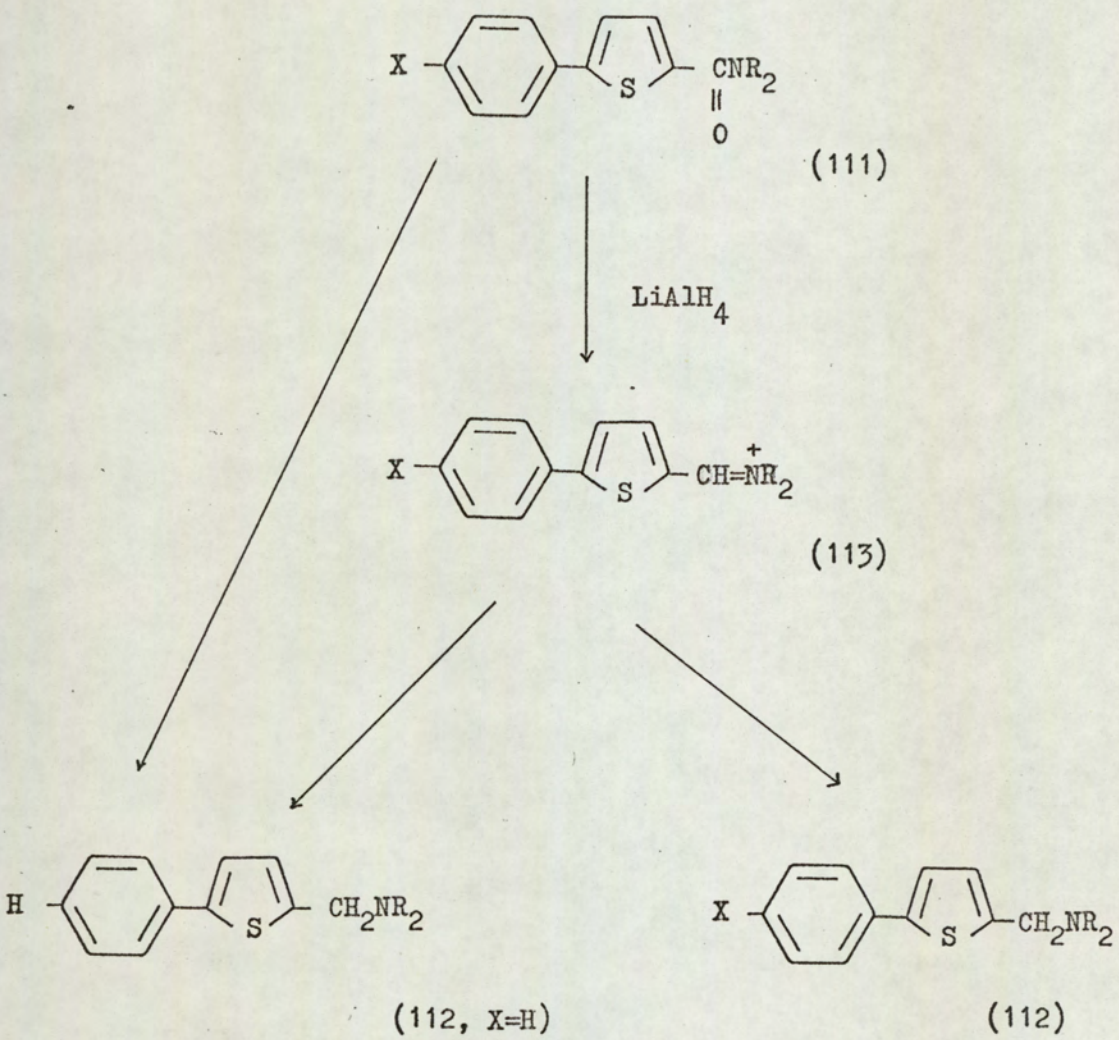
Table 1.

Amine	% from mass spectrum	% from analysis figures
112, X = Br, NR_2 = morpholino	17	29.4
112, X = Br, NR_2 = piperidino	7	7.8
112, X = Br, NR_2 = pyrrolidino	12	6.5
112, X = Br, NR_2 = NMe_2	62	80

Reduction of the amides (111, X = Br, NR_2 = morpholino, NMe_2) with the calculated quantity of lithium aluminium hydride gave the 5-*p*-bromophenylthien-2-ylmethylamines (112, X = Br, NR_2 = morpholino, NMe_2) in good yield. The melting points and n.m.r. spectra were identical with those of authentic samples prepared from the reaction of 2-*p*-bromophenyl-5-chloromethylthiophen (114, X = Br) with the appropriate secondary amine. Reduction of *N*-(5-*p*-bromophenylthien-2-ylmethyl)morpholine (111, X = Br, NR_2 = morpholino) with a four-fold excess of lithium aluminium hydride gave *N*-(5-phenylthien-2-ylmethyl)morpholine (112, X = H, NR_2 = morpholino) in excellent yield. The 5-*p*-bromophenylthien-2-ylmethylamines however, were resistant to further reduction and were obtained unchanged after treatment with lithium aluminium hydride in ether-benzene at reflux for 48 hr. (Scheme 8).

Similar nucleophilic aromatic substitutions of halogen by hydride ion have been reported. 8-Bromonaphthoic acid was reduced to naphthyl alcohol by lithium aluminium hydride in tetrahydrofuran.[163] When lithium

Scheme 8.



Equation 8.

$$ArX + 2\,LiAlH_4 \longrightarrow ArH + LiAl_2H_7 + LiX$$

aluminium deuteride was used, the deuterium appeared only at position 8 which suggests that benzyne formation does not occur and that the reaction involves direct nucleophilic substitution of the halogen by hydride ion. The reaction is facilitated by the presence of electron withdrawing groups in the molecule[164] and possible mechanisms have been suggested[165] which are in accordance with these observed facts.

The resistance of the 5-p-bromophenylthien-2-ylmethylamines to further reduction suggests that hydrogenolysis of the aromatic bromine occurs prior to the formation of the amine and probably at the amide (111) or intermediate imine (113) stage. It is thought that the electron-withdrawing effect of these 2-substituents assists the substitution of the halogen by hydride ion.

In the presence of the calculated amount of lithium aluminium hydride required to reduce the amide function, (0.5 mole), the amide (111, X = Br) yields the amine (112, X = Br) as the major product. It has been observed[165] that, in the reaction of equimolar amounts of lithium aluminium hydride and an aryl halide, initial hydrogenolysis is relatively rapid and utilises two moles of lithium aluminium hydride per mole of aryl halide (Equation 8). Subsequent reduction of the remaining aryl halide by the species $LiAl_2H_7$ takes place at a much slower rate. When at least a twofold excess of reducing agent is present, complete hydrogenolysis of the aryl halide can proceed according to equation 8, but if only a limited amount of lithium aluminium hydride is available, the initial concentration of the species $LiALH_4$ decreases rapidly and subsequent replacement of the halogen by hydride ions from less hydrogen-rich species will proceed more slowly. This would explain the preferential reduction of the amide function of 5-p-bromophenylthien-2-ylamides under these conditions.

No evidence was found for the displacement of chlorine by hydride ions in the reduction of the amides (111, X = Cl)and this is

consistent with the reported order of reactivity of the halogens towards nucleophilic displacement in this reaction.[165]

In order to avoid this problem encountered in the reduction of the amides (111, X = Br), the amines (112, X = Br) were prepared from the reaction of 5-p-bromophenyl-2-chloromethylthiophen (114, X = Br) with an excess of a secondary amine (Scheme 9). The 5-aryl-2-chloromethylthiophen (114) was obtained from the corresponding 2-arylthiophen (101) by direct chloromethylation with formalin and concentrated hydrochloric acid. This reaction, carried out at 0°, has been used to prepare 2-chloromethylthiophen,[166] but in the present work, optimum yields were obtained at 60°. The yields were only moderate due to the formation of bis-(5-arylthien-2-yl)methane as a side product.

The m.p. and n.m.r. spectrum of 2-chloromethyl-5-phenylthiophen (114, X = H) were identical with those of an authentic sample prepared from 5-phenylthiophen-2-carboxylic acid (104, X = H) (Scheme 9); thus, chloromethylation had occurred at the free α position as anticipated.

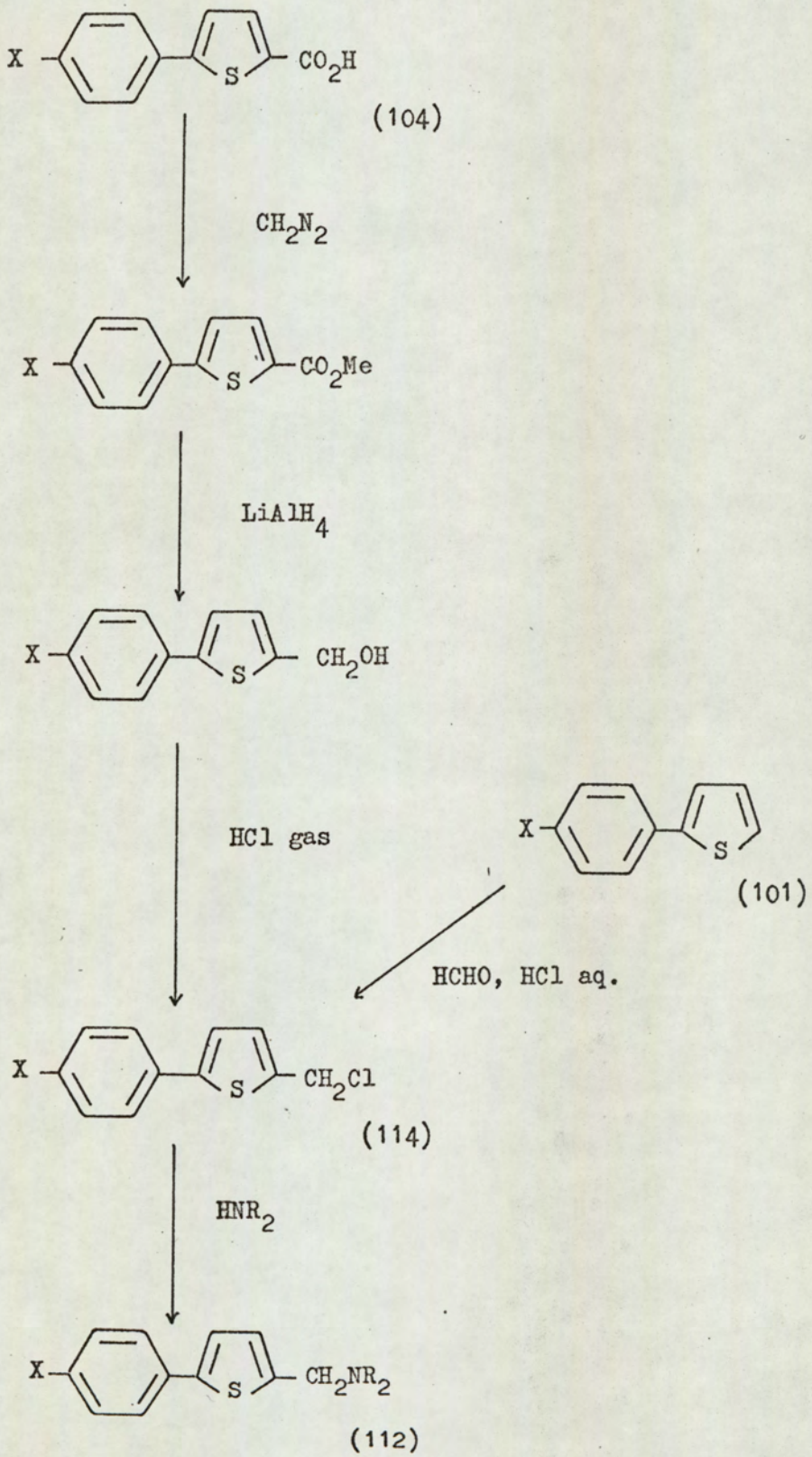
5-Arylthien-2-ylethylamines.

Two proposed routes to the 5-arylthien-2-ylethylamines (118, 120) are shown in Scheme 10.

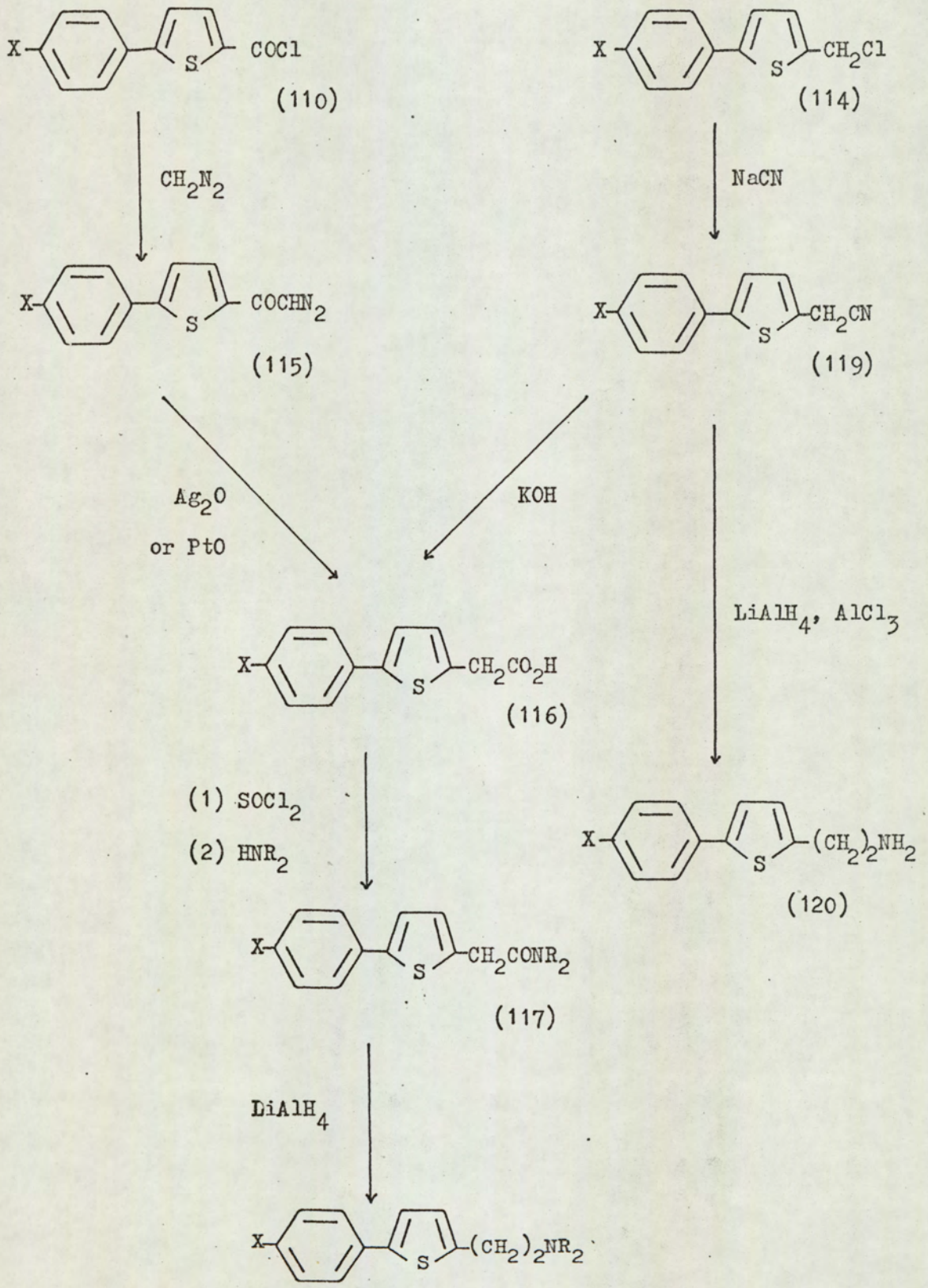
The Arndt-Eistert reaction offered a direct synthesis of the required 5-arylthien-2-ylacetic acids (116) from the corresponding carboxylic acids (104). Addition of the 5-arylthien-2-yl acid chlorides (110) to an excess of diazomethane gave the diazo-ketones (115), and subsequent treatment of these with platinum oxide or silver oxide in boiling methanol yielded the methyl-5-arylthien-2-ylacetates which were hydrolysed to the required acids (116).

The acids (116) were also prepared by the alkaline hydrolysis of the 5-aryl-2-cyanomethylthiophens (119) which were obtained from the

Scheme 9.


X
S
CO_2H
(104)
CH_2N_2
X
S
CO_2Me
$LiAlH_4$
X
S
CH_2OH
HCl gas
X
S
(101)
HCHO, HCl aq.
X
S
CH_2Cl
(114)
HNR_2
X
S
CH_2NR_2
(112)

Scheme 10.


X
S
COCl
(110)
CH_2N_2
$COCHN_2$
(115)
Ag_2O
or PtO
KOH
CH_2CO_2H
(116)
(1) $SOCl_2$
(2) HNR_2
CH_2CONR_2
(117)
$LiAlH_4$
$(CH_2)_2NR_2$
CH_2Cl
(114)
NaCN
CH_2CN
(119)
$LiAlH_4$, $AlCl_3$
$(CH_2)_2NH_2$
(120)

chloromethyl compounds (114) by treatment with sodium cyanide in dimethyl sulphoxide. These acids (116) could be converted into the amides (117) and amines (118) as previously described for the 5-arylthien-2-ylmethylamines (112).

5-Phenylthien-2-ylethylamine (120, X = H) was obtained from the reduction of 2-cyanomethyl-5-phenylthiophen (119, X = H) with a 1:1 molar ratio of lithium aluminium hydride and aluminium chloride in ether and benzene.

Amidines.

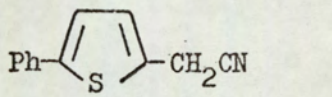
5-Phenylthien-2-ylacetamidine (122) was obtained in excellent yield by saturation of a solution of the nitrile (119, X = H) and ethanol in benzene with dry hydrogen chloride, and treatment of the intermediate imino-ether (121) with an excess of ammonia in ethanol (Scheme 11a).

When equimolar amounts of 5-phenylthien-2-ylmethylamine (112, X = H) and acetimidate hydrochloride (123) were mixed in dry ethanol, N,N'-di-(5-phenylthien-2-yl)acetamidine (124) was obtained and not the expected N-monosubstituted derivative.

The i.r. spectrum of the amidine hydrochloride (124) showed the expected C=N band at 1655 $cm.^{-1}$. In the n.m.r. spectrum, the two methylene groups appeared as a singlet at τ 5.36, and the N-proton was observed as a broad singlet at τ 4.45 which disappeared on the addition of D_2O.

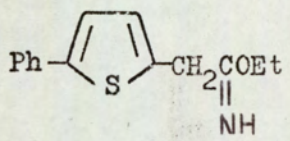
The mass spectrum showed a molecular ion peak at m/e 402 (17%). Elimination of a molecule of 5-phenylthien-2-ylmethylamine by cleavage of the bond γ to the thiophen ring with hydrogen rearrangement yields the radical-ion at m/e 213 (10%) which subsequently decomposes to the ion at m/e 171 (Scheme 11b). Cleavage of the bond β to the thiophen ring is the more favoured process, however, due to the stability of the 2-phenylthiopyrylium species which is generated and both of the two possible

Scheme 11a.



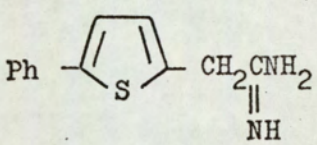
(119)

EtOH, HCl

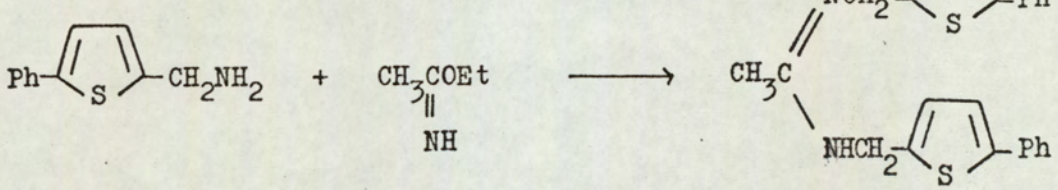


(121)

NH_3

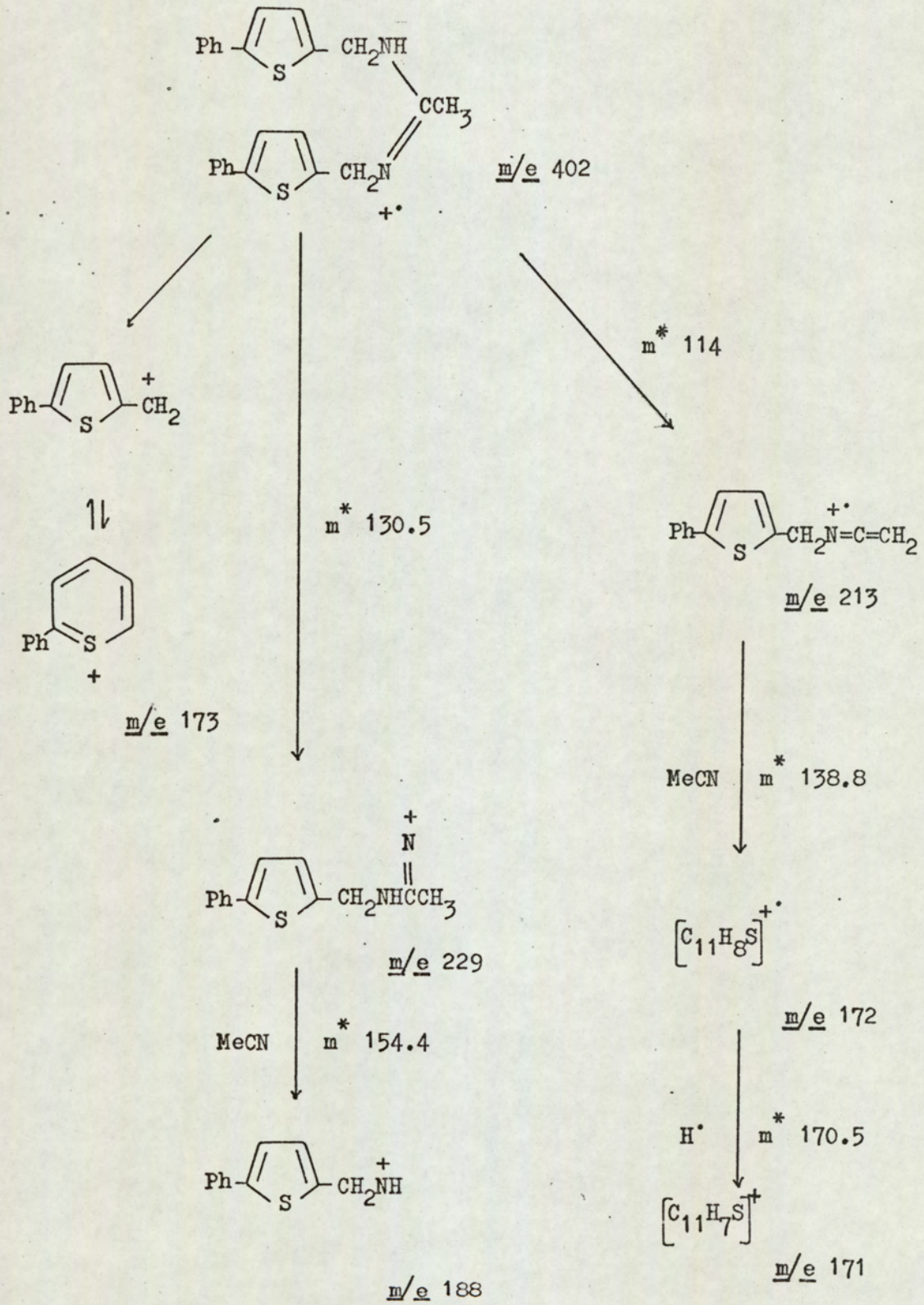


(122)



(112) (123) (124)

Scheme 11b.

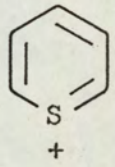

Ph
S
CH2NH
CCH3
CH2N
m/e 402
m* 114
m* 130.5
CH2
m/e 173
CH2N=C=CH2
m/e 213
MeCN
m* 138.8
CH2NHCCH3
m/e 229
MeCN
m* 154.4
[C11H8S]+·
m/e 172
H·
m* 170.5
[C11H7S]+
m/e 171
CH2NH
m/e 188

ions resulting from this fragmentation are observed at m/e 229 (65%) and m/e 173 (70%). The ion at m/e 229 eliminates a molecule of methyl cyanide to yield the ion at m/e 188 which forms the base peak of the spectrum. This ion is also prominent in the mass spectrum of 5-phenylthien-2-ylmethylamine and its stability could possibly be due to its existence as an aminothiopyrylium species. The subsequent decomposition of the ions at m/e 188 and m/e 173 are discussed in the mass spectrometry section.

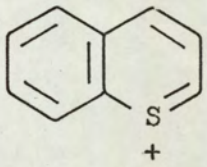
The formation of N-disubstituted amidines in the presence of an excess of amine has been discussed previously. In the present case however, no excess of amine was present, and since the di-substituted derivative was obtained in 87% yield, the initially formed mono-substituted acetamidine must react with the amine more rapidly than acetamidine hydrochloride itself.

Mass Spectrometry.

The mass spectra of thiophen and its deuterated derivatives have been reported,[167] and as anticipated, the molecular ion forms the base peak and fragmentation is similar to that of furan. The spectra of the alkylthiophens[168] differ considerably from the spectrum of the parent heterocycle and the fragmentation patterns resemble those of the alkylbenzenes. In the spectra of all the monoalkylthiophens, the most prominent feature is their fragmentation by β-cleavage to yield a common stable $C_5H_5S^+$ ion which has been formulated as the thiopyrylium ion (125).[169,170] The mass spectra of thirty-two substituted thiophens



(125)



(126)

have been published by Bowie et. al.,[171] and in general, their fragmentation pathways are similar to those of the corresponding benzene derivatives.

A study of the spectra of 2-, and 3-phenylthiophen and their pentadeuterophenyl analogues has shown that considerable hydrogen scrambling occurs on electron impact, but that the hydrogen atoms in the thiophen ring are the most labile.[172] A scheme has been suggested to account for the major fragmentation ions of 2-phenylthiophen,[171] and one of the most interesting features is the loss of sulphur from the molecular ion to give a phenylcyclobutadiene-type ion at m/e 128. A similar fragmentation is not observed in the spectra of the corresponding furan or pyrrole compounds.

The mass spectrum of benzo[b]thiophen[173] shows features similar to that of thiophen, and fragmentation of the molecular ion (100%) is dictated by the loss of S, C_2H_2, or CS.

Monoalkylbenzo[b]thiophens, like alkylthiophens, undergo β-fission to yield a common stable $C_9H_7S^+$ ion which forms the base peak of all of the spectra, and probably exists as a benzothiopyrylium cation (126).

1-(5-Chlorobenzo[b]thien-3-ylmethyl)guanidines (84, X = Cl).

The mass spectrum of 1-(5-chlorobenzo[b]thien-3-ylmethyl)-3-methylguanidine (84, X = Cl, R^2 = Me, R^1 = R^3 = H) shows a molecular ion peak at m/e 253 and, as for benzylguanidine, the major degradation pathways primarily involve the guanidine group in the neutral fragment (Scheme 12).

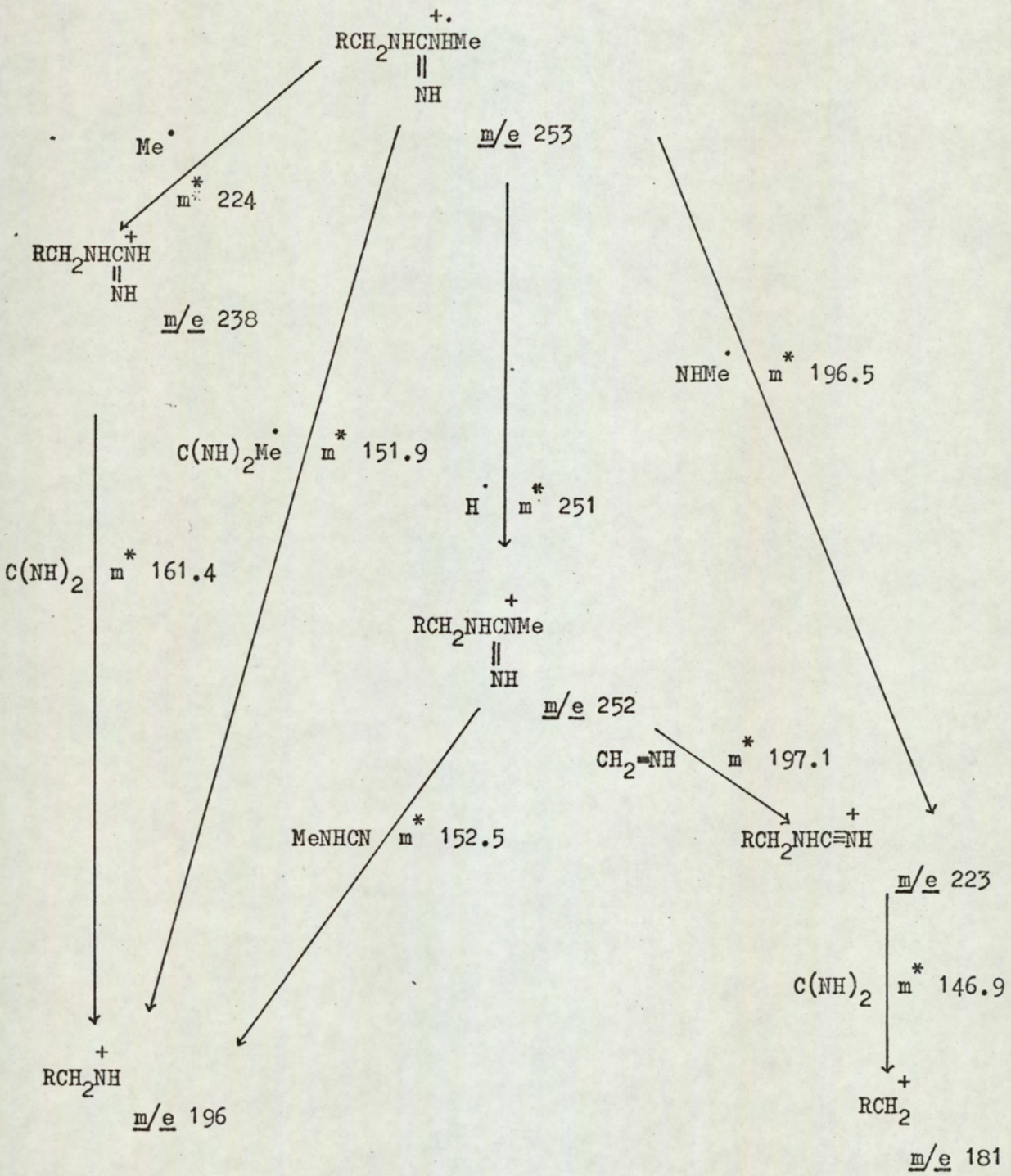
Loss of H$^\bullet$ or Me$^\bullet$ from the molecular ion gives the resonance stabilised ions at m/e 252 (90%) and 238 (6%) respectively, both of which subsequently decompose to the ion at m/e 196. This ion also arises directly from the molecular ion by the loss of a $C_2H_5N_2^\bullet$ radical, and may exist as an arylaminomethyl ion or can undergo rearrangement to form an aminobenzothiopyrylium ion.

Another possibility is that the molecular ion may fragment by elimination of MeNH$^\bullet$ to give the resonance-stabilised ion at m/e 223 which subsequently decomposes to the ion at m/e 181. The ion at m/e 223 can also arise by the loss of formimine from the $(M-I)^+$ ion.

Further substitution of the guanidine side-chain has little effect on the fragmentation pattern. However, for the 2,3-, and 3,3-dimethylguanidine derivatives (84, X = Cl, R^1 = R^3 = Me, R^2 = H, and R^2 = R^3 = Me, R^1 = H) the $(M-CH_3)^+$ ion shows an alternative fragmentation to the ion at m/e 222 by the loss of MeNH$^\bullet$. A corresponding loss of $NH_2^\bullet$ from the $(M-CH_3)^+$ ion of the monomethyl derivative is not observed.

In all of the spectra, the ion at m/e 196 fragments by the initial loss of HCN, with hydrogen rearrangement, to yield the ion at m/e 169, a similar degradation pathway to that observed in the mass spectrum of

Scheme 12.



R = 5-chlorobenzo[b]thien-3-yl

benzylguanidine.[174] Subsequent loss of Cl$^{\cdot}$ yields the radical-ion at m/e 134 which has the same molecular formula as that of the molecular ion of benzo[b]thiophen, and, if hydrogen rearrangement occurs, it could also have a similar structure. Further fragmentations are initiated by the loss of H$^{\cdot}$, S, or CS, as in the case of benzo[b]thiophen, but no evidence was found for the anticipated elimination of acetylene.

The ion at m/e 181 probably exists as the resonance-stabilised benzothiopyrylium cation, and forms the base peak in all of the spectra. The major degradation pathways for this ion, initiated by the loss of Cl$^{\cdot}$, or S and C_2H_2, are shown in Scheme 13. Although an ion is observed at m/e 149, which corresponds to the loss of S from the ion at m/e 181, the lack of any metastable peak to support this transition, and the presence of a metastable peak at m/e 83.6, suggests that S and C_2H_2 are lost simultaneously from the ion at m/e 181.

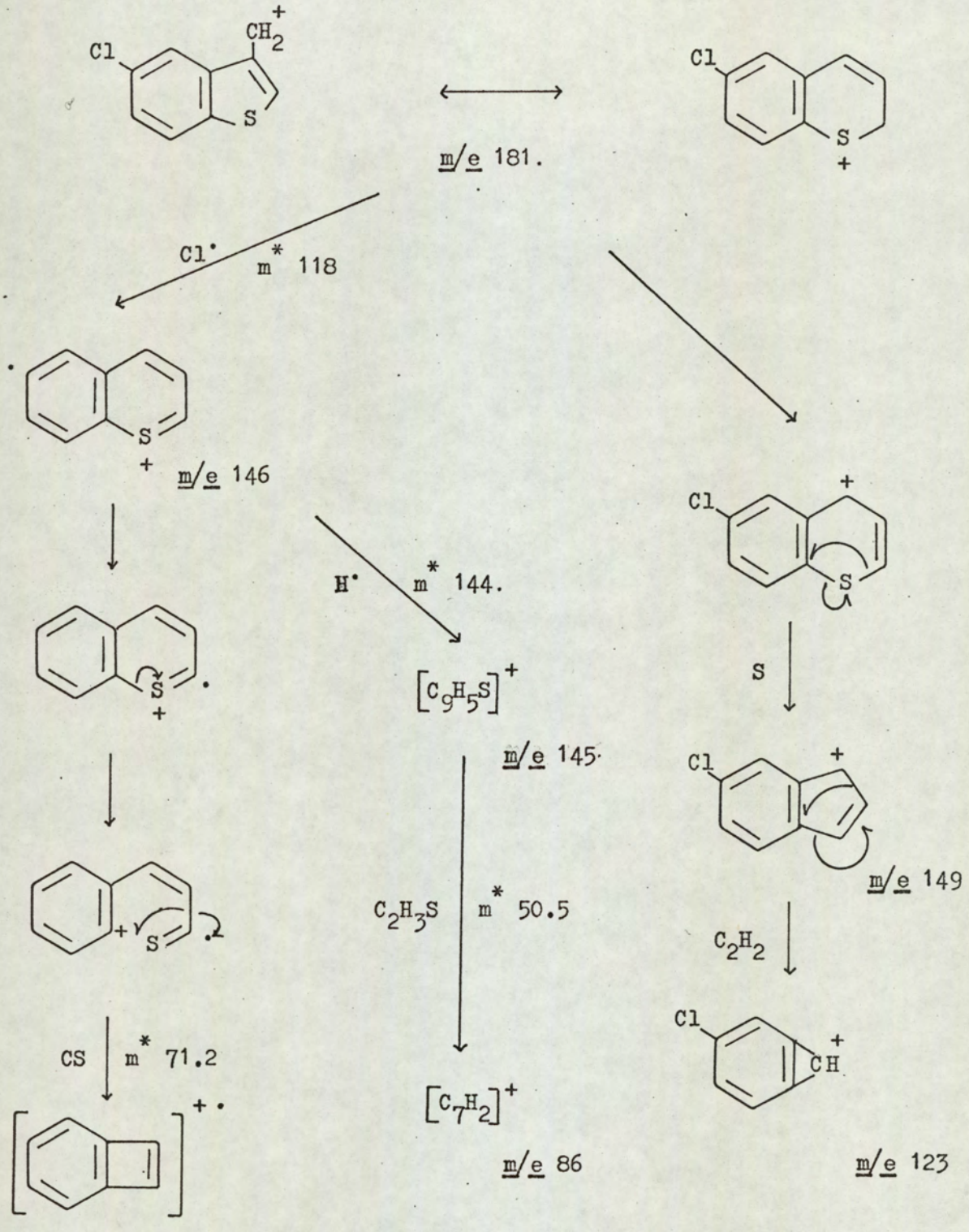
1-(5-Chlorobenzo[b]thien-3-ylethyl)guanidines (85, X = Cl).

The mass spectra of the ethylguanidines differ considerably from those of the corresponding methylguanidines previously discussed, and many of the prominent charged fragments are derived from the guanidine side-chain since cleavage of the C-N bond γ to the thiophen ring can no longer yield the highly resonance-stabilised ion at m/e 196.

The intensity of the molecular ion peak of 1-(5-chlorobenzo[b]thien-3-ylethyl)3-methylguanidine (85, X = Cl, R^2 = Me, R^1 = R^3 = H) is small, and the spectrum is dominated by the $MeNH^+$ ion at m/e 30 which forms the base peak.

This moleculer ion also decomposes to the aminoethyl ion at m/e 210 which subsequently eliminates a molecule of HCN to yield the ion at m/e 183, a fragmentation pathway similar to that involved in the formation of the ions at m/e 196 and 169 from the molecular ions of the methylguanidines. The ion at m/e 183 decomposes to the benzothiopyrylium ion at m/e 181 by two

Scheme 13.


Cl
CH2
S
m/e 181.
Cl
S
Cl·
m* 118
S
m/e 146
H·
m* 144.
[C9H5S]+
m/e 145
Cl
S
S
Cl
m/e 149
C2H3S
m* 50.5
C2H2
[C7H2]+
m/e 86
Cl
CH
m/e 123
CS
m* 71.2
m/e 102

successive losses of H$^{\cdot}$. A minor fragmentation pathway of the molecular ion, initiated by the loss of CH_2=NH, is observed too.

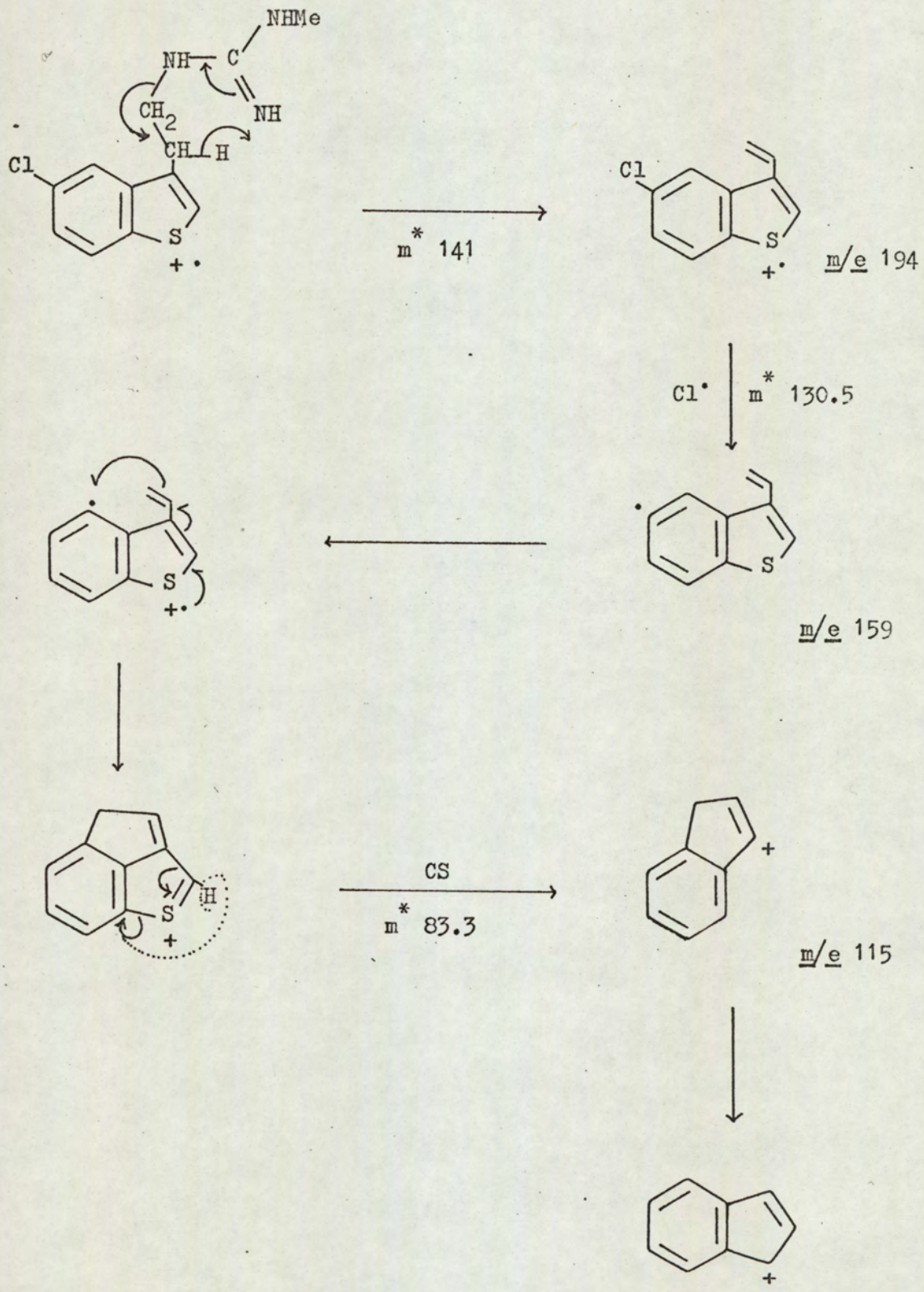
Elimination of a molecule of N-methylguanidine from the molecular ion to yield the radical-ion at m/e 194 also occurs. This fragmentation involves a hydrogen rearrangement which may be effected via a six-membered cyclic transition state (Scheme 14). The ion at m/e 194 fragments to the ion at m/e 115 (10%) which may exist as the resonance stabilised indene cation.

Similar fragmentation to the ion at m/e 194 is an important decomposition pathway for the molecular ions of the 2,3, and 3,3-dimethyl derivatives (85, X = Cl, $R^1 = R^3$ = Me, R^2 = H, and $R^2 = R^3$ = Me, R^1 = H) and, in addition, fragmentation to the ion at m/e 210 is observed to a small extent. Cleavage of the C-N bond γ to the thiophen ring also occurs, but in the case of these dimethyl derivatives, the positive charge is retained by the nitrogen fragment to give the radical-ion at m/e 87 (Scheme 15a). This ion subsequently fragments to the ion at m/e 72 or m/e 58 by the elimination of Me$^{\cdot}$ or CH_2=NH respectively; in the case of the 3,3-dimethyl derivative, elimination of CH_2=NH must be accompanied by some rearrangement of the methyl groups.

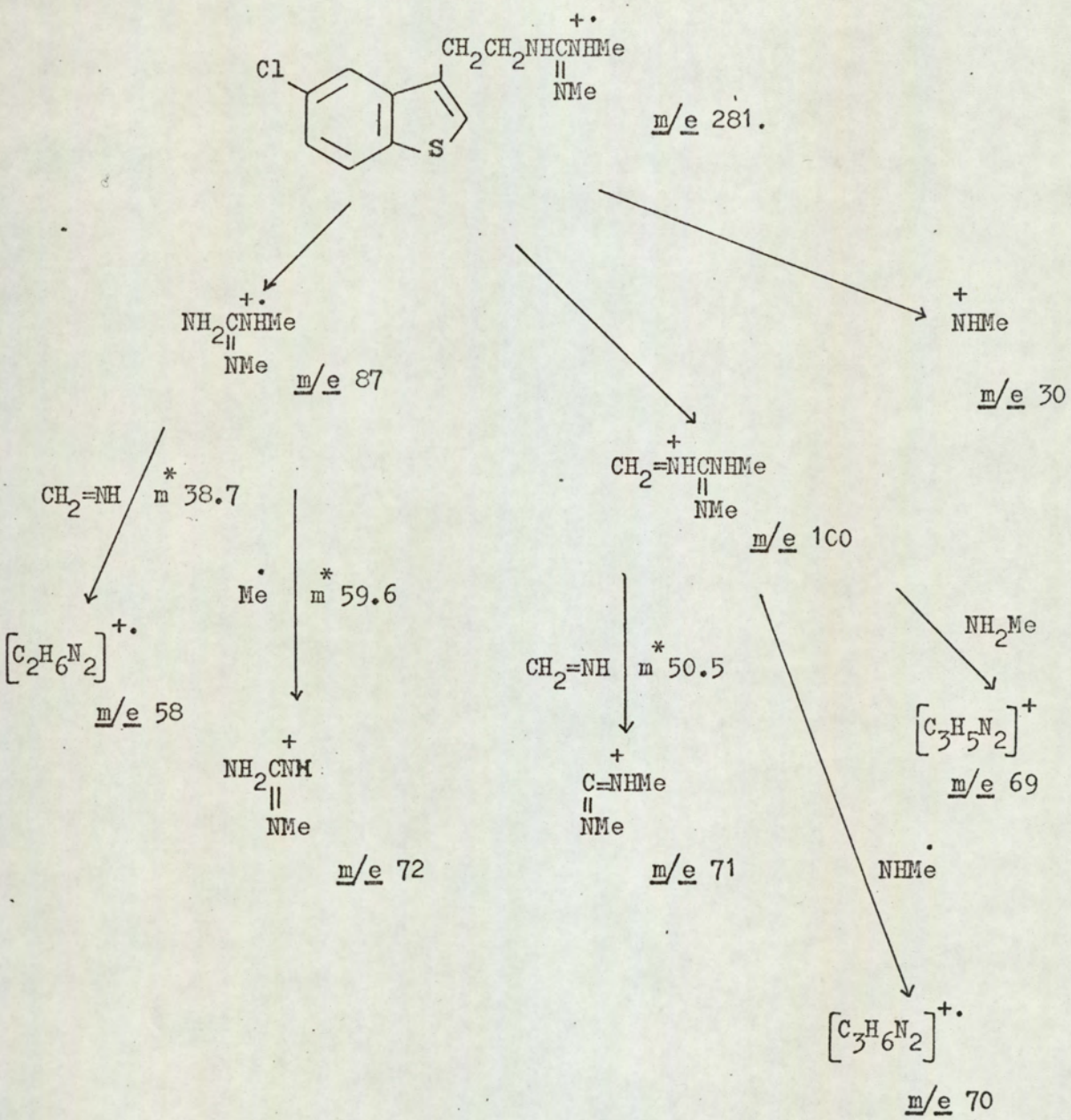
In the spectrum of the 2,3-dimethyl derivative, elimination of the terminal nitrogen as $MeNH^+$ yields the ion at m/e 30 (18%), but the major fragmentation of the molecular ion is cleavage β to the thiophen ring to give the guanidinium ion at m/e 100 which forms the base peak (Scheme 4a). This ion subsequently decomposes by the elimination of CH_2=NH or $MeNH_2$ to give the ions at m/e 71 (94%) and m/e 69 (27%) respectively; loss of MeNH$^{\cdot}$ occurs to a lesser extent to yield the ion at m/e 70 (7%) (Scheme 15a).

The spectrum of the 3,3-dimethyl derivative shows that elimination of the terminal nitrogen occurs to a small extent, and in this case, the charge is retained by the aralkylcarbodiimide fragment which is observed at

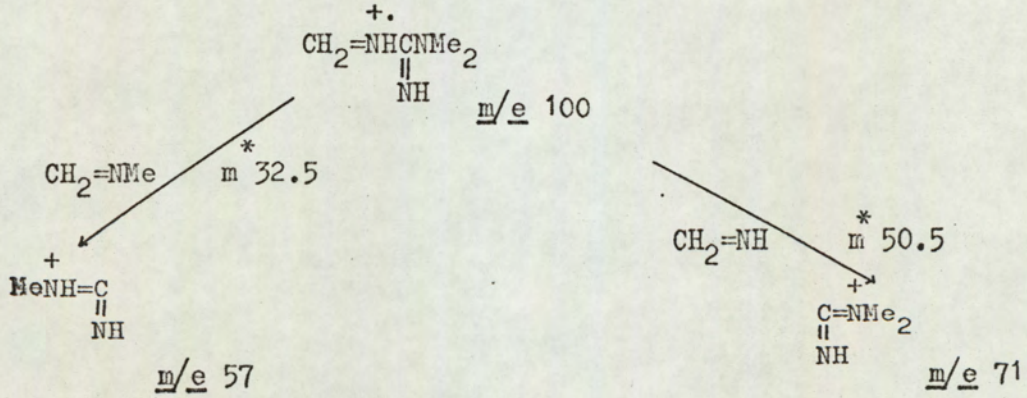
Scheme 14.


NHMe
NH
C
NH
CH2
CH
H
Cl
S
+•
m* 141
Cl
S
+•
m/e 194
Cl•
m* 130.5
S
m/e 159
S
+•
H
S
+
CS
m* 83.3
+
m/e 115
+

Scheme 15a.



Scheme 15b.



m/e 238 (3%). The major fragmentation is again β-cleavage to yield an ion at m/e 100 (100%) which subsequently decomposes with the elimination of CH_2=NH or CH_2=NMe to give the ions at m/e 71 (70%) and m/e 57 (45%) respectively. (Scheme 15b).

Fragmentation by β-cleavage leads to the stable benzothiopyrylium radical, and it is therefore surprising that this fragmentation is not a prominent feature in the spectrum of the monomethyl-substituted derivative where it only occurs to a very minor extent to yield the ion at m/e 86 (1%),

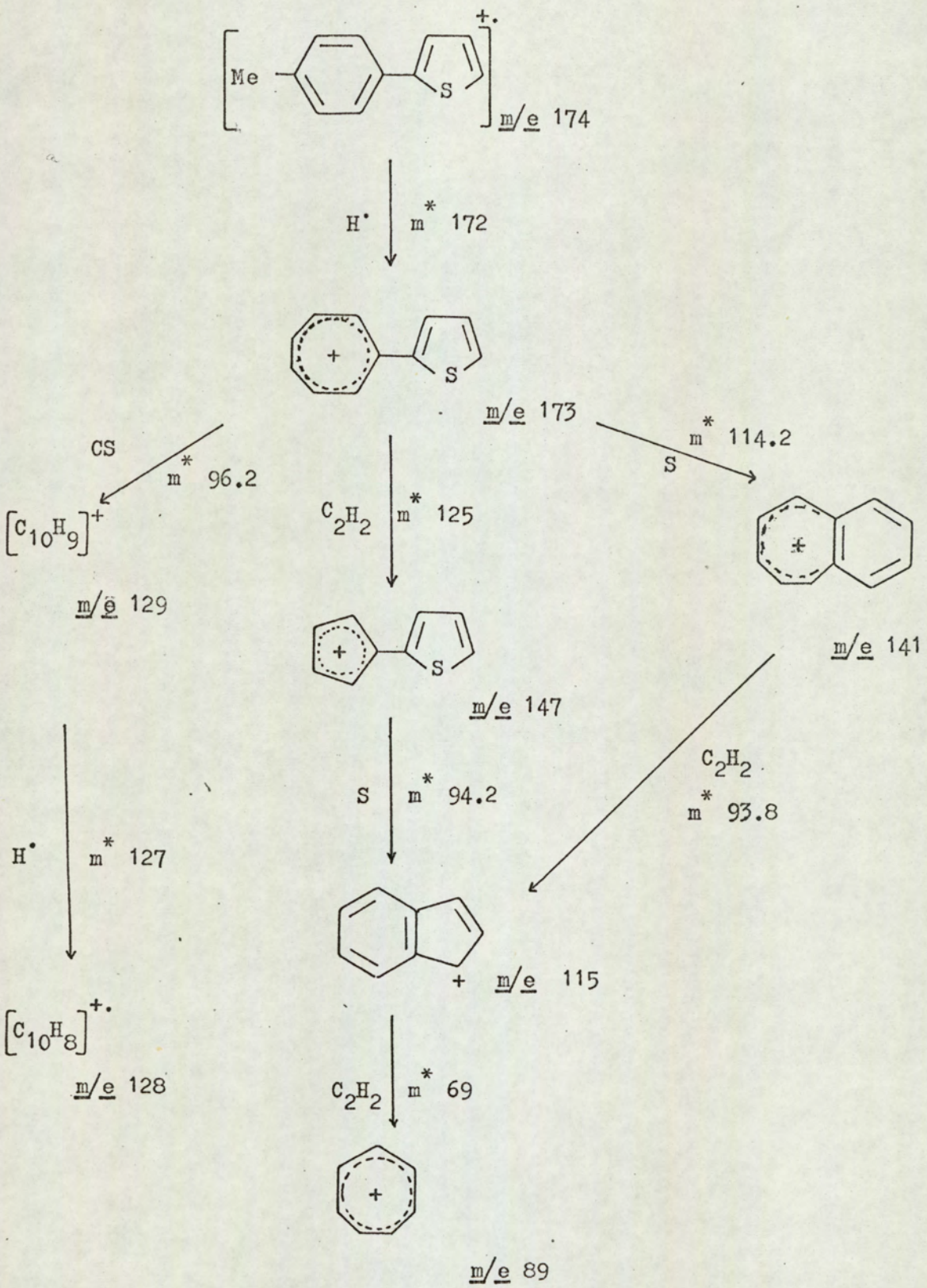
2-p-Tolylthiophen (101, X = Me).

The molecular ion of 2-p-tolylthiophen forms the base peak of the spectrum and fragments initially to the ion at m/e 173 (54%) by the loss of H·. The stability of the $(M-1)^+$ ion could be due to its existence as the thien-2-yltropylium ion, and the three main degradation pathways, initiated by the loss of CS, S, or C_2H_2 are shown in Scheme 16. Elimination of S from the molecular ion of 2-phenylthiophen has been noted and a cyclobutadine structure has been proposed for the resulting ion,[171] but in the case of 2-p-tolylthiophen, the ion at m/e 141 (14%) could also exist as a fused benzotropylium ion. This type of ion has been suggested for the alkylnaphthalenes,[175] and it fragments by the elimination of C_2H_2 to yield the ion at m/e 115 (11%).

2-t-Aminomethyl-5-arylthiophens (112).

In the mass spectrum of N-(5-phenylthien-2-ylmethyl) morpholine (112, X = H, NR_2 = morpholino), the anticipated decomposition of the molecular ion (1%) by cleavage of the bond α to the thiophen ring occurs to a small extent to yield the methyleneimmonium ion at m/e 100 (2%). The major degradation of the molecular ion is by cleavage of the C-N bond β to

Scheme 16.


Me
S
m/e 174
H·
m* 172
m/e 173
CS
m* 96.2
[C10H9]+
m/e 129
C2H2
m* 125
m* 114.2
S
m/e 141
m/e 147
S
m* 94.2
C2H2
m* 93.8
H·
m* 127
[C10H8]+·
m/e 128
m/e 115
C2H2
m* 69
m/e 89

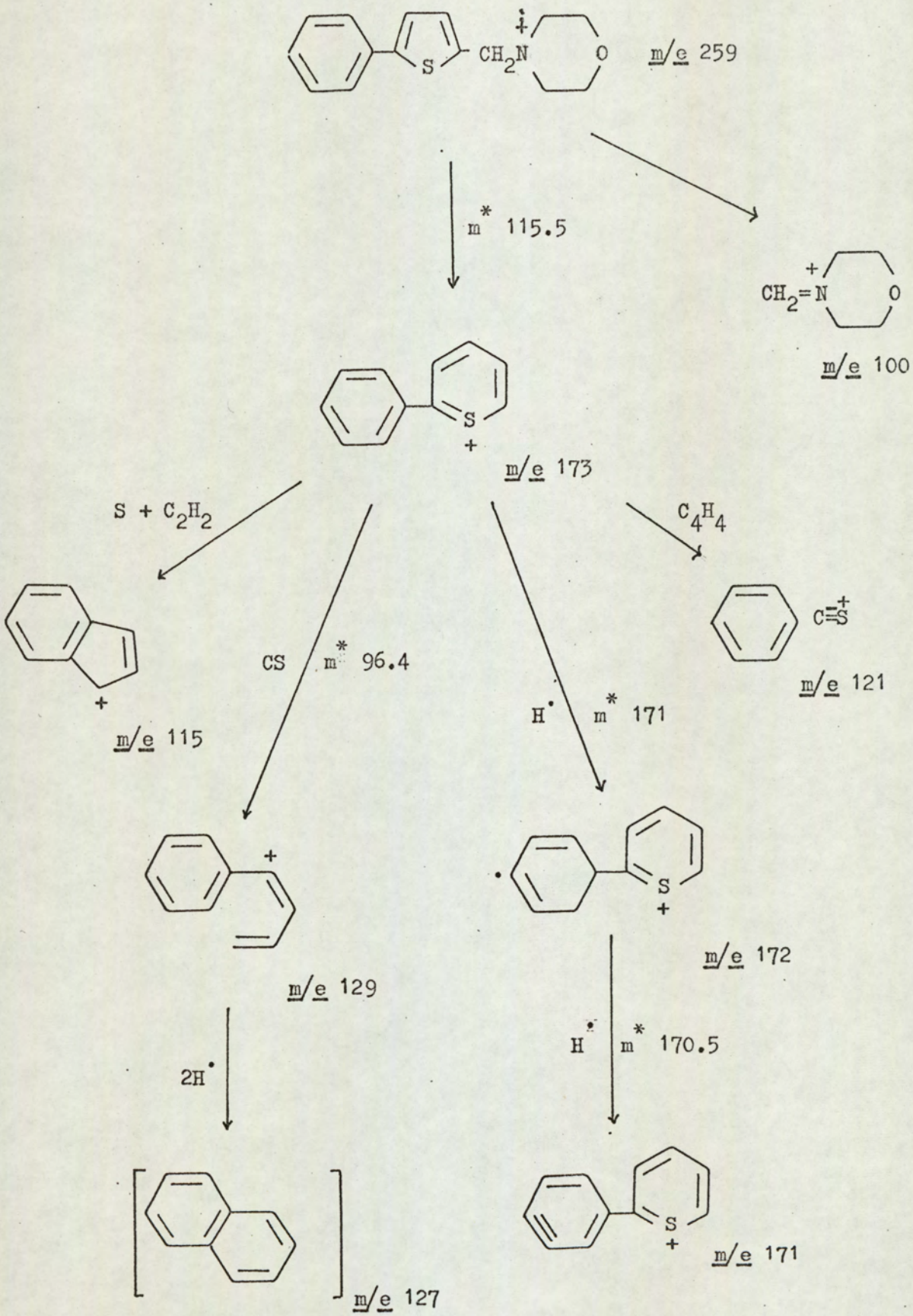
the thiophen ring to give the ion at m/e 173 which forms the base peak of the spectrum and which probably exists as a 2-phenylthiopyrylium ion. All subsequent fragmentation ion peaks are of low intensity. (Scheme 17).

The ion at m/e 173 may decompose by the loss of C_2H_2 and S, or by the loss of two molecules of C_2H_2. A metastable peak at m/e 125 which corresponds to the transition m/e 173 → m/e 147 suggests that both of these fragmentations could be two stage processes initiated by the elimination of C_2H_2 (Scheme 17a). The ion at m/e 173 may eliminate CS to give the ion at m/e 129 (4%) which subsequently decomposes to the ion at m/e 127 (Scheme 17b), or it may fragment by two successive losses of H$^{\bullet}$ to yield the benzyne thiopyrylium ion at m/e 171 (3%) (Scheme 17). Fragmentation of the base-peak ion to the ion at m/e 139 (3%) is also observed, but there is no evidence to indicate the process by which the elimination of H_2S occurs. A possible route would be the initial expulsion of HS$^{\bullet}$ utilising the o-hydrogen of the phenyl group, followed by the elimination of H$^{\bullet}$ (Scheme 17c).

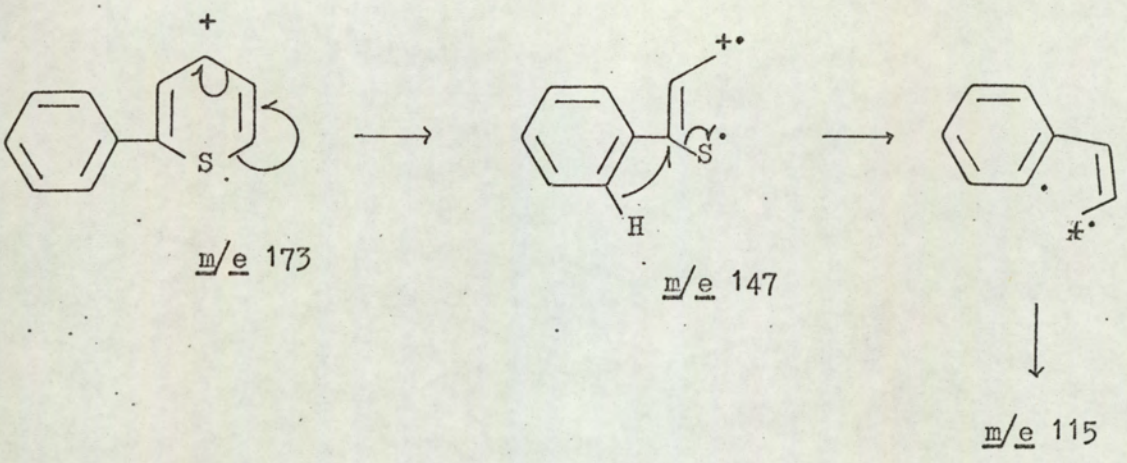
The presence of a p-chloro-, bromo-, or methyl-substituent in the benzene ring has little influence on the fragmentation pattern and the 2-arylthiopyrylium ion forms the base peak in every case. However, no fragmentation of this ion, initiated by the loss of CS, was observed, and the decomposition to the benzyne ion at m/e 171, initiated by the loss of the p-substituent and subsequent elimination of H$^{\bullet}$ became the most favoured degradation pathway, especially in the case of the p-halogeno-compounds.

Replacement of the morpholino-group by N,N-dimethylamino, increases the tendency of the molecular ion to undergo cleavage of the bond α to the thiophen ring, giving the ion $CH_2{=}\overset{+}{N}Me_2$ at m/e 58. However, cleavage of the bond β to the thiophen ring still dominates the spectra of the series of related N,N-dimethyl-5-arylthien-2-ylmethylamines (112, $NR_2 = NMe_2$) due to the high stability of the arylthiopyrylium ion which forms the base peak in every case. This ion shows all of the subsequent fragmentation pathways previously discussed for the morpholino-derivatives.

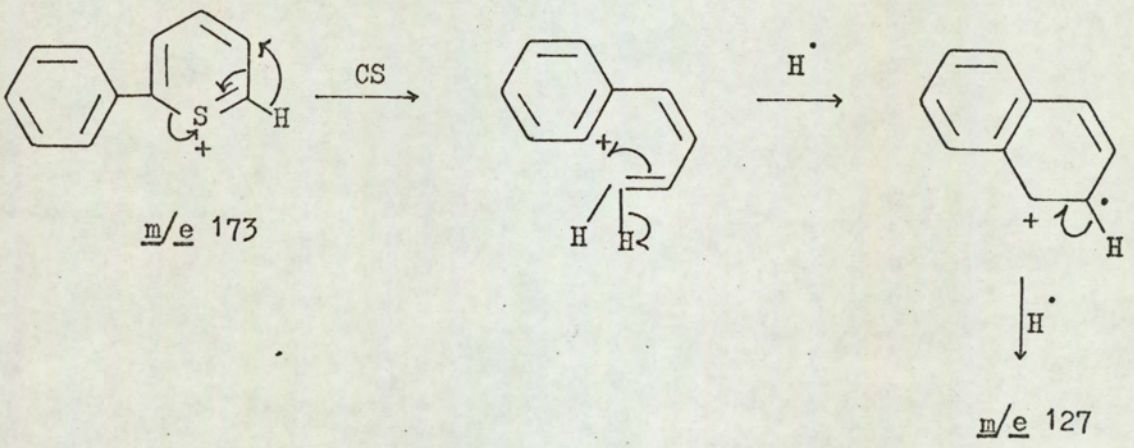
Scheme 17.


m/e 259
m* 115.5
m/e 100
m/e 173
S + C2H2
m/e 115
CS m* 96.4
C4H4
m/e 121
H• m* 171
m/e 129
m/e 172
2H•
H• m* 170.5
m/e 127
m/e 171

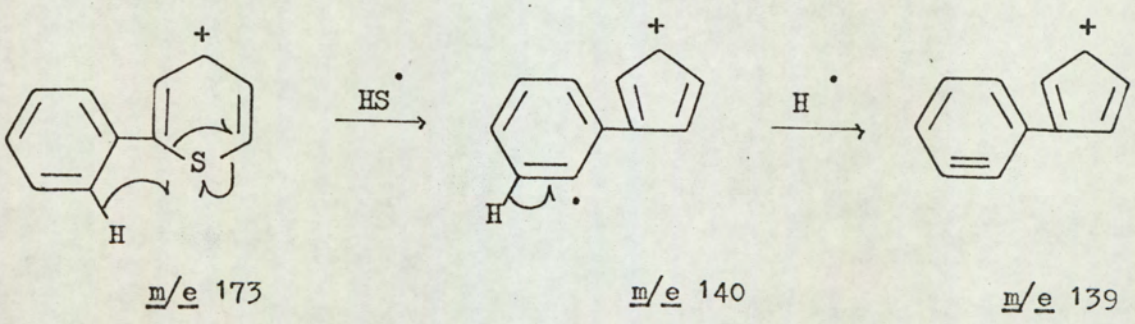
Scheme 17a.



Scheme 17b.



Scheme 17c.



2-Aminomethyl-5-arylthiophens (112, $NR_2 = NH_2$).

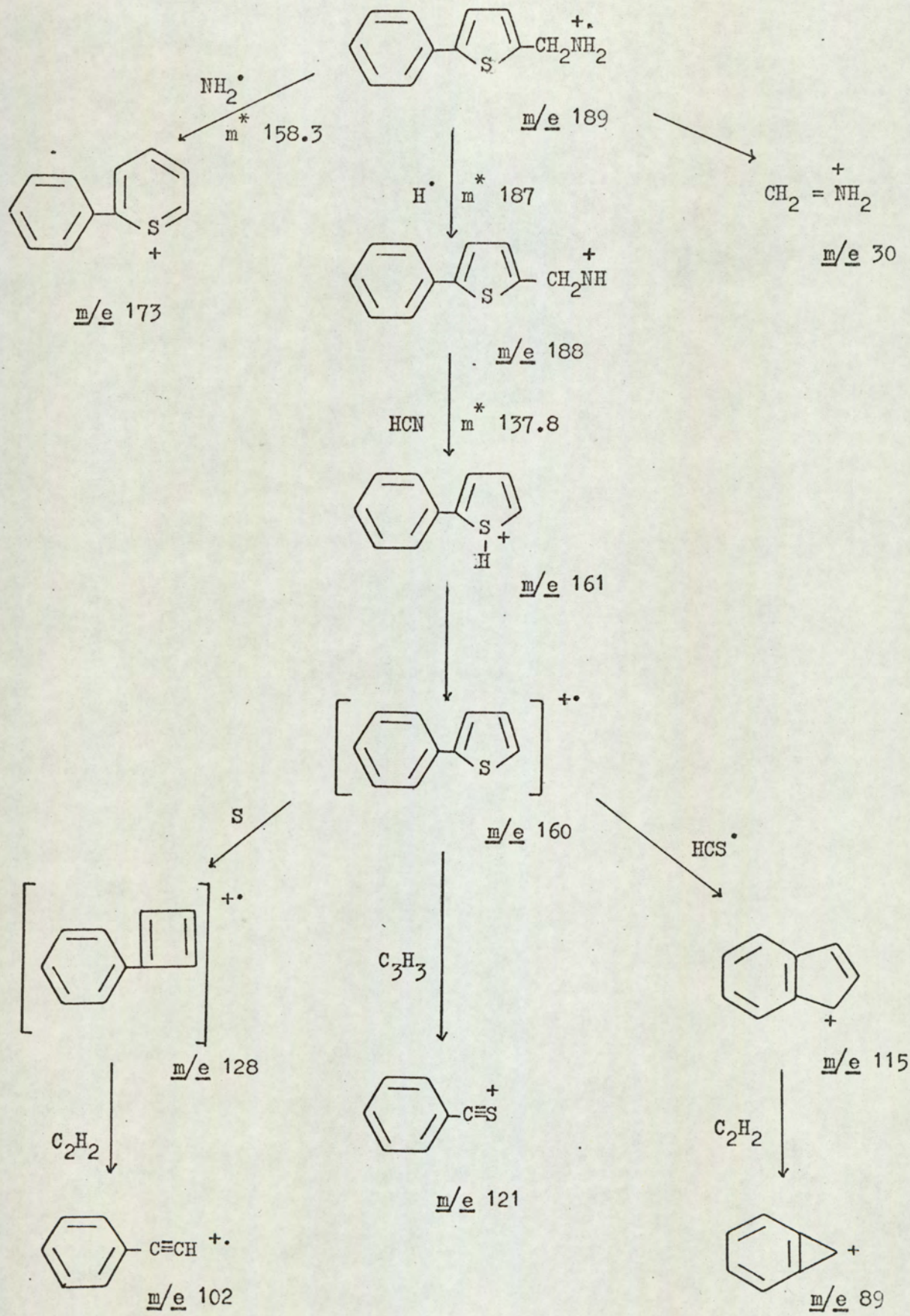
2-Aminomethyl-5-phenylthiophen (112, X = H, $NR_2 = NH_2$) is considerably more stable than the related tertiary amines to electron impact and the prominent molecular ion (80%) fragments by initial cleavage of the bond α or β to the thiophen ring to yield the ions at m/e 30 (25%) and m/e 173 (58%) respectively. The tendency for α-cleavage to occur is greater than that observed for the tertiary amines, but the most striking difference is the occurrence of a third decomposition pathway, initiated by the loss of H·, to yield a prominent $(M-1)^+$ ion at m/e 188 (53%) (Scheme 18). A similar loss of H· from the molecular ion of benzylamine also occurs.[176] The stable $(M-1)^+$ ion possibly exists as an aminothiopyrylium species, and fragments by the elimination of HCN, a process which requires rearrangement of some of the hydrogen atoms, and the ion at m/e 161 (6%) may exist as an S-protonated 2-phenylthiophen. Further decomposition is initiated by the loss of HS· or H·, and in the latter case, the resulting ion at m/e 160 subsequently shows the main fragmentation pathways described for 2-phenylthiophen itself.[171]

p-Substitution of the phenyl group by chlorine or methyl has little influence on the basic fragmentation pattern, but the S-protonated 2-arylthiophen cation now decomposes to the ion at m/e 160 by elimination of the p-substituent.

5-Arylthien-2-ylamides (111)

N-(5-Phenylthen-2-oyl)morpholine (111, X = H, NR_2 = morpholino) is more stable towards electron impact than the related methylamine, and fragmentation of the prominent molecular ion (27%) to the $(M-1)^+$ ion (1%) is substantiated by the presence of an appropriate metastable ion peak. Peaks are also present at m/e 240 (4%) and m/e 245 (1%) corresponding to

Scheme 18.

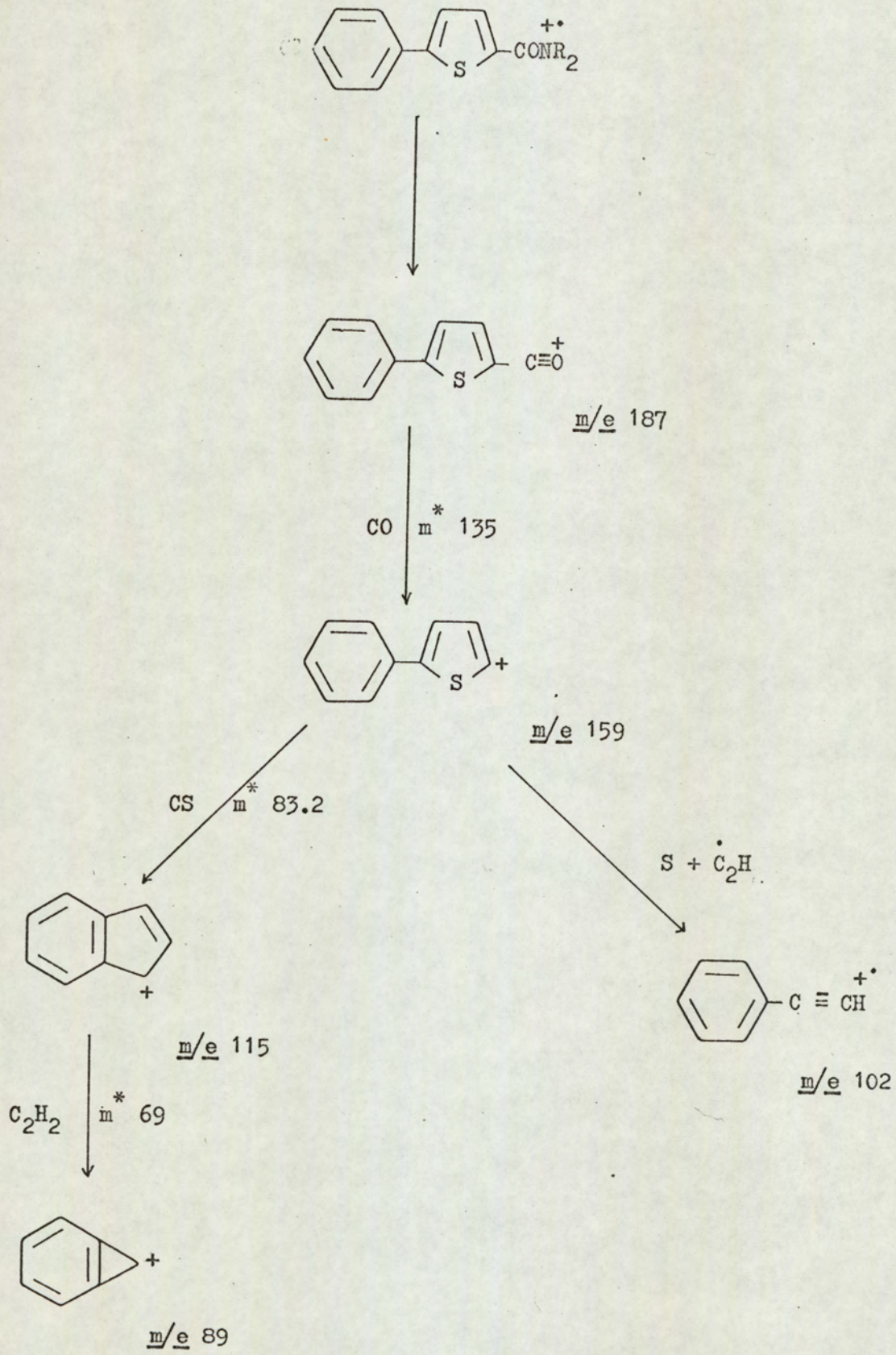

NH2•
m* 158.3
m/e 173
m/e 189
H•
m* 187
CH2 = NH2
m/e 30
m/e 188
HCN
m* 137.8
m/e 161
m/e 160
S
HCS•
C3H3
m/e 128
m/e 115
C2H2
C2H2
m/e 121
m/e 102
m/e 89

the elimination of HS and CO respectively from the molecular ion. The presence of skeletal rearrangement ions which originate by the loss of CO has been observed in the mass spectra of methyl- and phenyl-thien-2-yl ketones, and it is suggested that their formation involves the migration of the carbonyl substituent to the electron-deficient sulphur atom.[171] As anticipated, the major fragmentation of the molecular ion is initiated by cleavage of the bond β to the thiophen ring to yield the resonance-stabilised ion at m/e 187 (76%), which subsequently decomposes to the phenylthienyl cation at m/e 159 (2%) with the elimination of CO (Scheme 19). The loss of CS from this ion at m/e 159 gives an indene ion at m/e 115 which forms the base peak of the spectrum; fragmentation to the phenylacetylene ion at m/e 102 also occurs, but there is no evidence to indicate the mechanism of this process.

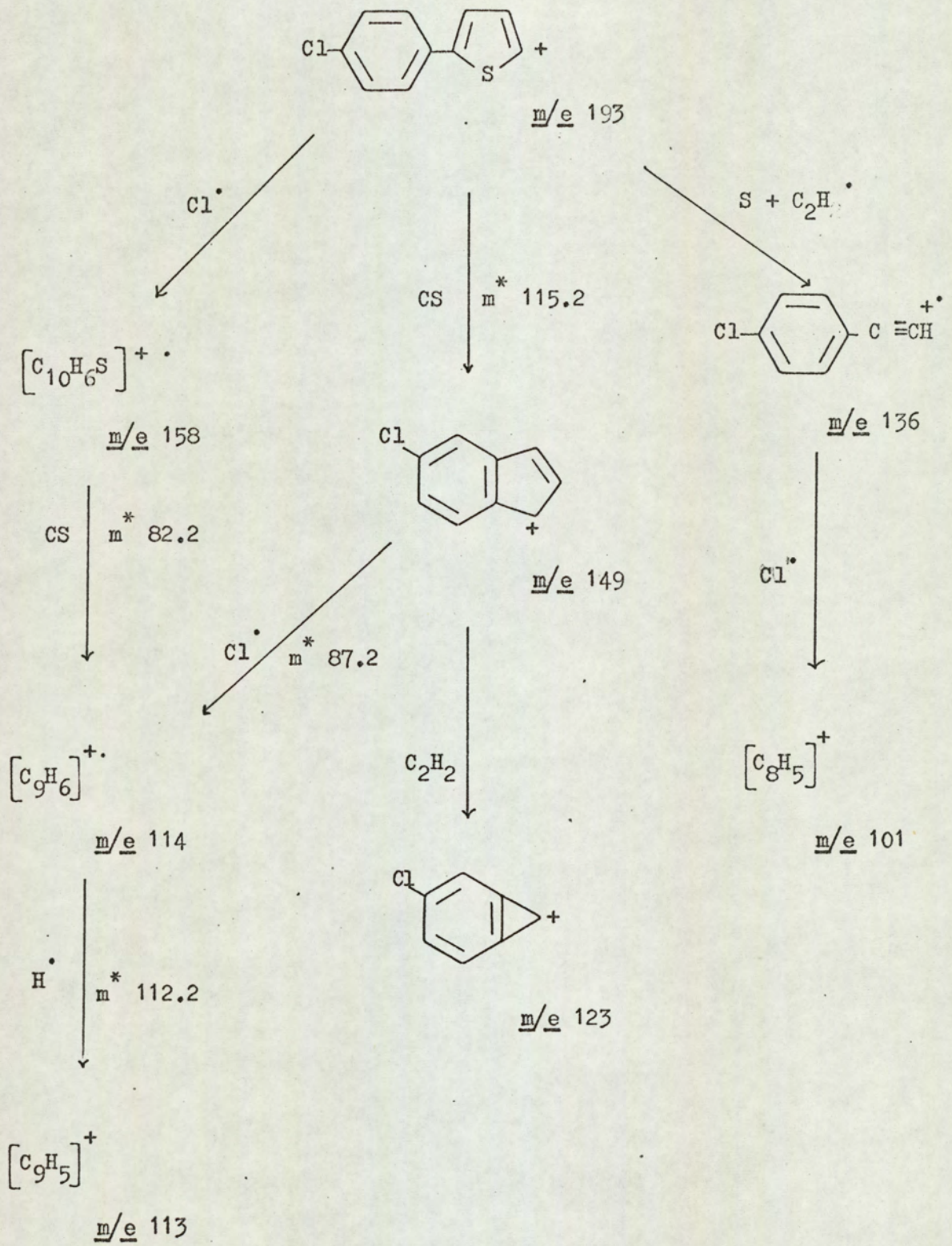
Replacement of the morpholino group by the dimethylamino group does not influence the basic fragmentation pattern, but the rearrangement ions due to the loss of HS or CO from the molecular ion are not observed in the spectrum of N,N-dimethyl-5-phenylthien-2-ylamide (111, X = H, NR_2 = NMe_2).

The primary fragmentation of the molecular ion to the arylthienyl cation remains the same for the corresponding 5-p-chlorophenyl-, and 5-p-tolyl-thien-2-ylamides (111, X = Cl, Me, NR_2 = morpholino, NMe_2). An alternative fragmentation by the loss of $Cl^{\bullet}$ is observed for the p-chlorophenylthienyl cation at m/e 193, for the chloroindene ion at m/e 149, and for the p-chlorophenylacetylene ion at m/e 136 (Scheme 20). For the p-tolylthienyl ion at m/e 173, similar fragmentations initiated by the loss of CS or $Me^{\bullet}$ are observed but the loss of $Me^{\bullet}$ is less favourable than the corresponding loss of $Cl^{\bullet}$. Degradation to an acetylenic derivative occurs in a slightly different manner, however and involves the loss of S and C_2H_2 (Scheme 21). It is possible that the ion at m/e 173 undergoes hydrogen rearrangement, involving the aryl methyl group, to yield the

Scheme 19.


CONR2
m/e 187
CO m* 135
m/e 159
CS m* 83.2
S + C2H
m/e 115
m/e 102
C2H2 m* 69
m/e 89

Scheme 20.


Cl
S
+
m/e 193
Cl•
CS
m* 115.2
S + C2H•
Cl
C ≡CH
+•
[C10H6S]+•
m/e 158
m/e 136
Cl
+
m/e 149
CS
m* 82.2
Cl•
Cl•
m* 87.2
Cl•
[C9H6]+•
m/e 114
C2H2
[C8H5]+
m/e 101
Cl
+
m/e 123
H•
m* 112.2
[C9H5]+
m/e 113

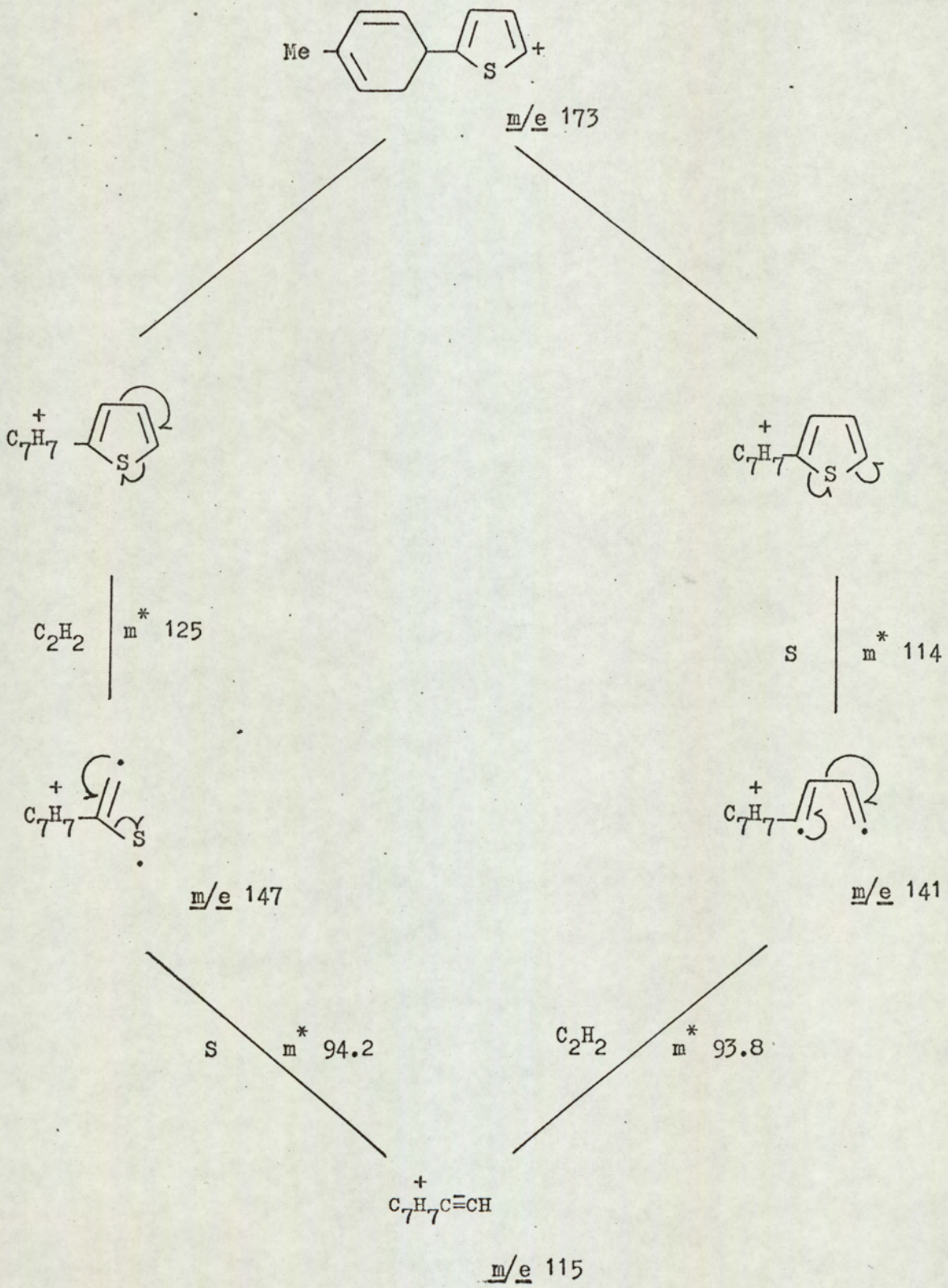
resonance-stabilised thien-2-yltropylium ion which subsequently decomposes to the acetylenic ion at m/e 115. Both of the possible fragmentation pathways, initiated by the loss of S or by the loss of C_2H_2, are observed.

In contrast to the situation observed for the amines, the mass spectra of the primary 5-arylthien-2-ylamides (111, X = H, Cl, Me, $NR_2 = NH_2$) closely resemble those of the corresponding tertiary amides. The primary amides are however more stable to electron impact than the tertiary derivatives, and the molecular ion of 5-p-tolylthien-2-ylamide (111, X = Me, $NR_2 = NH_2$) forms the base peak of its spectrum. The absence of the $(M-1)^+$ ion peaks suggests that the initial loss of H$^\bullet$ from the molecular ions of the tertiary amides is from one of the α carbon atoms of the N-substituent.

5-Arylthiophen-2-carboxylic acid hydrazides.

The mass spectra of the hydrazides are very similar to those of the corresponding primary amides, but the hydrazides are less stable to electron impact as indicated by the lower intensity of the molecular ion peaks. The molecular ion initially decomposes with elimination of an $N_2H_3^\bullet$ radical to yield the resonance-stabilised 5-arylthien-2-oyl cation which forms the base peak of the spectrum. Subsequent loss of CO gives the 5-arylthienyl cation which fragments in the manner previously described for the amides.

Scheme 21.


Me
S
+
m/e 173
$C_7H_7^+$
S
C_2H_2
m* 125
$C_7H_7^+$
S
S
m* 114
$C_7H_7^+$
m/e 147
$C_7H_7^+$
m/e 141
S
m* 94.2
C_2H_2
m* 93.8
$C_7H_7C{\equiv}CH^+$
m/e 115

EXPERIMENTAL

EXPERIMENTAL

Melting points were determined with a Gallenkamp hot stage apparatus, and are uncorrected.

Infrared (i.r.) spectra were recorded by a Unicam SP 200 spectrophotometer, and are polystyrene calibrated.

Nuclear magnetic resonance (n.m.r.) spectra were measured with a Varian A 60A spectrometer operating at 60 MHz., using tetramethylsilane as internal standard. Abbreviations used are, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, J = coupling constant in Hz.

Mass spectra were determined on an AEI MS9 spectrometer operating at 50 μa. and 70 EV. M^+ signifies the m/e value of the molecular ion peak.

Microanalyses were performed by Messrs. Reckitt and Sons, Hull, and by Dr. F. B. Strauss, Oxford.

Solvents.

Benzene, ether, toluene, and xylene were dried over sodium wire. Carbon tetrachloride and chloroform were dried over calcium chloride and filtered. Dimethylformamide was dried over a molecular sieve and distilled. Dimethyl sulphoxide was dried over calcium hydride and distilled. Ethanol was dried by treatment with magnesium, by the method of Lund and Bjerrum. Tetrahydrofuran was dried over sodium wire, and distilled from lithium aluminium hydride.

Unless otherwise stated, petrol denotes light petroleum, b.p. 60-80°.

THIOUREAS AND S-METHYLISOTHIOURONIUM IODIDES.

N,N'-Dimethylthiourea.

Methyl isothiocyanate (42 g., 0.58 mole) was added over a period of 1 hr. to a stirred solution of 25% aqueous methylamine (120 ml., 0.1 mole). The excess of methylamine was removed by warming the solution on a water-bath for 30 min., and the solution was evaporated down to a volume of 50 ml. On cooling, N,N'-dimethylthiourea (44 g., 74.3%) was deposited as colourless prisms, m.p. 58.5-60° (benzene-petrol) (lit.[144] 60-61°).

N,N,N'-Trimethylthiourea.

The procedure used for N,N'-dimethylthiourea was followed using a solution of 25% aqueous dimethylamine (200 ml., 0.1 mole) to obtain N,N,N'-trimethylthiourea (57 g., 84%) as colourless prisms, m.p. 87-88° (benzene-petrol) (lit.[145] 87-88°).

N,N-Dimethylthiourea.

A solution of dimethylamine (27 g., 0.6 mole) in dry benzene (100 ml.) was slowly added to a stirred solution of silicon tetraisothiocyanate[148] (19.6 g., 0.1 mole) in dry benzene (150 ml.) contained in a 1l. flask. When the exothermic reaction had subsided, the mixture was refluxed for 30 min. The benzene was evaporated, isopropyl alcohol (180 ml.) in water (20 ml.) was added to the residue and the resulting mixture was refluxed for 30 min. It was filtered hot, the gelatinous silica was washed with acetone (2 x 75 ml.) and the combined filtrate was evaporated to yield N,N-dimethylthiourea (20.7 g., 50%) as colourless prisms, m.p. 163-164° (benzene-petrol) (lit.[147] 164°)

S-Methylisothiouronium iodides.

Methyl iodide (14 ml., 0.22 mole) was added dropwise with shaking to a solution of the thiourea (0.2 mole) in dry ethanol (100 ml.), the mixture was warmed to 60° and maintained at that temperature for 3 hr. The ethanol was evaporated to yield the S-methylisothiouronium iodide.

In this way the following compounds were prepared.

S-Methyl-N-methylisothiouronium iodide (43.7 g., 94.2%), colourless prisms, m.p. 134-135° (dry ethanol-ether) (lit.[177] 135°).

S-Methyl-N-phenylisothiouronium iodide (57 g., 97%), colourless prisms, m.p. 146-147° (dry ethanol-ether) (lit.[178] 146-147°).

S-Methyl-N-allylisothiouronium iodide (48.3 g., 94%), colourless prisms, m.p. 68-69.5° (dry ethanol-ether) (lit.[178] 68.5 - 69.5°).

S-Methyl-N,N-dimethylisothiouronium iodide (47.7 g., 97%), colourless prisms, m.p. 100.5-101.5° (ethanol) (lit.[140] 100.5-102°) $\nu_{max.}$ (KCl disc) 3330 and 3150 (N-H), and 1635 (C=N) $cm.^{-1}$.

S-Methyl-N,N'-dimethylisothiouronium iodide (46.2 g., 96%) was obtained as a crystalline precipitate. The mixture was warmed at 60° for 40 min. only, cooled, and the crystals were collected, washed with ethanol and air-dried. No further purification was carried out. $\nu_{max.}$ (KCl disc) 3260 and 3180 (N-H), and 1610 (C=N) $cm.^{-1}$.

S-Methyl-N,N,N'-trimethylisothiouronium iodide (42.4 g., 81.6%) was obtained as a reddish oil which solidified on chilling for several days. Recrystallisation from cold ethanol-ether gave colourless prisms which were collected and stored at 0°. ν_{max} (liquid film) 3460 and 3200 (N-H), and 1610 (C=N) $cm.^{-1}$.

5-HALOGENOBENZO[b]THIEN-3-YLALKYLAMINES.

5-Halogenobenzo[b]thien-3-ylmethylamines (77).

3-Bromomethyl-5-chlorobenzo[b]thiophen (75, X = Cl) (34 g., 0.13 mole) was added, with stirring, to hexamethylene tetramine (20 g., 0.14 mole) in dry chloroform (250 ml.) and the mixture was refluxed for 6 hr. It was allowed to stand overnight, the white hexamine salt (76, X = Cl) was collected and dried *in vacuo*. A mixture of this salt (9 g., 0.03 mole), absolute ethanol (40 ml.), water (10 ml.), and concentrated hydrochloric acid (15 ml.) was refluxed for 2 hr., cooled, basified with 10% aqueous sodium hydroxide solution, and extracted with ether. The ethereal extracts were dried ($MgSO_4$), and treated with dry ethereal hydrogen chloride to precipitate 5-chlorobenzo[b]thien-3-ylmethylamine hydrochloride (77, X = Cl) as colourless plates, m.p. 270-271° (aqueous ethanol) (lit.[140] 263-264°), ν_{max} (KCl disc) 3150 - 2900 (NH_3^+), and 1595 (N-H)cm.$^{-1}$.

Basification of a hot aqueous solution of the hydrochloride with 10% aqueous sodium hydroxide solution gave the free base which was extracted with ether. The dried ($MgSO_4$) ethereal extracts were evaporated and the residue distilled to yield 5-chlorobenzo[b]thien-3-ylmethylamine (81%), as a colourless oil, b.p. 120-124°/0.1 mm.

Similarly prepared was 5-bromobenzo[b]thien-3-ylmethylamine hydrochloride (77, X = Br) as colourless plates, m.p. 283-284° (aqueous ethanol) (lit.[139] 274-275.5°)

5-Bromobenzo[b]thien-3-ylmethylamine (81%) was obtained from the hydrochloride as a colourless oil, b.p. 180-184°/0.1 mm., ν_{max} (KCl disc) 3450 and 1575 (N-H) cm.$^{-1}$.

3-Cyanomethyl-5-halogenobenzo[b]thiophen (78).

3-Bromomethyl-5-chlorobenzo[b]thiophen (75, X = Cl) (35 g., 0.134 mole) in the minimum amount of hot dry dimethyl sulphoxide was added dropwise to a stirred suspension of sodium cyanide (7.35 g., 0.15 mole) in dry dimethyl sulphoxide (10 ml.) at 70° over a period of 30 min. Stirring was continued for 2 hr. at 100°, the mixture was cooled to 50° and poured into cold water (600 ml.). The precipitated nitrile was collected, washed successively with water, dilute hydrochloric acid, and water, and dried *in vacuo*. The crude produce dissolved in the minimum volume of benzene was passed down a column of alumina (2.5 x 50 cm.) and eluted with benzene. The first few fractions contained small quantities of 2-cyanomethyl-5-chlorobenzo[b]thiophen, pale yellow prisms, m.p. 160-162° (benzene) (lit.[140] 160-162°) Evaporation of the solvent from the remaining fractions gave 3-cyanomethyl-5-chlorobenzo[b]thiophen (78, X = Cl) (23.7 g., 85%) as colourless plates, m.p. 133-134° (benzene) (lit.[140] 133-134°).

5-Bromo-3-cyanomethylbenzo[b]thiophen (78, X = Br) was similarly prepared (29.8 g., 87.6%) as colourless plates, m.p. 140-141° (benzene) (lit.[140] 139-140°) Small quantities of 5-bromo-2-cyanomethylbenzo[b]thiophen were similarly isolated from the crude reaction product as cream-coloured prisms, m.p. 170-171° (benzene) (lit.[140] 170-172°).

2-(5-Halogenobenzo[b]thien-3-yl)ethylamines (79).

Anhydrous aluminium trichloride (13.35 g., 0.1 mole) in dry ether (200 ml.) was slowly added to a stirred slurry of lithium aluminium hydride (4.18 g., 0.11 mole) in dry ether (100 ml.) under nitrogen. After 5 min., 5-chloro-3-cyanomethylbenzo[b]thiophen (20.75 g., 0.1 mole) in the minimum volume of dry benzene was added and the stirred mixture was

refluxed for 22 hr. The excess of reducing agent was destroyed by the addition of water, the mixture was basified with 10% aqueous sodium hydroxide solution, the organic layer was separated, and the aqueous layer was thoroughly extracted with ether. Treatment of the dried ($MgSO_4$) combined extracts with ethereal hydrogen chloride gave 2-(5-chlorobenzo[b]thien-3-yl)ethylamine (79, X = Cl) (20.25 g., 95.7%) as colourless plates, m.p. 245-246° (aqueous ethanol) (lit.[140] 245-246°).

The free base was obtained from the hydrochloride in the manner previously described as a colourless oil, (94%), b.p. 118-122°/0.07 mm.

2-(5-Bromobenzo[b]thien-3-yl)ethylamine hydrochloride (79, X = Br) was similarly prepared (24.7 g., 96.4%) as colourless plates, m.p. 250-251° (aqueous ethanol) (lit.[140] 249-250°)

The free base was obtained as a colourless oil (81.6%), b.p. 142-147°/0.05 mm.

5-HALOGENOBENZO[b]THIEN-3-YLALKYLGUANIDINES AND BIGUANIDES.

N-Substituted guanidine hydriodides (82 and 83).

The appropriate S-methylisothiouronium iodide (0.02 mole) was added to the appropriate freshly distilled amine (0.02 mole) in dry ethanol (100 ml.) and the resulting solution was refluxed for 6 hr., or until the smell of thiol had disappeared. The methylthiol produced was continuously removed by a slow stream of dry nitrogen, which then passed through two traps containing aqueous solutions of lead acetate and mercuric chloride respectively. The reaction mixture was cooled, filtered*, the filtrate was evaporated, and the residual oil was chilled to 0°, or triturated with dry ether to yield the solid N-substituted guanidine hydriodide, which was recrystallised from dry ethanol-ether.

N-Substituted guanidine hydrochlorides (84 and 85).

Method A.

The hydriodide in the minimum volume of hot water was basified with 10% aqueous sodium hydroxide solution, the mixture was cooled, and the free base was collected, washed with cold water, and air dried. It was dissolved in the minimum volume of dry ethanol, treated with ethereal hydrogen chloride until the mixture was acidic, and allowed to stand for 3 hr. Evaporation of the solvent yielded the required hydrochloride.

Method B.

A mixture of 5 g. of Amberlite IRA 401 resin (Cl^-) per 1 g. of hydriodidein dry ethanol (100 ml.) was stirred for 24 hr. at room temperature. The resin was removed by filtration, washed with warm, dry ethanol, and the combined filtrates were evaporated to give the required hydrochloride which was recrystallised from dry ethanol-ether, unless otherwise stated.

In this way the following compounds were prepared.

S-Methyl-N-methylisothiouronium iodide and 5-chlorobenzo[b]thien-3-ylmethylamine gave 1-(5-chlorobenzo[b]thien-3-ylmethyl)-3-methylguanidine hydriodide (82, X = Cl, R^3 = Me, R^1 = R^2 = H) (86.5%) as pale pink prisms, m.p. 168–169° (Found: C, 34.7; H, 3.4; N, 10.9. $C_{11}H_{13}ClIN_3S$ requires C, 34.6; H, 3.4; N, 11.0%), $\nu_{max.}$ (Nujol) 3200 (N-H), and 1625 (C=N) $cm.^{-1}$.

This was converted by Method A into the hydrochloride (84, X = Cl, R^3 = Me, R^1 = R^2 = H) (93.1%), colourless prisms, m.p. 200 - 201° (Found: C, 45.6; H, 4.5; N, 14.5; M^+, 253. $C_{11}H_{13}Cl_2N_3S$ requires C, 45.5; H, 4.5; N, 14.5%; M^+ [free base], 253), $\nu_{max.}$ (Nujol) 3100 (N-H) and 1640 (C=N) $cm.^{-1}$.

S-Methyl-N-phenylisothiouronium iodide and 5-chlorobenzo[b]thien-3-ylmethylamine gave 1-(5-chlorobenzo[b]thien-3-ylmethyl)-3-phenylguanidine hydriodide (82, X = Cl, R^3 = Ph, R^1 = R^2 = H) (94.7%), as colourless prisms, m.p. 150.5-151.5° (Found: C, 43.3; H, 4.3; N, 9.2. $C_{16}H_{15}ClIN_3S$ requires C, 43.3; H, 4.3; N, 9.5%).

This was converted by Method A into the hydrochloride (84, X = Cl, R^3 = Ph, R^1 = R^2 = H) (95%), colourless prisms, m.p. 165-166° (Found: C, 54.6; H, 4.3; N, 11.8. $C_{16}H_{15}Cl_2N_3S$ requires C, 54.5; H, 4.3; N, 11.9%).

S-Methyl-N-allylisothiouronium iodide and 5-chlorobenzo[b]thien-3-ylmethylamine gave 1-(5-chlorobenzo[b]thien-3-ylmethyl)-3-allylguanidine hydriodide (82, X = Cl, R^3 = allyl, R^1 = R^2 = H) (87.7%) as colourless prisms, m.p. 122-123° (Found: C, 38.7; H, 3.7; N, 10.2. $C_{13}H_{15}ClIN_3S$ requires C, 38.3; H, 3.7; N, 10.3%), ν_{max} (KCl disc) 3300 and 3180 (N-H), 1645 and 1625 (C=N and C=C) $cm.^{-1}$.

This was converted by Method B into the hydrochloride (84, X = Cl, R^3 = allyl, R^1 = R^2 = H) (94%), colourless prisms, m.p. 135-136° (Found: C, 49.2; H, 4.7; N, 13.3. $C_{13}H_{15}Cl_2N_3S$ requires C, 49.3; H, 4.8; N, 13.3%), $\nu_{max.}$ (KCl disc) 3370 and 3200 (N-H), 1660 and 1640 (C=N and C=C) $cm.^{-1}$.

S-Methyl-N,N'-dimethylisothiouronium iodide and 5-chlorobenzo[b]thien-3-ylmethylamine gave 1-(5-chlorobenzo[b]thien-3-ylmethyl)-2,3-dimethylguanidine hydriodide (82, X = Cl, R^1 = R^3 = Me, R^2 = H) (71%) as pale brown prisms, m.p. 170-171° (Found: C, 36.48; H, 3.7; N, 10.35. $C_{12}H_{15}ClIN_3S$ requires C, 36.42; H, 3.8; N, 10.62%), $\nu_{max.}$ (KCl disc) 3300 (N-H) and 1630 (C=N) $cm.^{-1}$.

This was converted by Method A into the hydrochloride (84, X = Cl, R^1 = R^3 = Me, R^2 = H) (95.5%), colourless prisms, m.p. 180-181° (Found: C, 46.9; H, 5.0; N, 13.9; M^+, 267. $C_{12}H_{15}Cl_2N_3S$ requires

C, 47.3; H, 4.97; N, 13.8%; $\underline{M}^+$ [free base], 267), $\nu_{max.}$ (KCl disc) 3300 and 3200 (N-H), and 1620 (C=N) $cm.^{-1}$.

S-Methyl-N,N-dimethylisothiouronium iodide and 5-chlorobenzo[b]thien-3-ylmethylamine gave 1-(5-chlorobenzo[b]thien-3-ylmethyl)-3,3-dimethylguanidine hydriodide (82, X = Cl, $R^2 = R^3$ = Me, R^1 = H) (69.4%) as colourless prisms, m.p. 214-215° (Found: C, 36.3; H, 3.8; N, 10.6. $C_{12}H_{15}ClIN_3S$ requires C, 36.4; H, 3.8; N, 10.62%), $\nu_{max.}$ (KCl disc) 3350 and 3200 (N-H), and 1635 (C=N) $cm.^{-1}$.

This was converted by Method A into the hydrochloride (84, X = Cl, $R^2 = R^3$ = Me, R^1 = H) (68%), colourless prisms, m.p. 238-239° (Found: C, 47.3; H, 5.0; N, 13.8; $\underline{M}^+$, 267. $C_{12}H_{15}Cl_2N_3S$ requires C, 47.3; H, 5.0; N, 13.8; $\underline{M}^+$ [free base], 267) $\nu_{max.}$ (Nujol) 3050 (N-H) and 1645 (C=N) $cm.^{-1}$.

S-Methyl-N,N,N'-trimethylisothiouronium iodide and 5-chlorobenzo[b]thien-3-ylmethylamine gave 1-(5-chlorobenzo[b]thien-3-ylmethyl)-2,3,3-trimethylguanidine hydriodide (82, X = Cl, $R^1 = R^2 = R^3$ = Me) (21%) as pale brown prisms, m.p. 112-113° (Found: C, 38.0; H, 4.17; N, 9.8. $C_{13}H_{17}ClIN_3S$ requires C, 38.1; H, 4.15; N, 10.2%), $\nu_{max.}$ (KCl disc) 3350 (N-H) and 1620 (C=N) $cm.^{-1}$.

S-Methylisothioronium iodide and 5-bromobenzo[b]thien-3-ylmethylamine gave 1-(5-bromobenzo[b]thien-3-ylmethyl) guanidine hydriodide (82, X = Br, $R^1 = R^2 = R^3$ = H) (95.8%) as colourless prisms, m.p. 207-208° (Found: C, 29.34; H, 2.74; N, 9.94. $C_{10}H_{11}BrIN_3S$ requires C, 29.13; H, 2.67; N, 10.2%), $\nu_{max.}$ (Nujol) 3300 and 3150 (N-H), 1655 and 1635 (C=N) $cm.^{-1}$.

This was converted by Method A into the hydrochloride (84, X = Br, $R^1 = R^2 = R^3 = H$) (91.7%), colourless prisms, m.p. 183-184° (Found: C, 49,8; H, 4.14; N, 10.0. $C_{10}H_{11}BrClN_3S$ requires C, 49.7; H, 4.14; N, 10.23%) $\nu_{max.}$(Nujol) 3350 and 3175 (N-H), and 1660 (C=N) $cm.^{-1}$.

S-Methyl-N-methylisothiouronium iodide and 5-bromobenzo[b]thien-3-ylmethylamine gave 1-(5-bromobenzo[b]thien-3-ylmethyl)-3-methylguanidine hydriode (82, X = Br, R^3 = Me, $R^1 = R^2 = H$) (93%) as pale yellow prisms, m.p. 171-172° (Found: C, 31.2; H, 3.0; N, 9.6. $C_{11}H_{13}BrIN_3S$ requires C, 31.0, H, 3.0; N, 9.87%), $\nu_{max.}$(KCl disc) 3280 (N-H) and 1640 (C=N) $cm.^{-1}$.

This was converted by Method A into the hydrochloride (84, X = Br, R^3 = Me, $R^1 = R^2 = H$) (90%), colourless prisms, m.p. 221-222° (Found: C, 39.6; H, 3.94; N, 12.3. $C_{11}H_{13}BrClN_3S$ requires C, 39.5; H, 3.89; N, 12.56%), $\nu_{max.}$(KCl disc) 3200 (N-H) and 1640 (C=N) $cm.^{-1}$.

S-Methyl-N-phenylisothiouronium iodide and 5-bromobenzo[b]thien-3-ylmethylamine gave 1-(5-bromobenzo[b]thien-3-ylmethyl)-3-phenylguanidine hydriode (82, X = Br, R^3 = Ph, $R^1 = R^2 = H$) (89%) as colourless prisms, m.p. 188-189° (Found: C, 39.25; H, 3.0; N, 8.7. $C_{16}H_{15}BrIN_3S$ requires C, 39.34; H, 3.1; N, 8.6%), $\nu_{max.}$(KCl disc) 3200 and 3000 (N-H), 1645 and 1630 (C=N) $cm.^{-1}$.

This was converted by Method B into the hydrochloride (84, X = Br, R^3 = Ph, $R^1 = R^2 = H$) (85.9%), colourless prisms, m.p. 151.5-152.5° (Found: C, 48.2; H, 3.7; N, 10.6. $C_{16}H_{15}BrClN_3S$ requires C, 48.4; H, 3.8; N, 10.6%), $\nu_{max.}$(KCl disc) 3150 (N-H) and 1660 (C=N) $cm.^{-1}$.

S-Methyl-N-allylisothiouronium iodide and 5-bromobenzo[b]thien-3-ylmethylamine gave 1-(5-bromobenzo[b]thien-3-yl)-3-allylguanidine hydriode (82, X = Br, R^3 = allyl, $R^1 = R^2 = H$) (92.5%) as colourless

prisms, m.p. 151.5-152.5° (Found: C, 34.34; H, 3.4; N, 9.2. $C_{13}H_{15}BrIN_3S$ requires C, 34.51; H, 3.3; N, 9.3%), $\nu_{max.}$ (KCl disc) 3350 (N-H), 1625, and 1580 (C=N and C=C) $cm.^{-1}$.

This was converted by Method B into the hydrochloride (84, X = Br, R^3 = allyl, $R^1 = R^2$ = H) (82.7%), colourless prisms, m.p. 136-137° (Found: C, 43.58; H, 4.25; N, 11.55. $C_{13}H_{15}BrClN_3S$ requires C, 43.27; H, 4.16; N, 11.65%), $\nu_{max.}$ (Nujol) 3370 (N-H), 1650 and 1630 (C=N) $cm.^{-1}$.

S-Methyl-N,N'-dimethylisothiouronium iodide and 5-bromobenzo[b]thien-3-ylmethylamine gave 1-(5-bromobenzo[b]thien-3-ylmethyl)-2,3-dimethylguanidine hydriode (82, X = Br, $R^1 = R^3$ = Me, R^2 = H) (77%) as pale yellow prisms, m.p. 185-186° (Found: C, 32.5; H, 3.6; N, 9.6. $C_{12}H_{15}BrIN_3S$ requires C, 32.7; H, 3.4; N, 9.45%).

This was converted by Method B into the hydrochloride (84, X = Br, $R^1 = R^3$ = Me, R^2 = H), colourless prisms, m.p. 196-198°, $\nu_{max.}$ (KCl disc) 3200 (N-H) and 1630 (C=N) $cm.^{-1}$, for which correct analysis figures could not be obtained.

S-Methyl-N,N-dimethylisothiouronium iodide and 5-bromobenzo[b]thien-3-ylmethylamine gave 1-(5-bromobenzo[b]thien-3-ylmethyl)-3,3-dimethylguanidine hydriodide (82, X = Br, $R^2 = R^3$ = Me, R^1 = H) (74.9%) as pale yellow prisms, m.p. 211-212° (Found: 32.9; H, 3.5; N, 9.3. $C_{12}H_{15}BrIN_3S$ requires C, 32.73; H, 3.4; N, 9.45%), $\nu_{max.}$ (KCl disc) 3250 (N-H) and 1640 (C=N) $cm.^{-1}$.

This was converted by Method B into the hydrochloride (84, X = Br, $R^2 = R^3$ = Me, R^1 = H) (87.4%), colourless prisms, m.p. 252-253° (Found: C, 41.49% H, 4.58; N, 11.71. $C_{12}H_{15}BrClN_3S$ requires C, 41.32; H, 4.3; N, 12.05%), $\nu_{max.}$ (KCl disc) 3100 (N-H) and 1650 (C=N) $cm.^{-1}$.

S-Methyl-N-methylisothiouronium iodide and 5-chlorobenzo[b]thien-3-ylethylamine gave 1-(5-chlorobenzo[b]thien-3-ylethyl)-3-methylguanidine hydriodide (83, X = Cl, R^3 = Me, R^1 = R^2 =H) (94.1%) as colourless prisms, m.p. 123-124° (Found: C, 36.4; H, 4.0; N, 10.5. $C_{12}H_{15}ClIN_3S$ requires C, 36.4; H, 3.8; N, 10.6%), $\nu_{max.}$(KCl disc) 3350 and 3200 (N-H), and 1640 (C=N) $cm.^{-1}$.

This was converted by Method A into the hydrochloride (85, X = Cl, R^3 = Me, R^1 = R^2 = H) (89.6%), colourless prisms, m.p. 138-140° (Found: C, 47.05; H, 4.8; N, 13.6; M^+, 267. $C_{12}H_{15}Cl_2N_3S$ requires C, 47.36; H, 5.0; N, 13.8%; M^+ [free base], 267), $\nu_{max.}$ (Nujol) 3250 and 3100 (N-H), and 1635 (C=N) $cm.^{-1}$.

S-Methyl-N-phenylisothiouronium iodide and 5-chlorobenzo[b]thien-3-ylethylamine gave 1-(5-chlorobenzo[b]thien-3-ylethyl)-3-phenylguanidine hydriode (83, X = Cl, R^3 = Ph, R^1 = R^2 = H) (83.4%) as colourless prisms, m.p. 164-165° (Found: C, 44.4; H, 3.75; N, 9.2. $C_{17}H_{17}ClIN_3S$ requires C, 44.6; H, 3.72; N, 9.2%), $\nu_{max.}$(KCl disc) 3350 and 3200 (N-H), and 1640 (C=N) $cm.^{-1}$.

This was converted by Method A into the hydrochloride (85, X = Cl, R^3 = Ph, R^1 = R^2 = H) (90%), colourless prisms, m.p. 188-189° (Found: C, 55.5; H, 4.7; N, 11.5. $C_{17}H_{17}Cl_2N_3S$ requires C, 55.7; H, 4.6; N, 11.5%), $\nu_{max.}$ (KCl disc) 3400 and 3100 (N-H), 1660 and 1620 (C=N) $cm.^{-1}$.

S-Methyl-N,N'-dimethylisothiouronium iodide and 5-chlorobenzo[b]thien-3-ylethylamine gave 1-(5-chlorobenzo[b]thien-3-ylethyl)-2,3-dimethylguanidine hydriode (83, X = Cl, R^1 = R^3 = Me, R^2 = H) (77.4%) as colourless prisms, m.p. 191-192° (Found: C, 37.9, H, 4.25; N, 10.3. $C_{13}H_{17}ClIN_3S$ requires C, 38.1; H, 4.15; N,10.3%), $\nu_{max.}$ (KCl disc) 3300 (N-H) and 1635 (C=N) $cm.^{-1}$.

This was converted by Method A into the hydrochloride (85, X = Cl, $R^1 = R^3 = Me$, $R^2 = H$) (93%), colourless crystals, m.p. 230-231° (Found: C, 49.15; H, 5.4; N, 13.25; M^+, 281. $C_{13}H_{17}Cl_2N_3S$ requires C, 49.16; H, 5.35; N, 13.2%; M^+ [free base], 281), $\nu_{max.}$ (KCl disc) 3200 (N-H) and 1630 (C=N) $cm.^{-1}$.

S-Methyl-N,N-dimethylisothiouronium iodide and 5-chlorobenzo[b]thien-3-ylethylamine gave 1-(5-chlorobenzo[b]thien-3-ylethyl)-3,3-dimethylguanidine hydriode (83, X = Cl, $R^2 = R^3 = Me$, $R^1 = H$) (83.3%) as colourless prisms, m.p. 209-210° (Found: C, 38.2; H, 4.25; N, 10.0. $C_{13}H_{17}ClIN_3S$ requires C, 38.1; H, 4.15; N, 10.26%), $\nu_{max.}$ (Nujol) 3230 and 3100 (N-H) and 1635 (C=N) $cm.^{-1}$.

This was converted by Method A into the hydrochloride (85, X = Cl, $R^2 = R^3 = Me$, $R^1 = H$) (94.2%), colourless crystals, m.p. 217.5-218.5° (Found: C. 48.95; H, 5.45; N, 13.05; M^+, 281. $C_{13}H_{17}Cl_2N_3S$ requires C, 49.16; H, 5.35; N, 13.2%; M^+[free base], 281), $\nu_{max.}$ (Nujol) 3250 and 3080 (N-H), and 1625 (C=N) $cm.^{-1}$.

S-Methylisothiouronium iodide and 5-bromobenzo[b]thien-3-ylethylamine gave 1-(5-bromobenzo[b]thien-3-ylethyl)guanidine hydriode (83, X = Br, $R^1 = R^2 = R^3 = H$) (66.1%) as colourless prisms, m.p. 198-199° (Found: C, 31.11; H, 3.34; N, 9.57. $C_{11}H_{13}BrIN_3S$ requires C, 30.98; H, 3.05; N, 9.87%), $\nu_{max.}$ (Nujol) 3300 and 3100 (N-H), 1650 and 1630 (C=N) $cm.^{-1}$.

This was converted by Method B into the hydrochloride (85, X = Br, $R^1 = R^2 = R^3 = H$) (88.4%), colourless prisms, m.p. 183.5-184.5° (Found: C, 39.71; H, 3.87; N, 12.68. $C_{11}H_{13}BrClN_3S$ requires C, 39.48; H, 3.89; N, 12.56%), $\nu_{max.}$ (Nujol) 3250 and 3100 (N-H), and 1650 (C=N) $cm.^{-1}$.

S-Methyl-N-methylisothiouronium iodide and 5-bromobenzo[b]thien-3-ylethylamine gave 1-(5-bromobenzo[b]thien-3-ylethyl)-3-methylguanidine hydriode (83, X = Br, R^3 = Me, R^1 = R^2 = H) (81%) as pink prisms, m.p. 137-138° (Found: C, 32.8; H, 3.35; N, 9.6. $C_{12}H_{15}BrIN_3S$ requires C, 32.7; H, 3.4; N, 9.45%), ν_{max} (Nujol) 3200 and 3100 (N-H), and 1630 (C=N) cm.$^{-1}$.

This was converted by Method A into the hydrochloride (85, X = Br, R^3 = Me, R^1 = R^2 = H) (90%), colourless prisms, m.p. 108-110° (aqueous ethanol) (Found: C, 40.3; H, 4.15; N, 11.8. $C_{12}H_{15}BrClN_3S\frac{1}{2}H_2O$ requires C, 40.3; H, 4.4; N, 11.75%), $\nu_{max.}$(KCl disc) 3400 and 3200 (N-H), and 1640 (C=N) cm.$^{-1}$.

S-Methyl-N-phenylisothiouronium iodide and 5-bromobenzo[b]thien-3-ylethylamine gave 1-(5-bromobenzo[b]thien-3-ylethyl)-3-phenylguanidine hydriode (83, X = Br, R^3 = Ph, R^1 = R^2 = H) (93.2%) as colourless prisms, m.p. 199-200° (Found: C, 40.56; H, 3.44; N, 8.5. $C_{17}H_{17}BrIN_3S$ requires C, 40.63; H, 3.4; N, 8.4%), $\nu_{max.}$(Nujol) 3400 and 3100 (N-H), and 1630 (C=N) cm.$^{-1}$.

This was converted by Method A into the hydrochloride (85, X = Br, R^3 = Ph, R^1 = R^2 = H) (91.7%), colourless prisms, m.p. 183-184° (Found: C, 49.8; H, 4.14; N, 10.0. $C_{17}H_{17}BrClN_3S$ requires C, 49.7; H, 4.14; N, 10.2%), $\nu_{max.}$(KCl disc) 3200 (N-H) and 1640 (C=N) cm.$^{-1}$.

S-Methyl-N,N'-dimethylisothiouronium iodide and 5-bromobenzo[b]thien-3-ylethylamine gave 1-(5-bromobenzo[b]thien-3-ylethyl)-2,3-dimethylguanidine hydriode (83, X = Br, R^1 = R^3 = Me, R^2 = H) (66%) as colourless prisms, m.p. 202-203° (Found: C, 34.6; H, 3.7; N, 9.3. $C_{13}H_{17}BrIN_3S$ requires C, 34.36; H, 3.7; N, 9.3%), $\nu_{max.}$(KCl disc) 3450 and 3100 (N-H), and 1655 (C=N) cm.$^{-1}$.

This was converted by Method A into the hydrochloride (85, X = Br, $R^1 = R^3 = Me$, $R^2 = H$) (86.7%), colourless prisms, m.p. 212-213° (Found: C, 42.96; H, 4.82; N, 11.8. $C_{13}H_{17}BrClN_3S$ requires C, 43.03; H, 4.7; N, 11.58%), $\nu_{max.}$(Nujol) 3200 (N-H) and 1620 (C=N) $cm.^{-1}$.

S-Methyl-N,N-dimethylisothiouronium iodide and 5-bromobenzo[b]thien-3-ylethylamine gave 1-(5-bromobenzo[b]thien-3-ylethyl)-3,3-dimethylguanidine hydriode (83, X = Br, $R^2 = R^3 = Me$, $R^1 = H$) (79.6%) as colourless prisms, m.p. 188-189° (Found: C, 34.5; H, 3.75; N, 9.1. $C_{13}H_{17}BrIN_3S$ requires C, 34.4; H, 3.74; N, 9.25%), $\nu_{max.}$(Nujol) 3220 and 3100 (N-H), and 1630 (C=N) $cm.^{-1}$.

This was converted by Method B into the hydrochloride (85, X = Br, $R^2 = R^3 = Me$, $R^1 = H$) (93.7%), colourless prisms, m.p. 195-196° (Found: C, 42.84; H, 4.45; N, 11.29. $C_{13}H_{17}BrClN_3S$ requires C, 43.03; H, 4.69; N, 11.58%), $\nu_{max.}$(KCl disc) 3300 and 3100 (N-H), 1640 and 1625 (C=N) $cm.^{-1}$.

* On filtering the cooled reaction mixture, a small quantity of crystalline material (5-50 mg.) was obtained. This was the N,N-dimethyl derivative of the original amine hydriodide. It was converted by Method A into a hydrochloride and recrystallised from absolute ethanol.

Reactions involving 5-chlorobenzo[b]thien-3-ylmethylamine yielded colourless needles which were converted by Method A into N,N-dimethyl-5-chlorobenzo[b]thien-3-ylmethylamine hydrochloride, colourless prisms, m.p. 217-218°(lit.[138] 217-218°) (Found: M^+, 225. $C_{11}H_{13}Cl_2NS$ requires M^+ [free base], 225).

Reactions involving 5-bromobenzo[b]thien-3-ylmethylamine yielded colourless needles which were converted by Method A into N,N-dimethyl-5-bromobenzo[b]thien-3-ylmethylamine hydrochloride, colourless prisms, m.p. 226-227° (lit.[138] 225-226°).

Reactions involving 5-chlorobenzo[b]thien-3-ylethylamine yielded colourless needles which were converted by Method A into N,N-dimethyl-5-chlorobenzo[b]thien-3-ylethylamine, colourless prisms, m.p. 219-220° (lit.[140] 219-220°).

Reactions involving 5-bromobenzo[b]thien-3-ylethylamine yielded colourless needles which were converted by Method A into N,N-dimethyl-5-bromobenzo[b]thien 3-ylethylamine, colourless prisms, m.p. 222-223° (lit.[140] 221-222°).

The m.p.s. were not depressed on admixture with authentic samples.

All of these compounds showed a band in the i.r. spectrum at 2800-2760 cm.$^{-1}$ due to N-Me.

1-(5-Halogenobenzo[b]thien-3-ylalkyl)-3,3-dimethylguanidines (80).

An intimate mixture of amine hydrochloride (0.02 mole) and dimethyl cyanamide[149] (0.022 mole) was slowly heated in an oil-bath until fusion occurred, and the fusion temperature was maintained for 90 min. The cooled reaction mixture was extracted with ethanol, the extracts were filtered, and evaporated. The residual oil was triturated with dry ether to yield the solid guanidine (80) which was recrystallised from dry ethanol-ether. Details are recorded in Table I.

Table I.

Compound	Yield %	m.p.(°C)	Fusion Temp.(°C)
80, X = Cl, n = 1	84.7	238-239	160
80, X = Cl, n = 2	81.4	218-219	180
80, X = Br, n = 1	77.0	252-253	190
80, X = Br, n = 2	71.0	195-196	190

Fusion temperature measured is that of the external oil-bath.

The m.p.s. were not depressed on admixture with authentic samples.

1-(5-Chlorobenzo[b]thien-3-ylmethyl)biguanides (81).

An intimate mixture of 5-chlorobenzo[b]thien-3-ylmethylamine hydrochloride (2.34 g., 0.01 mole) and dicyandiamide (0.84 g., 0.01 mole) was heated in an oil-bath at 150-180° for 6 hr. The cooled reaction mixture was extracted with absolute ethanol, the extracts were filtered and evaporated to yield 1-(5-chlorobenzo[b]thien-3-ylmethyl)biguanide hydrochloride (81, X = Cl, R = H) (76.7%) as colourless prisms, m.p. 229-230° (dry ethanol-ether) (Found: C, 41.6; H, 3.95; N, 21.5. $C_{11}H_{13}Cl_2N_5S$ requires C, 41.7; H, 4.05; N, 21.1%), $\nu_{max.}$ (KCl disc) 1640 and 1580 (C=N) cm.$^{-1}$ (broad peaks).

An intimate mixture of 5-chlorobenzo[b]thien-3-ylmethylamine hydrochloride (2.34 g., 0.01 mole) and p-chlorophenyldicyandiamide (1.95 g., 0.01 mole) was heated in an oil-bath at 160-180° for 6 hr. The cooled reaction mixture was extracted with absolute ethanol, the extracts were filtered and evaporated to low bulk. Treatment with dry ethereal hydrogen chloride gave 1-(5-chlorobenzo[b]thien-3-ylmethyl)-5-p-chlorophenylbiguanide dihydrochloride (81, X = Cl, R = $pClC_6H_4$) (83.9%) as colourless prisms, m.p. 216-217° (dry ethanol-ether) (Found: C, 43.7; H, 3.6; N, 15.0 $C_{17}H_{17}Cl_4N_5S$ requires C, 43.9; H, 3.6; N, 15.0%), $\nu_{max.}$ (KCl disc) 1675 and 1625 (C=N) cm.$^{-1}$ (broad peaks).

5-HALOGENOBENZO[b]THIEN-3-YLACETAMIDINES.

Ethyl-5-halogenobenzo[b]thien-3-ylacetimidate hydrochlorides (86).

5-Chloro-3-cyanomethylbenzo[b]thiophen (4.15 g., 0.02 mole) and dry ethanol (1.0 g., 0.021 mole) in dry benzene (40 ml.) containing just sufficient dioxan to prevent precipitation of the nitrile at 0° was saturated at 0° with dry hydrogen chloride. Dry ether (150 ml.) was added,

the solution was chilled overnight and the crystals of the required acetimidate hydrochloride (95%) were collected, colourless prisms, m.p. 206-208° (d) (lit.[151] 206-208°).

In a similar way, ethyl-5-bromobenzo[b]thien-3-ylacetimidate hydrochloride was obtained as colourless prisms, m.p. 231-233° (d) (lit.[151] 231-233°). These compounds were sufficiently pure to be used directly in the next stage of the synthesis.

N-Methyl-5-bromobenzo[b]thien-3-ylacetamidine (87, X = Br).

Methylamine (0.39 g., 0.013 mole) in dry ethanol (50 ml.) was added dropwise over a period of 15 min. to a stirred suspension of ethyl-5-bromobenzo[b]thien-3-ylacetimidate hydrochloride (4.2 g., 0.013 mole) in dry ethanol (50 ml.) at 0°. Stirring was continued for 30 min., the solvent was evaporated, and the residual oil was triturated with dry ether to give solid N-methyl-5-bromobenzo[b]thien-3-ylacetamidine hydrochloride (64.7%), as colourless prisms, m.p. 253-254° (Found: C, 41.55; H, 4.0; N, 8.48. $C_{11}H_{12}BrClN_2S$ requires C, 41.31; H, 3.8; N, 8.76%), $\nu_{max.}$ (Nujol) 1660 and 1550 (C=N) cm.$^{-1}$.

N,N'-Dimethyl-5-halogenobenzo[b]thien-3-ylacetamidines. (89).

Ethyl-5-halogenobenzo[b]thien-3-ylacetimidate hydrochloride (4g., 0.014 mole) was added portionwise, with shaking, to methylamine (15 g., 0.5 mole) in ethanol (50 ml.) at 0°, and the resulting solution was chilled for 12 hr. Evaporation of the solvent gave N,N'-dimethyl-5-chlorobenzo[b]thien-3-ylacetamidine hydrochloride (89, X = Cl) (92.9%), colourless needles, m.p. 241-242° (absolute ethanol) (Found: C, 49.7; H, 4.8; N, 9.85. $C_{12}H_{14}Cl_2N_2S$ requires C, 49.8; H, 4.8; N, 9.7%), $\nu_{max.}$ (KCl disc) 1660 and 1540 (C=N) cm.$^{-1}$.

$\tau_{(D_2O)}$ 7.17 (6H, s, NCH_3), 6.13 (2H, s, CH_2); 2.97 (1H, q, J=8.5 and 2Hz, benzo[b]thienyl-6-H), 2.58-2.40 (3H, m, aromatic-H).

In a similar way N,N'-dimethyl-5-bromobenzo[b]thien-3-ylacetamidine hydrochloride (89, X = Br) was obtained (94%), colourless needles, m.p. 244-245° (absolute ethanol) (Found: C, 43.1; H, 3.9; N, 8.3. $C_{12}H_{14}BrClN_2S$ requires C, 43.2; H, 4.2; N, 8.4%), $\nu_{max.}$ (KCl disc) 1670 and 1555 (C=N) $cm.^{-1}$.

N,N-Dimethyl-5-halogenobenzo[b]thien-3-ylacetamidines. (88).

Ethyl-5-chlorobenzo[b]thien-3-ylacetimidate (2 g., 0.07 mole) was added portionwise, with shaking, to dimethylamine (5 g., 0.11 mole) in dry ethanol (50 ml.) at 0° and the resulting solution was chilled overnight. Evaporation of the solvent gave N,N-dimethyl-5-chlorbenzo[b]thien-3-ylacetamidine hydrochloride (88, X = Cl) (80.3%), colourless prisms, m.p. 217-218° (absolute ethanol) (Found: C, 49.75, H, 4.8; N, 10.0. $C_{12}H_{14}Cl_2N_2S$ requires C, 49.8; H, 4.8; N, 9.7%), $\nu_{max.}$ (KCl disc) 1680, 1635 and 1530 (C=N) $cm.^{-1}$.

$\tau_{(D_2O \text{ at } 40^\circ)}$ 6.99 (3H, s, NCH_3), 6.92 (3H, s, NCH_3), 6.11 (2H, s, CH_2), 2.97 (1H, q, J = 8.5 and 2Hz, benzo[b]thienyl-6-H), 2.56-2.40 (3H, m, aromatic-H).

Signals at 6.99 and 6.92 coalesce to give a single signal at τ6.94 (6H, s, $N(CH_3)_2$), in D_2O at 60°.

In a similar way N,N-dimethyl-5-bromobenzo[b]thien-3-ylacetamidine hydrochloride (88, X = Br) was obtained (86.6%), colourless prisms, m.p. 222-223° (absolute ethanol) (Found: C, 43.2; H, 4.0; N, 8.6. $C_{12}H_{14}BrClN_2S$ requires C, 43.2; H, 4.2; N, 8.4%), $\nu_{max.}$ (Nujol) 1660, 1630, and 1530 (C=N) $cm.^{-1}$.

ATTEMPTED SYNTHESIS OF 1-(6-BROMO-1-METHYL-1,2,3,4-TETRAHYDROTHIANAPHTHENO-[2,3-c]-PYRIDINE)GUANIDINE.

N-Acetyl-5-bromobenzo[b]thien-3-ylethylamine (90, X = Br).

Acetic anhydride (25 ml.) was added portionwise, with shaking, to a cooled suspension of 5-bromobenzo[b]thien-3-ylethylamine (12.5 g., 0.05 mole) in 20% aqueous sodium hydroxide (85 ml.), and the mixture was allowed to stand. The solid acetyl derivative was collected, washed with cold water, and dried in vacuo, (13.9 g., 95.5%), pale brown needles, m.p. 137-138° (benzene) (Found: C, 48.6; H, 4.0; N, 4.65. $C_{12}H_{12}BrNOS$ requires C, 48.33; H, 4.0; N, 4.6%).

6-Bromo-1-methyl-3,4-dihydrothianaphtheno-(2,3-c)-pyridine (91, X = Br).

The N-acetyl derivative (1.5 g.), phosphorus pentoxide (2.5 g.), and redistilled phosphorus oxychloride (2.5 g.) were refluxed in dry xylene (30 ml.) for 3 hr. Ice-cold water was added to the cooled reaction mixture, the organic layer was separated, and shaken with dilute hydrochloric acid. The tarry residue was boiled with water for 15 min. and hot-filtered. The combined aqueous extracts were shaken with ether, and then basified with 20% aqueous sodium hydroxide, and the liberated free base was extracted with ether. The dried ($MgSO_4$) ethereal extracts were evaporated and the residue was sublimed to give 6-bromo-1-methyl-3,4-dihydrothianaphtheno-(2,3-c) pyridine (81.2%), colourless plates, m.p. 128-129° (d) (benzene), $\nu_{max.}$ (KCl disc) 2930 (C-H) and 1610 (C=N) $cm.^{-1}$. Correct analytical figures could not be obtained.

Treatment of the free base in dry ether with dry hydrogen chloride gave the hydrochloride (98.4%), yellow-brown crystals, m.p. 299.5-300.5° (Found: C, 45.3; H, 3.5; N, 4.4. $C_{12}H_{11}BrClNS$ requires C, 45.5; H, 3.5; N, 4.4%).

6-Bromo-1-methyl-1,2,3,4-tetrahydrothianaphtheno-(2,3-c) pyridine (92, X = Br).

Sodium borohydride (1.2 g.) was added portionwise, with shaking, to the dihydro-derivative (0.7 g., 0.002 mole) in dry methanol (10 ml.) and the resulting clear solution was allowed to stand at 0° for 12 hr. It was refluxed for 1 hr. and the excess of sodium borohydride was destroyed with aqueous acetic acid. The methanol was evaporated, the solution was basified with 20% aqueous sodium hydroxide, and extracted with ether. The dried ($MgSO_4$) ethereal extracts were treated with ethereal hydrogen chloride to precipitate 6-bromo-1-methyl-1,2,3,4-tetrahydrothianaphtheno-(2,3-c)-pyridine hydrochloride (87.2%), colourless prisms, m.p. 305-306° (d) (Found: C, 45.0, H, 4.1; N, 4.4. $C_{12}H_{13}BrClNS$ requires C, 45.2, H, 4.1; N, 4.4%), $\nu_{max.}$ (KCl disc) 2940 (C-H), 2720 and 2680 (N-H), and 1580 (N-H) $cm.^{-1}$.

6-Bromo-1-methyl-1,2,3,4-tetrahydrothianaphtheno-(2,3-c)-pyridineguanidine (93, X = Br).

An intimate mixture of the amine (92, X = Br) hydrochloride (3.18 g., 0.01 mole) and cyanamide (0.42 g., 0.01 mole) was heated in an oil-bath until fusion occurred (210°) and this temperature was maintained for 2 hr. The cooled mixture was extracted with ethanol, the extracts were filtered and evaporated to give the guanidine hydrochloride (93, X = Br), (71.4%), m.p. 292-293° (d) (dry ethanol-ether), $\nu_{max.}$ (Nujol) 3300 and 3140 (N-H), 2720 and 2480 (NH_2^+ and NH^+), and 1620 (C=N) $cm.^{-1}$. Correct analytical figures could not be obtained.

2-ARYLTHIOPHENS.

(a) From an epoxyacetylene

Phenylpropargyloxirane (95).

A stirred solution of methylsulphinyl carbanion[157] (0.1 mole) in dry dimethyl sulphoxide (50 ml.) and dry tetrahydrofuran (50 ml.) was cooled to -30° and treated with trimethylsulphonium iodide (20.4 g., 0.1 mole) in dry dimethyl sulphoxide (80 ml.) over 3 min. The mixture was stirred for 1 min., and phenylpropargylaldehyde (11 g., 0.085 mole) in dry tetrahydrofuran (100 ml.) was added dropwise at -30°. The mixture was stirred at -30° for 15 min., and at room temperature for 60 min. It was diluted with water (1 l.) and extracted with ether. Evaporation of the dried (K_2CO_3) ethereal extracts and vacuum distillation of the residue gave phenylpropargyloxirane (2.3 g., 19%), colourless oil, b.p. 78-81°/1.0 mm., $\nu_{max.}$ (CS_2) 3020 and 2960 (C-H), 2250 (C≡C), and 1230 (C-O) $cm.^{-1}$.

τ (liquid) 7.13 (2H, d, J=3Hz, CH_2-O), 6.48 (1H, t, J=3Hz, CH-O), 2.53-2.80 (5H, m, aromatic-H).

The n.m.r. spectrum indicated the presence of dimethyl sulphoxide and the oxirane was not purified for analysis.

2-Phenylthiophen (96).

A slow stream of hydrogen sulphide was passed through a stirred mixture of the oxirane (1g., 0.007 mole), barium hydroxide (1g.), and water (15 ml.) for 22 hr. at room temperature. The mixture was acidified with 30% aqueous acetic acid (15 ml.), extracted with ether, and the dried (Na_2SO_4) extracts were evaporated. Steam distillation of the

residue gave 2-phenylthiophen (0.78 g., 70%), colourless plates, m.p. 42-43° (ethanol) (lit.[109] 42°).

(b) From methylthioglycollate (54),

5-Phenylthiophen-2-carboxylic acid (98).

A stirred mixture of methylthioglycollate (5.3 g., 0.05 mole) and 2 N methanolic potassium hydroxide solution (50 ml.) cooled in an ice-salt bath, was treated with α-bromocinnamaldehyde (10.55 g., 0.05 mole) in methanol (50 ml.) and the mixture was stirred for 1 hr. at room temperature. It was poured into water (500 ml.), extracted with ether, and the dried (Na_2SO_4) extracts were evaporated to give α-bromocinnamaldehyde (2.44 g., 23%), pale cream needles, m.p. 72-73° (aqueous ethanol) (lit.[179] 72-73°).

The mother liquors were acidified with concentrated hydrochloric acid, the orange oil was extracted with ether, and the dried (Na_2SO_4) extracts were evaporated to yield 5-phenylthiophen-2-carboxylic acid (3.67 g., 46.8%), pale cream flakes, m.p. 186-187° (chloroform) (lit.[115] 187-188°), $\nu_{max.}$ (Nujol) 1720 (C=O) $cm.^{-1}$.

$\tau_{(CDCl_3)}$ 2.25 - 2.75 (7H, m, aromatic-H), -0.6 (1H, broad s, CO_2H).

2-Phenylthiophen (96).

5-Phenylthiophen-2-carboxylic acid was decarboxylated using copper powder and quinoline, by the method of Rinkes[159] to yield 2-phenylthiophen (72.4%), colourless plates, m.p. 42-43° (ethanol), $\nu_{max.}(CHCl_3)$ 3100 (C-H), 1605, 1500, and 1440 (C=C) $cm.^{-1}$.

Reaction of methylthioglycollate and phenylpropargylaldehyde.

A stirred solution of methylthioglycollate (5.3 g., 0.05 mole) and 2% aqueous sodium hydroxide (200 ml.) was treated with phenylpropargyl-

aldehyde (6.5 g., 0.05 mole) in methanol (50 ml.) and the mixture was stirred for 24 hr. It was extracted with ether, the dried ($MgSO_4$) extracts were evaporated, and the residue was vacuum distilled to give phenylacetylene (4.1 g., 80.4%), colourless oil, b.p. 26-28°/4 mm. (lit. 49-50°/14 mm.), $\nu_{max.}$ ($CHCl_3$) 3310 (C-H), 2160 (C≡C), 1610, 1500, and 1456 (C=C) $cm.^{-1}$.

$\tau_{(liquid)}$ 7.01 (1H, s, C≡CH), 2.46-2.96 (5H, m, phenyl-H).

The mother liquors were acidified with dilute sulphuric acid, extracted with ether, and the dried ($MgSO_4$) extracts were evaporated to give phenylpropargylcarboxylic acid (0.72 g.), colourless needles, m.p. 136-137° (carbon tetrachloride) (lit.[180] 136-137°), $\nu_{max.}$ (Nujol) 3500 (O-H), 2250 (C≡C), and 1670 (C=O) $cm.^{-1}$.

(c) From α-mercapto-β-styrylacrylic acid (99).

Oxidative cyclisation of α-mercapto-β-styrylacrylic acid with chlorine in carbon tetrachloride, using the method of Chakrabarti,[105] yielded 5-phenylthiophen-2-carboxylic acid (85-90%). The acid was decarboxylated as previously described, using Rinke's method, to obtain 2-phenylthiophen.

(d) From a Gomberg reaction.

The p-substituted aniline (0.4 mole) dissolved in water (160 ml.) and concentrated hydrochloric acid (90 ml.) was diazotised with sodium nitrite (29 g.) in water (100 ml.), and thiophene (350 g.) was added to the stirred solution at 0°. Anhydrous sodium acetate (160 g.) in water (400 ml.) was added dropwise, and stirring was continued for 3 hr. at 0-5°, and for 24 hr. at room temperature. The organic layer was separated and the aqueous layer was extracted with ether. Evaporation of the combined

dried (Na_2SO_4) organic extracts and vacuum-, or steam-distillation of the residue gave the p-substituted 2-arylthiophen.

In this way, the following 2-arylthiophens were prepared.

2-p-Bromophenylthiophen (101, X = Br) (38%), pale yellow plates, m.p. 99-100° (ethanol) (lit.[109] 100°), $\nu_{max.}$($CHCl_3$) 2950 (C-H), 1535 and 1490 (C=C) $cm.^{-1}$.

$\tau_{(CDCl_3)}$ 3.14-2.80 (3H, m, thienyl-H), 2.67 (4H, s, phenyl-H).

2-p-Chlorophenylthiophen (101, X = Cl) (31%), colourless plates, m.p. 83-84° (ethanol) (lit.[109] 83°), $\nu_{max.}$ (Nujol) 3100 (C-H), 1495 and 1435 (C=C) $cm.^{-1}$.

2-p-Tolylthiophen (101, X = Me) (18%), colourless plates, m.p. 82-83° (ethanol) (lit.[134] 77-78°) (Found: M^+, 174. $C_{11}H_{10}S$ requires M^+, 174), $\nu_{max.}$($CHCl_3$) 3100 and 2980 (C-H), 1510 and 1440 (C=C)$cm.^{-1}$.

$\tau_{(CDCl_3)}$ 7.74 (3H, s, CH_3), 2.90 (2H, d, J=8Hz., phenyl-H), 3.10-2.80 (3H, m. thienyl-H), 2.54 (2H, d, J=8Hz., phenyl-H).

5-ARYLTHIEN-2-YLALDEHYDES AND THEIR DERIVATIVES.

5-Arylthien-2-ylaldehydes (102).

Redistilled phosphorus oxychloride (4.62 g., 0.03 mole) was added dropwise to dry dimethylformamide (10 ml.) at 0°, and the solution was added to 2-arylthiophen (0.02 mole) in dry toluene (50 ml.) at 0°. The mixture was heated for 3 hr. on a water-bath, refluxed for 30 min., cooled, treated with anhydrous sodium acetate (30 g.) in water (200 ml.), and allowed to stand overnight. The organic layer was separated, the aqueous layer was extracted with ether, and the combined dried (Na_2SO_4) extracts were evaporated. Vacuum distillation of the residue gave the required aldehyde which was recrystallised from aqueous ethanol.

In this way, the following aldehydes were prepared.

5-p-Bromophenylthien-2-ylaldehyde (102, X = Br) (68.4%), colourless needles, m.p. 111-112° (Found: C, 49.62; H, 2.40. $C_{11}H_7BrOS$ requires C, 49.45; H, 2.62%), $\nu_{max.}(CHCl_3)$ 2800 (C-H), 1665 (C=O), 1400, 1260, and 1185 $cm.^{-1}$.

$\tau_{(CDCl_3)}$ 2.60 (1H, d, J=3.8Hz., thienyl-4-H), 2.44 (4H, s, phenyl-H), 2.25 (1H, d, J=3.8Hz., thienyl-3-H). 0.08 (1H, s, CHO).

5-p-Chlorophenylthien-2-ylaldehyde (102, X = Cl) (71.2%), colourless needles, m.p. 89-90° (lit.[181] 82-83°), $\nu_{max.}(CHCl_3)$ 2850 (C-H), 1670 (C=O), 1410, and 1230 $cm.^{-1}$.

$\tau_{(CDCl_3)}$ 2.78-2.36 (5H, m, phenyl-H, and thienyl-4-H), 2.32 (1H, d, J = 3.6 Hz., thienyl-3-H), 0.12 (1H, s, CHO).

5-Arylthien-2-ylthiosemicarbazones (103).

5-Arylthien-2-ylaldehyde (0.01 mole) in ethanol (25 ml.), water (10 ml.), and glacial acetic acid (0.5 ml.) was treated with thiosemicarbazide (0.91 g., 0.01 mole) and the mixture was warmed, with shaking, until a solution was obtained. It was refluxed for 1 hr., cooled, and the crystalline thiosemicarbazone was collected, and recrystallised from ethanol.

In this way the following compounds were prepared.

5-p-Bromophenylthien-2-ylthiosemicarbazone (103, X = Br) 3.15 g., 93%), yellow needles, m.p. 211-213° (Found: C, 41.93; H, 2.8; N, 11.93. $C_{12}H_9BrN_3S_z$ requires C, 42.4; H, 2.7; N, 12.4%), $\nu_{max.}$ (Nujol) 3450-3200 (N-H, multiple bands), 1605 and 1590 (C=N and C=S) $cm.^{-1}$.

5-p-Chlorophenylthien-2-ylthiosemicarbazone (103, X = Cl)

(2.7 g., 91.5%), orange-yellow prisms, m.p. 225-226° (Found: C, 48.3; H, 3.3; N, 14.0. $C_{12}H_9ClN_3S_2$ requires C, 48.9; H, 3.1; N, 14.7%), $\nu_{max.}$(Nujol) 3550-3200 (N-H, multiple bands), 1605 and 1590 (C=N and C=S) $cm.^{-1}$.

Oxidation of 5-p-bromophenylthien-2-ylaldehyde.

A suspension of silver oxide, prepared by the addition of silver nitrate (3.4 g.) in water (25 ml.) to a stirred solution of sodium hydroxide (1.7 g.) in water (25 ml.), was treated with the aldehyde (2.94 g., 0.011 mole) in methanol (40 ml.) at room temperature. The mixture was stirred vigorously for 24 hr., filtered, the precipitate was washed with copious amounts of hot water, and the combined filtrates were extracted with ether, and acidified with concentrated hydrochloric acid. The liberated acid was extracted with ether and the dried (Na_2SO_4) ethereal extracts were evaporated to yield 5-p-bromophenythiophen-2-carboxylic acid (104, X = Br) (80.6%), colourless prisms, m.p. 263-264° (aqueous ethanol) (Found: C, 46.92; H, 2.38; S, 11.70. $C_{11}H_7BrO_2S$ requires C, 46.64; H, 2.47; S, 11.3%), $\nu_{max.}$(Nujol) 3500 (O-H) and 1680 (C=O) $cm.^{-1}$.

Condensation of 5-p-bromophenylthien-2-ylaldehyde with malonic acid.

The aldehyde (2.67 g., 0.01 mole), malonic acid (2.04 g., 0.02 mole), dry pyridine (15 ml.), and piperidine (0.5 ml.) were heated together for 2.5 hr. on a steam-bath, and for 5 min. at reflux. The cooled solution was poured into water (100 ml.), treated with concentrated hydrochloric acid (50 ml.), and allowed to stand for 30 min. The solid 5-p-bromophenylthien-2-ylacrylic acid (105, X = Br) (70.9%) was collected,

bright yellow prisms, m.p. 234-236° (ethanol) (Found: C, 50.31; H, 2.8; S, 10.62. $C_{13}H_9BrO_2S$ requires C, 50.48; H, 2.9; S, 10.35%), $\nu_{max.}$ (Nujol) 3450 (O-H), 1680 (C=O), and 1625 (C=C) $cm.^{-1}$.

5-ARYLTHIOPHEN-2-CARBOXYLIC ACIDS AND THEIR DERIVATIVES.

5-Arylthiophen-2-carboxylic acids (104).

n-Butyllithium[161] (4.5 g., 0.07 mole) in dry ether (100 ml.) was added dropwise to a stirred solution of 2-arylthiophen (0.05 mole) in dry ether (50 ml.). The mixture was stirred for 15 min., poured on to a slurry of crushed solid carbon dioxide in ether, and the excess carbon dioxide was allowed to evaporate. Water (200 ml.) was added, the ethereal layer was separated, and the aqueous layer was acidified with concentrated hydrochloric acid. The liberated acid was extracted with ether, and the dried (Na_2SO_4) ethereal extracts were evaporated to give the 5-arylthiophen-2-carboxylic acid.

In this way, the following acids were obtained.

5-p-Bromophenylthiophen-2-carboxylic acid (104, X = Br) (86.2%), colourless prisms, m.p. 263-264° (aqueous ethanol).

5-p-Chlorophenylthiophen-2-carboxylic acid (104, X = Cl) (81.4%), colourless prisms, m.p. 253-254° (acetic acid) (lit.[134] 254°).

5-p-Tolylthiophen-2-carboxylic acid (104, X = Me) (78.2%), colourless prisms, m.p. 217-218° (chlorobenzene) (lit.[134] 217°).

5-Arylthien-2-yl acid hydrazides.

A suspension of the acid (0.02 mole) in ether (40 ml.) was treated with an ethereal solution of diazomethane at 0-5° until a permanent yellow

colour persisted, and the solution was allowed to stand overnight. Evaporation of the ether yielded the methyl ester which was dissolved in ethanol (50 ml.) and treated with hydrazine hydrate (1.5 g., 0.03 mole). The mixture was refluxed for 6 hr., cooled, and the crystalline acid hydrazide was collected and recrystallised from ethanol.

In this way, the following compounds were prepared.

5-Phenylthien-2-yl acid hydrazide (62.7%), pale cream flakes, m.p. 164-165° (Found: C, 60.80; H, 4.47; N, 12.56; M^+, 218. $C_{11}H_{10}N_2OS$ requires C, 60.54; H, 4.58; N, 12.85%; M^+, 218), $\nu_{max.}$ (Nujol) 3350 and 3250 (N-H), 1620 (C=O), and 1550 (N-H and C=N combination bands) $cm.^{-1}$.

5-p-Chlorophenylthien-2-yl acid hydrazide (70.7%), cream flakes, m.p. 179-180° (Found: C, 52.48, H, 3.62; N, 10.83; M^+, 252. $C_{11}H_9ClN_2OS$ requires C, 52.27; H, 3.56; N, 11.09%; M^+, 252), $\nu_{max.}$ (Nujol) 3350 and 3250 (N-H), 1620 (C=O), and 1545 (N-H and C=N combination bands) $cm.^{-1}$.

5-p-Tolylthien-2-yl acid hydrazide (64.7%), colourless flakes, m.p. 175-176° (Found: C, 62.01; H, 5.13; N, 12.21; M^+, 232. $C_{12}H_{12}N_2OS$ requires C, 62.07; H, 5.17; N, 12.07%; M^+, 232), $\nu_{max.}$ (Nujol) 3350 and 3250 (N-H), 1615 (C=O), and 1545 (N-H and C=N combination bands) $cm.^{-1}$.

N-Substituted 5-arylthien-2-ylamides (111).

5-Arylthiophen-2-carboxylic acid (0.05 mole) and redistilled thionyl chloride (15 ml.) was refluxed together for 1 hr., the excess of thionyl chloride was evaporated, and the residue was distilled under reduced pressure to give the 5-arylthien-2-yl acid chloride (110). The acid chloride (0.02 mole) in dry benzene (40 ml.) was cooled, treated with the appropriate amine (0.1 mole) in dry benzene (40 ml.), and the mixture was allowed to stand for 1 hr. It was extracted with dilute hydrochloric

acid and the dried (Na_2SO_4) organic layer was evaporated to yield the N-substituted 5-arylthien-2-ylamide which was recrystallised from carbon tetrachloride unless otherwise stated.

In this way, the following compounds were prepared.

5-Phenylthien-2-yl acid chloride and morpholine gave N-(5-phenylthen-2-oyl)morpholine (111, X = H, NR_2 = morpholino) (97.8%), colourless needles, m.p. 122-123° (Found: C, 65.88; H, 5.39; N, 4.95; M^+, 273. $C_{15}H_{15}NO_2S$ requires C, 65.94; H, 5.49; N, 5.12%; M^+, 273), $\nu_{max.}$ (CCl_4) 1635 (C=O) $cm.^{-1}$.

$\tau_{(CDCl_3)}$ 6.38 (8H, broad s, morpholino-CH_2), 2.86-2.4 (7H, m, aromatic-H).

5-Phenylthien-2-yl acid chloride and piperidine gave N-(5-phenylthen-2-oyl)piperidine (111, X = H, NR_2 = piperidino) (97.7%), colourless needles, m.p. 102 - 103° (aqueous ethanol) (Found: C, 68.75; H, 6.25; N, 4.91. $C_{16}H_{17}NOS\frac{1}{2}H_2O$ requires C, 68.59; H, 6.33; N, 4.99%), $\nu_{max.}$ ($CHCl_3$) 1615 (C=O) $cm.^{-1}$.

$\tau_{(CDCl_3)}$ 8.40 (6H, m, piperidino-3,4,5-CH_2), 6.41 (4H, m, NCH_2), 2.83-2.34 (7H, m, aromatic-H).

5-Phenylthien-2-yl acid chloride and pyrrolidine gave N-(5-phenylthen-2-oyl)pyrrolidine (111, X = H, NR_2 = pyrrolidino) (82.4%), colourless needles, m.p. 132-133° (Found: C, 70.38; H, 5.91; N, 5.49. $C_{15}H_{15}NOS$ requires C, 70.05, H, 5.84; N, 5.45%), $\nu_{max.}$ (Nujol) 1600 (C=O) $cm.^{-1}$.

$\tau_{(CDCl_3)}$ 8.06 (4H, m, pyrrolidino-3,4-CH_2), 6.3 (4H, m, NCH_2), 2.83-2.29 (7H, m, aromatic-H).

5-Phenylthien-2-yl acid chloride and dimethylamine gave N,N-dimethyl-5-phenylthien-2-ylamide (111, X = H, NR_2 = NMe_2) (95.9%),

colourless needles, m.p. 113-114° (Found: C, 67,80; H, 5.81; N, 6.31; $\underline{M}^+$, 231. $C_{13}H_{13}NOS$ requires C, 67.53; H, 5.63; N, 6.06%; $\underline{M}^+$, 231), $\nu_{max.}(CHCl_3)$ 1610 (C=O) $cm.^{-1}$.

$\tau_{(CDCl_3)}$ 6.88 (6H, s, $N(CH_3)_2$), 2.90-2.32 (7H, m, aromatic-H).

5-p-Bromophenylthien-2-yl acid chloride and morpholine gave N-(5-p-bromophenylthen-2-oyl)morpholine (111, X = Br, NR_2 = morpholino) (89.2%), cream crystals, m.p. 160-161° (Found: C, 51.35, H, 3.91, N, 3.68; $\underline{M}^+$, 351,353. $C_{15}H_{14}BrNO_2S$ requires C, 51.15; H, 3.98; N, 3.98%; $\underline{M}^+$, 351, 353), $\nu_{max.}(CHCl_3)$ 1615 (C=O) $cm.^{-1}$.

$\tau_{(CDCl_3)}$ 6.25 (8H, broad s, morpholino-CH_2), 2.80 (1H, d, J=3.5Hz., thienyl-H) 2.77 (1H, d, J=3.5Hz., thienyl-H), 2.52 (4H, s, phenyl-H).

5-p-Bromophenylthien-2-yl acid chloride and piperidine gave N-(5-p-bromophenylthen-2-oyl)piperidine (111, X = Br, NR_2 = piperidino) (92.5%), colourless crystals, m.p. 79-80° (aqueous ethanol) (Found: C, 53.7; H, 4.56; N, 4.01. $C_{16}H_{16}BrNOS\frac{1}{2}H_2O$ requires C, 53.5; H, 4.73; N, 3.9%), $\nu_{max.}(CHCl_3)$ 1610 (C=O) $cm.^{-1}$.

$\tau_{(CDCl_3)}$ 8.36 (6H, m, piperidino-3,4,5-CH_2), 6.34 (4H, m, NCH_2), 2.85-2.4 (6H, m, aromatic-H).

5-p-Bromophenylthien-2-yl acid chloride and pyrrolidine gave N-(5-p-bromophenylthen-2-oyl)pyrrolidine (111, X = Br, NR_2 = pyrrolidino) (89.9%), colourless needles, m.p. 189-190° (ethanol) (Found: C, 53.76; H, 4.24; N, 4.10. $C_{15}H_{14}BrNOS$ requires C, 53.42; H, 4.15; N, 4.15%), $\nu_{max.}$(Nujol) 1600 (C=O) $cm.^{-1}$.

$\tau_{(CDCl_3)}$ 8.06 (4H, m, pyrrolidino-3,4-CH_2), 6.28 (4H, m, NCH_2), 2.88-2.70 (2H, m, thienyl-H), 2.52 (4H, s, phenyl-H).

5-p-Bromophenylthien-2-yl acid chloride and dimethylamine gave N,N-dimethyl-5-p-bromophenylthien-2-ylamide (111, X = Br, NR_2=NMe_2) (93.1%), colourless flakes, m.p. 136-137° (Found: C, 50.51; H, 3.83; N, 4.29; M^+, 309, 311. $C_{13}H_{12}BrNOS$ requires C, 50.31; H, 3.87; N, 4.51%; M^+, 309, 311), $\nu_{max.}$ ($CHCl_3$) 1615 (C=O) $cm.^{-1}$.

$\tau_{(CDCl_3)}$ 6.83 (6H, s, $N(CH_3)_2$), 2.84 (1H, d, J=4Hz., thienyl-H), 2.70 (1H, d, J=4Hz., thienyl-H), 2.55 (4H, s, phenyl-H).

5-p-Chlorphenylthien-2-yl acid chloride and morpholine gave N-(5-p-chlorophenylthen-2-oyl)morpholine (111, X = Cl, NR_2=morpholino) (96.7%), colourless needles, m.p. 147-148° (Found: C, 58.03, H, 4.52; N, 4.85; M^+, 307. $C_{15}H_{14}ClNO_2S$ requires C, 58.54; H, 4.55; N, 4.55%, M^+, 307), $\nu_{max.}$ ($CHCl_3$) 1620 (C=O) $cm.^{-1}$.

$\tau_{(CDCl_3)}$ 6.31 (8H, broad s, morpholino-CH_2), 2.82 - 2.31 (6H, m, aromatic-H).

5-p-Chlorophenylthien-2-yl acid chloride and piperidine gave N-(5-p-chlorophenylthen-2-oyl)piperidine (111, X = Cl, NR_2=piperidino) (96.9%), colourless flakes, m.p. 109-110° (Found: C, 62.93; H, 5.21; N, 4.63. $C_{16}H_{16}ClNOS$ requires C, 62.85; H, 5.24; N, 4.58%), $\nu_{max.}$ ($CHCl_3$) 1610 (C=O) $cm.^{-1}$.

$\tau_{(CDCl_3)}$ 8.37 (6H, m, piperidino-3,4,5-CH_2), 6.32 (4H, m, NCH_2), 2.88-2.34 (6H, m, aromatic-H).

5-p-Chlorophenylthien-2-yl acid chloride and pyrrolidine gave N-(5-p-chlorophenylthen-2-oyl)pyrrolidine (111, X = Cl, NR_2 = pyrrolidino) (71.8%), colourless needles, m.p. 189-190° (Found: C, 61.47; H, 4.91; N, 4.97. $C_{15}H_{14}ClNOS$ requires C, 61.75; H, 4.80; N, 4.80%), $\nu_{max.}$ ($CHCl_3$) 1600 (C=O) $cm.^{-1}$.

$\tau_{(CDCl_3)}$ 8.06 (4H, m, pyrrolidino-3,4-CH_2), 6.28 (4H, m, NCH_2), 2.84-2.31 (6H, m, aromatic-H).

5-p-Chlorophenylthien-2-yl acid chloride and dimethylamine gave N,N-dimethyl-5-p-chlorophenylthien-2-ylamide (111, X = Cl, NR_2 = NMe_2) (87.1%), colourless plates, m.p. 140-141° (Found: C, 58.52; H, 4.84; N, 5.00; M^+, 265. $C_{13}H_{12}ClNOS$ requires C, 58.77; H, 4.52; N, 5.27%, M^+, 265), $\nu_{max.}$($CHCl_3$) 1615 (C=O) $cm.^{-1}$.

$\tau_{(CDCl_3)}$ 6.85 (6H, s, $N(CH_3)_2$), 2.85-2.34 (6H, m, aromatic-H).

5-p-Tolylthien-2-yl acid chloride and morpholine gave N-(5-p-tolylthen-2-oyl)morpholine (111, X = Me, NR_2 = morpholino) (87.6%), colourless flakes, m.p. 134-135° (Found: C, 66.77; H, 5.80; N, 4.72; M^+, 287. $C_{16}H_{17}NO_2S$ requires C, 66.9; H, 5.92; N, 4.88%; M^+, 287), $\nu_{max.}$($CHCl_3$) 1620 (C=O) $cm.^{-1}$.

$\tau_{(CDCl_3)}$ 7.68 (3H, s, CH_3), 6.35 (8H, broad s, morpholino-CH_2), 2.92-2.45 (6H, m, aromatic-H).

5-p-Tolylthien-2-yl acid chloride and piperidine gave N-(5-p-tolylthen-2-oyl)piperidine (111, X = Me, NR_2 = piperidino) (79.4%),

colourless silky needles, m.p. 132-133° (Found: C, 71.30; H, 6.65; N, 5.06. $C_{17}H_{19}NOS$ requires C, 71.58; H, 6.67; N, 4.91%), $\nu_{max.}(CHCl_3)$ 1610 (C=O) cm.$^{-1}$.

$\tau_{(CDCl_3)}$ 8.45 (6H, broad s, piperidino-3,4,5-CH_2), 7.73 (3H, s, CH_3), 6.40 (4H, broad s, NCH_2), 2.98-2.5 (6H, m, aromatic-H).

5-p-Tolylthien-2-yl acid chloride and pyrrolidine gave N-(5-p-tolylthen-2-oyl)pyrrolidine (111, X = Me, NR_2 = pyrrolidino) (76.2%), colourless flakes, m.p. 156-157° (ethanol) (Found: C, 70.81; H, 6.09; N, 4.99. $C_{16}H_{17}NOS$ requires C, 70.85; H, 5.9; N, 5.16%), $\nu_{max.}(CHCl_3)$ 1600 (C=O) cm.$^{-1}$.

$\tau_{(CDCl_3)}$ 8.06 (4H, m, pyrrolidino-3,4-CH_2), 7.68 (3H, s, CH_3), 6.31 (4H, m, NCH_2), 2.96-2.49 (6H, m, aromatic-H).

5-p-Tolylthien-2-yl acid chloride and dimethylamine gave N,N-dimethyl-5-p-tolylthien-2-ylamide (111, X = Me, NR_2 = NMe_2) (91.5%), colourless needles, m.p. 136-137° (Found: C, 68.29; H, 6.12; N, 5.83; M^+, 245. $C_{14}H_{15}NOS$ requires C, 68.56; H, 6.12; N, 5.72%; M^+, 245), $\nu_{max.}(CHCl_3)$ 1615 (C=O) cm.$^{-1}$.

$\tau_{(CDCl_3)}$ 7.68 (3H, s, CH_3), 6.84 (6H, s, $N(CH_3)_2$), 2.82-2.43 (6H, m, aromatic-H).

5-Arylthien-2-ylamides.

The acid chloride (0.02 mole) in dry benzene (40 ml.) was added dropwise to a cooled, stirred, saturated solution of ammonia in dry

methanol (100 ml.). The mixture was stirred for 1 hr., the precipitate was collected, washed well with cold water and air-dried to give the 5-arylthien-2-ylamide, which was recrystallised from ethanol.

In this way the following compounds were prepared.

5-Phenylthien-2-yl acid chloride gave 5-phenylthien-2-ylamide (111, X = H, NR_2 - NH_2) (66%), colourless prisms, m.p. 200-201° (Found: C, 64.76; H, 4.64; N, 6.68; M^+, 203. $C_{11}H_9NOS$ requires C, 65.03; H, 4.43; N, 6.89%; M^+, 203), $\nu_{max.}$ (Nujol) 3420 and 3200 (N-H), 1650 (C=O), and 1615 (N-H and C-N combination bands) $cm.^{-1}$.

5-p-Bromophenylthien-2-yl acid chloride gave 5-p-bromophenylthien-2-ylamide (111, X = Br, NR_2 = NH_2) (61.7%), broad colourless needles, m.p.209-211° (Found: C, 46.68; H, 2.86; N, 4.71. $C_{11}H_8BrNOS$ requires C, 46.82; H, 2.84; N, 4.74%), $\nu_{max.}$ (Nujol) 3420 and 3200 (N-H), 1650 (C=O), and 1615 (N-H and C-N combination bands) $cm.^{-1}$.

5-p-Chlorophenylthien-2-yl acid chloride gave 5-p-chlorophenylthien-2-ylamide (111, X = Cl, NR_2 = NH_2) (71.8%), colourless long needles, m.p. 207-208° (Found: C, 55.36; H, 3.33; N, 5.62; M^+, 237. $C_{11}H_8ClNOS$ requires C, 55.59; H, 3.37; N, 5.89%; M^+, 237), $\nu_{max.}$ (Nujol) 3420 and 3180 (N-H), 1650 (C=O), and 1615 (N-H and C-N combination bands) $cm.^{-1}$.

5-p-Tolylthien-2-yl acid chloride gave 5-p-tolylthien-2-ylamide (111, X = Me, NR_2 = NH_2) (69.2%), colourless flakes, m.p. 214-215° (Found: C, 65.98; H, 5.05; N, 6.29; M^+, 217. $C_{12}H_{11}NOS$ requires C, 66.36; H,5.07; N, 6.45%; M^+, 217), $\nu_{max.}$ (Nujol) 3420 and 3180 (N-H), 1650 (C=O), and 1615 (N-H and C-N combination bands) $cm.^{-1}$.

Arndt-Eistert reaction.

5-phenylthien-2-yl acid chloride (5 g., 0.022 mole) in dry ether (100 ml.) was added dropwise over a period of 1 hr. to a stirred solution of diazomethane (2.8 g., 0.067 mole) in dry ether (100 ml.) at 0°. The mixture was allowed to stand overnight and the solvent was evaporated to yield 5-phenylthien-2-yl diazo-ketone (115, X = H) (5.1 g., 97.6%), long yellow needles, m.p. 123-124° (d) (ether) (Found: C, 63.6; H, 3.5; N, 11.9. $C_{12}H_8N_2OS$ requires C, 63.2; H, 3.5; N, 12.3%), $\nu_{max.}$ ($CHCl_3$) 2140 (N≡N) and 1605 (C=O) cm.$^{-1}$.

$\tau_{(CDCl_3)}$ 4.3 (1H, s, CH), 2.80-2.37 (7H, m, aromatic-H)

A mixture of the diazo-ketone (2.2g., 0.01 mole), dry ethanol (40 ml.) and platinum oxide (0.1 g.) was refluxed for 6 hr. with the addition of further portions of platinum oxide (0.2 g.) at 1 hr. intervals. The mixture was refluxed for a further 20 hr., filtered while hot, and the ethanol was evaporated to yield ethyl-5-phenylthien-2-yl acetate., $\nu_{max.}$ ($CHCl_3$) 2910 (C-H), 1630 (C=O), and 1240 (C-O) cm.$^{-1}$.

$\tau_{(CDCl_3)}$ 8.78 (3H, t, J=7Hz., $CH_2\underline{CH_3}$), 6.23 (2H, s, CH_2), 5.82 (2H, q, J=7Hz., $\underline{CH_2}CH_3$), 3.15 (1H, d, J-3.5Hz., thienyl-3-H), 2.92-2.32 (6H, m, phenyl-H and thienyl-4-H).

The crude ester was dissolved in ethanol (40 ml.), treated with 20% aqueous sodium hydroxide solution (40 ml.) and heated on a steam-bath for 1 hr. The ethanol was evaporated, the residue was diluted with water (50 ml.), extracted with ether, and acidified with concentrated hydrochloric acid. The liberated acid was extracted with ether and the dried (Na_2SO_4)

ethereal extracts were evaporated to yield 5-phenylthien-2-ylacetic acid (116; X=H) (1.37 g., 62.8%), colourless flakes, m.p. 228-230° (carbon tetrachloride) (Found: C, 66.0, H, 4.6; S, 14.9. $C_{12}H_{10}O_2S$ requires C, 66.06; H, 4.6; S, 14.7%), $\nu_{max.}$ (Nujol) 2700 (O-H), and 1700 (C=O) $cm.^{-1}$.

Freshly prepared silver oxide (0.2 g.) was refluxed in dry methanol (15 ml.) for 30 min. until a silver mirror began to form. The diazo-ketone (2 g., 0.009 mole) in dry methanol (40 ml.) was added and the mixture was refluxed for 6 hr. with the addition of further portions of silver oxide (0.1 g.) at 1 hr. intervals. The mixture was refluxed for a further 20 hr., filtered hot, and the filtrate was heated with 20% aqueous sodium hydroxide solution (40 ml.) for 1 hr. on a steam-bath. The required 5-phenylthien-2-ylacetic acid (1.1 g., 54%), extracted as previously described, separated as colourless flakes, m.p. 228-230° (carbon tetrachloride).

5-ARYLTHIEN-2-YLMETHYLAMINES AND THEIR DERIVATIVES.

Reduction of 5-arylthien-2-ylamides.

The amide (0.015 mole) in dry benzene (40 ml.) was added to a stirred suspension of lithium aluminium hydride (0.76 g., 0.02 mole) in dry ether (20 ml.). The mixture was refluxed for 12 hr., cooled, and the excess of reducing agent was destroyed by the addition of 10% aqueous sodium hydroxide solution. The precipitate of lithium aluminium oxide was filtered off and washed with ether. Treatment of the combined, dried ($MgSO_4$) filtrates with dry hydrogen chloride precipitated the amine hydrochloride (112) which was recrystallised from ethanol unless otherwise stated.

The following reactions were carried out as above.

Reduction of N-(5-phenylthen-2-oyl)morpholine gave N-(5-phenylthien-2-ylmethyl)morpholine hydrochloride (112, X = H, NR_2 = morpholino) (95.5%), colourless needles, m.p. 235-236° (d) (Found: C, 60.77; H, 6.23; N, 4.93; M^+, 259. $C_{15}H_{18}ClNOS$ requires C, 66.92; H, 6.09; N, 4.74%; M^+, [free base], 259), $\nu_{max.}$ (Nujol) 2520 and 2460 (C-H) $cm.^{-1}$.

$\tau_{(CDCl_3)}$ 7.35 (4H, m, morpholino-NCH_2), 6.29 (4H, m, morpholino-OCH_2), 3.01 (1H, d, J=3.4Hz., thienyl-3-H), 2.88-2.48 (6H, m, phenyl-H and thienyl-4-H).

Reduction of N-(5-phenylthen-2-oyl)piperidine gave N-(5-phenylthien-2-ylmethyl)piperidine hydrochloride (112, X = H, NR_2 = piperidino) (98.1%), colourless needles, m.p. 211-212° (Found: C, 65.53; H, 7.00; N, 4.66. $C_{16}H_{20}ClNS$ requires C, 65.41; H, 6.82; N, 4.77%), $\nu_{max.}$ (Nujol) 2660 and 2580 (C-H) $cm.^{-1}$.

$\tau_{(CDCl_3)}$ 8.45 (6H, m, piperidino-3,4-5-CH_2), 7.44 (4H, m, piperidino-NCH_2) 6.21 (2H, s, CH_2), 3.05 (1H, d, J=3.5Hz., thienyl-3-H), 2.92-2.51 (6H, m, phenyl-H and thienyl-4-H).

Reduction of N-(5-phenylthen-2-oyl)pyrrolidine gave N-(5-phenylthien-2-ylmethyl)pyrrolidine hydrochloride (112, X = H, NR_2 = pyrrolidino) (92.5%), colourless needles, m.p. 228.5-229.5° (Found: C, 64.29; H, 6.50; N, 5.10. $C_{15}H_{18}ClNS$ requires C, 64.4; H, 6.44; N, 5.01%), $\nu_{max.}$ (Nujol) 2640 and 2560 (C-H) $cm.^{-1}$.

Reduction of N,N-dimethyl-5-phenylthien-2-ylamide gave N,N-dimethyl-5-phenylthien-2-ylmethylamine hydrochloride (112, X = H, NR_2 = NMe_2) (96.4%), colourless needles, m.p. 229-230° (Found: C, 61.34; H, 6.23; N, 5.47; M^+, 217. $C_{13}H_{16}ClNS$ requires C, 61.53; H, 6.31; N, 5.52%; M^+ [free base], 217), $\nu_{max.}$ (Nujol) 2520 (C-H) $cm.^{-1}$.

Reduction of N-(5-p-chlorophenylthen-2-oyl)morpholine gave N-(5-p-chlorophenylthien-2-ylmethyl)morpholine hydrochloride (112, X = Cl, NR_2 = morpholino) (94.2%), colourless flakes, m.p. 233-234° (d) (Found: C, 54.77; H, 5.33; N, 4.39; M^+, 293. $C_{15}H_{17}Cl_2NOS$ requires C, 54.55; H, 5.15; N, 4.24%; M^+, [free base], 293), $\nu_{max.}$ (Nujol) 2550 and 2500 (C-H) $cm.^{-1}$.

Reduction of N-(5-p-chlorophenylthen-2-oyl)piperidine gave N-(5-p-chlorophenylthien-2-ylmethyl)piperidine hydrochloride (112, X = Cl), NR_2 = piperidino) (91.6%), colourless needles, m.p. 220-221° (Found: C, 58.81; H, 5.77; N, 4.34. $C_{16}H_{19}Cl_2NS$ requires C, 58.53; H, 5.79; N, 4.27%), $\nu_{max.}$ (Nujol) 2640 and 2570 (C-H) $cm.^{-1}$.

Reduction of N-(5-p-chlorophenylthen-2-oyl)pyrrolidine gave N-(5-p-chlorophenylthien-2-ylmethyl)pyrrolidine hydrochloride (112, X = Cl, NR_2 = pyrrolidino) (85.2%). The hydrochloride proved difficult to crystallise and the amine in dry ethanol was converted into the methiodide by treatment with a 10% excess of methyl iodide. The methiodide precipitated as colourless flakes, m.p. 179-181° (d) (ethanol) (Found: C, 45.57; H, 4.40; N, 3.14. $C_{16}H_{19}ClINS$ requires C, 45.77; H, 4.53; N, 3.34%).

Reduction of N,N-dimethyl-5-p-chlorophenylthien-2-ylamide gave N,N-dimethyl-5-p-chlorophenylthien-2-ylmethylamine hydrochloride (112, X = Cl, NR_2 = NMe_2) (92.6%), colourless needles, m.p. 230-231° (Found: C, 54.44; H, 5.35; N, 5.05; M^+, 251. $C_{13}H_{15}Cl_2NS$ requires C, 54.16; H, 5.21; N, 4.86%; M^+ [free base], 251), $\nu_{max.}$ (Nujol) 2520 (C-H) $cm.^{-1}$.

Reduction of N-(5-p-tolylthen-2-oyl)morpholine gave N-(5-p-tolylthien-2-ylmethyl)morpholine hydrochloride (112, X=Me, NR_2=morpholino) (84.6%), colourless needles, m.p. 242-243° (d) (Found: C, 62.04; H, 6.65; N, 4.63; M^+, 273. $C_{16}H_{20}ClNOS$ requires C, 62.03; H, 6.47; N, 4.52%; M^+ [free base], 273), $\nu_{max.}$ (Nujol) 2924 and 2450 (C-H) $cm.^{-1}$.

Reduction of N-(5-p-tolylthen-2-oyl)piperidine gave N-(5-p-tolylthien-2-ylmethyl)piperidine hydrochloride (112, X = Me, NR_2 = piperidino) (81.3%), colourless broad needles, m.p. 233-234° (Found: C, 66.08; H, 7.32; N, 4.56. $C_{17}H_{22}ClNS$ requires C, 66.35; H, 7.16; N, 4.55%), $\nu_{max.}$ (Nujol) 2640, 2520, and 2450 (C-H) $cm.^{-1}$.

Reduction of N-(5-p-tolylthen-2-oyl)pyrrolidine gave N-(5-p-tolylthien-2-ylmethyl)pyrrolidine hydrochloride (112, X = Me, NR_2 = pyrrolidino) (84.7%), colourless needles, m.p. 244-245° (d) (Found: C, 65.32; H, 6.89; N, 4.57. $C_{16}H_{20}ClNS$ requires C, 65.41; H, 6.82; N, 4.77%), $\nu_{max.}$ (Nujol) 2600 and 2520 (C-H) $cm.^{-1}$.

Reduction of N,N-dimethyl-5-p-tolylthien-2-ylamide gave N,N-dimethyl-5-p-tolylthien-2-ylmethylamine hydrochloride (112, X = Me,

NR_2=NMe_2) (94.1%), colourless needles, m.p. 250-251° (Found: C, 62.57; H, 6.83; N, 5.46; $\underline{M}^+$, 231. $C_{14}H_{18}ClNS$ requires C, 62.80; H, 6.73; N, 5.23%; $\underline{M}^+$[free base], 231), $\nu_{max.}$(Nujol), 2580 and 2540 (C-H) $cm.^{-1}$.

Reduction of 5-phenylthien-2-ylamide (refluxing for 24 hr.) gave 5-phenylthien-2-ylmethylamine hydrochloride (112, X = H, NR_2 = NH_2) (89.8%), colourless flakes, m.p. 253-254° (d) (dry ethanol-ether) (Found: C, 58.51; H, 5.36; N, 6.13; $\underline{M}^+$ 189. $C_{11}H_{12}ClNS$ requires C, 58.53; H, 5.32; N, 6.21%; $\underline{M}^+$[free base], 189), $\nu_{max.}$(Nujol) 1605 (N-H) $cm.^{-1}$.

Reduction of 5-p-chlorophenylthien-2-ylamide (refluxing for 24 hr.) gave 5-p-chlorophenylthien-2-ylmethylamine hydrochloride (112, X = Cl, NR_2 = NH_2) (82.9%), colourless flakes, m.p. 254-255° (aqueous ethanol) (Found: C, 50.71; H, 4.28; N, 5.61; $\underline{M}^+$, 233. $C_{11}H_{11}Cl_2NS$ requires C, 50.77; H, 4.23; N, 5.38%; $\underline{M}^+$[free base], 233), ν_{max} (Nujol) 1615 (N-H) $cm.^{-1}$.

Reduction of 5-p-tolylthien-2-ylamide (refluxing for 24 hr.) gave 5-p-tolylthien-2-ylmethylamine hydrochloride (112, X = Me, NR_2 = NH_2) (54.7%), colourless silky needles, m.p. 256-258° (d) (Found: C, 59.93; H, 5.95; N, 5.59; $\underline{M}^+$, 203. $C_{12}H_{14}ClNS$ requires C, 60.13; H, 5.84; N, 5.84%; $\underline{M}^+$ [free base], 203), $\nu_{max.}$(Nujol) 1615 (N-H) $cm.^{-1}$.

Reduction of p-bromophenylthien-2-ylamides (111, X = Br).

(a) Using the method previously described.

Reduction of N-(5-p-bromophenylthen-2-oyl)morpholine gave a cream solid which was a mixture of N-(5-p-bromophenylthien-2-ylmethyl)morpholine

and N-(5-phenylthien-2-ylmethyl)morpholine hydrochlorides. Analytical figures were consistent with a 70.6% reduction of the aromatic bromine.

Reduction of N-(5-p-bromophenylthen-2-oyl)piperidine gave a cream solid which was a mixture of N-(5-p-bromophenylthien-2-ylmethyl)piperidine and N-(5-phenylthien-2-yl)piperidine hydrochlorides. Analytical figures were consistent with a 92.2% reduction of the aromatic bromine.

Reduction of N-(5-p-bromophenylthen-2-oyl)pyrrolidine gave colourless crystals which were a mixture of N-(5-p-bromophenylthien-2-ylmethyl)pyrrolidine and N-(5-phenylthien-2-ylmethyl)pyrrolidine hydrochlorides. Analytical figures were consistent with a 93.5% reduction of the aromatic bromine.

Reduction of N,N-dimethyl-5-p-bromophenylthien-2-ylamide gave colourless needles which were a mixture of N,N-dimethyl-5-p-bromophenylthien-2-ylmethylamine and N,N-dimethyl-5-phenylthien-2-ylmethylamine hydrochlorides. Analytical figures were consistent with a 20% reduction of the aromatic bromine.

(b) Using a four-fold excess of lithium aluminium hydride.

The amide (0.002 mole) in dry benzene (40 ml.) was added dropwise to a stirred suspension of lithium aluminium hydride (152 mg., 0.004 mole) in dry ether (20 ml.) and the mixture was refluxed for 48 hr. The amine hydrochloride was isolated as previously described.

In this way, N-(5-p-bromophenylthen-2-oyl)morpholine gave N-(5-phenylthien-2-ylmethyl)morpholine hydrochloride (412 mg., 91.3%), colourless flakes, m.p. 235-236° (d).

Similarly, N,N-dimethyl-5-p-bromophenylthien-2-ylamide gave N,N-dimethyl-5-phenylthien-2-ylmethylamine hydrochloride (466 mg., 92%), colourless needles, m.p. 229-230°.

The melting points were not depressed on admixture with authentic samples of the N-substituted-5-phenylthien-2-ylmethylamine hydrochlorides.

(c) Using the calculated amount of lithium aluminium hydride.

The amide (0.002 mole) in dry benzene (40 ml.) was added dropwise to a stirred suspension of lithium aluminium hydride (38 mg. 0.001 mole) in dry ether (20 ml.) and the mixture was refluxed for 6 hr. The amine hydrochloride was precipitated as previously described, and evaporation of the filtrate, obtained on removal of the amine hydrochloride, yielded a small quantity of the original amide.

In this way, N-(5-p-bromophenylthen-2-oyl)morpholine gave N-(5-p-bromophenylthien-2-ylmethyl)morpholine hydrochloride (112, X = Br, NR_2 = morpholino) (490 mg., 65.4%), colourless flakes, m.p. 236-238° (ethanol) (Found: C, 48.22; H, 4.52; N, 3.63; M^+, 337, 339. $C_{15}H_{17}BrClNOS$ requires C, 48.05; H, 4.54; N, 3.74%; M^+ [free base], 337, 339), $\nu_{max.}$ (Nujol) 2420 (C-H) $cm.^{-1}$.

$\tau_{(CDCl_3)}$ 7.35 (4H, m, morpholin-NCH_2), 6.28 (4H, m, morpholino-OCH_2), 6.13 (2H, s, CH_2), 2.95 (1H, d, J=3.4Hz., thienyl-H), 2.84 (1H, d, J=3.4Hz., thienyl-H), 2.56 (4H, s, phenyl-H).

Evaporation of the filtrate gave N-(5-p-bromophenylthen-2-oyl) morpholine (97 mg., 13.8%), cream crystals, m.p. 160-161° (carbon tetrachloride).

Similarly, N,N-dimethyl-5-p-bromophenylthien-2-ylamide gave N,N-dimethyl-5-p-bromophenylthien-2-ylmethylamine hydrochloride (112, X = Br, NR_2 = NMe_2) (479 mg., 72%), colourless needles, m.p. 239-240° (ethanol) (Found: C, 47.03; H, 4.52; N, 4.24; M^+, 297, 295. $C_{13}H_{15}BrClNS$ requires C, 46.92; H, 4.5; N, 4.21%; M^+ [free base], 297, 295), $\nu_{max.}$ (Nujol) 2600 and 2650 (C-H) $cm.^{-1}$.

$\tau_{(CDCl_3)}$ 7.80 (6H, s, $N(CH_3)_2$), 3.03 (1H, d, J=3.4Hz., thienyl-H), 2.81 (1H, d, J=3.4Hz., thienyl-H), 2.65 (4H, s, phenyl-H).

Evaporation of the filtrate gave N,N-dimethyl-5-p-bromophenylthien-2-ylamide (62 mg., 10%), colourless flakes, m.p. 136-137° (carbon tetrachloride).

5-p-Bromophenylthien-2-ylamide (refluxed for 24 hr.) gave 5-p-bromophenylthien-2-ylmethylamine hydrochloride (112, X = Br, NR_2 = NH_2) (371 mg., 60%), colourless flakes, m.p. 264-266° (d) (aqueous ethanol) (Found: C, 42.84; H, 3.56; N, 4.5. $C_{11}H_{11}BrClNS$ requires C, 43.3; H, 3.6; N, 4.6%), $\nu_{max.}$ (Nujol) 3200 and 1600 (N-H) $cm.^{-1}$.

N-Substituted-5-p-bromophenylthien-2-ylmethylamines (112, X = Br).

2-p-Bromophenyl-5-chloromethylthiophen (114, X = Br) (2.87 g., 0.01 mole) in dry benzene (40 ml.) was added dropwise to a stirred solution of the appropriate amine (0.1 mole) in benzene (20 ml.). The mixture was allowed to stand at room temperature for 3 days, basified with 20% aqueous

sodium hydroxide solution, the organic layer was separated and the aqueous layer was extracted with benzene. The dried ($MgSO_4$) combined extracts were evaporated, the excess of amine was evaporated under reduced pressure, and the residual oil was triturated with petrol. The solid N-substituted-5-p-bromophenylthien-2-ylamine was collected, dissolved in dry benzene and treated with dry hydrogen chloride to give the amine hydrochloride which was recrystallised from ethanol.

In this way, using morpholine, N-(5-p-bromophenylthien-2-ylmethyl)morpholine hydrochloride (2.8 g., 75%) was obtained as colourless prisms, m.p. 236-238°.

Similarly, using dimethylamine, N,N-dimethyl-5-p-bromophenylthien-2-ylmethylamine hydrochloride (2.56 g., 77%) was obtained as colourless needles, m.p. 239-240°.

In some cases, the amine hydrochloride was obtained as an oil which proved difficult to crystallise. The amine, in dry ethanol was therefore treated with methyl iodide (10% excess) to give the methiodide which was recrystallised from ethanol.

In this way, using piperidine, N-(5-p-bromophenylthien-2-ylmethyl) piperidine methiodide (3.16 g., 66.3%) was obtained, colourless flakes, m.p. 222-224° (d) (Found: C, 42.92; H, 4.4; N, 2.7. $C_{17}H_{21}BrINS$ requires C, 42.7; H, 4.4; N, 2.9%), $\nu_{max.}$ (Nujol) 2680 and 2550 (C-H) $cm.^{-1}$.

Similarly, using pyrrolidine N-(5-p-bromophenylthien-2-ylmethyl) pyrrolidine methiodide (2.87 g., 61.4%) was obtained, colourless flakes, m.p. 184-185° (d) (Found: C, 41.6; H, 4.1; N, 2.8. $C_{16}H_{19}BrINS$ requires C, 41.4; H, 4.1; N, 3.0%).

Aminomethylation of 2-phenylthiophen.

A vigorously stirred mixture of 2-phenylthiophen (6.2 g., 0.032 mole), ammonium chloride (3.6 g., 0.067 mole), and 36% aqueous formaldehyde (4 g., 0.13 mole, 11 ml.) was warmed to 65°, and this temperature was maintained for 30 min. The mixture was stirred at room temperature for 12 hr. and extracted with ether to remove unchanged 2-phenylthiophen (1.2 g.). The remaining aqueous mixture was treated with methanol (20 ml.) and allowed to stand for 5 hr. at room temperature. The low boiling constituents were evaporated, the residue was treated with 40% aqueous sodium hydroxide solution (10 ml.), allowed to stand for 2 hr, and extracted with ether. The dried ($MgSO_4$) ethereal extracts were treated with dry hydrogen chloride to precipitate 5-phenylthien-2-ylmethylamine hydrochloride (5.15 g., 73%), colourless flakes, m.p. 253-254°. The melting point was not depressed on admixture with an authentic sample prepared by the reduction of 5-phenylthien-2-ylamide.

Reaction of 5-phenylthien-2-ylmethylamine with ethyl acetimidate hydrochloride.

Ethyl acetimidate hydrochloride (0.62 g., 0.005 mole) was added portionwise to a stirred solution of 5-phenylthien-2-ylmethylamine (0.005 mole) in dry ethanol (50 ml.) cooled in ice water. The resulting solution was allowed to stand overnight at 0°, the deposited crystals were collected, and a further quantity of crystals were obtained on the addition of dry ether. Recrystallisation from ethanol gave N,N'-di-(5-phenylthien-2-yl) acetamidine hydrochloride (124) (0.91 g., 87%), colourless prisms, m.p. 233-234° (Found: C, 65.6; H, 5.25; N, 6.36; $\underline{M}^+$, 402. $C_{24}H_{23}ClN_2S_2$ requires C, 65.7; H, 5.24; N, 6.39%; $\underline{M}^+$ [free base], 402), $\nu_{max.}$ (Nujol) 1655 (C=N) $cm.^{-1}$.

τ ($CDCl_3$) 8.1 (3H, s, CH_3), 5.36 (4H, s, CH_2), 4.55 (1H, broad s, removed with D_2O, NH), 3.15-2.35 (16H, m, aromatic-H).

2-ARYL-5-CYANOMETHYLTHIOPHENS (119).

2-Aryl-5-chloromethylthiophen (114).

40% Aqueous formaldehyde (300 ml.) and concentrated hydrochloric acid (200 ml.) were added to the 2-arylthiophen (0.1 mole) in chloroform (150 ml.), and the vigorously stirred mixture was maintained at 60° while a slow stream of hydrogen chloride was bubbled through it for 2 hr. The mixture was poured into cold water (1.5 l.), the organic layer was separated, and the aqueous layer was extracted with chloroform. The dried ($MgSO_4$) combined organic layer and extracts were evaporated to give the 2-aryl-5-chloromethylthiophen which was recrystallised from petrol.

Only the 2-p-bromophenyl-5-chloromethylthiophen was sufficiently stable to be analysed.

In this way, the following compounds were prepared.

2-Chloromethyl-5-phenylthiophen (114, X = H) (9.03 g., 43.3%), colourless plates, m.p, 59-61° (d)

$\tau_{(CDCl_3)}$ 5.47 (2H, s, CH_2), 3.23 (1H, d, J=3.5Hz., thienyl-3-H), 3.10 (1H, d, J=5Hz., thienyl-4-H), 2.97-2.60 (5H, m, aromatic-H).

2-Chloromethyl-5-p-chlorophenylthiophen (114, X = Cl) (13.2 g., 54.2%), pale cream flakes, m.p. 85-87° (d) (lit.[181] 81.5-83.5°).

$\tau_{(CDCl_3)}$ 5.42 (2H, s, CH_2), 3.25-2.69 (6H, m, aromatic-H).

2-p-Bromophenyl-5-chloromethylthiophen (114, X = Br) (17.1 g., 59.6%), pale brown prisms, m.p. 96-97° (d) (Found: C, 46.23; H, 2.81; S, 10.89. $C_{11}H_8BrClS$ requires C, 45.91; H, 2.78; S, 11.13%)

$\tau_{(CDCl_3)}$ 5.40 (2H, s, CH_2), 3.12 (1H, d, J=4Hz., thienyl-3-H), 2.85 (1H, d, J=4Hz., thienyl-4-H), 2.59 (4H, s, phenyl-H).

2-Chloromethyl-5-phenylthiophen.

A stirred suspension of 5-phenylthiophen-2-carboxylic acid (4.1 g., 0.02 mole) in ether (50 ml.), cooled in ice water, was treated with diazomethane (1.4 g., 0.03 mole) in ether (100 ml.), and the excess of diazomethane was allowed to evaporate. The dried (Na_2SO_4) ethereal solution of the methyl ester was added dropwise to a stirred slurry of lithium aluminium hydride (0.95 g., 0.025 mole) in dry ether (20 ml.), the mixture was refluxed for 24 hr., cooled, and the excess of reducing agent was destroyed with water. 20% Sulphuric acid (50 ml.) was added and the mixture was stirred for 10 min. The ethereal layer was separated, the aqueous layer was extracted with ether, and the dried (Na_2SO_4) combined ethereal layer and extracts were evaporated. Distillation of the residual oil under reduced pressure gave 5-phenylthien-2-ylmethyl alcohol (3.04 g., 80%), colourless flakes, m.p. 89-90° (aqueous ethanol) (Found: C, 69.59; H, 5.2. $C_{11}H_{10}OS$ requires C, 69.5; H, 5.2%), $\nu_{max.}$ (Nujol) 3480 (O-H), 1300 and 1075 (C-O) $cm.^{-1}$.

A solution of the alcohol (1.9 g., 0.01 mole) in dry benzene (50 ml.), containing a few lumps of anhydrous calcium chloride was saturated with hydrogen chloride. The solvent was evaporated and the residual oil was distilled under reduced pressure to give 2-chloromethyl-5-phenylthiophen (1.25 g., 60%), colourless flakes, m.p. 59-61° (d) (petrol).

2-Aryl-5-cyanomethylthiophens (119).

2-Aryl-5-chloromethylthiophen (0.06 mole) in the minimum volume of dry dimethyl sulphoxide was added dropwise to a stirred suspension of sodium cyanide (4.9 g., 0.1 mole) in dry dimethyl sulphoxide (10 ml.) at 70°, and

stirring was continued at 70° for 2 hr. The mixture was poured into water (1.5 l.), extracted with chloroform and the dried (Na_2SO_4) extracts were evaporated. The residue was distilled under reduced pressure to give the required 2-aryl-5-cyanomethylthiophen.

In this way, the following compounds were prepared.

2-Cyanomethyl-5-phenylthiophen (119, X = H) (8.13 g., 68.2%), colourless broad needles, m.p. 82-83° (ethanol) (Found: C, 72.49; H, 4.7; N, 6.8. $C_{12}H_9NS$ requires C, 72.36; H, 4.5; N, 7.0%), $\nu_{max.}$($CHCl_3$) 2260 (C≡N) $cm.^{-1}$.

$\tau_{(CDCl_3)}$ 6.59 (2H, s, CH_2), 3.36 (1H, d, J=3.5Hz., thienyl-3-H), 3.18 (1H, d, J=3.5Hz., thienyl-4-H), 3.06-2.56 (5H, m, phenyl-H).

2-p-Chlorophenyl-5-cyanomethylthiophen (119, X = Cl) (8.6 g., 61.4%), colourless flakes, m.p. 108-109° (ethanol) (Found: C, 61.53; H, 3.4; N, 5.9. $C_{12}H_8ClNS$ requires C, 61.67; H, 3.4; N, 6.0%), $\nu_{max.}$(Nujol) 2260 (C≡N)$cm.^{-1}$.

$\tau_{(CDCl_3)}$ 6.2 (2H, s, CH_2), 3.06 (1H, d, J=3.5Hz., thienyl-3-H), 2.93 (1H, d, J=3.5Hz., thienyl-4-H), 2.88-2.62 (4H, m, phenyl-H).

2-p-Bromophenyl-5-cyanomethylthiophen (119, X = Br) (11.3 g., 67.8%), pale yellow needles, m.p. 125-126° (ethanol) (Found: C, 51.7; H, 2.8; N, 4.8. $C_{12}H_8BrNS$ requires C, 51.8; H, 2.9; N, 5.0%), $\nu_{max.}$($CHCl_3$) 2260 (C≡N) $cm.^{-1}$.

$\tau_{(CDCl_3)}$ 6.24 (2H, s, CH_2), 3.0 (1H, d, J=3.5Hz., thienyl-3-H), 2.92 (1H, d, J=3.5Hz., thienyl-4-H), 2.63 (4H, s, phenyl-H).

5-Phenylthien-2-ylacetamidine (122).

A solution of 2-cyanomethyl-5-phenylthiophen (4g., 0.02 mole) and dry ethanol (1.0 g,, 0.021 mole) in dry benzene (20 ml.) and dry ether (20 ml.) was saturated at 0° with dry hydrogen chloride, and allowed to stand for 24 hr. at 0°. The crystalline ethyl-5-phenylthien-2-ylacetimidate hydrochloride (121) (3.94 g., 70%) was collected and dried in vacuo. The imino ether (1.4 g., 0.005 mole) was added portionwise to a cooled, stirred, saturated solution of ammonia in dry ethanol (50 ml.) and the resulting clear solution was allowed to stand at 0° for 12 hr. The addition of dry ether precipitated 5-phenylthien-2-ylacetamidine hydrochloride (1.15 g., 91%), cream needles, m.p. 230-232° (d) (ethanol) (Found: C, 56.8; H, 5.2; N, 11.1. $C_{12}H_{13}ClN_2S$ requires C, 57.0, H, 5.2; N, 11.1%), $\nu_{max.}$ (Nujol) 1690 (C=N) $cm.^{-1}$.

Reduction of 2-cyanomethyl-5-phenylthiophen.

Anhydrous aluminium trichloride (1.46 g., 0.011 mole) in dry ether (20 ml.) was added to a stirred slurry of lithium aluminium hydride (0.42 g., 0.011 mole) in dry ether (10 ml.) under dry nitrogen, and the mixture was stirred for 5 min. The nitrile (1.99 g., 0.1 mole) in dry benzene (50 ml.) was added dropwise to the stirred mixture, which was then refluxed for 22 hr., cooled, and the excess of reducing agent was destroyed with 20% aqueous sodium hydroxide solution. The lithium aluminium oxide was filtered off, washed with ether, and the combined, dried (Mg, SO_4) filtrates were treated with dry ethereal hydrogen chloride to precipitate 2-(5-phenylthien-2-yl)ethylamine hydrochloride (120, X = H) (2.1 g., 87.5%), colourless flakes, m.p, 266-267° (ethanol) (lit.[182] 266°), $\nu_{max.}$ (Nujol) 3340 and 1610 (N-H) $cm.^{-1}$.

Hydrolysis of 2-aryl-5-cyanomethylthiophens.

A mixture of the nitrile (0.01 mole), ethanol (25 ml)., and 8% aqueous potassium hydroxide solution (25 ml.) was refluxed for 20 hr., the ethanol was evaporated, the residue diluted with water (50 ml.) and extracted with chloroform. The aqueous layer was acidified with concentrated hydrochloric acid, extracted with ether, and the dried (Na_2SO_4) ethereal extracts were evaporated to give 5-arylthien-2-ylacetic acid.

The following compounds were obtained in this way.

5-phenylthien-2-ylacetic acid (1.3 g., 59.6%), colourless flakes, m.p. 228-230° (carbon tetrachloride).

5-p-Bromophenylthien-2-ylacetic acid (1.49 g., 51%), pale cream flakes, m.p. 165-166° (aqueous ethanol) (Found: C, 48.77; H, 3.04; S, 11.05. $C_{12}H_9BrO_2S$ requires C, 48.5; H, 3.03; S, 10.8%), $\nu_{max.}$ (Nujol) 2905 (O-H) and 1700 (C=O) $cm.^{-1}$.

MASS SPECTRAL TABLES.

1-(5-Chlorobenzo[b]thien-3-ylmethyl)-3-methylguanidine (84, X = Cl, R^3 = Me, R^1 = R^2 = H)

m/e (I%)							
	254(35)	253(18)	252(90)	251(10)	238 (6)	223 (5)	222 (6)
	221 (8)	199 (4)	198 (5)	197(10)	196 (7)	195(22)	184 (6)
	183(35)	182(16)	181(100)	169(12)	168 (5)	160 (5)	159 (5)
	149 (5)	147 (5)	146(14)	145(22)	134(22)	133 (9)	127 (4)
	102(14)	101 (8)	89 (7)	86 (7)	85(21)	75 (5)	75 (5)
	69 (9)	59 (5)	58(82)	57(92)	45(20)	43(55)	38(28)
	36(76)	35 (7)	32(25)	30(60).			

m*			
	250.8(253 → 252),	224(253 → 238),	221(223 → 222)
	197.1(252 → 223),	196.5(253 → 223),	161.4(238 → 196)
	152.5(252 → 196),	151.9(253 → 196),	146.9(223 → 181)
	118(181 → 146),	116.4(181 → 145),	106.3(169 → 134)
	71.2(146 → 102),	50.5(145 → 86).	

1-(5-Chlorobenzo[b]thien-3-ylmethyl)-3,3-dimethylguanidine (80, X = Cl, n=1)

m/e (I%)							
	268(14)	267 (6)	266(41)	252 (6)	224 (5)	223 (4)	222(12)
	221 (4)	199 (6)	198(11)	197(19)	196(45)	194(12)	183(34)
	182(15)	181(100)	169 (4)	168 (3)	159 (4)	149 (5)	147 (3)
	146(10)	145(16)	134 (8)	133 (6)	132 (3)	123 (3)	117 (6)
	110 (5)	102(11)	101 (5)	89 (5)	86 (6)	82 (4)	77 (6)
	76(12)	75 (6)	72(28)	71(30)	69 (8)	57(45)	50 (8)
	46(22)	45(15)	43(12)	42(10)	38(16)	36(49)	31 (9)
	30 (9)						

m*			
	265.1(267 → 266),	237.8(267 → 252),	195.6(252 → 222)
	147.6(222 → 181),	146.9(223 → 181),	144.5(267 → 196)
	145.7(196 → 169).		

1-(5-Chlorobenzo[b]thien-3-ylmethyl)-2,3-dimethylguanidine. (84, X = Cl, $R^1 = R^3 = Me$, $R^2 = H$).

m/e (I%)							
	268(27)	267(18)	266(66)	265(10)	254 (3)	252 (9)	237 (6)
	236(10)	235(37)	234(18)	222 (7)	211 (2)	209 (6)	207 (4)
	205 (5)	200 (5)	198(10)	197(22)	196(18)	195(63)	193(35)
	184 (6)	183(34)	182(18)	181(100)	169 (4)	149 (4)	147 (4)
	146(17)	145(17)	134 (7)	133 (4)	115 (4)	102(10)	101 (6)
	99(12)	72(60)	71(66)	69 (9)	57 (9)	55 (7)	45(10)
	44 (8)	42(11)	38(18)	36(51)	30(29).		

m*			
	265(267 → 266),	237.8(267 → 252),	233(235 → 234),
	207.6(266 → 235),	195.6(252 → 222),	183.1(234 → 207),
	152.5(252 → 196),	144.4(266 → 196),	143.9(267 → 196),
	140(234 → 181),	106.3(169 → 134),	97.7(134 → 102),
	50.5(145 → 86).		

1-(5-Chlorobenzo[b]thien-3-ylethyl)-3-methylguanidine. (85, X = Cl, $R^3 = Me$, $R^1 = R^2 = H$).

m/e (I%)							
	267 (1)	266 (1)	253 (1)	238 (1)	212 (2)	210 (7)	196 (3)
	195 (1)	194 (6)	184(10)	183 (8)	182(28)	181(16)	149 (2)
	147 (4)	146 (3)	145 (6)	115 (2)	102 (4)	101 (2)	86 (1)
	69 (3)	59 (2)	58(21)	45 (4)	38 (7)	36(22)	30(100).

m*			
	212.2(267 → 238),	181(183 → 182),	180(182 → 181),
	165.2(267 → 210),	159.5(210 → 183),	141(267 → 194),
	130.3(194 → 159),	118(181 → 146),	116.5(181 → 145).

1-(5-Chlorobenzo[b]thien-3-ylethyl)-3,3-dimethylguanidine. (80, X = Cl, n = 2).

m/e (I%)						
	282 (6)	281 (3)	280(17)	238 (3)	210 (2)	196(14)
	195 (9)	194(38)	184 (2)	183(11)	182 (6)	181(27)
	160 (7)	159 (7)	158 (3)	149 (3)	147 (3)	146 (3)
	145 (4)	115 (9)	102 (3)	101(11)	100(100)	88 (7)
	87(41)	72(11)	71(70)	58(11)	57(45)	56 (5)
	55 (8)	36 (6)	35(10)	34(10).		

m*			
	201.6(281 → 238),	181(183 → 182),	180(182 → 181)
	157(281 → 210),	133.9(281 → 194)	130.3(194 → 159)
	83.2(159 → 115),	59.5(87 → 72),	50.5(100 → 71)
	38.7(87 → 58),	32.5(100 → 57).	

1-(5-Chlorobenzo[b]thien-3-ylethyl)-2,3-dimethylguanidine (85, X = Cl, $R^1 = R^3 = Me$, $R^2 = H$)

m/e (I%)						
	282 (7)	281 (4)	280(19)	210 (3)	196(25)	195(14)
	194(62)	188 (6)	182 (4)	181(14)	160 (8)	159(10)
	149 (2)	146 (3)	145 (3)	115(11)	101(12)	100(100)
	89 (8)	87(36)	72(14)	71(94)	70 (7)	69 (27)
	58(31)	57(22)	56 (4)	55 (6)	45 (4)	44(14)
	42 (9)	38(11)	36(34)	35 (4)	30(18).	

m*			
	181(183 → 182),	180(182 → 181),	159.5(210 → 183)
	133.9(281 → 194),	130.3(194 → 159),	118(181 → 146)
	116.5(181 → 145),	83.3(159 → 115),	59.6(87 → 72)
	50.5(100 → 71),	38.7(87 → 58).	

2-p-Tolylthiophen (101, X = Me)

m/e (I%)						
	174(100)	173(54)	147 (5)	141(14)	129(15)	128(11)
	127 (5)	115(11)	89 (4)	87 (4)	86 (4)	77 (5)
	74 (4)	69 (4)	65 (4)	63 (7)	51 (5)	45(11)

m* 172(173 → 172), 127(129 → 128), 125(173 → 147)
114.2(173 → 141), 96.2(173 → 129), 93.8(141 → 115)
94.1(147 → 115), 69(115 → 89).

N-(5-phenylthien-2-ylmethyl)morpholine (112, X = H, NR_2=morpholino)

m/e (I%)							
	259(19)	186 (5)	174(15)	173(100)	172 (1)	171 (3)	139 (2)
	134 (2)	129 (4)	128 (4)	127 (2)	121 (2)	115 (3)	100 (2)
	99 (5)	86(13)	77 (3)	56(13)	45 (7)	38(11)	36(33)

m* 171(173 → 172), 170.3(172 → 171), 127.2(129 → 128)
125(173 → 147), 115.5(259 → 173) 96.4(173 → 129).

N-(5-p-bromophenylthien-2-ylmethyl)morpholine (112, X = Br, NR_2-morpholino)

m/e (I%)						
	339 (2)	337 (2)	266 (5)	264 (5)	254(20)	253(100)
	252(20)	251(100)	201 (2)	199 (2)	173 (8)	172(13)
	171(22)	139 (6)	129 (1)	128 (9)	127 (3)	120 (3)
	115 (2)	114 (4)	100 (9)	86(35)	85 (6)	56(32)
	45 (6)	42 (7)	38 (23)	36(52)		

m* 188.8(339 → 253), 187(337 → 251), 170.5(172 → 171),
118(253 → 172), 117(251 → 172), 94.4(171 → 127).

N-(5-p-chlorophenylthien-2-ylmethyl)morpholine. (112, X = Cl, NR_2 = morpholino)

m/e (I%)						
	295(10)	294 (6)	293(28)	220 (6)	209(39)	208(15)
	207(100)	173 (6)	172 (4)	171(10)	149 (2)	139 (2)
	129 (3)	128 (6)	127 (3)	86 (3)	56 (8)	45 (3)

m^* 170.5(172 → 171), 146.2(293 → 207), 143(207 → 172)
127.3(129 → 128).

N-(5-p-tolylthien-2-ylmethyl)morpholine . (112, X = Me, NR_2=morpholino)

m/e (I%)							
	273(12)	200 (3)	189 (6)	188(17)	187(100)	173 (2)	172 (2)
	171 (4)	128 (5)	127 (2)	115 (3)	100 (2)	99 (3)	93 (4)
	86 (6)	56 (7)	45 (3)	42 (3)	38 (4)	36(14)	

m^* 170.5(172 → 171), 158.2(187 → 172), 128(173 → 187)
36.6(273 → 100).

N,N-Dimethyl-5-phenylthien-2-ylmethylamine. (112, X = H, NR_2 = NMe_2)

m/e (I%)							
	217(14)	216 (4)	174(14)	173(100)	172 (2)	171 (3)	140 (3)
	139 (4)	134 (3)	129 (4)	128 (6)	127 (3)	121 (5)	115 (9)
	102 (2)	89 (3)	77 (6)	71 (3)	69 (3)	63 (3)	58(11)
	51 (4)	45 (6)	42(15)	36 (6)			

m^* 171(173 → 172), 170.2(172 → 171), 137.8(217 → 173),
127(120 → 128), 125.1(173 → 147), 96.2(173 → 129).

N,N-Dimethyl-5-p-bromophenylthien-2-ylmethylamine. (112, X = Br, NR_2 = NMe_2)

m/e (I%)							
	296(16)	295 (7)	294(16)	293 (6)	253(100)	252(14)	
	251(100)	201 (1)	199 (1)	173 (1)	172 (6)	171(13)	
	140 (1)	139 (3)	128 (4)	120 (1)	115 (1)	114 (2)	113 (1)

108 (2) 58 (8) 45 (3) 42 (7) 36 (6)

m^* 294(296 → 295), 292(294 → 293), 216.2(296 → 253), 214.4(294 → 251), 170.3(172 → 171), 117.8(251 → 172), 117(253 → 172).

N,N-Dimethyl-5-p-chlorophenylthien-2-ylmethylamine. (112, X = Cl, $NR_2 = NMe_2$)

m/e (I%) 253 (7) 251(20) 209(52) 208(20) 207(100) 172 (2)
171(10) 170 (6) 169(17) 157 (2) 155 (5) 151 (2)
149 (6) 139 (5) 128 (7) 127 (5) 115 (3) 114 (3)
113 (3) 89 (2) 75 (5) 71 (5) 69 (5) 63 (4)
58(34) 57 (6) 45(11) 42(32) 36(27).

m^* 170.8(251 → 207), 170.3(172 → 171), 143(207 → 172) 127(129 → 128).

N,N-Dimethyl-5-p-tolylthien-2-ylmethylamine (112, X = Me, $NR_2 = NMe_2$)

m/e (I%) 231(16) 230 (4) 188(14) 187(100) 172 (2) 171 (4)
139 (2) 128 (5) 127 (2) 115 (4) 114 (3) 58(10)
45 (3) 42(10) 36(10)

m^* 170.5(172 → 171), 151.4(231 → 187)

5-Phenylthien-2-ylmethylamine. (112, X = H, $NR_2 = NH_2$)

m/e (I%) 190(12) 189(80) 188(53) 174 (8) 173(58) 172 (3)
171 (6) 160 (7) 156(11) 129(15) 128(100) 127(52)
121(15) 115(25) 112(14) 102 (8) 89(10) 77(95)
76(11) 75 (9) 74 (6) 69(14) 68 (6) 63(33)
51(75) 50(55) 45(13) 38(13) 37(23) 35(18)
34 (9) 30(25)

m^* 187(189 → 188), 171(173 → 172), 170.5(172 → 171)
158.3(189 → 173), 137.8(188 → 161) 128.6(189 → 156)
127(129 → 128), 125.9(128 → 127), 125(173 → 147).

5-p-Chlorophenylthien-2-ylmethylamine (112, X = Cl, $NR_2 = NH_2$)

m/e (I%) 224(38) 223(100) 222(64) 209(37) 207(59) 196 (8)
195(11) 194(14) 191 (9) 190(23) 173(21) 172 (8)
171(24) 162 (9) 161 (5) 160(25) 155(14) 151(10)
149(31) 136(14) 128(19) 127(16) 126 (9) 125 (8)
115(40) 114(18) 113(19) 112(35) 111(15) 102 (8)
101(14) 99(10) 98 (7) 95 (9) 94 (9) 93(20)
89(18) 87(13) 86(12) 78(14) 77(14) 76(21)
75 (8) 74(49) 73(31) 71(29) 69(32) 68(59)
67(20) 51(24) 50(19) 45(32) 36(38) 30(56).

m^* 221(223 → 222), 171(222 → 195), 143(207 → 172)
131.3(195 → 160).

5-p-Tolylthien-2-ylmethylamine (112, X = Me, $NR_2 = NH_2$)

m/e (I%) 204(15) 203(97) 202(53) 188(14) 187(70) 175 (9) 174(11)
173(10) 172 (5) 171(14) 170(23) 160 (8) 154 (6)
153(13) 152(13) 147(21) 142(30) 141(33) 139(30)
136(13) 135(29) 134(25) 129(56) 128(64) 127(30)
121(11) 116(17) 115(100) 114(10) 113(10) 112(61)
103(10) 102(17) 101(10) 91(33) 89(22) 78(23)
77(24) 69(13) 68(22) 65(17) 63(19) 51(15)
45(17) 39(29) 38(17) 36(47) 35(13) 30(53).

m^* 151.8(202 → 175), 146.3(175 → 160), 140.2(142 → 144), 127(187 → 154), 125(187 → 153), 115.2(175 → 142), 46.4(91 → 65).

N-(5-phenylthen-2-oyl)morpholine (111, X = H, NR_2 = morpholino)

m/e (I%)							
273(27)	245 (1)	240 (4)	188(10)	187(76)	160 (4)	159 (2)	
116(10)	115(100)	114 (5)	102(18)	89 (8)	86(14)	77 (8)	
65 (5)	63 (5)	58(13)	56 (9)	51 (6)	43(48)		

m^* 271(273 → 272), 220(273 → 245), 211(273 → 240), 135(187 → 159), 83.2(159 → 115).

N-(5-p-chlorophenylthen-2-oyl)morpholine (111, X = Cl, NR_2 = morpholino)

m/e (I%)							
309(14)	308(11)	307(40)	279 (1)	276 (1)	274 (3)	223(20)	
222 (7)	221(61)	210 (1)	208 (3)	196 (4)	194(12)	193 (2)	
186 (4)	158 (3)	152 (2)	151(26)	150 (9)	149(100)	136 (2)	
125 (2)	123 (3)	114 (4)	113 (3)	86 (4)	79 (5)	75 (8)	
56 (8)	51 (4)	45 (4)	42(10)				

m^* 254(307 → 279), 244.6(307 → 274), 170.4(221 → 194), 168.8(221 → 193), 115.2(113 → 149), 112.2(114 → 113), 87.2(149 → 114), 82.2(158 → 114).

N-(5-p-tolylthen-2-oyl)morpholine. (111, X = Me, NR_2 = morpholino)

m/e (I%)							
287(27)	259 (1)	254 (1)	253 (5)	203 (6)	202(16)	201(100)	
187 (2)	174 (4)	173 (1)	171 (2)	129(16)	128 (3)	127 (2)	
116 (2)	86 (2)	56 (2)					

m^* 233.5(287 → 259), 224.8(287 → 254), 149(201 → 173), 127.2(129 → 128), 125.2(173 → 147), 96.2(173 → 129).

N,N-Dimethyl-5-phenylthien-2-ylamide (111, X = H, NR_2 = NMe_2)

m/e (I%)							
	231(13)	188 (6)	187(46)	161 (4)	160(18)	159 (4)	158 (4)
	116(10)	115(100)	114 (6)	113 (3)	102 (8)	89(13)	77 (7)
	76 (6)	75 (5)	72 (6)	69 (5)	65 (6)	63(12)	51(11)
	50 (5)	45 (4)	44 (5)	42(15)	39 (9)		

m* 229(231 → 230), 151.3(231 → 187), 135(187 → 159), 112.2(114 → 113), 83.3(159 → 115), 69(115 → 89).

N,N-Dimethyl-5-p-bromophenylthien-2-ylamide. (111, X = Br, NR_2 = NMe_2).

m/e (I%)							
	312(10)	311(61)	310(13)	309(61)	268(13)	267(100)	266(13)
	265(100)	240 (4)	238 (4)	195(21)	193(21)	187 (6)	186 (3)
	158 (2)	115 (2)	114 (3)	113 (1)	72 (2)	44 (4)	42 (6)

m* 229(311 → 267), 227(309 → 265), 214(267 → 239), 212(265 → 237), 142.4(267 → 195), 140.7(265 → 193), 112.2(114 → 113), 82.2(158 → 114), 68.5(195 → 115), 67.8(195 → 113).

N,N-Dimethyl-5-p-chlorophehylthien-2-ylamide. (111, X = Cl, NR_2 - NMe_2)

m/e (I%)						
	267(12)	266 (6)	265(34)	223(34)	222(12)	221(100)
	196 (2)	194 (6)	186 (4)	173 (6)	158(11)	151(25)
	149(83)	138 (2)	136 (7)	115 (8)	114(17)	113(12)
	101 (7)	99 (5)	87 (5)	75(10)	74 (6)	72 (8)
	69 (6)	63 (9)	51 (7)	45 (5)	44 (9)	42(17)

m* 221(223 → 222), 168.8(221 → 193), 112.2(114 → 113), 87.2(149 → 114).

N,N-Dimethyl-5-p-tolylthien-2-ylamide. (111, X = Me, NR_2 = NMe_2)

m/e (I%)							
	246 (6)	245(41)	203 (5)	202(13)	201(100)	174 (6)	173 (4)
	172 (3)	171 (6)	158 (3)	147 (3)	145 (3)	130 (8)	129(80)
	128(20)	127(10)	115(15)	102 (4)	91 (4)	89 (6)	77 (7)
	72 (6)	69 (4)	65 (6)	63 (9)	45 (5)	44 (7)	42(11)
	39 (7)						

m* 165(245 → 201), 149(201 → 173), 127.2(129 → 128), 125(173 → 147), 114.8(173 → 141), 96.2(173 → 129) 94.2(147 → 115).

5-Phenylthien-2-ylamide. (111, X = H, NR_2 = NH_2).

m/e (I%)							
	204(11)	203(86)	188(13)	187(100)	160 (1)	159 (2)	158 (3)
	121 (3)	116 (8)	115(79)	114 (5)	113 (3)	102 (6)	89 (9)
	79 (7)	77 (6)	76 (5)	69 (5)	65 (4)	63(10)	51 (8)
	50 (5)	45 (4)	44 (8)	39 (7)			

m* 172.2(203 → 187), 135.5(187 → 159), 83.2(159 → 115), 69(115 → 89).

5-p-Chlorophenylthien-2-ylamide. (111, X = Cl, NR_2 = NH_2)

m/e (I%)						
	240(17)	239(16)	238 (6)	237(40)	223(27)	221(100)
	173 (2)	158 (4)	151(11)	149(35)	138(1)	136 (4)
	115(49)	114 (7)	113 (6)	101 (4)	99 (3)	93 (3)
	79 (5)	75 (6)	69 (4)	63 (7)	45(4)	44 (8)
	39 (3)					

m* 206(237 → 221), 168.9(221 → 193), 100.5(221 → 149), 87.2(149 → 114).

5-p-Tolylthien-2-ylamide (111, X = Me, NR_2 = NH_2).

m/e (I%) 218(17) 217(100) 202 (7) 201(47) 174 (1) 173 (3) 171 (3)
147 (1) 145 (1) 130 (2) 129(26) 128 (8) 127 (4) 115 (6)
101 (2) 100 (3) 89 (3) 77 (3) 63 (5) 45 (4) 44 (6)
39 (6)

m* 186(217 → 201), 149(201 → 173), 127.2(129 → 128),
125(173 → 147), 114.8(173 → 141), 96.4(173 → 129),
93.8(141 → 115).

5-Phenylthiophen-2-carboxylic acid hydrazide.

m/e (I%) 218(10) 188(11) 187(100) 159(41) 116(8) 115(80) 102(8)
89(10) 77 (5) 76 (5) 63 (9) 51 (9) 50 (6) 45 (4)
39 (6) 31(11).

m* 160.4(218 → 187), 135.2(187 → 159).

5-p-Chlorophenylthiophen-2-carboxylic acid hydrazide.

m/e (I%) 254 (3) 252 (9) 223(30) 221(100) 207 (5) 193 (1) 186 (4)
158 (9) 151(29) 150 (9) 149(86) 136 (9) 114(13) 113 (9)
101 (5) 76 (8) 69 (5) 63 (8) 31 (9).

m* 168.5(221 → 193), 120.6(193 → 136), 112(114 → 113).

5-p-Tolylthiophen-2-carboxylic acid hydrazide.

m/e (I%) 232(14) 202(15) 201(100) 173 (3) 172 (2) 171 (3) 158 (2)
130 (6) 129(53) 128(14) 127 (6) 116 (8) 115(11) 91 (8)
77 (4) 63 (5) 51 (4) 45 (3) 39 (5) 31 (8)

m^* 174.2(232 → 201), 149(201 → 173), 127(129 → 128), 126(128 → 127), 125(173 → 147), 114.8(173 → 141), 96.4(173 → 129).

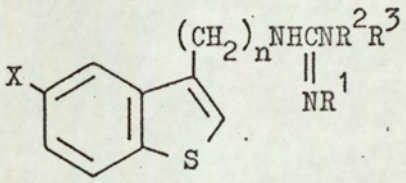
N,N'-Di-(5-phenylthien-2-yl) acetamidine (124).

m/e (I%)						
	402(17)	344 (2)	331 (1)	242 (2)	229(65)	213(10)
	200 (3)	196 (8)	188(100)	187 (3)	186 (4)	173(70)
	172(13)	171(12)	161(15)	159 (3)	147 (2)	139 (5)
	134 (4)	129 (8)	128(20)	121(10)	115(13)	102 (3)
	89 (3)	77 (5)	51 (3)	45(15)	42(28)	36(25)
	38 (7)					

m^* 185.8(188 → 187), 171(173 → 172), 170.5(172 → 171), 154.4(229 → 188), 138.5(213 → 172), 137.9(188 → 161), 130.5(402 → 229), 127(129 → 128), 125(173 → 147), 101.8(161 → 128), 114(402 → 213), 96.2(173 → 129).

Antibacterial Screening Results.

Table 2.



X	n	R^1	R^2	R^3	A	B	C	D
Cl	1	H	H	Me	125	500	250	125
Cl	1	H	H	Ph	31.25	1000	62.5	125
Cl	1	Me	H	Me	125	1000	500	250
Cl	1	H	Me	Me	62.5	250	250	62.5
Cl	2	H	H	Me	125	500	500	250
Cl	2	H	H	Ph	21.25	1000	125	125
Cl	2	Me	H	Me	250	1000	1000	500
Cl	2	H	Me	Me	125	1000	500	250
Br	1	H	H	Me	31.2	250	250	125
Br	1	H	H	Ph	15.6	1000	62.5	62.5

The values given are the minimum inhibitory concentrations in μg/ml. against the following bacteria,

A = S. aureus.

B = S. pyogenes.

C = E. coli.

D = P. vulgaris.

The minimum inhibitory concentrations of a selection of 5-halogenobenzo[b]thien-3-ylalkylguanidines (84, 85) against four strains of bacteria are shown in Table 2. All of the compounds showed some antibacterial activity; the most favourable results were obtained against S. aureus, and S. pyogenes was the most resistant of the bacterial strains in all cases.

In general, the methylguanidines (84) were more effective than the corresponding ethylguanidines (85) and highest activity was shown by the 5-bromo-substituted compounds. The most active compounds were the monosubstituted 5-halogenobenzo[b]thien-3-ylalkylguanidines (84, 85, R^1 = R^3 = H, R^2 = Me, Ph.) and the N-phenyl derivatives were superior to the N-methyl compounds against all of the bacterial strains except S. pyogenes. Disubstitution decreased the activity in most cases and the 3,3-dimethyl derivatives (84, 85, R^2 = R^3 = Me, R^1 = H) were often more effective than the corresponding 2,3-dimethyl compounds (84, 85, R^1 = R^2 = Me, R^3 = H).

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