SOME HETEROCYCLIC SYSTEMS AS AMBIDENT ELECTROPHILES

by

John Suschitzky

A Thesis Submitted for the Degree of Doctor of Philosophy of the University of Leicester.

August 1970

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

"...To explore new worlds;

To seek out new life and civilisations;

To boldly go where no man has gone before."

Star Trek

STATEMENT

The accompanying thesis submitted for the degree of Doctor of Philosophy is based on work conducted by the author in the Department of Chemistry of the University of Leicester and at Smith Kline, and French Laboratories, Welwyn Garden City, Herts.

All the work recorded in this thesis is original unless otherwise acknowledged in the text or by references. None of the work has been submitted for another degree in this or any other University.

Signed August, 1970

J. Suschitzky

(J. Suschitzky)

Acknowledgements

I would like to record my sincere thanks to Professor C.W. Rees for his constant guidance and encouragement over the past three years, and to Dr. A.M. Roe for his help during and after my stay in industry. I am also grateful to the Science Research Council for a Research Studentship under the CAPS scheme and to Smith Kline, and French Laboratories for their generous financial help in my final year which enabled me to complete my work.

Finally, I would like to thank all the physical organic chemists at Smith Kline, and French Laboratories for their assistance, as well as Dr. Slater with whom I had many useful discussions.

ABSTRACT

Some Heterocyclic Systems as Ambident Electrophiles.

Some heterocyclic systems were investigated for ambident electrophilic behaviour. Of the cases reported in the literature, the majority involve nucleophilic attack, most frequently by cyanide on a halomethyl aromatic system to give as the major product, the expected cyanomethyl compound ('normal' product) accompanied by the compound derived from S_N1' or S_N2' attack of cyanide ('abnormal' product).

In the present work, the halomethyl derivatives of the following systems were investigated: benzothiophene, thiophene, benzofuran, furan, and pyrazine. Triphenylmethylchloride was also investigated for comparison. The ability of these systems to display ambident electrophilic behaviour is correlated with their structure. Solvent effects are also investigated.

2-Furfuryl was taken as a model system because of its great tendency to give abnormal products. The system was made to rearrange under conditions in which the temperature and the nature of the nucleophile and leaving group were varied. The competition between 'normal' and 'abnormal' product formation appears to be kinetically controlled.

The interesting transformation of 2-bromomethyl-5-methylthiophene to 3-bromo-2,5-dimethylthiophene has

been reported to occur. A detailed examination of this reaction was undertaken and the mechanism is discussed.

At the end of the Thesis, a report of the work completed in industry* as part of the CAPS scheme is given. The objective of this work was to examine synthetic procedures for obtaining the enantiomers of 4(5)-(2-aminopropyl)imidazole (α-methylhistamine) and 4(5)-(2-amino-1-methylethyl)imidazole (β-methylhistamine) in order to provide new compounds for biological testing. A new synthesis of α-methylhistamine from L-histidinol has been devised; the optical purity of the product is unknown. β-Methylhistamine has been obtained in quantity and has been partially resolved with D-camphor-10-sulphonic acid.

An unsuccessful attempt to prepare 4(5)-(2-amino-1-methylethyl)-2-methylimidazole by a method which has been used for 4(5)-(2-aminoethyl)-2-methylimidazole (2-methylhistamine) is also described.

* At Smith Kline, and French Laboratories Ltd., Welwyn Garden City, Herts.

CONTENTS

	Page
Introduction	
Acyclic Ambident Electrophiles	4
Ambident Electrophiles in Heterocyclic Systems	10
Furans	13
Imidazoles	19
Pyrroles	21
Thiophenes	22
Pyrazines	30
Benzenoid compounds	32
Correlation between Structure and Ambifunctionality	36
Experimental	41
Instrumentation	42
Thiophenes	45
Furans	76
Benzothiophenes	90
Benzofurans	100
Thiazoles	104
Ferrocenes	124
Tritylchloride	130
Discussion	133
The Synthesis of α-Haloalkyl Aromatic Compounds	136
1. Direct Synthesis	136
2. Halomethylation	138

Discussion (Cont'd) Page

3. Halogenation of Side-chains 142

4. Conversion of Alcohols into Halomethyl Compounds 145

Stability of Halomethyl Compounds 146

Reactions of Halomethyl Compounds with Cyanide 149

Correlation between Structure and Ambifunctionality 153

The Energy Profile 158

Order of Reactions 160

Thermodynamic v. Kinetic Control 162

Effect of Temperature 168

Effect of Nucleophile 169

Effect of Leaving Group 171

Effect of Solvent 172

Miscellaneous 179

1. Ferrocenes 179

2. Reaction of Furfurylthiocyanate and Isothiouronium Salts with Cyanide 180

3. Benzothiophenes 184

The 'Lecocq' Rearrangement 189

Methylhistamines 203

Discussion 204

Experimental 213

Bibliography 223

I N T R O D U C T I O N

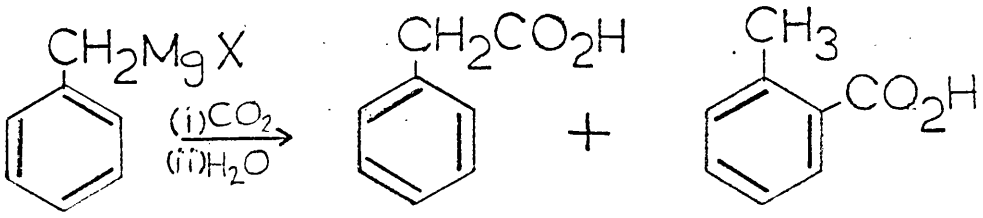
INTRODUCTION

The present work deals with reactions of ambident electrophilic species of heterocyclic systems. Since this subject has not been reviewed and the information is widely dispersed in the literature, this section is mainly devoted to a discussion of the existing knowledge in this field.

Generally an ambident species (also referred to as an ambient or ambifunctional species) may be defined as a system containing two centres susceptible to either electrophilic or nucleophilic (or homolytic) attack, but in which only one of these centres can take part directly in one transition state. Of the heterolytic cases, ambident nucleophiles are well documented and therefore only briefly considered before presenting a detailed account of ambident electrophiles.

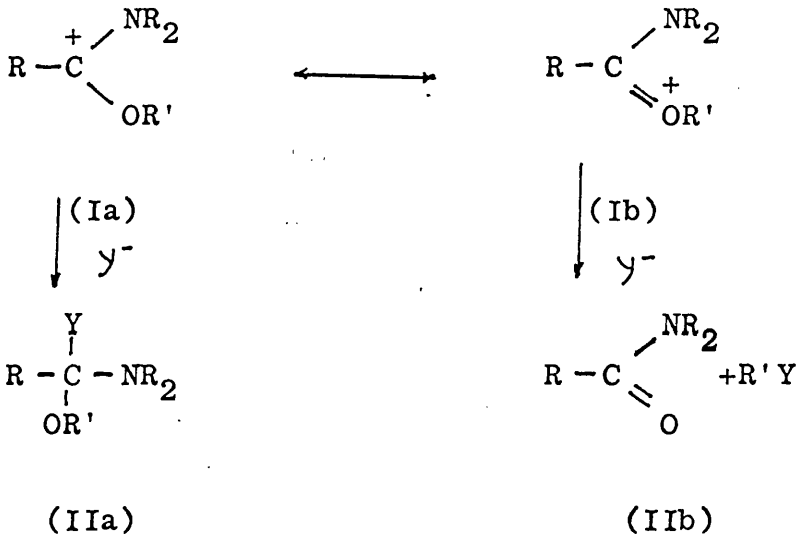
Reactions involving ambident nucleophiles are known in great numbers and have been comprehensively reviewed by Gompper[1]. Among the simpler cases are amides in which the nitrogen atom usually acts as the nucleophile, but the oxygen atom can also attack electrophilic species or the cyanide anion which can react via the carbon atom to form nitriles or through the nitrogen atom when isonitriles are obtained. Another example is found in the alkylation of indole sodium salt[2]. It is worth mentioning that a number of 'allylic' Grignard compounds when treated with standard reagents can give

abnormal products[3-10], as exemplified in Scheme 1. These reactions as we shall see, are formally similar to the ambident electrophiles under study in the present work.



SCHEME 1

In contrast to ambident nucleophiles, examples of transformations involving ambident electrophilic species are uncommon. Broadly, ambident cations can be divided into two types. The first category includes simple carbonium ions in which the positive charge can also rest on a neighbouring hetero atom (nitrogen, oxygen, or sulphur usually). Attack by a nucleophile can result in a mixture of the carbon and the heteroatom-substituted compound or products derived from these. For instance, in Scheme 2 the carbonium ion (Ia) also exists as the mesomeric oxonium ion (Ib). Attack by a nucleophile ($\bar{Y}$) can therefore give rise to the amino ether (IIa) or the amide (IIb), the latter being formed by the elimination of R'.



SCHEME 2

Hünig[11] has recently reviewed this first class of ambident electrophiles. The present work, however, is concerned with the second type of ambident electrophile, which has the positive charge in a reaction intermediate delocalised in a polyene system. Examples of this type will now be discussed under two headings.

1. ACYCLIC AMBIDENT ELECTROPHILES

Some mechanistic work has been done on acyclic allylic compounds which rearrange via ambident carbonium ions (for reviews see references 12 to 15). In Scheme 3 the allylic substrate (III) may be treated with a nucleophile ($\overline{Y}$) to give the 'normal' product (IVa) or the 'abnormal' product (IVb) in which the nucleophile has become attached to the γ-carbon atom.

$$R\text{-}CH{=}CH\text{-}CH_2X \xrightarrow{Y^-} R\text{-}CH{=}CH\text{-}CH_2Y \;+\; R\text{-}CHY\text{-}CH{=}CH_2$$

(III) (IVa) (IVb)

SCHEME 3

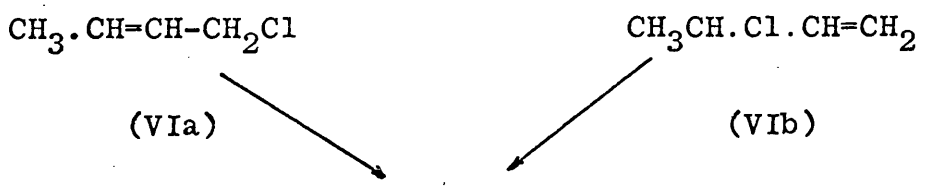
Three possible mechanisms by which this process may occur are now considered.

The S_N1' mechanism: When the above transformation occurs unimolecularly, the mesomeric carbonium ion (Va$\longleftrightarrow$Vb) can be visualised as the intermediate and the reaction is said to go by an S_N1' mechanism.

$$R.CH{=}CH\text{-}CH_2^+ \longleftrightarrow R.\overset{+}{C}H\text{-}CH{=}CH_2$$

(Va) (Vb)

Typically, when α,β-unsaturated halides are treated with sodium carbonate in water or with various metallic acetates in acetic acid, rearrangement by an S_N1' mechanism occurs[16,17,18]. A simple unimolecular reaction is not always observed, however. If it were, then the α,β-unsaturated halides (VIa) and (VIb) on treatment with hydroxide ion should each give the alcohols (VIIa) and (VIIb) in the same proportion. It was found that on treatment with 0.8M sodium hydroxide at 25°, 1-chlorobut-2-ene (VIa) gave 1-hydroxybut-2-ene (VIIa) and 3-hydroxybut-1-ene (VIIb) in the ratio 3:2, whereas 3-chlorobut-1-ene (VIb) gave the two isomers in the ratio 2:3[12].

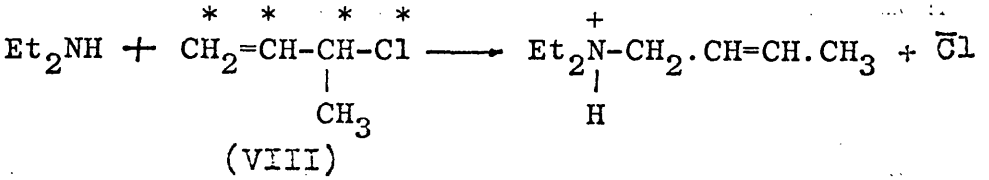


$CH_3.CH=CH.CH_2OH$ (VIIa)

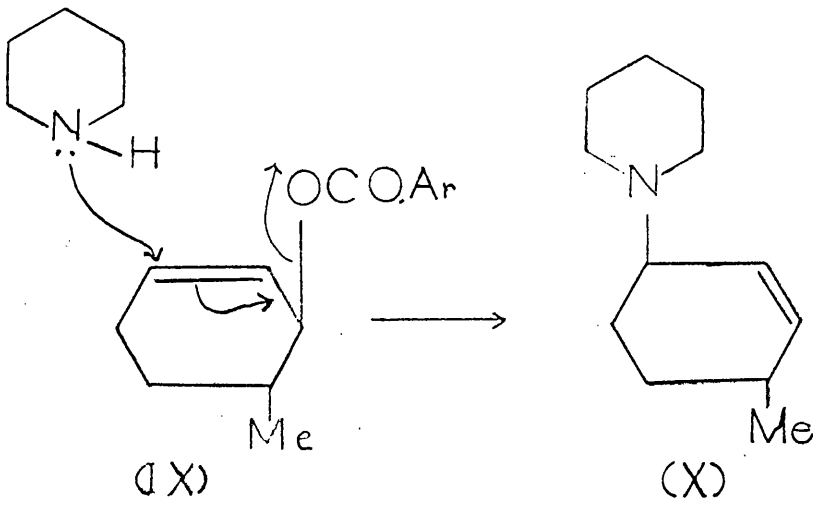
$CH_3.CH(OH).CH=CH_2$ (VIIb)

This phenomenon is known as 'product spread' and it usually occurs in the direction of the starting compound as in the above example. Further, when $H_2C=CH.CMe_2Cl$ was treated with acetic acid, the two isomeric acetates were obtained, but also some $Cl.CH_2CH=CMe_2$[19]. (The rate of formation of rearranged chloride was unaffected by the addition of external Cl). These facts indicate that the first step in these reactions is formation of an ion pair, which undergoes a considerable amount of internal return.

S_N2' mechanism: In rare cases abnormal product formation may occur by a bimolecular (S_N2') mechanism. These usually occur when 'normal', attack is sterically hindered. Thus 3-chlorobut-1-ene (VIII) is substituted by diethylamine in an S_N2' process, which was confirmed by the kinetic isotope effect displayed when the atoms marked with an asterisk were successively labelled[20].



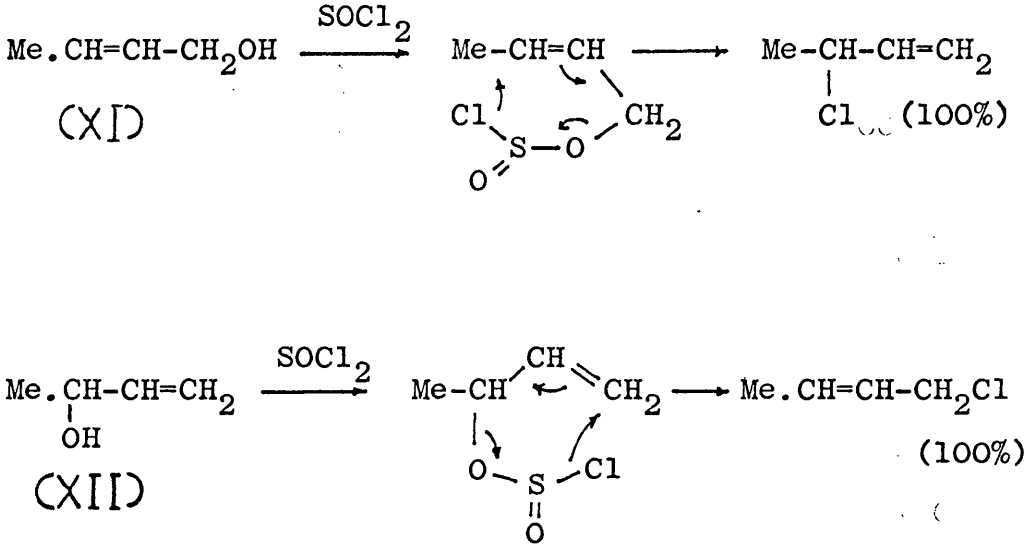
Stereochemically the S_N2' process is as expected. The nucleophile attacks in the 'abnormal' position on the same side from which the leaving group is expelled. An S_N2 process involves backside attack by the nucleophile on the carbon bearing the leaving group. Thus, if the leaving group is pushed out upwards, the π-electrons of the double bond attack from below, which implies that the nucleophile has attacked from above. This is shown diagramatically for a case where the stereochemistry has been proved; trans-(IX) gives rise to trans-(X)[21] Scheme 4.



SCHEME 4

S_Ni' mechanism: When an allylic molecule has a leaving group which can also act as an internal nucleophile reaction can occur by an S_Ni' mechanism. This

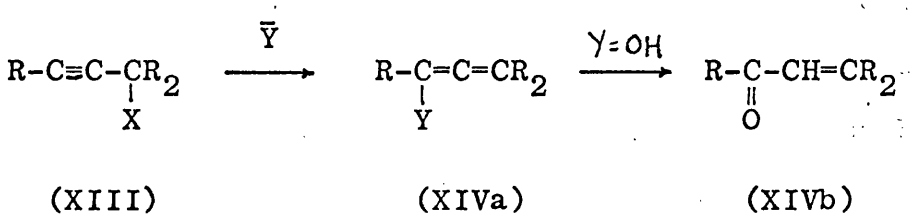
S_Ni' mechanism has been demonstrated with but-2-en-1-ol (XI) and but-3-en-2-ol (XII)[13], which undergo 100% rearrangement on treatment with thionyl chloride, providing good evidence for an intramolecular reaction (Scheme 5).



SCHEME 5

The case already mentioned, where a simple leaving group (e.g. Cl) separates to form an internal ion pair and then returns to the allylic position, can also be thought of as an S_Ni' mechanism.

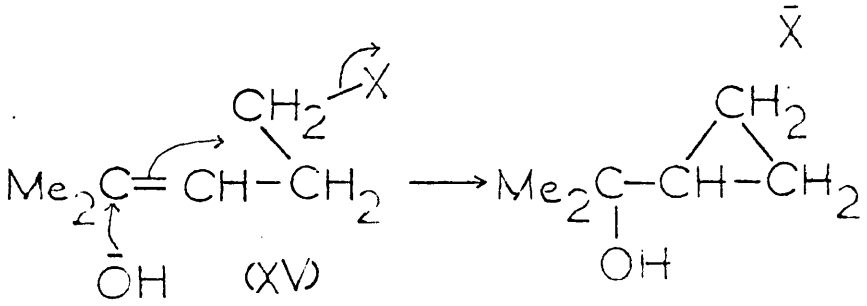
Allylic rearrangements are also known in propargyl systems[22], as shown in Scheme 6.



SCHEME 6

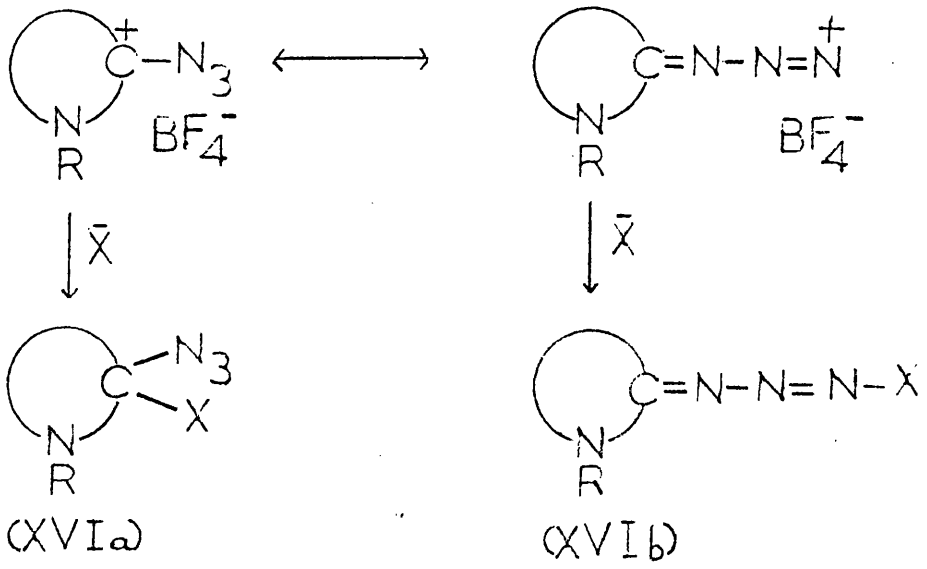
The acetylene (XIII) can give the allene (XIVa) on abnormal attack by a nucleophile ($\bar{Y}$). If Y = OH then tautomerism to the α,β-unsaturated ketone occurs. (XIVb).

An unusual type of "allylic" shift has been demonstrated in a homoallylic system (XV), where a cyclopropyl ring was formed, presumably by an S_N2' type of mechanism[23].



(XV)

Finally, it has recently been shown[24] that heterocyclic azidinium salts can display ambident electrophilic behaviour, giving rise to C-(XVIa) or N-(XVIb) substitution when attacked by nucleophiles. (Scheme 7).



(XVIa) (XVIb)

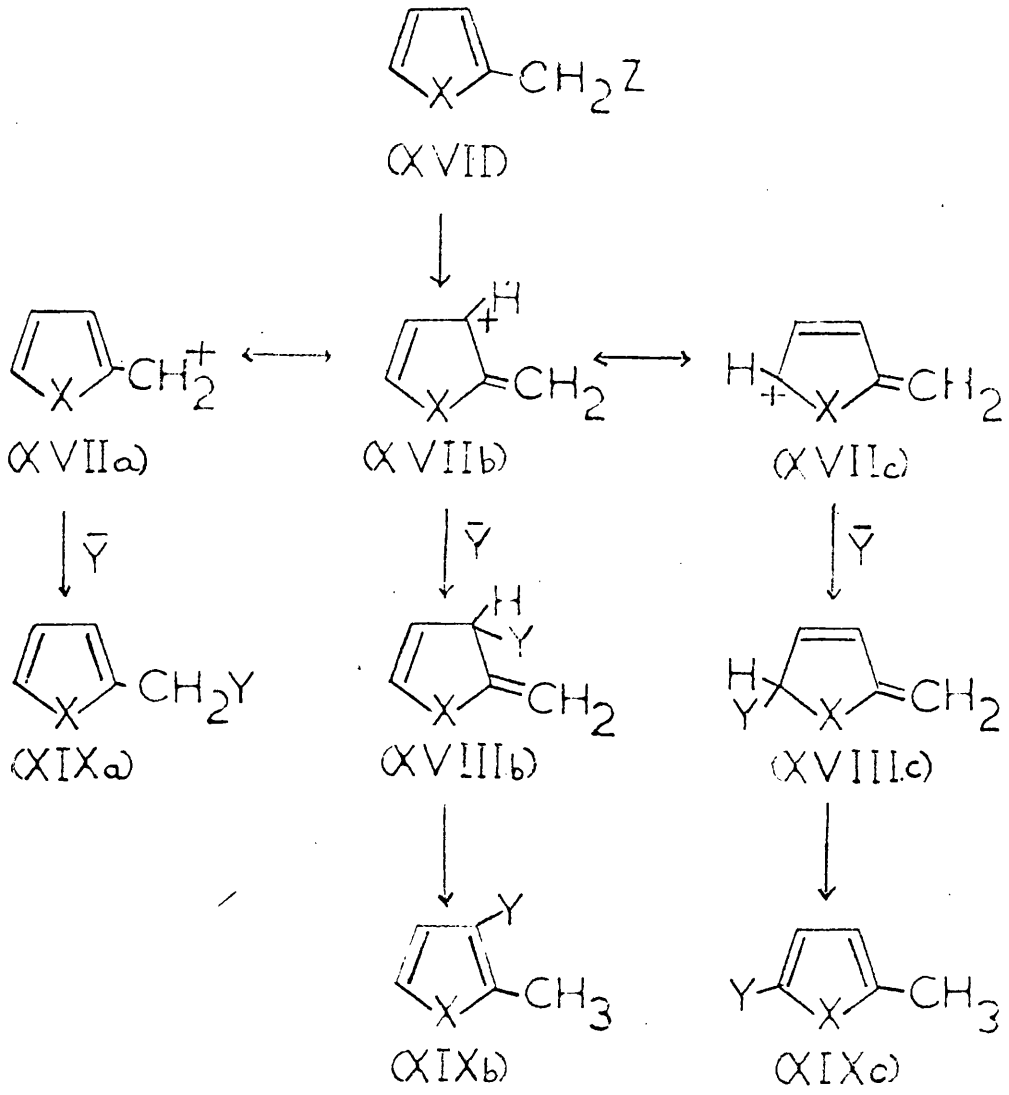
SCHEME 7

2. AMBIDENT ELECTROPHILES IN HETEROCYCLIC SYSTEMS.

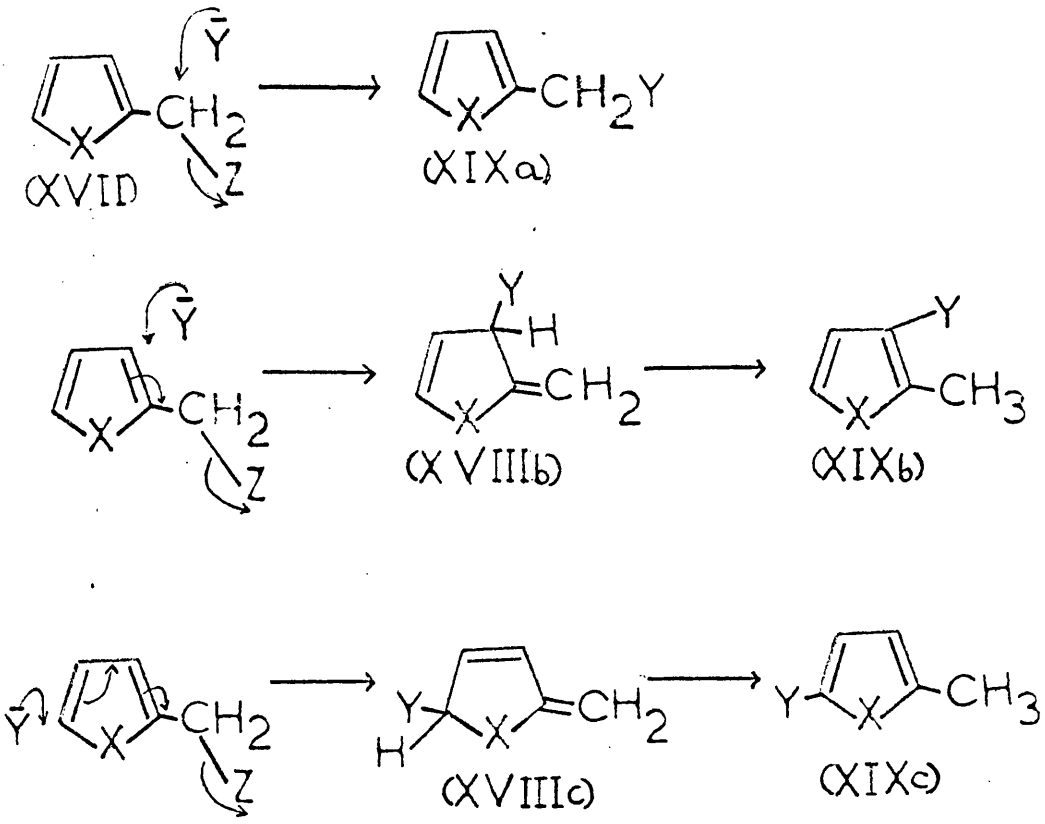
The present work is concerned with electrophiles where the positive charge is delocalised around a heterocyclic ring system. The known examples are usually observed in five-membered π-rich systems (such as pyrroles, furans and thiophenes). In Scheme 8a the heterocyclic compound (XVII, X = O, S, NH, NR etc; Z = Br, Cl or NR_2 usually) is attacked by a nucleophile, $\bar{Y}$. Cyanide is far and away the most frequently encountered nucleophile, but hydroxide, alkoxide or piperidine have also given allylic rearrangements in systems of this type.

The halomethyl (or aminomethyl) compound can formally be thought to dissociate into the carbonium ion (XVIIa) which is mesomeric with (XVIIb) and (XVIIc) in which the positive charge rests on the 3- and 5-carbon atom of the heterocyclic ring. Attack by the nucleophile ($\bar{Y}$) on one of the carbon atoms bearing the positive charge can lead to three possible products, namely the 'normal' or expected product (XIXa) or the rearrangement products (XIXb and XIXc). The exocyclic methylene derivatives (XVIIIb and c) are analogous to the final products in the acylic allylic systems already discussed. In the heterocyclic systems, however, the final product is the re-aromatised compound (XIXb or XIXc).

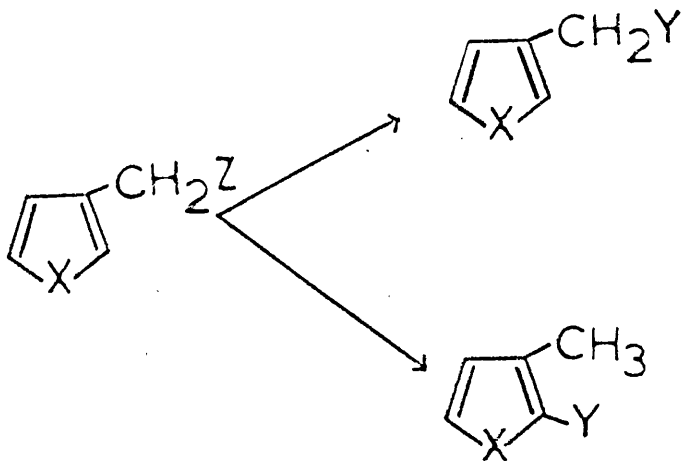
Scheme 8a implies an S_N1' mechanism, whereas an S_N2' (or conceivably S_Ni') mechanism may actually


CH2Z
(XVII)
CH2+
(XVIIa)
H+
CH2
(XVIIb)
H+
CH2
(XVIIc)
Y⁻
CH2Y
(XIXa)
H
Y
CH2
(XVIIIb)
H
Y
CH2
(XVIIIc)
Y
CH3
(XIXb)
Y
CH3
(XIXc)

SCHEME 8a



SCHEME 8b



SCHEME 8c

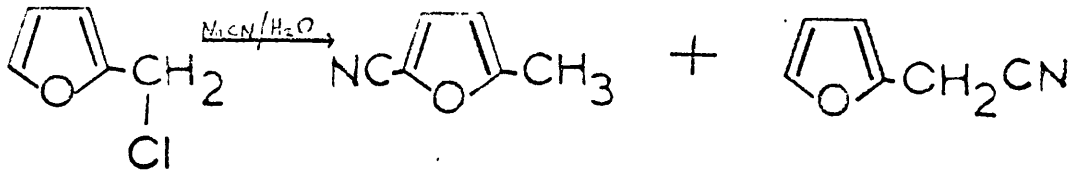
operate. In fact in certain cases a homolytic reaction may not be ruled out. Scheme 8b shows how an S_N2' (concerted) mechanism can give rise to the same abnormal products.

Reasoning analogous to the above shows that only one 'abnormal' product can be expected when a nucleophile attacks a 3-halomethyl group in a 5-membered heterocyclic compound. (Scheme 8c).

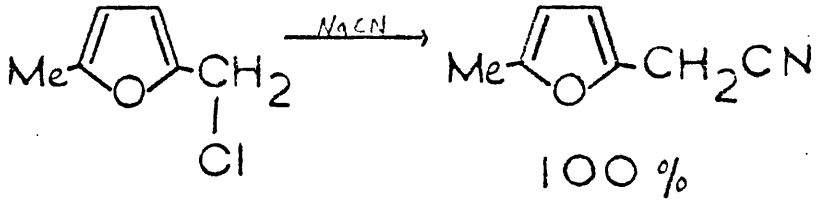
The rest of this chapter will be concerned with rearrangements of the above type which have been reported in the literature.

ALLYLIC REARRANGEMENTS OF FURANS

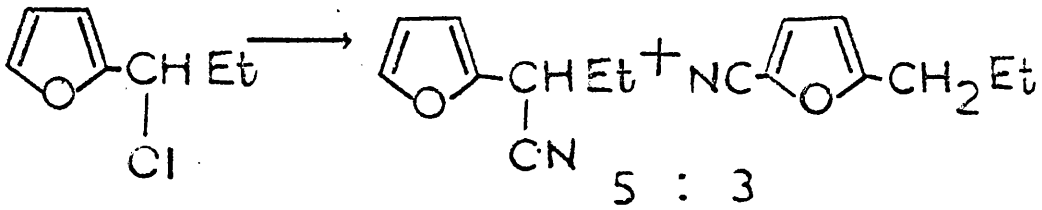
The earliest example in the literature of an ambident electrophile in a heterocyclic system is due to Reichstein[25]. In the two-phase reaction of 2-chloromethylfuran in water with sodium cyanide, 2-cyano-5-methyl furan was obtained in high yield, as well as a small amount of 2-cyanomethylfuran. (Scheme 9a). Later it was shown that, if the 5-position is blocked by a methyl group no rearrangement occurs[26,27]; 2-chloromethyl-5-methylfuran on treatment with sodium cyanide gave only the normal product, 2-cyanomethyl-5-methylfuran. (Scheme 9b). It may be noted that rearrangement could still occur in this case to give 3-cyano-2-methylfuran, but this does not appear to happen.



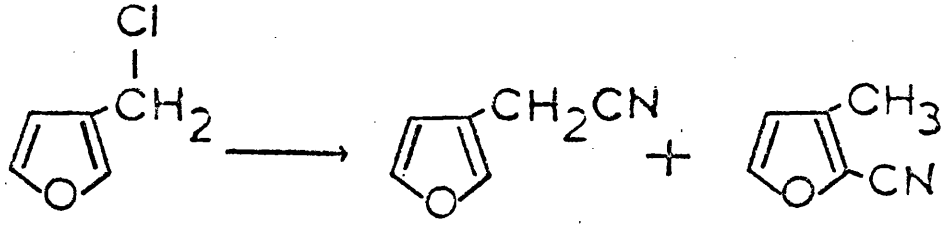
(a)



(b)



(c)



(d)

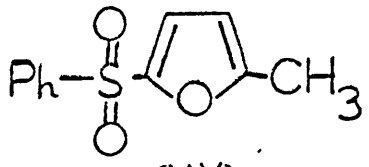
SCHEME 9

In the above work on furfuryl halides, the cyanides were characterised only by hydrolysis to the corresponding acids. The reasonable assumption was made that rearrangement was not taking place during the hydrolysis of the nitriles. The rearrangement of 2-α-chloropropylfuran[38] (Scheme 9c) and of 3-chloromethylfuran (Scheme 9d)[39] with sodium cyanide are also known.

The rearrangement of 2-chloromethylfuran has recently been studied in some detail[28-37]. Effect of solvent has been reported[29-51], but will be considered later (p.172). Suffice it to say for the moment that aprotic solvents give no rearrangement, whereas protic solvents invariably do. The effect of temperature on the yield of the normal product in aprotic solvents has been investigated[30], but the variation with temperature of the product ratio of 'normal' to 'abnormal' products, when competition between allylic and 'normal' substitution is occuring, is not reported.

The effect of using nucleophiles other than cyanide has not been studied in detail, though there are reports of 2-chloromethylfuran giving only the normal product on reaction with sodium thiocyanate[28,32]. In this reaction some 2-furfurylisothiocyanate is formed, i.e. the thiocyanate anion is behaving as an ambident nucleophile, but no thiocyanate or isothiocyanate is incorporated into an allylic position. Reaction of

benzenesulphinate with 2-chloromethylfuran yields the 5-substituted-2-methylfuran (XX)[36].



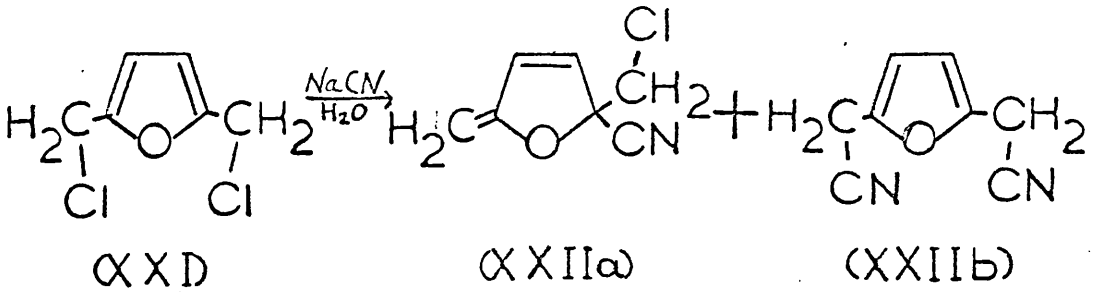
(XX)

The reaction of methoxide with 2-chloromethylfuran[33,36] is discussed below.

Published kinetic work on the allylic rearrangement is limited. In more recent publications[36,37] it has been stated that abnormal products are formed by an S_N1' mechanism, but no kinetic data are available. For an S_N1' mechanism with cyanide as nucleophile the nature of the leaving group should not influence the formation of the abnormal product.

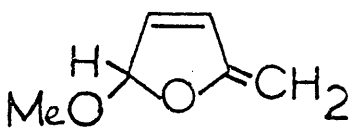
As we have seen, blocking of the 5-position of 2-chloromethylfuran was originally thought to give rise to no abnormal products on attack with cyanide. In this case we are not, of course, preventing the ambident electrophilic intermediate from being formed, nor is attack by the incoming nucleophile prohibited, though some steric hindrance may occur. Tautomeric change of the non-aromatic exocyclic methylene intermediate (XVIIIc) (Scheme 8a) to give the aromatic system (XIXc) (Scheme 8a) is, however, impossible in

this case. Thus the overall driving force for allylic reaction has been greatly reduced. Nevertheless, Novitskii[35] has actually isolated the exocyclic methylene compound (XXIIa) formed by the reaction of aqueous sodium cyanide with 2,5-bis(chloromethyl)furan (XXI) (Scheme 10) in benzene at 60° for 4 hr. The normal product (XXIIb) was also formed.

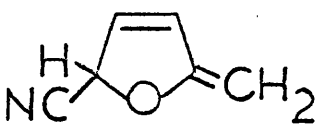


SCHEME 10

Two other examples of the isolation of an exocyclic methylenefuran via ambident cation formation are known, namely the products (XXIIIa) and (XXIIIb) derived from abnormal attack of methoxide ion[33,36] and cyanide ion[37] on 2-chloromethylfuran.



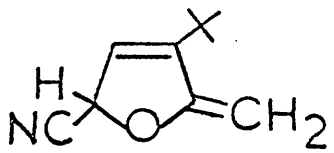
(XXIIIa)



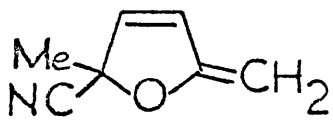
(XXIIIb)

The latter intermediate (XXIIIb) was characterised and partially isolated in spite of the fact that prototropy can and does occur to give the re-aromatised product. The reaction between 2-chloromethylfuran and potassium cyanide was carried out under the same aqueous conditions used by Reichstein[5,25] but at 0°. Evidence for the presence of the exocyclic methylene compound (XXIIIb) in the product mixture was obtained by NMR analysis. The chemical shifts of the protons in the exocyclic methylene group (δ, 4.2 and δ, 4.4) were in good agreement with values in known 2-methenylfurans[40]. These and the other peaks attributed to the intermediate (XXIIIb) disappeared rapidly, enhancing the peaks due to the re-aromatised product. On neutralising the reaction product the 2-methenylfuran (XXIIIb) was found to be surprisingly stable.

Two further exocyclic methylene compounds (XXIV) and (XXV) were detected in solution by Divald[37] from the reaction of aqueous potassium cyanide with 3-t-butyl-2-chloromethylfuran and 2-chloromethyl-5-methylfuran. The compounds could not be isolated, however,



(XXIV)



(XXV)

IMIDAZOLES

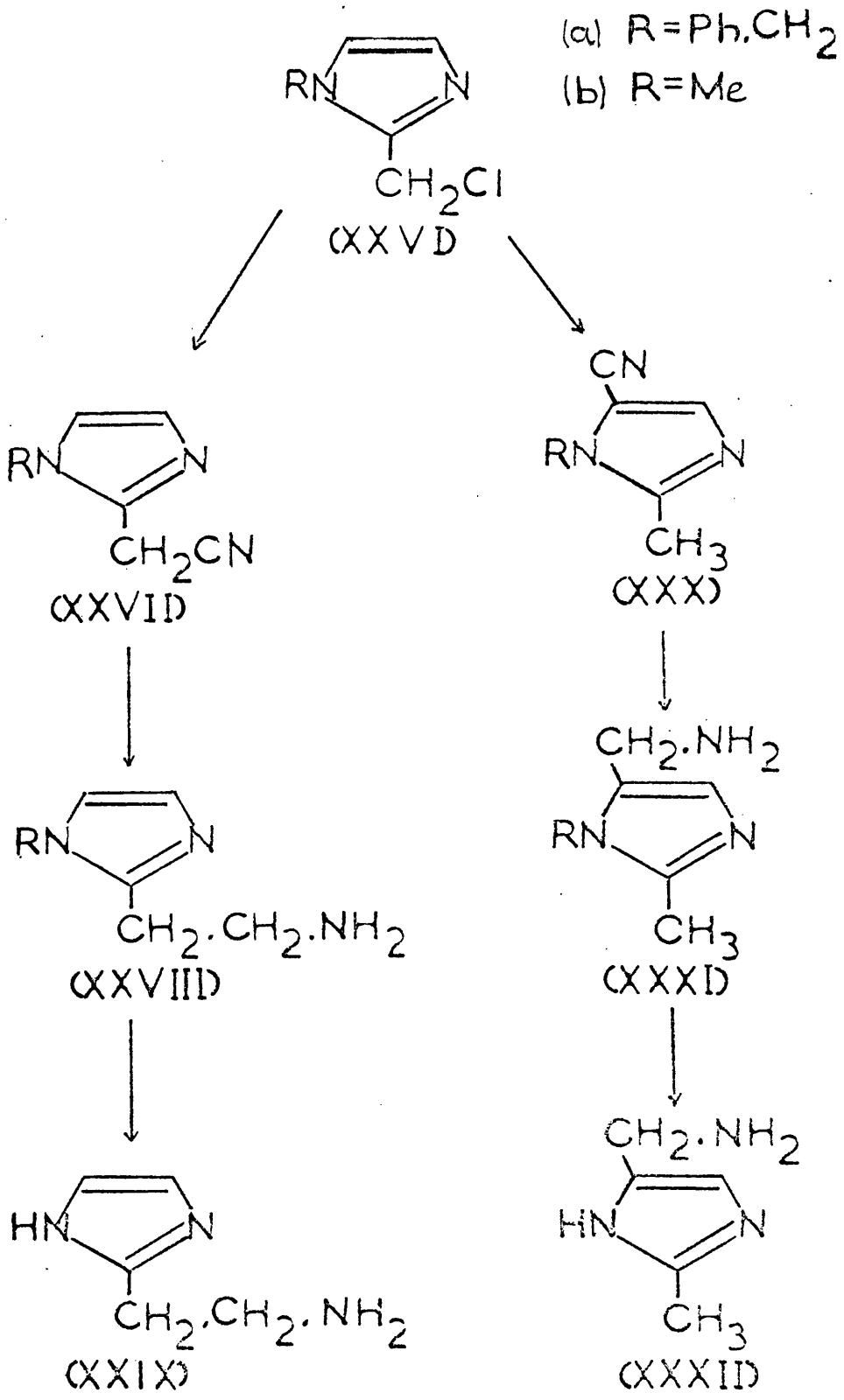
In 1949 Jones[41] claimed to have made 2-β-aminoethylimidazole (isohistamine; XXIX) from 1-benzyl-2-chloromethylimidazole (XXVIa) by the route shown in Scheme 11.

Treatment of this chloromethyl compound with aqueous cyanide appeared to give 1-benzyl-2-cyanomethylimidazole (XXVIIa) which was reduced catalytically to yield the cyanoethyl compound (XXVIIIa) and debenzylated to give an amine formulated as isohistamine (XXIX). The surprising absence of histamine-like activity of this compound had been much discussed[42] until it was discovered[43,44] by NMR analysis that attack by cyanide ion on 1-benzyl-2-chloromethylimidazole (XXVIa) gives quantitatively the abnormal product 1-benzyl-5-cyano-3-methylimidazole (XXXa) associated with an ambident electrophilic intermediate. On reduction, to give (XXXIa), and debenzylation 5-aminomethyl-2-methylimidazole (XXXII), a compound which is pharmacologically not at all analogous to histamine, is formed.

1-Methyl-2-chloromethylimidazole (XXVIb) has also been shown to undergo partial rearrangement with aqueous cyanide, but with sodium diethyl acetamidomalonate, the chloromethylimidazoles (XXVIa) and (XXVIb) do not give abnormal products[44].

Isohistimine (XXIX) has now been unambiguously synthesised[43] and its biological activity resembles

SCHEME II

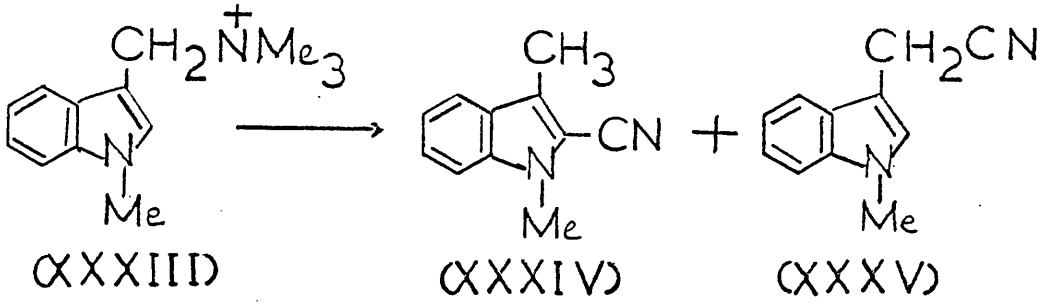

(a) R=Ph.CH2
(b) R=Me
RN
N
CH2Cl
(XXV)
CH2CN
(XXVI)
CN
CH3
(XX)
CH2.CH2.NH2
(XXVII)
CH2.NH2
(XXI)
HN
(XXIX)
(XXII)

that of histamine, but it is much less potent.

In aprotic media (dimethylformamide[45] and dimethylsulphoxide[46]) no rearrangement takes place, as is the case in the furans already considered. Indeed these solvents provide a good medium for the synthesis of the 2-cyanomethylimidazoles (XXVIIa) and (XXVIIb).

PYRROLES

No examples of simple pyrroles behaving as ambident electrophiles are known. However, the indole 1-methyl-3-N,N-dimethylaminomethylindole methiodide (1-methylgramine methiodide) (XXXIII) has been shown by Snyder and Eliel[7] to give a small amount (4.3%) of the abnormal product 2-cyano-1,3-dimethylindole (XXXIV) when treated with aqueous sodium cyanide, though the major product is the normal nitrile, 3-cyanomethyl-1-methylindole (XXXV) (Scheme 12).

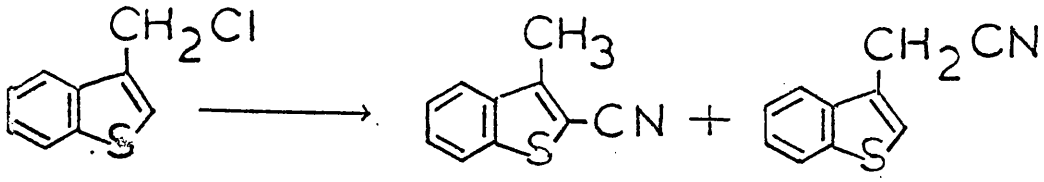


(XXXIII) (XXXIV) (XXXV)

SCHEME 12

The two isomeric nitriles (XXXIV) and (XXXV) were separated by distillation followed by fractional crystallisation. The abnormal isomer (XXXIV) was characterised from a nitrile absorption in the infrared spectrum which showed a shift of 36 cm^{-1} toward shorter wave number compared with the normal isomer; this is typical of a nitrile which is conjugated with a double bond or an aromatic system.

THIOPHENES

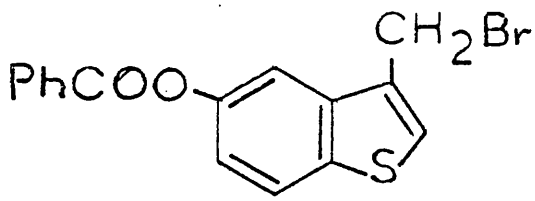


(XXXVI) (XXXVII) (XXXVIII)

SCHEME 13

Campaigne and Neiss[48] have obtained from 3-Chloromethylbenzo[b]thiophene (XXXVI) in dimethyl sulphoxide as solvent, the normal product, 3-cyano-methylbenzo[b]thiophene (XXXVIII), (98%) as well as a small amount (2%) of the abnormal product, 2-cyano-3-methylbenzo[b]thiophene (XXXVII) (Scheme 13). Small quantities of the abnormal isomer were isolated by preparative GLC, and physical data (NMR, IR and UV)

were compared with the unambiguously synthesised nitrile (XXXVII). Further evidence for the structure of (XXXVII) was provided by the NMR spectrum. 3-Substituted benzothiophenes show the splitting into a doublet of protons α to the ring by the hydrogen atom on the 2-carbon atom of the thiophene ring. For example in the normal product of the above reaction (XXXVIII) the methylene protons are split into a doublet by the 2-hydrogen atom. In the abnormal isomer (XXXVIII) no such splitting is observed, providing evidence that this compound is 2-substituted. The same authors have shown[49] that 5-benzoyloxy-3-bromomethyl-benzothiophene (XXXIX) also undergoes allylic rearrangement.

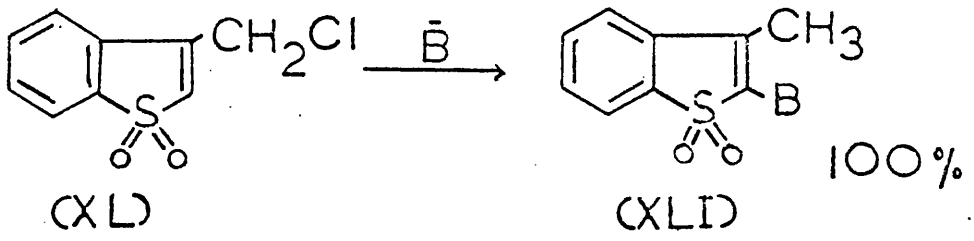


(XXXIX)

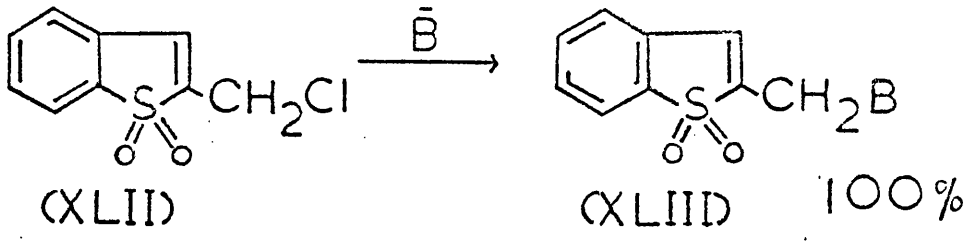
In the above cases rearrangement was effected in a dipolar aprotic solvent. Further, no rearrangement was detected when a protic medium (ethanol/water) was used[48]. This is in contradiction to the solvent effects observed in the study of the furans and

imidazoles already mentioned. This anomaly will be discussed in the appropriate section (p172).

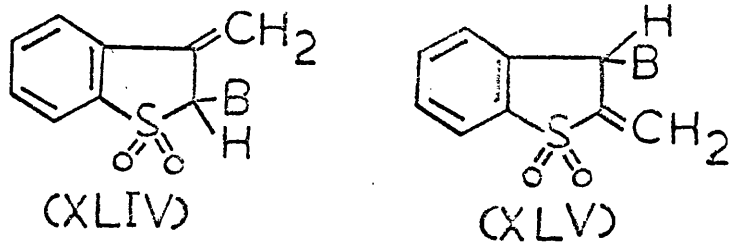
The 3-chloromethyl derivative of the non-aromatic system benzo[b]thiophene-1,1-dioxide (XL) (Scheme 14) when treated with a variety of nucleophilic reagents (piperidine, thiourea, sodium phenoxide or morpholine) leads exclusively to the 2-substituted-3-methyl benzo [b]thiophenedioxide (XLI)[50]. In contrast the dioxide of 2-chloromethylbenzo[b]thiophene (XLII) underwent only normal substitution with the same nucleophiles under the same conditions.



(XL) (XLI)



(XLII) (XLIII)



(XLIV) (XLV)

SCHEME 14

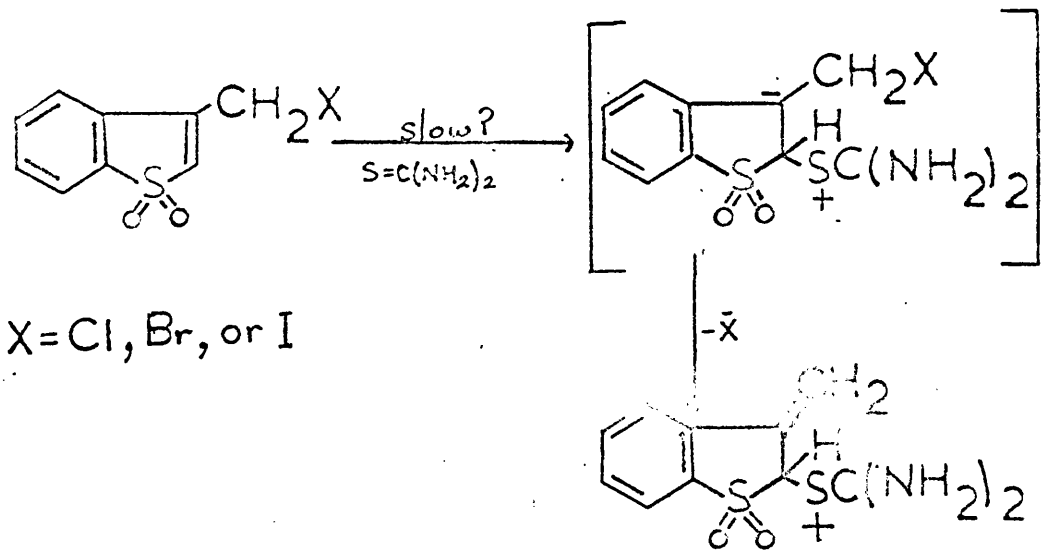
The authors explain this phenomenon in terms of the relative stability of the intermediates (XLIV) and (XLV) of these reactions. Substitution of 3-chloromethylbenzo[b]thiophene-1,1-dioxide (XL) produces an intermediate (XLIV) in which the exocyclic methylene group is conjugated with the benzene ring, whilst in (XLV) it is not. (Conjugation cannot of course occur through the sulphur atom which has its maximum co-ordination). The activation energy in the latter case would, therefore, be sufficiently raised for only normal substitution to take place. It may be noted that, if the reaction under discussion is analogous to the rearrangement of the furan system already described, then the exocyclic methylene compounds (XLIV) and (XLV) would be (isolable) primary products of the reaction and may not in any way resemble the transition state of the reaction, as assumed in the above argument. In this case it may be argued that the reaction is thermodynamically controlled and that abnormal product formation is more likely to occur in the case where the exocyclic methylene compound (now the product of the reaction) is more stable (i.e. compound XLIV).

Bordwell, Sokol and Spainhour[51] have conducted a kinetic study of these reactions using thioformamide as nucleophile and have shown that the rate of the reaction is first order with respect to both halide and nucleophile. This indicates that an S_N2' mechanism is

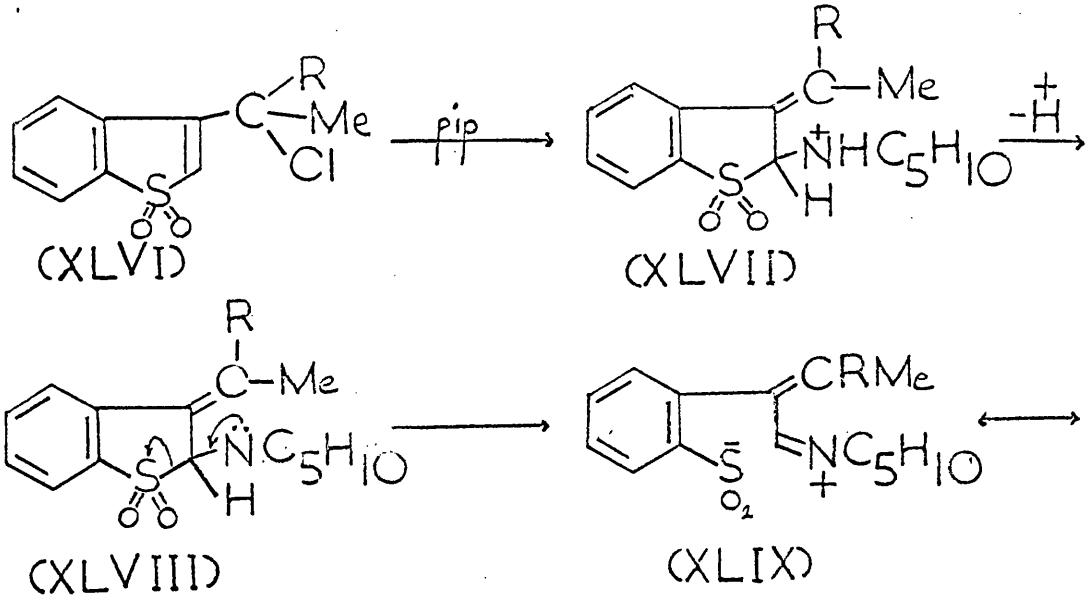
probably operating. A second order addition-elimination mechanism as shown (Scheme 15) was ruled out by a study of the relative rates of reaction of the chloro, bromo, and iodo compounds. A rate enhancement of 1 : 79 : 230 (Cl:Br:I) confirmed that halogen-carbon bond cleavage must occur in the rate-determining step, which is incompatible with the addition-elimination mechanism.

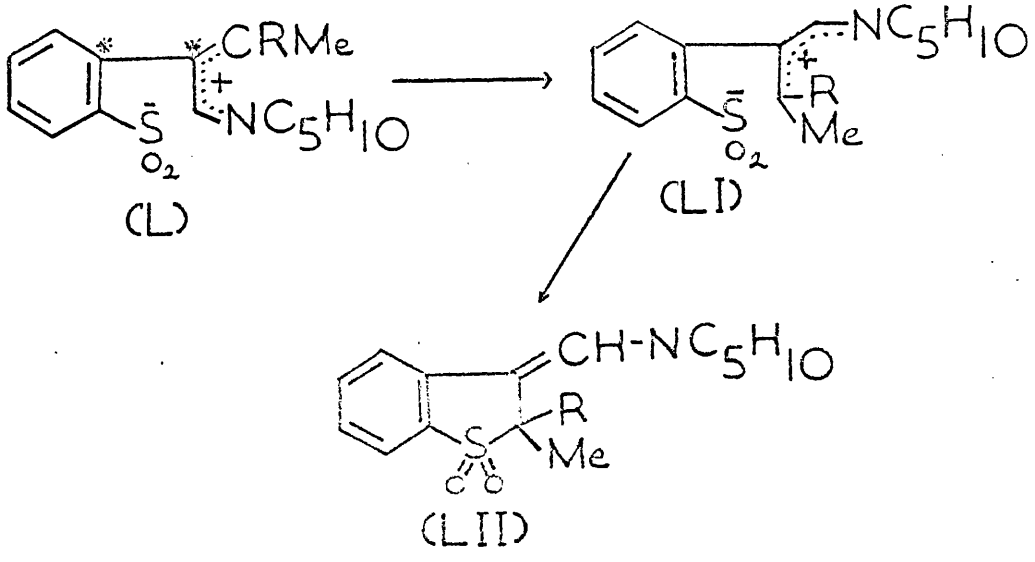
The above system undergoes a very interesting rearrangement when the 3-chloromethyl group of compound (XL) is replaced by the 3-(α-chloro)-ethyl or 3-(α-chloro--α-methyl)-ethyl group[52] (Scheme 16).

Attack on these molecules (XLVI; R = H or Me) by piperidine leads initially to the abnormally substituted intermediate (XLVII). This intermediate does not undergo prototropy in the usual way, but loses a proton (to give XLVIII) followed by attack of the piperidine nitrogen atom on the α-carbon atom producing the ring opened intermediate (XLIX) in which the carbon-sulphur bond has been cleaved. This zwitterion can be thought of as the localised form (XLIX) or the delocalised, nonclassical form (L) which can undergo conformational change by rotation about the bond marked ** to the species (LI). Ring closure follows to give the exocyclic methylene compound (LII) which is in fact the experimentally observed product. The mechanism has been borne out by a detailed study, including kinetics,



SCHEME 15

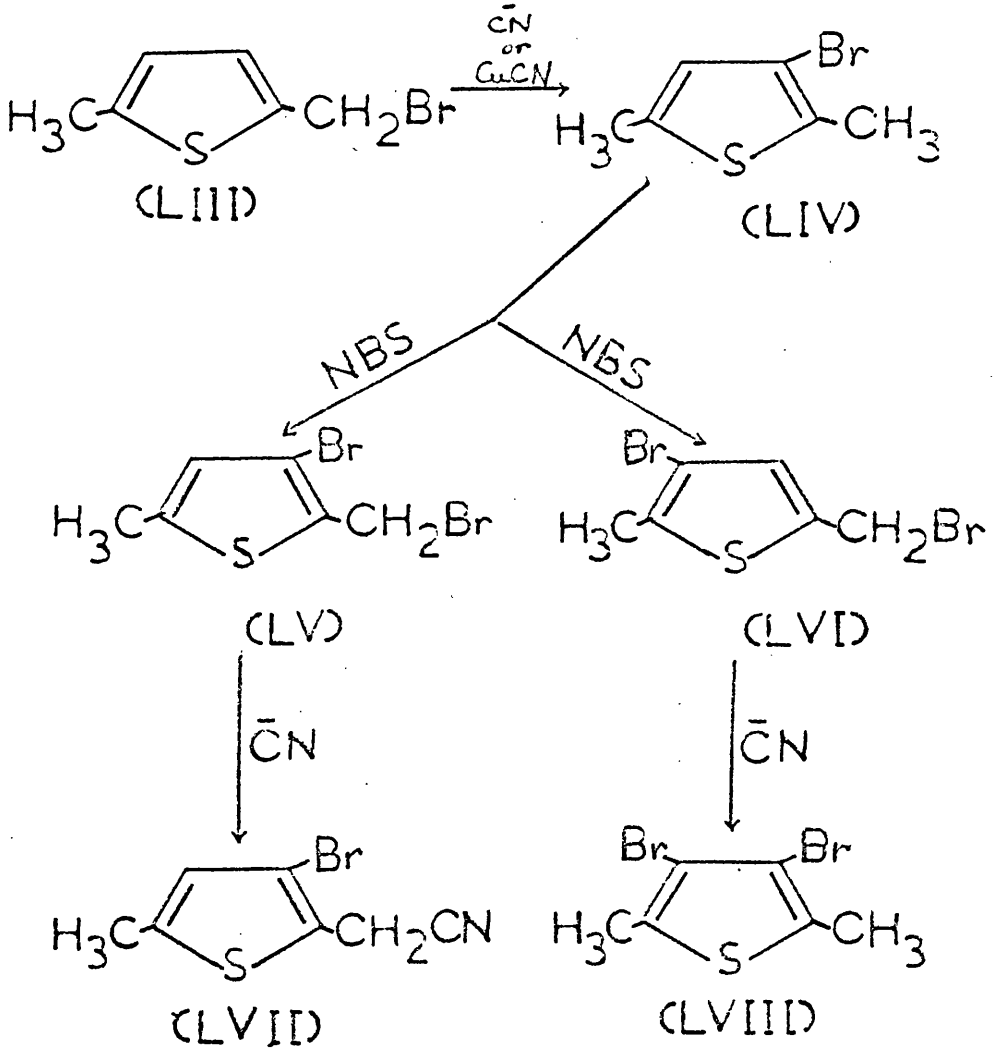




SCHEME 16

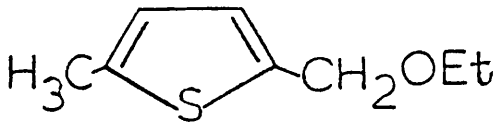
of this reaction[52].

No simple thiophenes have been reported to give rearrangements of the type so far discussed. However, an interesting intramolecular transformation has been studied by Lecocq[6,53,54] (Scheme 17).



SCHEME 17

Treatment of 2,5-dimethylthiophene (thioxene) with N-bromosuccinimide (NBS) in carbon tetrachloride gave 2-bromomethyl-5-methylthiophene (LIII), as a distillable but unstable oil. This compound (LIII) on treatment with cuprous cyanide in the absence of solvent gave an exothermic reaction from which 3-bromo-2,5-dimethyl-thiophene (LIV) was isolated in high yield[53,54]. This rearrangement also occurs when 2-bromomethyl-5-methyl-thiophene (LIII) is made to react with potassium cyanide in dioxan. When alcohol is used as solvent, 2-ethoxy-methyl-5-methylthiophene (LIX) is the major product, though rearrangement (to LIV) still occurs[54].



(LIX)

The sodium salt of diethylmalonate also effects the above transformation. Further, if the product of rearrangement (LIV) is brominated with NBS, the two isomeric bromo-methylthiophenes (LV) and (LVI) are formed. These were separated and it was found on treatment with cyanide that 4-bromo-2-bromomethyl-5-methylthiophene (LVI) gave the product of rearrangement (LVIII) in which no cyanide had incorporated, whereas 3-bromomethyl-5-methylthiophene

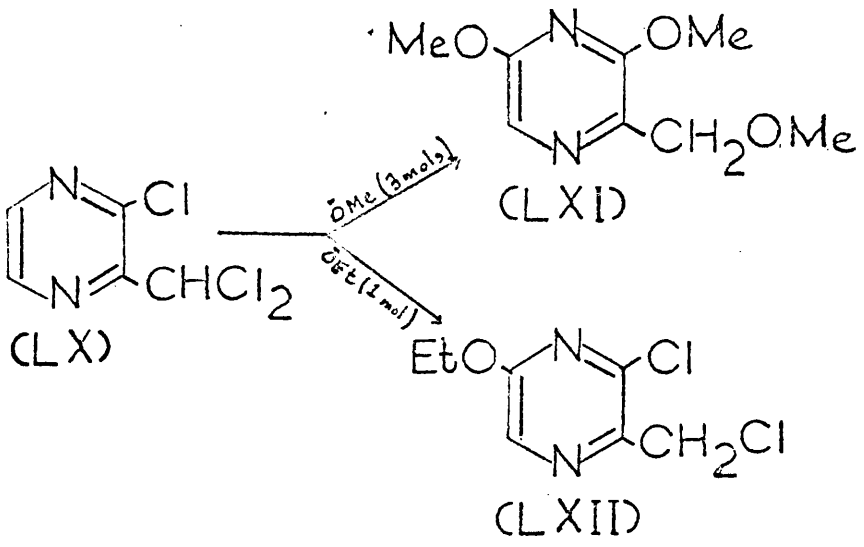
(LV) gave the 'normal' product, 3-bromo-2-cyanomethyl-5-methylthiophene (LVII) exclusively. This shows that migration of the bromine atom occurs specifically to the adjacent carbon atom of the thiophene ring (a 2-bromomethyl group becomes a 3-bromo-2-methyl group) and may be thought to provide some evidence that an intramolecular reaction is taking place. This reaction will be discussed in detail in the light of further data obtained in the present work.

PYRAZINES

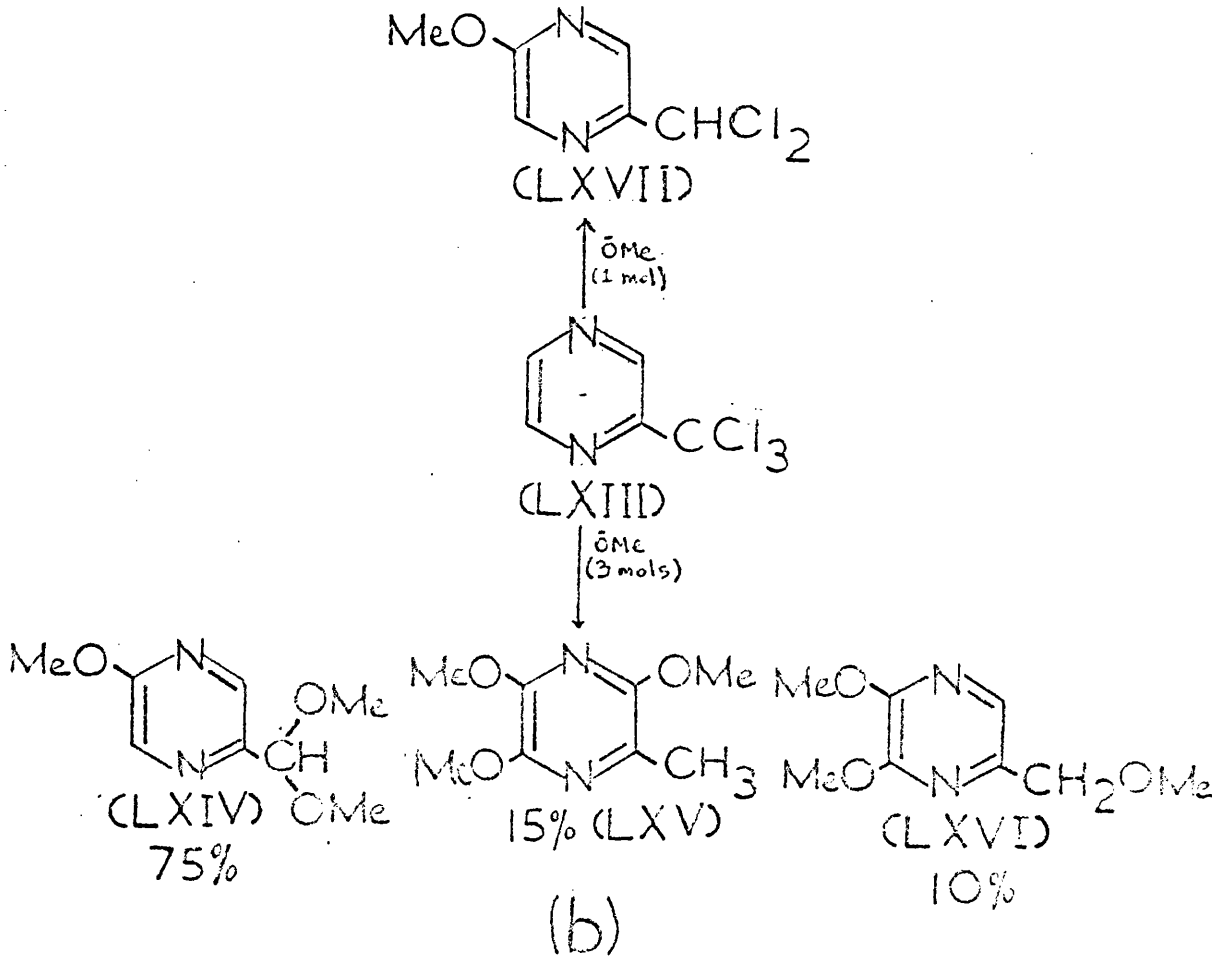
One of the few examples of a six-membered, 6 π - electron molecule undergoing allylic rearrangement is reported by Grabowski[55]. This work is summarised in Schemes 18a and 18b.

Treatment of 2-chloro-3-dichloromethylpyrazine (LX) with methoxide ion (3 moles) under reflux in methanol gave the product 3,5-dimethoxy-2-methoxymethylpyrazine (LXI), in which one chlorine atom on the dichloromethyl group had been normally and the other had been allylically substituted. The nuclear chlorine atom is, of course, substituted in the normal way. Treatment of the same compound with one mole of ethoxide ion (in ethanol at 0°) gave the abnormal product 3-chloro-2-chloromethyl-4-ethoxypyrazine (LXII) as the sole isolable material. Similar rearrangements occurred when trichloromethyl-pyrazine (LXIII) was treated with methoxide ion (3 moles).

SCHEME 18


MeO
OMe
CH2OMe
(LXI)
Cl
CHCl2
(LX)
ŌMe (3 mols)
ŌEt (1 mol)
EtO
Cl
CH2Cl
(LXII)

(a)


MeO
CHCl2
(LXVII)
ŌMe
(1 mol)
CCl3
(LXIII)
ŌMe
(3 mols)
MeO
OMe
CH
OMe
(LXIV)
75%
MeO
OMe
MeO
CH3
15% (LXV)
MeO
MeO
CH2OMe
(LXVI)
10%

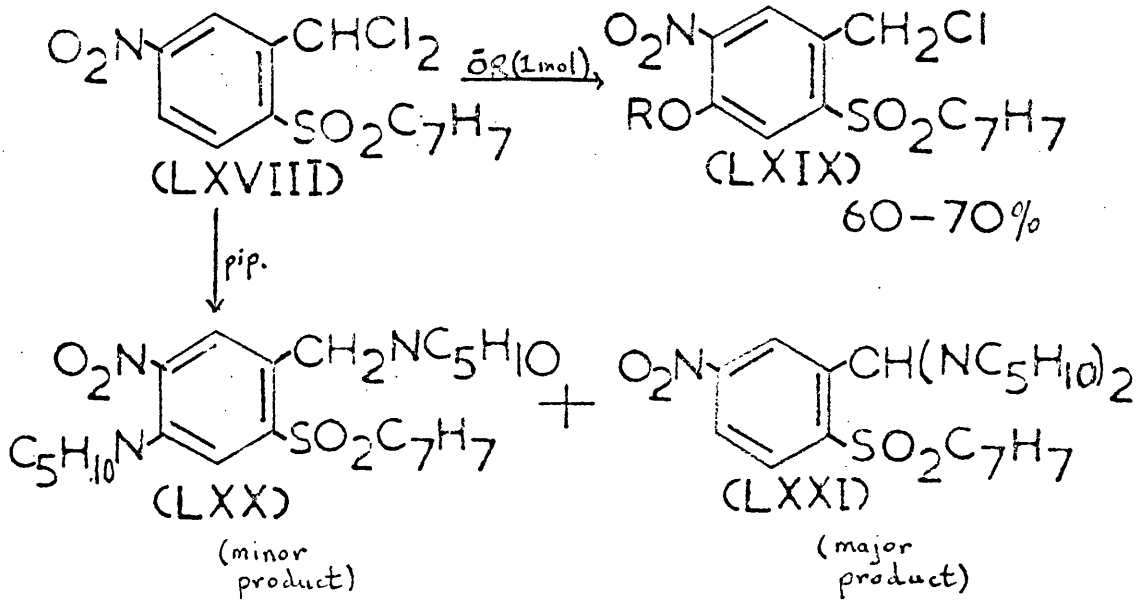
(b)

A mixture of the three isomeric trimethoxymethylpyrazines (LXIV, LXV, and LXVI) were obtained, resulting from one, three, or two abnormal substitutions respectively. Reaction of trichloromethylpyrazine (LXIII) with one mole of methoxide gave the abnormal product 2-dichloromethyl-5-methoxypyrazine (LXVII) which was converted into the three isomeric pyrazines (LXIV, LXV, and LXVI) in the same proportion as before.

BENZENOID COMPOUNDS

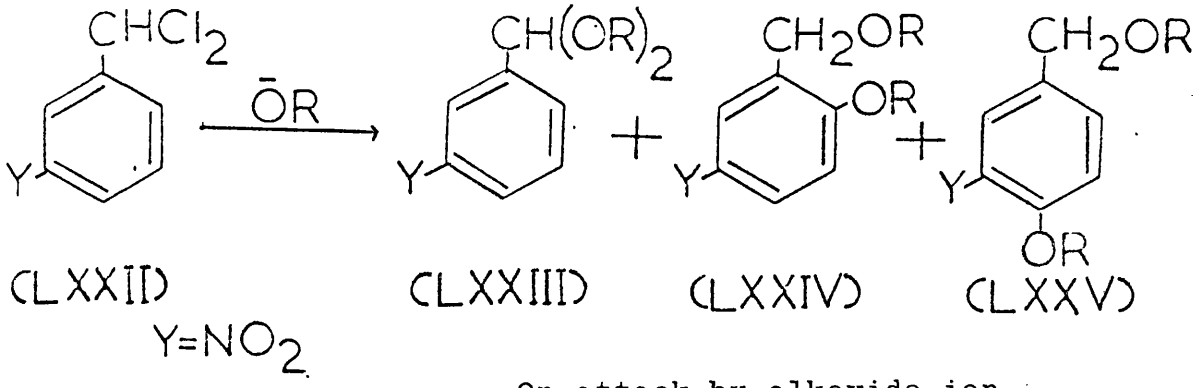
No simple benzenoid compounds are known to rearrange when acting as ambident electrophiles. However, two examples of halomethyl benzenes which are also substituted by strongly electron withdrawing groups, namely p-toluenesulphonyl- and/or nitro-, have been shown to give abnormal products[56,57,58]. In a benzene system the nucleophile may enter ortho or para to the halomethyl group, thus one normal and two (or three if the two ortho positions are not equivalent) abnormal products are possible.

Attack by alkoxide ion on 1-dichloromethyl-5-nitro-2-p-toluenesulphonylbenzene (LXVIII) gives as the major product the compound (LXIX) in which the alkoxide group has entered para to the dichloromethyl group[56].



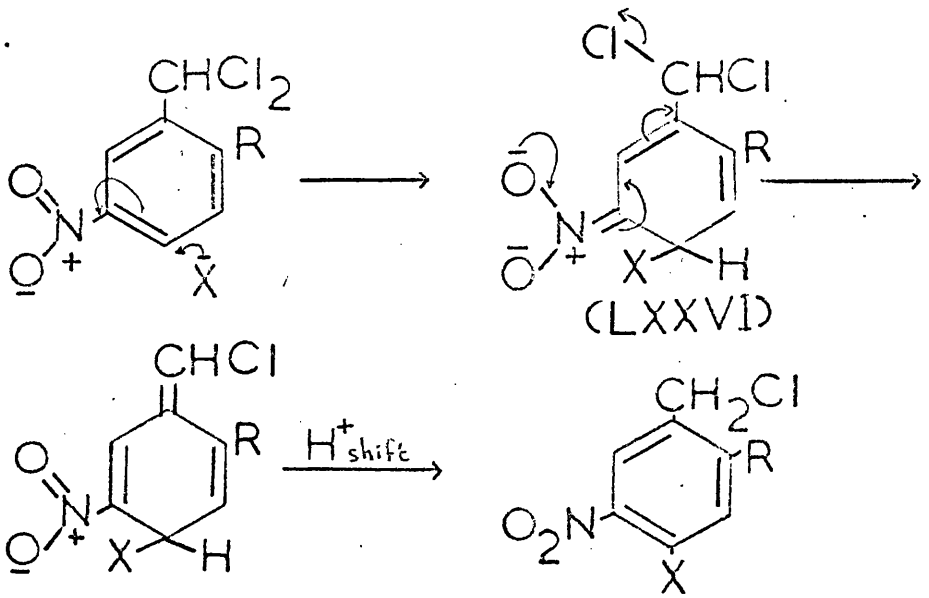
Piperidine always displaced both chlorine atoms of the dichloromethyl compound (LXVIII). The major product was the benzylidene bispiperidyl compound (LXXI), but a small amount of the compound (LXX) in which one piperidine molecule substituted normally, and the second substituted abnormally in the para position was also obtained.

The second case of abnormal substitution in a nitrobenzene was reported by Kliegl and Hölle[58].



On attack by alkoxide ion, 1-Dichloromethyl-3-nitrobenzene (LXXII) gives mainly the acetal but also a little of the two abnormal isomers (LXXIV) and (LXXV) was isolated. The proportion of rearranged products increased in the order OMe < OEt < O_nPr. For reaction with ethoxide the yields doubled to 6% (LXXIV) and 16% (LXXV) with the dibromide instead of the dichloride.

Loudon and Smith[57] invoke participation by the nitro group to explain these reactions as shown in Scheme 19.



SCHEME 19

The intermediate (LXXVI) in which the negative charge from the nucleophile rests on the nitro group would have a low energy content and would lower the activation energy for abnormal substitution.

The authors state that those circumstances which operate against direct replacement of halogen are liable to encourage abnormal product formation. Thus the dibromomethyl group as substrate is more likely to give products of rearrangement and so are large nucleophiles (steric effect). Similarly a large substituent ortho to the leaving group would favour abnormal product formation. Electron withdrawing groups on the ring also decrease the rate of normal substitution[59]*, thus the fact that abnormal substitution is particularly favoured by the bulky electron withdrawing p-toluenesulphonyl group is explained.

* This is true of an S_N1 reaction. However, for a substitution reaction in which the nucleophile-carbon bond formation occurs in the rate determining step, electron withdrawing groups would favour reaction.

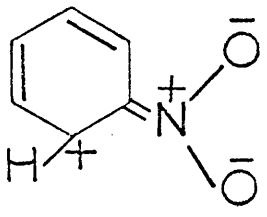
Correlation between Structure and Ambifunctionality.

Because of the limited number of known examples of ambident electrophiles, a theory correlating the structure of a system and its ability to undergo rearrangement is difficult to evolve. Though a large number of nucleophilic displacements on allylic systems have been reported as leading only to normal products, the abnormal product when present as 'impurity' perhaps even as much as 20% might easily have been missed. This would apply particularly to work published before the advent of NMR and GLC.

One trend does emerge from known examples of ambident electrophiles. The greater the diene or localised character as opposed to aromatic stabilisation or delocalisation of the system, the greater is its tendency to rearrange. Thus, the halomethyl derivatives of simple benzenoid compounds, which have a large resonance stabilisation, have never been observed to give abnormal products. At the other end of the scale, completely non-aromatic systems such as simple acyclic mono-enes (e.g. see ref.[12]), or benzothiophene 1,1-dioxide [50-52] rearrange to a considerable extent, when their halomethyl derivatives are treated with a variety of nucleophiles under suitable conditions. In between these two extremes are aromatic systems with relatively small resonance stabilisations, which tend to rearrange to a greater or lesser extent. For instance furans, which

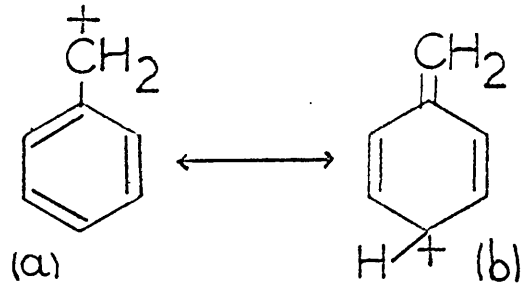
can be thought of as dienes (and in fact undergo Diels-Alder reactions) give abnormal products[25-39], whereas the more aromatic thiophenes do not show ambident electrophilic character (but see p. 28). The double bond in the thiophene ring of benzo[b] thiophene is probably more localised than in thiophene, due to the asymmetry of the former system and consequently 3-chloromethylbenzothiophene behaves to some degree as an ambident electrophile.

The introduction of more than one hetero-atom into an aromatic system, greatly reduces its aromatic character. Thus, while simple benzenes rarely display ambident behaviour, pyrazines give high yields of abnormal products[55]. Similarly simple pyrroles do not behave abnormally whereas imidazoles[43,44] do. Perturbations of the aromatic systems also occur by introduction of strongly electron withdrawing groups. Thus the 6π -electron cloud in nitrobenzene is partially distorted towards the nitro-group, as is evident from the contributing structures (e.g. LXXVII). It is not surprising, therefore, to find that chloromethylnitrobenzenes display ambident electrophilic behaviour[56-58].



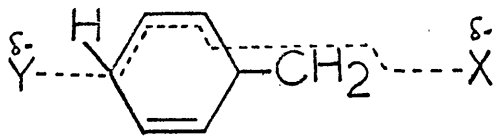
(LXXVII)

The reason for the connection between aromaticity and absence of abnormal behaviour is easy to see. The transition state in an S_N1 mechanism may be thought of as the mesomeric carbonium ion (LXXVIII).



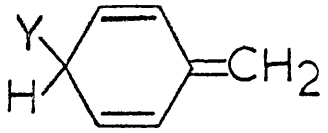
(LXXVIII)

In simple terms it may be said that the greater the contribution of the exocyclic methylene mesomer (LXXVIIIb), the larger the yield of the allylically substituted isomer. Since structures of type (LXXVIIIb) become less important as the resonance energy of the parent increases, the formation of the abnormal product becomes kinetically disfavoured. The same would apply to an S_N2 reaction where the intermediate (LXXIX) has also lost its aromaticity.



(LXXIX)

Though the final product of allylic attack is the re-aromatized system, the primary product is the exocyclic methylene compound (LXXX), Which has lost



(LXXX)

its aromatic character. In cases where this is accompanied by considerable loss in resonance energy abnormal substitution would not be expected in the thermodynamically controlled reaction.

Sherman[39] suggested the following order of decreasing tendency toward formation of abnormal or allylic reaction products: α-furfuryl > β-furfuryl > thenyl > cinnamyl > benzyl. The object of the present work was to extend this series and to correlate structure and ambident electrophilic behaviour. Effects other than structural ones (e.g. nature of solvent, of nucleophile, leaving group and temperature) which are only sparsely dealt with in the literature are also investigated and are discussed elsewhere.

	1	2	3
	Simple acyclic mono-enes	imidazole, furan (α and β-furfuryl) indole	naphthalene benzene
A.	Benzothiophene-1,1-dioxide	(3-chloromethyl)-benzothiophene nitrobenzene pyrazine	
B.		thiazole benzofuran (2-chloromethyl)-benzothiophene	pyrrole thiophene ferrocene

In the accompanying table various systems are arranged in columns according to aromatic stability 1.non-aromatic systems 2.aromatic systems with a low resonance energy 3.highly resonance stabilised aromatic systems . Row A lists systems which have been the subject of literature study whereas selected derivatives of compounds in row B were considered for the present work. Thus compounds in block 2B are prone to rearrange whereas those in block 3B are less likely to show ambident electrophilic behaviour.

EXPERIMENTAL SECTION

INSTRUMENTATION

^{1}H NMR spectra were recorded on a Varian A 60 or a Varian T 60 spectrometer. Samples were run in solution of deuteriochloroform except when otherwise stated. Coupling constants (J values) are given in cycles per second.

Mass spectra were determined on an A.E.I. M.S.9 instrument working at low resolution. In each case the mass peak is given first, followed by those of structural significance.

Infrared spectra (IR) were recorded on a Perkin-Elmer 237 or 257 spectrometer and were taken as thin liquid films unless otherwise stated.

Melting points were taken on a Koffler block and are uncorrected.

G.L.C. analysis was performed on a Perkin-Elmer F 11 instrument using a 2 metre "Silicone gum rubber D.E. 120 column".

General Details

In this section "in the usual way" refers to the following working up procedure: The quantities given are approximately those used per gramme of starting material. The reaction product was poured into water (10 ml.) and extracted with ether (3 x 200 ml.). The combined ether extracts were dried (for at least 3 hr.) over anhydrous sodium sulphate. The sodium sulphate

was filtered off and the ether solution was evaporated under reduced pressure.

Dimethyl sulphoxide (DMSO) was purified by distillation under reduced pressure on to molecular sieves, type 10X. Typically the fraction boiling at b_7 = 64-66° was collected. All reactions were carried out under $CaCl_2$ or with self-indicating silica guard tubes. Dry ethanol was obtained by drying commercial 'absolute' ethanol. Ethanol was warmed gently with magnesium turnings (ca. 5% by weight) and a crystal of iodine until reaction occurred. The mixture was heated under reflux for 2 hr. and distilled collecting the fraction boiling at 77 - 79°. Methanol was dried similarly.

Standardisation of n-Butyl-lithium.

1. n-Butyl-lithium (1.00 ml.) was poured cautiously into water and the resulting solution was titrated with standard M/10 HCl using phenolphthalein. The molarity (xM) was calculated.

2. n-Butyl-lithium (1.00 ml.) was added slowly to a solution of benzyl chloride (1.5 ml.) in ether (5 ml.). Water (10 ml.) was added and the resulting solution titrated as before. The molarity (yM) was calculated.

xM represents the molarity of the total lithium, whereas the molarity of lithium present as lithium hydroxide or lithium butoxide (i.e. 'non-active' lithium) is yM. The molarity of the metallating constituent

(butyl-lithium) present in the reagent is therefore (x - y)M. The molarity of the samples used (obtained from Kodak Co.) was usually around 2.4 M.

THIOPHENES

2,5-Dimethylthiophene.

2,5-Dimethylthiophene was prepared by the method of Paal[60]. Lower yields were obtained by Farrar and Levine's[61] method.

Halomethylation of thiophene.

2-Chloromethylthiophene was prepared by the method of Hensley[62] i.e. chloromethylation of thiophene with formaldehyde and hydrogen chloride. This route resembles closely the preparation cited in Organic Synthesis[63]. Distillation of the crude product gave pure 2-chloromethylthiophene, $b_2 = 43^o$, as a colourless oil.

Bromomethylation of thiophene according to Inaba et al.[64] using trioxane and concentrated hydrobromic acid gave, after distillation, pure 2-bromomethylthiophene, $b_2 = 47^o$.

2-Bromomethyl- and 2-chloromethylthiophene were both prepared immediately before use.

2-Bromomethyl-5-methylthiophene.

2,5-Dimethylthiophene (thioxene) was brominated using N-bromosuccinimide as described by Buu-Hoi and Lecocq[6]. Crude 2-bromomethyl-5-methylthiophene was purified by distillation, $b_2 = 50^o$, and was used immediately. On standing for several hours at 0^o, the liquid turned violet and after 24 hr. only a black polymeric material could be recovered.

Chlorination of 2,5-dimethylthiophene.

A mixture of thioxene (11.2 g.; 0.1 mole), N-chlorosuccinimide (13.3 g.; 0.1 mole) and carbon tetrachloride (50 ml.) were warmed gently on a water-bath. A vigorous reaction with a variable induction period occurred. After the reaction was complete, i.e. when the N-chlorosuccinimide is converted into succinimide and rises to the top of the reaction mixture, the mixture was cooled in ice and the succinimide filtered off. Evaporation of the solution gave a yellow oil which was fractionated under reduced pressure through a Vigreux column and yielded two products. 3-Chloro-2,5-dimethylthiophene (4.1 g.; 28%), $b_5 = 42^o$; ν max. 2900, 2850 (CH), 1560 (C=C); 1450, 1330, 1190; 830 (aromatic) cm^{-1}; ^1H NMR δ 6.5 (s, ^1H), 2.35 (s, 3H), 2.30 (s,3H). (Found: C, 48.9; H, 4.55; Cl, 24.1. C_6H_7Cls requires C, 49.5; H, 4.8; Cl, 24.2%). 2-Chloromethyl-5-methylthiophene (too unstable for analysis) (6.3 g.; 43%), $b_{0.5} = 50-53^o$; ν max. 3080, 2970, 2950 (CH), 1550 (C=C), 1480, 1435, 1330; 1260, 1195, 1160, 1140, 1045, 1015; 820, 800 (aromatic) cm^{-1}; ^1H NMR δ 6.65 (d, ^1H, J = 3.5); 6.4 (d, ^1H, J = 3.5), 4.5 (s, 2H), 2.25 (s, 3H).

It may be noted that the ratio of ring to side chain substituted products varied. A number of factors operate here. For example new samples of N-chlorosuccinimide gave a long initiation time and led mainly to the ring

substituted product, 3-chloro-2,5-dimethylthiophene. In one run benzoyl peroxide was used to initiate the reaction and the ring substituted product was formed with only a trace of 2-chloromethyl-5-methylthiophene.

Alternative preparation of 2-chloromethyl-5-methylthiophene

2-Hydroxymethyl-5-methylthiophene (see later) (3 g., 0.0234 mole) was dissolved in benzene (5 ml.) and stirred at 3°. Thionyl chloride (5 g., 0.042 mole) was added dropwise with vigorous stirring. The temperature was allowed to rise slowly to 25° when stirring was continued for 1 hr. Finally the mixture was heated under reflux for a further hour. The benzene and thionyl chloride were removed under reduced pressure leaving a brown oil which was redistilled to give 2-chloromethyl-5-methylthiophene (2.2 g., 63%) as a colourless liquid. Physical data (b.p., IR and NMR spectra) were identical to the compound produced by chlorination of 2,5-dimethylthiophene.

Reaction of 3-methylthiophene with N-chlorosuccinimide.

cf. refs.[7] and[65].

3-Methylthiophene (20 g., 0.2 mole) was dissolved in carbon tetrachloride (60 ml.). N-Chlorosuccinimide (27 g., 0.2 mole) was added, followed by dry benzoyl peroxide* (0.5 g.). The mixture was heated under reflux

* The reaction could not be initiated without benzoyl peroxide.

on a water-bath for 5 hr. The suspension of succinimide was filtered off and washed with carbon tetrachloride (50 ml.). The organic phases were combined and the carbon tetrachloride was removed under reduced pressure and the brown oil thus obtained was distilled through a Vigreux column. Three products were isolated. 2-Chloro-3-methylthiophene (9.7 g., 36.5%), b_9 = 40-45°. $\nu_{max.}$ 3110, 2930, 2880 (CH); 1560 (C=C); 1440, 1415 (C-H), 1225, 1185, 1040, 930; 835, 700 (aromatic) cm^{-1}. ^1H NMR. δ, 6.78 (d, 1H, $J_{H/H}$=6), 6.55 (d, 1H, $J_{H/H}$=6), 2.0 (s, 3H). (Found: C, 45.2; H, 3.6; Cl, 26.6; S, 24.4. C_5H_5ClS requires C, 45.2; H, 3.8; Cl, 26.8; S, 24.4%). 3-Chloromethylthiophene (too unstable for analysis) (100 mg., 0.38%), b_2 = 47-55°, as a pale violet oil which turned black rapidly on standing. $\nu_{max.}$ 3100, 2920 (CH); 1555 (C=C); 1440, 1055, 935; 835, 700 (aromatic) cm^{-1}. 2,5-Dichloro-3-methylthiophene (12.7 g., 38%), b_2 = 87-89°, $\nu_{max.}$ 320, 2910, 2880 (CH); 1640 (CS); 1560 (C=C); 1440, 1380; 1180, 1055, 990, 930, 825 (aromatic); 695 (C-Cl) cm^{-1}; ^1H NMR. δ 6.62 (s, 1H); 1.98 (s, 3H). (Found: C, 35.7; H, 2.2; Cl, 42.7; S, 18.9. $C_5H_4Cl_2S$ requires C, 35.9; H, 2.4; Cl, 42.5; S, 19.2%).

2-Chloro-5-methylthiophene.

2-Methylthiophene (20 g., 0.2 mole) was treated with N-chlorosuccinimide as described for 3-methylthiophene. The crude oil obtained from the carbon tetrachloride solution was distilled to give 2-chloro-5-methylthiophene

(8 g., 62%) as a colourless liquid $b_{1.4}$ = 33°; $\nu_{max.}$ 3100, 2930, 2880 (CH); 1720 (CS); 1550, 1460 (CH); 1220, 1160, 1060, 1020, 960; 800, 700 (aromatic) cm^{-1}; ^1H NMR δ, 6.55 (d, 1H, $J_{H/H}$ = 3.5), 2.2 (s, 3H). (Found: C, 44.9; H, 4.0; Cl, 26.8; S, 24.7. C_5H_5ClS requires C, 45.2; H, 3.8; Cl, 26.8; S, 24.4).

Reaction of 3-methylthiophene with N-bromosuccinimide in carbon tetrachloride.

cf. refs.[7] and [65].

3-Methylthiophene (8.0 g., 0.08 moles) was dissolved in carbon tetrachloride (40 ml.) and N-bromosuccinimide (14.2 g., 0.08 moles) was added. The solution was heated under reflux for 3 hr. as described for reactions with N-chlorosuccinimide. The brown oil obtained was fractionated through a Vigreux column. Two impure fractions were obtained: Fraction A: a pale brown oil containing 2-bromo-3-methylthiophene and 3-bromomethylthiophene (1:1) (6.2 g., 43%), $b_{1.5}$ = 40-50°. Fraction B: 2-bromo-3-methylthiophene and 3-bromomethylthiophene (3:1) (2.7 g., 18.5%), $b_{1.5}$ = 60-70°. The ratios were calculated from the NMR spectra. Though the two isomers could not be separated NMR spectra could be allocated as follows: 2-bromo-3-methylthiophene; δ, 7.0 and 6.65 (2H, aromatics); 2.1 (s, 3H); 3-bromomethylthiophene, δ, 7.0, 6.6, 6.52 (3H aromatic); 4.25 (s, 2H).

Reaction of 3-methylthiophene with N-bromosuccinimide in benzene.

3-Methylthiophene (11 g., 0.112 mole) was treated with N-bromosuccinimide (17.8 g., 0.1 mole) in benzene (35 ml.) using dibenzoyl peroxide (0.4 g.) as initiator as described in Organic Synthesis[65], which is derived from the method of Campaigne and LeSuer[7]. A yellow oil was obtained which was fractionated to give three colourless fractions. Fraction A: 3-methylthiophene (3.5 g.), b_{10} = 40-44°. Fraction B: 2-bromo-3-methylthiophene (5.0 g.), b_{10} = 90-92°. This fraction was shown by NMR to contain 3-bromomethylthiophene (c.a. 20%). Fraction C: 3-bromomethylthiophene (4.5 g.), b_4 = 95-98°. $\gamma_{max.}$ 3100, 2950 (CH); 1690 (CS); 1410 1235, 1210, 820; 780 (aromatic) 665, 690 (C-Br) cm^{-1}; ^1H NMR. δ, 7.4-7.0 (m, 3H), 4,45 (s, 2H). This fraction contained 2-bromo-3-methylthiophene (c.a. 5%) based on the following NMR allocations: δ, 7.2-7.1 (m, 2H); 2.2 (s, 3H). Further distillation of this fraction failed to eliminate the impurity.

The total yield of all thiophene products was 79.5%.

Chloromethylation of 2-methylthiophene.

Concentrated hydrochloric acid (8.75 ml.) and formalin (7.5 ml.) in a 50 ml. 3-neck flask were cooled to 0° and hydrogen chloride gas was passed into the

solution. 2-Methylthiophene (9.8 g., 0.1 mole) was added slowly at 0.5°. The mixture was stirred for 1 hr. allowing the temperature to rise to 25°, then cooled to 0°. Work-up in the usual way but using anhydrous potassium carbonate as the drying agent gave a pale green oil which was distilled twice to give analytically pure 1,2-bis(5-methyl-2-thienyl)ethylene (6 g., 60%), $b_{0.5}$ = 120-123°, m.p. 29-30°; $\nu_{max.}$ 3050, 2900, 2850 (CH); 1710 (CS), 1600 (C=C); 1280, 1240, 1220, 1150, 1040, 970; 800, 740, 700 (aromatic) cm^{-1} ^1H NMR δ, 6.55 (m, 4H), 4.1 (s, 2H), 2.3 (s, 6H). m/e, 220, 194, 97. $\lambda_{max.}$ = 242 (E, 4000). (Found: C, 65.3; H, 5.5. $C_{12}H_{12}S_2$ requires C, 65.0; H, 5.5).

Emerson[66] claimed the above compound to be bis(5-methyl thienyl)methane, but our UV and mass spectral evidence support the proposed olefin structure. Also the reaction of the compound with neutral permanganate (using 2-methylthiophene as a blank) gave in the cold a precipitate of manganese dioxide after 3 min.

The above experiment was repeated on a quarter scale, except that sodium sulphate (instead of potassium carbonate) was used to dry the crude product. An unstable brown oil (1.8 g., 72%) was obtained which could only be distilled with much decomposition giving an impure, unstable yellow oil (100 mg., 4%). Mass spectra and NMR evidence showed the compound to be 1-chloro-1,2-bis(5-methylthienyl)ethane (too unstable for analysis).

$^{m}/e$ 256, 222, 194, 97. ^{1}H NMR δ 6.5 (m, 4H), 3.9 (t, 1H), 3.3 (d, 2H), 2.4 (s, 3H), 2.38 (s, 3H).

Reaction of 2-chloromethyl-5-methylthiophene with formalin.

2-Chloromethyl-5-methylthiophene (2.5 g.) was stirred vigorously with an excess of 40% aqueous formaldehyde (3 ml.) for 24 hr. at room temperature. Work-up in the usual way afforded a brown oil (130 mg., 5.3%) which was distilled from cotton wool in a sublimation tube to give impure 1-chloro-1,2-bis(5-methylthienyl) ethane.

Similar results were obtained if the above experiment was carried out while bubbling HCl gas into the reaction mixture.

Addition of sodium carbonate solution to the unstable 1-chloro-1,2-bis(5-methylthienyl)ethane was accompanied by evolution of carbon dioxide from which 1,2-bis(5-methyl-2-thienyl)ethylene could be isolated nearly quantitatively.

Attempted chloromethylation of 3-methylthiophene.

Treatment of 3-methylthiophene with formalin and hydrogen chloride as described in the preparation of 2-methylthiophene gave only polymeric material.

Preparation of N-chlorobenzotriazole.

N-Chlorobenzotriazole was prepared by Storr and Rees'

method[67]. From benzotriazole (100 g.), N-chlorobenzotriazole (120 g., 95%), m.p. 104°, was obtained.

Reaction of N-chlorobenzotriazole with 2,5-dimethylthiophene.

N-Chlorobenzotriazole (13.8 g., 0.09 mole) was added slowly to 2,5-dimethylthiophene (5 g., 0.045 mole) in carbon tetrachloride (50 ml.) at 0°. The mixture was stirred, allowing the temperature to rise slowly. After 6 hr. the mixture was filtered to remove benzotriazole hydrochloride. On distillation of the crude product obtained on evaporating the carbon tetrachloride solution, only traces of 2-chloromethyl-5-methylthiophene (IR evidence) were formed.

The crude product (3.6 g.) was chromatographed on a silica column and eluted with 20% ether/petrol to give an acidic product which was dissolved in 2N sodium hydroxide. The solution was filtered, washed with ether, acidified and extracted with ether to yield, after recrystallisation from water, white crystals of 5-methylthiophene-2-carboxylic acid (100 mg.), m.p. 138-140°. (Rinkes[68] gives m.p. 138-139°).

Elution of the column with ether gave a grey solid which was recrystallised from petrol/carbon tetrachloride to yield white needles of 1-(5-methyl-2-thenyl)benzotriazole (2.5 g., 24.5%) m.p. 105-7°. One further recrystallisation gave an analytical specimen of m.p. 109-110°.

$\nu_{max.}$ 2900, 2840 (CH); 1640, 1595 (C=C); 1270, 1245, 1230, 1170, 1110, 1050, 955; 870, 790, 765, 670 (aromatic) cm^{-1}; ^1H NMR δ, 8.0 and 7.4 (m, 4H), 6.85 (d, 1H, J=3), 6.55 (d, 1H, J = 3), 5.85 (s, 2H), 2.3 (s, 3H), $^m/e$ 229, 111 (Found: C, 62.9; H, 4.8; N, 18.3; S, 14.0. $C_{12}H_{11}N_3S$ requires C, 62.8; H, 4.8; N, 18.3; S, 13.9%).

Reaction of the sodium salt of benzotriazole with 2-chloromethyl-5-methylthiophene.

Benzotriazole (5 g., 0.042 mole) was stirred with sodium-dried ether (200 ml.). Sodium hydride (1.1 g., 0.046 mole) was added cautiously. Precipitation of the sodium salt occurred rapidly.

A solution of 2-chloromethyl-5-methylthiophene (4.8 g., 0.033 mole) in anhydrous ether (75 ml.) was added slowly to the suspension of the sodium salt. After 3 hr. the reaction mixture was poured into water and the ether was separated and then thoroughly washed with water (3 x 400 ml.). The ether layer was dried (anhydrous sodium sulphate) and evaporated leaving a brown oil which crystallised on scratching. Recrystallisation from petrol (b.p. 60-80°) gave needles of pure 1-(5-methyl-2-thenyl)benzotriazole (1.1 g., 11%) m.p. and mixed m.p. 108-9°. The reaction was also performed in dimethyl formamide (8% yield).

Thermolysis of 1-(5-methyl-2-thenyl)-benzotriazole.

When 1-(5-methyl-2-thenyl)-benzotriazole (250 mg.) was heated in a test-tube fitted with an air condenser at 160° for 12 hr. only starting material was obtained.

Reaction of 1-(5-methyl-2-thenyl)-benzotriazole with potassium cyanide.

A mixture of potassium cyanide (65 mg.) dimethyl sulphoxide and 1-(5-methyl-2-thenyl)-benzotriazole (250 mg.) when kept at 50° for 2 days gave on work-up only starting material.

2-Acetyl-5-methylthiophene.

2-Methylthiophene (31.0 g., 0.32 mole) was acetylated with acetic anhydride and orthophosphoric acid by the method of Hartough[69] to give pure 2-acetyl-5-methylthiophene (33.5 g., 77%) $b_{2.0}$ = 74.5-75°.

5-Methylthiophene-2-carboxylic acid.

2-Acetyl-5-methylthiophene (10 g., 0.07 mole) was oxidised with sodium hypochlorite by the method of Hartough[69], which is a modification of an Organic Synthesis[70] preparation of 2-naphtholic acid. 5-Methylthiophene-2-carboxylic acid (6.5 g., 65%), m.p. 137-137.5° was obtained.

2-(α-Hydroxyethyl)-5-methylthiophene.

Sodium borohydride (2.1 g., 0.055 mole) in water (10 ml.) and tetrahydrofuran (100 ml.) was added to 2-acetyl-2-methylthiophene (10 g., 0.071 mole) in tetrahydrofuran (100 ml.) and the mixture was stirred for 24 hr., the reaction being followed with TLC. The reaction product was acidified with N-sulphuric acid (to pH 5) and extracted with ether. The ether extracts were washed (water) and dried (Na_2SO_4). The colourless oil produced was distilled to yield pure 2-(α-hydroxyethyl)-5-methylthiophene (9.2 g., 91%) $b_{0.1} = 60^o$, $b_{0.9} = 83^o$, $b_{1.5} = 101^o$. $\nu_{max.}$ 3345 (OH); 2975, 2915, 2860 (CH); 1625; 1070 (→C-O-), 890, 805 (aromatic) cm^{-1}. ^1H NMR δ 6.6 (d, 1H J = 4); 6.4 (d, 1H, J = 4), 4.75 (quartet, 1H, J = 6); 3.77 (s, 1H); 2.31 (s, 3H); 1.4 (d, 3H, J = 6).

Reaction of 2-(α-hydroxyethyl)-5-methylthiophene with thionyl chloride.

A solution of 2-(α-hydroxyethyl)-5-methylthiophene (3 g., 0.02 mole) in benzene (5 ml.) was treated with thionyl chloride (5.0 g., 0.042 mole) in benzene (5 ml.) by dropwise addition with vigorous stirring at 0^o. The temperature was allowed to rise slowly and finally the mixture was heated under reflux for 10 min. The excess of benzene and thionyl chloride was taken off under reduced pressure. The brown oil produced decomposed spontaneously and rapidly. Decomposition occurred within

one hour even when the compound was kept in a solvent such as benzene or ether.

Attempts to prepare 2-(α -chloroethyl)-5-methylthiophene under carefully contrived conditions (such as under nitrogen and in the presence of pyridine to neutralise excess of hydrogen chloride and using purified[71] thionyl chloride) led invariably to the same unstable, brown oil, impure 2-(α -chloroethyl)-5-methylthiophene)(too unstable for analysis). On one occasion IR and NMR spectra were taken before decomposition occurred. $\nu_{max.}$ 3080, 2980, 2935, 2880 (CH); 1490, 1450, 1380; 1240, 1050; 805 (aromatic); 710 (C-Cl) cm^{-1} ^1H NMR δ, 7.0 - 6.5 (m, 2H), 5.3 (quartet, 1H); 2.5 (d + s; 3H + 3H). Integration of the aromatic region showed the compound to be at least 60% pure.

Immediate reaction of the crude product with cyanide led to polymeric material assumed to be the same as that formed from the spontaneous decomposition of the α-chloroethyl compound.

Reduction of 5-methylthiophene-2-carboxylic acid with lithium aluminium hydride.

5-Methylthiophene-2-carboxylic acid (7.5 g., 0.053 mole) was added in small portions to a suspension of lithium aluminium hydride (2.01 g., 0.053 mole) in dry ether (75 ml.) and the mixture was stirred at room temperature overnight. Water (5 ml.) was added dropwise to destroy the excess of lithium aluminium hydride.

The acidity of the reaction mixture was adjusted to pH5 with 2N sulphuric acid. Work-up in the usual way afforded a cloudy oil which was redistilled to give 2-hydroxymethyl-5-methylthiophene (5.1 g., 76%), b_4 = 80-2° as a colourless liquid. $\nu_{max.}$ 3340 (OH); 3080, 2940, 2880 (CH); 1500, 1460; 1020 (C-O); 810 (aromatic)cm^{-1}. ^1H NMR δ, 6.7 (d, 1H, J = 3); 6.5 (d, J = 3); 4.55 (s, 2H), 3.4 (s, 1H); 2.4 (s, 3H).

Bromopinacolone.

Bromopinacolone was prepared by the method of Bayer[72], (a modification of Hill and Kropa's method[73]) from pinacolone (4.2 g., 0.42 mole) and bromine (66 g., 0.42 mole) in ether (350 ml.). The crude bromo-compound was redistilled to give bromopinacolone (55.3 g., 73.5%), $b_{5.8}$ = 75-6°.

Ethyl 6,6-dimethylheptan-2,5-dione-3-carboxylate.

The preparation of the sodium salt of ethyl aceto-acetate is based on the method described in Organic Synthesis[74]. Its reaction with bromopinacolone has been mentioned by Messina and Brown[75], but no experimental details are given.

Sodium (4.6 g., 0.2 mole) was dissolved in absolute ethanol (80 ml.) and ethyl acetoacetate (28.6 g., 0.22 mole) was added slowly to the solution with rapid stirring. Bromopinacolone (35.8 g., 0.20 mole) was introduced dropwise with stirring. The mixture was

stirred for 24 hr., cooled to 5° and the sodium bromide was filtered off and washed with ethanol. The ethanol phases were combined and the solvent was removed. The remaining oil was filtered through a small sinter funnel and fractionated to give ethyl 6,6-dimethyl-2,5-dioxoheptan-3-carboxylate (ethyl α-pinacolylacetoacetate) (36.7 g., 80.5%), b_{18} = 147-8° as a colourless liquid. $\nu_{max.}$ 2950, 2915, 2890, 2860 (CH); 1740, 1705 (>C=O); 1480, 1395, 1365, 1100, 860 cm^{-1}. ^1H NMR δ, 4.1 (quartet + t appearing as quintet, 2H + 1H); 3.05 (d, 2H, J = 9); 2.3 (s, 3H): 1.2 (t, 3H, J = 7); 1.15 (s, 9H).

6,6-Dimethylheptan-2,5-dione.[75]

Ethyl α-pinacolyacetoacetate (40 g., 0.176 mole) was stirred at room temperature for 4 days with dilute aqueous potassium hydroxide (10.8 g. dissolved in 400 ml. of water; 0.192 mole). The solution was acidified to pH 1 with 2N-sulphuric acid, stirred for 1 hr. * and extracted with ether. The extracts were washed with water, 10% aqueous sodium carbonate, water and finally

---

* Decarboxylation does not appear to be complete under basic conditions but occurs rapidly in acid. Stirring for a short time at low pH prevents any free acid from being isolated and increases the yield of the diketone by ca. 5%.

dried (Na_2SO_4). The product was distilled to give pure 6,6-dimethylheptan-2,5-dione (16.5 g., 60%), b_{15} = 93-4° as a colourless liquid. $\nu_{max.}$ 2950, 2895, 2860 (C-H); 1715, 1705 (C=O), 1480, 1395, 1365, 1230, 1185, 1160, 1085, 1050, 995 cm^{-1} ^1H NMR δ, 5.4 (t + t appearing as quintet, 2H + 2H), 4.3 (s, 3H), 2.3 (s, 9H).

2-t-Butyl-5-methylthiophene.

2-t-Butyl-5-methylthiophene was prepared by the method of Messina and Brown[75]. From 6,6-dimethylheptan-2,5-dione (7.8 g., 0.05 mole) and phosphorus pentasulphide (8.2 g., 0.038 mole), pure 2-t-butyl-5-methylthiophene (3.6 g., 47%), b_{15} = 70-2°, b_{760} = 182-6° (lit.[75] b_{19} = 74-5°) was obtained as a colourless liquid. $\nu_{max.}$ 3060, 2950, 2850, (CH); 1450, 1350, 1245; 780 (aromatic) cm^{-1}. ^1H NMR δ, 6.55 (m, 2H), 2.4 (s, 3H), 1.15 (s, 9H).

Chlorination of 2-t-butyl-5-methylthiophene with N-chlorosuccinimide.

A. A solution of 2-t-butyl-5-methylthiophene (2.31 g., 0.015 mole) in carbon tetrachloride (20 ml.) was treated with N-chlorosuccinimide (2.00 g., 0.015 mole). The solution was heated under reflux for 6 hr. Reaction which could be followed by NMR occurred and only under vigorous reflux. The solution was filtered, dried (Na_2SO_4) and the solvent removed leaving a pale brown oil.

B. The experiment was repeated using 2 equivalents of N-chlorosuccinimide.

C. The experiment was performed using dibenzoyl peroxide as an initiator and 1 equivalent of N-chlorosuccinimide. Reaction was in each case complete in 2 hr. A product analysis based on the following NMR allocations is given in Table 1.

(i) 2-t-butyl-5-methylthiophene (see previous experiment).

(ii) 2-t-butyl-5-chloromethylthiophene*[76] (too unstable for analysis); b_2 = 80-1° δ, 6.82 (d, 1H, J = 4); 6.65 (d, 1H, J = 4), 4.68 (s, 2H), 135 (s, 9H). $\nu_{max.}$ 2960, 2860 (CH); 14-75, 1365, 803 (aromatic); 695 (C-Cl) cm^{-1}.

(iii) 2-t-butyl-3-chloro-5-methylthiophene:** δ, 6.55 (s, 1H), 2.43 (s, 3H), 1.46 (s, 9H).

(iv) 2-t-butyl-4-chloro-5-methylthiophene:** δ, 6.58 (s, 1H), 2.35 (s, 3H); 1.38 (s, 9H).

(v) 2-t-butyl-3,4-dichloro-5-methylthiophene: δ, 2.15 (s, 3H), 1.35 (s, 9H).

---

* 2-t-butyl-5-chloromethylthiophene was the only chlorinated thiophene obtained in a pure state (see Table 1), hence IR data are given for this compound.

** The 3- and 4-chloro derivatives of 2-t-butyl-5-methylthiophene could not be separated. NMR allocations are based on the assumption that the more sterically hindered 3-chloro-compound is formed in lower yield.

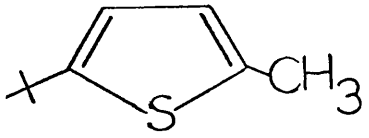
Table I

Experiment	Reaction Time (hr.)	Amount of N.C.S. used (moles)	Crude Product Analysis	Fractions after distillation of crude product
A	6	1	(i):(ii) 2:1	(a)(i)(150 mg.) b_6 = 60-70°
	12		As above (2.2 g.)	(b)(i);(ii) 1:2 (1.3 g.) 1.3 g. b_5 = 78-84° (c)(ii)(300 mg.) b_2 = 80-1°
B	9	2	(ii):(iii):(iv):(v) (6:5:8:25) (1.8 g.)	Could not be fractionated

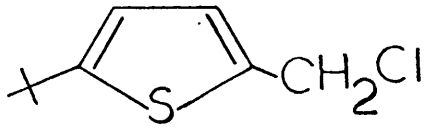
Experiment	Reaction Time (hr.)	Amount of N.C.S. used (moles)	Crude Product Analysis	Fractions after distillation of crude product
C*	1	1	(i):(ii): (iii)+(iv) (7:3:6)	
	2		(ii): (iii)+(iv) 3:6:6 (1.9 g.)	(a)(ii): (iii)+(iv) 1:3 (1.0 g.) b_{10} = 98-104° (b)(ii): (iii)+(iv) 9:1 (200 mg.) b_{10} = 110 - 115°

*Initiator: dibenzoyl peroxide.

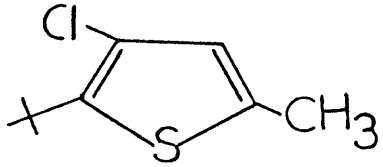
Key to table I



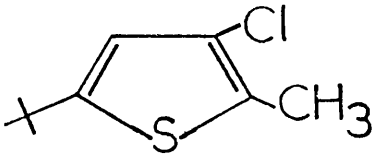
(i)



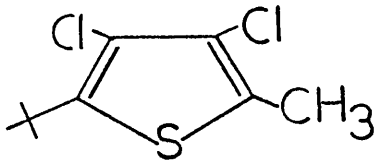
(ii)



(iii)



(iv)



(v)

Reactions of halomethylthiophenes.

The halomethylthiophenes whose preparations have been described were made to react with a number of nucleophiles (mainly cyanides) in a variety of solvents as shown in Table 2. Work-up was in the usual way except where cuprous or silver cyanide were used as reagents, when ether was added to the reaction mixture and the solution was filtered to remove insoluble inorganic salts. The product was then isolated in the usual way. Physical data of the reaction products in the table are as follows:

3-Chloro-2,5-dimethylthiophene (see p.47) $b_{10} = 53\text{-}4^{\circ}$

3-Bromo-2,5-dimethylthiophene[6,53,54] $b_{20} = 60^{\circ}$

$\nu_{max.}$ 2900 (CH), 1552, 1445, 1320, 1182, 1003, 820, 800 cm^{-1}. ^1H NMR δ, 6.5 (s, 1H); 2.35 (s, 3H); 2.3 (s, 3H).

2-Cyanomethylthiophene[77] $b_{0.5} = 60^{\circ}$

$\nu_{max.}$ 3080, 2910 (CH); 2250 (CN); 1415, 855, 835, 655 (aromatic) cm^{-1}; ^1H NMR δ, 7.25 (m, 1H); 7.1-6.9 (m, 1H); 3.85 (s, 2H).

Thiophene	Reagent
2-chloromethyl-	NaCN
(9 g., 0 068 mole)	(3.8 g., 0.078 mole)
2-chloromethyl	CuCN
(5 g., 0.038 mole)	(4 g., excess)
2-bromomethyl	NaCN
(5.8 g., 0.038 mole)	(1.9 g., 0.04 mole)
2-bromomethyl	CuCN
(4 g., 0.023 mole)	(excess)
3-bromomethyl	KCN
(2.0 g., 0.011 mole)	(0.975 g., 0.015 mole)
3-bromomethyl	KCN
(2.0 g., 0.011 mole)	(0.975 g., 0.015 mole
2-t-butyl-5-chloromethyl	KCN
(0.5 g., 0.003 mole)	(0.195 g., 0.003 mole)
2-t-butyl-5-chloromethyl	CuCN
(0.1 g., 0.0005 mole)	(excess)
2-α-chloro ethyl-5-methyl	CuCN
(0.5 g.)	KCN
2-bromomethyl-5-methyl	CuCN
(4.5 g., 0.024 mole	(5.5 g., 0.062 mole)
2-bromomethyl-5-methyl	KCN
(4.5 g., 0.024 mole)	
2-chloromethyl-5-methyl	CuCN
(4.0 g., 0.027 mole)	(6.3 g., 0.07 mole)

Solvent	Product(s) (Thiophenes)	Identified by
DMSO	2-cyanomethyl	IR NMR
(20 ml.)	(5 g., 60%)	GLC
no solvent	polymeric	TLC IR
or ether (15 ml.)	material	
DMSO	2-cyanomethyl	TLC GLC
(15 ml.)	(2.8 g., 69.5%)	NMR IR
no solvent	polymeric	TLC IR
or ether (12 ml.)	material	
DMSO	3-cyanomethyl	NMR IR
(10 ml.)	(0.88 g., 63.5%)	
EtOH (5 ml.)	3-cyanomethyl (0.6 g., 42%)	NMR IR
+ H_2O (5 ml.)	3-ethoxymethyl (0.2 g., 15%)	
DMSO	2-t-butyl-5-cyanomethyl	NMR IR
(5 ml.)	(0.32 g., 67.5%)	Analysis
no solvent	polymeric	IR NMR
or ether	material	TLC
no solvent	polymeric	IR TLC
DMSO	material	
-	3-bromo-2,5-dimethyl	IR NMR
	(4.0 g., 88%)	MS
DMSO	3-bromo-2,5-dimethyl	IR NMR
(10 ml.)	(1.9 g., 39%)	
-	3-chloro-2,5-dimethyl	TLC NMR
	(3.0 g., 75%)	IR MS Anal.

Thiophene	Reagent
2-chloromethyl-5-methyl (4.0 g., 0.027 mole)	CuCN (6.3 g., 0.07 mole)
2-chloromethyl-5-methyl (0.3 g., 0.020 mole)	NaCN (1.3 g., 0.027 mole)
2-chloromethyl-5-methyl (3.0 g., 0.02 mole)	-
2-chloromethyl-5-methyl (3.0 g., 0.02 mole)	KCN (1.7 g., 0.026 mole)
2-chloromethyl-5-methyl (3.0 g., 0.02 mole)	KBr (2.5 g., 1 mole)
2-chloromethyl-5-methyl (3.0 g., 0.02 mole)	CuCN (0.2 g., 0.002 mole)
2-chloromethyl-5-methyl (3.0 g., 0.02 mole)	$CH_3.CN^+$ (3 mole, excess)
2-chloromethyl-5-methyl (1.8 g., 0.012 mole)	AgCN (1.6 g., 0.012 mole)
2-chloromethyl-5-methyl (2.5 g., 0.017 mole)	AgCN (2.3 g., 0.017 mole)
2-chloromethyl-5-methyl (2.0 g., 0.014 mole	KCN (1.2 g., 0.018 mole)
2-chloromethyl-5-Me ** (1.0 g., 0.007 mole)	CuCN (1.0 g., 0.11 mole)

Solvent	Product (s) (Thiophenes)	Identified by
ether (12 ml.)	3-chloro-2,5-dimethyl (3.0 g., 75%)	TLC NMR IR MS Anal.
DMSO (10 ml.)	3-chloro-2,5-dimethyl (2.0 g., 67%)	TLC IR NMR
DMSO (10 ml.)	2-chloromethyl-5-methyl + a little polymer (2.7 g., 90%)	IR NMR
DMSO (10 ml.)	2-chloro-2,5-dimethyl (2.5 g., 83%)	IR NMR
DMSO (10 ml.)	3-chloro-2,5-dimethyl (0.7 g., 23%)	IR NMR
no solvent	3-chloro-2,5-dimethyl (0.21 g., 69%)	IR NMR
-	3-chloro-2,5-dimethyl (0.2 g., 7%)	
no solvent or EtOH or Et_2O	3-chloro-2,5-dimethyl (1.2 g., 67%)	
DMSO (10 ml.)	3-chloro-2,5-dimethyl (2.1 g., 84%)	IR NMR
H_2O (10 ml.)	3-chloro-2,5-dimethyl	IR NMR
petrol (bp 40-60° 10 ml.)	(0.4 g., 20%) 2-cyanomethyl-5-Me (1.1 g., 55%)	
-	polymeric material only	TLC IR NMR

Thiophene	Reagent
2-chloromethyl-5-Me ** (1.2 g., 0.008 mole)	KCN (0.58 g., 0.009 mole)

+ The solution turned pink on addition of acetonitrite

* The reaction mixture was shaken for 24 hr.

** Prepared from 2-hydroxymethyl-5-methylthiophene and thionyl chloride.

Solvent	Product (s) (Thiophenes)	Identified by
DMSO (7 ml.)	2-cyanomethyl-5-Me (0.61 g., 54%)	TLC NMR IR

3-Ethoxymethylthiophene. $b_{4.5} = 92\text{-}5^{o}$

$\nu_{max.}$ 3100, 2970 (CH), 1415, 1090 (CO), 772, 690 (aromatic) cm^{-1}. ^{1}H NMR δ, 7.4-6.95 (m, 3H); 3.65 (s, 2H); 3.55 (q, 2H, J = 6); 1.15 (t, 3H, J = 6). (Found: C, 59.5; H, 6.8; S, 22.1. $C_7H_{10}OS$ requires C, 59.2; H, 7.0 (5); S, 22.5).

3-Cyanomethylthiophene.[79] $b_{15} = 96^{o}$

$\nu_{max.}$ 3100, 2980, 2960 (CH), 2258 (CN), 1420, 1003, 860, 840, 775, 695 (aromatic) cm^{-1}. ^{1}H NMR δ, 7.45-6.90 (m, 3H); 3.7 (s, 2H).

2-t-Butyl-5-cyanomethylthiophene. (cf. ref.[76])

$\nu_{max.}$ 2960 (CH), 2255 (CN), 1260, 1010, 800, 730 (aromatic) cm^{-1}. ^{1}H NMR δ, 6.6 (d, 1H, J = $3\frac{1}{2}$); 6.4 (d, 1H, J = $3\frac{1}{2}$); 3.55 (s, 2H); 1.25 (s, 9H).

2-Cyanomethyl-5-methylthiophene. (cf. ref.[76]) $b_3 = 70^{o}$

$\nu_{max.}$ 2910 (CH), 2270 (CN), 1495, 1460, 1420, 1050, 810 (aromatic) cm^{-1}. ^{1}H NMR δ, 6.83 (d, 1H, J = $3\frac{1}{2}$); 6.6 (d, 1H, J = $3\frac{1}{2}$); 3.8 (s, 2H); 2.4 (s, 3H).

Comparison of 2-chloromethyl-5-methylthiophene prepared by different methods.

2-Chloromethyl-5-methylthiophene was prepared by each of the two routes described previously (reaction of 2-hydroxymethyl-5-methylthiophene with thionyl chloride

[B] and chlorination of thioxene with N-chlorosuccinimide [A]). The experiments set out in Table 3 below are designed to show that an impurity in [A] causes rearrangement. In each case the thiophene (or thiophene mixture) was added to potassium cyanide.

Table 3

Expt.	Quantities used	Products (thiophene)
Blank	0.5 g. [A]	3-chloro-2,5-dimethyl 0.32 g., 64%
Blank	0.5 g. [B]	2-cyanomethyl-5-methyl 0.24 g., 48%
1.	0.6 g. [B] + 0.05 g. [A]	2-cyanomethyl-5-methyl 0.32 g., 53%
2.	0.4 g. [B] + 0.2 g. [A]	2-cyanomethyl-5-methyl 0.1 g., 17% 3-chloro-2,5-dimethyl 0.31 g., 52%

(1.25 molar equivalent) in DMSO (5 ml.). After the usual work-up procedure products were distilled from cotton wool in a sublimation tube and the colourless oils obtained were analysed by NMR.

Hydrolysis of 2-chloromethyl-5-methylthiophene.

2-Chloromethyl-5-methylthiophene (14.6 g., 0.1 mole) was dissolved in tetrahydrofuran (100 ml.). Potassium hydroxide (5.6 g., 0.1 mole) in water (20 ml.) was added. The mixture was stirred for 18 hr. at room temperature. The crude brown oil obtained* (11.2 g.) by work-up in the usual way was distilled giving two fractions.

1. 2-Hydroxymethyl-5-methylthiophene as a colourless liquid (6.3 g., 49.5%) $b_{10} = 70^{o}$. See p for physical data.

2. bis(Thenyl-5-methyl)ether as a colourless liquid (3.5 g., 29.5%) $b_{0.05} = 140^{o}$. $\nu_{max.}$ 2910, 2850 (CH), 1680 (CS), 1490, 1445 (CH bending), 1360, 1225, 1110, 1065 (C-O), 800 (aromatic) cm^{-1}. ^{1}H NMR δ, 6.8 (d, 2H, J = 3), 6.55 (d, 2H, J = 3), 4.5 (s, 4H), 2.4 (s, 6H). (Found: C, 60.2; H, 5.9; S, 26.5. $C_{12}H_{14}OS_2$ requires C, 60.5; H, 5.9; S, 26.9.)

Under the conditions of the above experiment 2-hydroxymethyl-5-methylthiophene remained unchanged. On heating this compound above 100^{o} for 2 hr. the liquid darkened and formed the ether in 60% yield. (The loss was due to polymerisation, but only traces of the alcohol were present after thermal treatment).

* No bis(thenyl-5-methyl)ether was present in the crude product (IR, NMR).

On standing 2-hydroxymethyl-5-methylthiophene formed small amounts of the ether, detectable (IR, NMR) after two to three weeks.

Reaction of p-methylbenzylchloride with cuprous cyanide.

A mixture of p-methylbenzylchloride (10.0 g., 0.071 mole) and cuprous cyanide (8g., 0.089 mole) was stirred. No reaction occurred below 120°, at which temperature the mixture was heated for 12 hr. The dark brown oil obtained contained only one simple aromatic compound (TLC, NMR) which was isolated by distillation and shown to be pure p-methylbenzylnitrile (3.1 g., 33%) b_9 = 111° (lit.[78] b_{13} = 122°).

2-Hydroxymethylthiophene.

2-Thenaldehyde (22.4 g., 0.2 mole) in tetrahydrofuran (THF) (100 ml.) was treated with sodium borohydride (5.7 g., 0.15 mole). The reaction was followed on TLC and was shown to be complete in 18 hr. The product was poured on to ice/water (200 g.), the THF removed under reduced pressure and the residue extracted with ether (4 x 200 ml.). The ether extracts yielded a colourless oil which was distilled to give pure 2-hydroxymethylthiophene (cf. ref.[80]) (18.7 g., 83%); b_6 = 81°. $\nu_{max.}$ 3600-3000 (OH); 2920, 2865 (CH); 1435, 1210, 1160, 1005 (CO), 850, 830, 700 (aromatic) cm^{-1}. ^1H NMR δ, 7.15 (m, 1H); 6.85 (m, 2H); 4.55 (s, 2H); 4.35 (s, 1H).

Attempted thermolysis of 2-hydroxymethylthiophene under the conditions which yielded bis(5-methylthenyl) ether from 5-methyl-2-hydroxymethylthiophene gave no reaction. Though 2-hydroxymethylthiophene darkened slowly on standing for several weeks, no simple thiophenes could be isolated or detected.

2-Thenylisothiouronium chloride.

Thiourea (3.6 g., 0.05 mole) was added to a mixture of water (5 ml.) and 12.5 N hydrochloric acid (4 ml.). The solid was dissolved by gentle heating and the solution was cooled to 30°, when 2-hydroxymethylthiophene (5.7 g., 0.05 mole) was added. The solution was warmed to 50° and stirred for 6 hr. and then allowed to stand overnight at 0°. The white crystals which precipitated were collected and recrystallised from isopropanol, yielding pure 2-thenylisothiouronium chloride (7.4 g., 71%); m.p. 167-71° (lit.[81] 160-1°). $\nu_{max.}$ (nujol). 3400-2800, 1645, 1450, 1250, 1063, 730, 680 cm^{-1}, ^1H NMR (d^6 DMSO) δ, 9.55 (s, 4H); 7.6 (d, 1H, J = 5); 7.35 (d, 1H, J = $3\frac{1}{2}$); 7.1 (d of doublets, 1H, J = $3\frac{1}{2}$ and 5); 5.50 (s, 2H).

Bis(2-thenyl)disulphide.

A solution of 2-thenylisothiouronium chloride (3.0 g., 0.014 mole) in water (10 ml.) was added dropwise to a stirred solution of potassium cyanide (2.92 g., 0.045 mole) in water (10 ml.). The solution darkened rapidly

and stirring was continued for 24 hr. The product was poured into water and filtered. Both solution and solid were washed with ether and the combined ether extracts yielded an oil (1.3 g.) which was redistilled to give pure bis(2-thenyl)disulphide (0.91 g., 48%); b_2 = 164°; $\nu_{max.}$ 3100, 2960, 2900 (CH), 1430, 1405, 1245, 1220, 1103, 1035, 850, 825, 695 (aromatic) cm^{-1}. ^1H NMR δ, 7.2 (m, 1H); 6.95 (m, 2H); 3.9 (s, 2H); m.s. 258 (p^+), 226 (-S), 194 ($-S_2$), 129 ($Th-CH_2\overset{+}{S}$), 97 ($Th-\overset{+}{C}H_2-$). (Found: C, 46.2; H, 4.1; S, 48.8(5). $C_{10}H_{10}S_4$ requires C, 46.5; H, 3.8(5); S, 49.5).

FURANS

2-Chloromethylfuran.

Furfuryl alcohol was redistilled (b_8 = 62.3°) and dried over molecular sieves. Pyridine was distilled over potassium hydroxide before use.

Furfuryl alcohol in pyridine and ether was treated with thionyl chloride by the method of Kirner[82]. 2-Chloromethylfuran was obtained in up to 85% yield after distillation of the crude yellow oil (b_{10} = 35°); $\nu_{max.}$ 3105, 2950, (CH), 1500, 1330, 1150, 1015, 940, 790, 695 cm^{-1}.

^1H NMR δ, 7.35 (m, 1H); 6.3 (m, 2H); 4.5 (s, 2H).

Preparation of the Bunte Salt of 2-chloromethylfuran.

Furfuryl chloride (23.1 g., 0.2 mole) was added slowly to a solution of sodium thiosulphate (52 g., 0.21 mole) in water (80 ml.) with rapid stirring. After the initial exothermic reaction had subsided, the reaction mixture was heated under reflux for 1 hr., cooled and poured onto ice (800 g.). The aqueous solution was extracted with ether (3 x 150 ml.). The ether extracts were discarded, the yellow aqueous solution was concentrated (to 50 ml.) and the Bunte salt was allowed to crystallise overnight at 0°. This crude salt (13.4 g., 31.3%) was found to contain a mixture of sodium 2-furfurylthiosulphate and sodium 5-methyl-2-furylthiosulphate in the ratio 5 : 2 resp. based on the following NMR allocations:

Sodium 2-furfurylthiosulphate δ, 7.55 (m, 1H); 6.4 (m, 2H); 4.3 (s, 2H) and sodium 5-methyl-2-furylthiosulphate δ, 6.9 (d, 1H, J_{HH}= 3); 6.25 (d, 1H, J_{HH} = 3); 2.35 (s, 3H).

The mixture of isomers was recrystallised from water, but all fractions contained the two isomers in practically the same ratio (10.6 g., 24.8%). (Found: C, 27.6; H, 1.9; S, 29.5. $C_5H_5NaO_4S_2$ requires C, 27.8; H, 2.3 (1); S, 29.6%).

Reaction of the Bunte salt with chlorine.

To a solution of the crude Bunte salt made from 0.2 mole or furfuryl chloride was added acetic acid (50 ml.). The mixture was poured on to crushed ice to make a total volume of ca. 1500 ml. Chlorine was passed into the reaction mixture with rapid stirring. Ice was occasionally added to keep the temperature at 0°. When the solution remained green-yellow, the suspension was stirred for a further 5 min. and extracted with methylene chloride (3 x 100 ml.), washed with 5% sodium metabisulphite solution (2 x 200 ml.), water (3 x 100 ml.) and dried (Na_2SO_4). On evaporation of the methylene chloride a dark brown oil was obtained which was distilled to yield a colourless unstable liquid of 5-methyl-2-furylsulphonylchloride (2.6 g., 11.3%). $\nu_{max.}$ 3120, 2960 (CH); 1590, 1495, 1395, 1185 (SO_2), 1140, 1050; 800, 670, 640 (aromatic) cm^{-1}. ^1H NMR δ, 7.2

(d, 1H; J = 4); 6.3 (d, 1H, J = 4); 2.5 (s, 3H).

2-Furfurylisothiouronium chloride cf. [83,84]

Thiourea (38 g., 0.5 mole), water (50 ml.) and 12.5 N hydrochloric acid (40 ml.) were placed in a round flask. The solid was dissolved by gentle heating and the solution cooled to 30°. Furfuryl alcohol (49 g., 43.4 ml; 0.5 mole) was added over a period of 10 min. The temperature was kept below 60° by cooling intermittently in an ice bath. The reaction mixture was allowed to stand overnight.

The aqueous solution was evaporated to dryness under reduced pressure. Aliquots of n-propanol were added and evaporated (to azeotrope off last traces of water). On addition of ether and scratching, the hydrochloride crystallised out and was filtered off and washed with ether. Recrystallisation from aceto-nitrile gave 2-furfurylisothiouronium chloride (59.5 g., 62%) $\nu_{max.}$ (nujol mull) 3400 2900 (broad hydro-chloride absorption), 1620, 1010, 935, 815, 735 cm^{-1}; ^1H NMR δ, 9.5 (s, 4H); 7.8 (m, 1H); 6.55 (m, 2H); 4.85 (s, 2H). (Found: C, 37.1; H, 4.8; Cl, 18.7; N, 14.7; S, 16.1%. $C_6H_9ClN_2OS$ requires C, 37.4; H, 4.7; Cl, 18.4; N, 14.5; S, 16.6%). m.p.= 148-9° (lit.[84] m.p.=142)

Reaction of 2-furfuryl-isothiouronium chloride with cyanide.

2-Furfurylisothiouronium chloride (9.6 g., 0.05 mole)

in water (10 ml.) was stirred at room temperature with potassium cyanide (9.75 g., 0.15 mole). The solution darkened almost immediately. Stirring was continued overnight and the reaction mixture was poured into water and filtered to remove tarry material. The filtrate was extracted with ether (3 x 200 ml.). The combined ether extracts were washed with water (3 x 200 ml.) and dried (Na_2SO_4). A brown liquid was obtained which was redistilled to give bisfurfuryl disulphide[85] as a pale yellow oil (b_5 = 141°, $b_{0.8}$ = 120°; $b_{0.5}$ = 112°) (2.0 g., 34.1%). $^m/e$ 226 (p^+), 194, 162, 81 ^{1}H NMR δ, 7.35 (m, 1H); 6.25 (m, 2H) 3.65 (s, 2H). $\nu_{max.}$ 3120, 2980, 2920 (CH); 1505, 1405, 1150, 1015, 940, 890; 810, 740 (aromatic) cm^{-1}. (Found: C, 52.8; H, 4.1; S, 27.8%. $C_{10}H_{10}O_2S_2$ requires C, 53.1; H, 4.4; S, 28.3%).

2-Furfuryl mercaptan.

2-Furfuryl mercaptan was prepared according to Organic Synthesis[83] from 2-furfurylisothiouronium chloride and sodium hydroxide in 50% yield. $\nu_{max.}$ 4140, 2925, (CH); 2560 (SH); 1590, 1500, 1250, 1150, 1070, 1010, 925, 730 cm^{-1}. ^{1}H NMR δ, 7.3 (m, 1H); 6.2 (m, 2H); 3.7 (d, 2H, J = 8); 1.85 (t, 1H, J = 8).

The following experiments were designed to show that 2-furfuryl mercaptan is not converted into the dithio-compound under the conditions of the reaction between KCN and 2-furfuryl isothiouronium chloride (see p.82-3).

Experiment (i) serves as an unambiguous synthesis of the dithio-compound.

(i) 2-furfuryl mercaptan (4 g., 0.036 mole) was dissolved in methanol (20 ml.) and an aqueous solution of sodium hydroxide (0.5 g., 0.013 mole) in water (20 ml.) was added. Air was bubbled slowly through the reaction mixture at 50° for 18 hr. Work-up in the usual way afforded bis(2-furfuryl)bisulphide (2.4 g., 60%). No starting material was present in the reaction mixture (IR and NMR evidence). At room temperature reaction occurred more slowly, being incomplete after 2 days. With concentrated NaOH reaction was complete in a few minutes.

(ii) The above experiment was repeated in the absence of base. After 24 hr. a product analysis (NMR) showed the presence of the dithio-compound (0.6 g., 15%) and starting material (2.3 g., 62%).

(iii) Experiment (ii) was repeated but in the presence of potassium cyanide (5 g., 0.077 mole). Starting material (2.6 g., 65%) and the dithio-compound (0.8 g., 29%) were obtained after 24 hr.

Nucleophilic attack on 2-furfuryl chloride.

In the following reactions, 2-furfuryl chloride (5 g., 0.043 mole) was stirred at room temperature for 24-48 hr. with a variety of nucleophiles in a number of solvents. Work-up was in the usual way. Where a water-soluble solvent (e.g. methanol, dimethylsulphoxide and

dimethylformamide, or formamide) was used, thorough extraction of the organic layer with water was necessary to remove the solvent from the organic layer. The product analyses are based on NMR data. Physical data for the isolated compounds are given below.

Physical data for compounds.

2-Cyanomethylfuran $b_{10} = 95^{\circ}$; $\nu_{max.}$ 3120, 2960 (CH), 2255 (CN, medium), 1600, 1505, 1410, 1145, 1010, 950, 930, 810, 740 (aromatic) cm^{-1}. ^1H NMR δ, 7.35 (m, 1H); 6.25 (m, 2H): 3.7 (s,2H).

2-Cyano-5-methylfuran.[25] $b_7 = 88\text{-}90^{\circ}$

$\nu_{max.}$ 3120, 2920, (CH), 2220 (CN, strong); 1520, 1140, 1020, 945, 795, 740 (aromatic) cm^{-1}. ^1H NMR δ, 7.0 (d, 1H, J = $3\frac{1}{2}$); 6.15 (d, 1H, J = $3\frac{1}{2}$), 2.35 (s, 3H). ms 107 (p^+), 92, 81. (Found: C, 67.4; H, 4.3; N, 13.1. Calc. for C_6H_5NO: C, 67.3; H, 4.7; N, 13.1%).

2-Ethoxymethylfuran. $b_9 = 47\text{-}50^{\circ}$

$\nu_{max.}$ 2970, 2875, (CH), 1660, 1585, 1370, 1340, 1220, 1110 (CO), 100, 895, 810, 735 (aromatic) cm^{-1}. ^1H NMR δ, 7.4 (m, 1H); 6.35 (m, 2H); 4.45 (s, 2H); 3.65 (q, 2H, J = 8); 1.25 (t, 3H, J = 8).

2-Furfurylthiocyanate.[28,32] $b_5 = 71\text{-}4^{\circ}$

$\nu_{max.}$ 3120, 3000 (CH), 2150 (CN); 1500, 1410, 1245, 1150, 1110, 938, 742 (aromatic) cm^{-1}. ^1H NMR δ, 7.4

(m, 1H); 6.25 (m, 2H), 3.7 (s, 2H).

2-Furfurylisothiocyanate [32]

$\nu_{max.}$ 2080 (CN) cm^{-1}. ^1H NMR δ, 4.5.

2-Furfurylacetate.[34] $b_5 = 53\text{-}6^{o}$

$\nu_{max.}$ 3120, 2940 (CH), 1735 (C=O), 1230, (C-O), 1150, 1015, 920, 740 (aromatic) cm^{-1}. ^1H NMR δ, 7.4 (m, 1H); 6.4 (m, 2H); 5.05 (s, 2H); 2.0 (s, 3H).

1-Piperidylmethylfuran.[86] $b_{0.5} = 79\text{-}81^{o}$

$\nu_{max.}$ 2930 (CH), 1710, 1500, 1150, 1010, 915, 730 (aromatic cm^{-1}. ^1H NMR δ, 7.4 (m, 1H); 6.25 (m, 2H); 4.6 (s, 2H); 2.4 (t, 4H); 1.5 (m, 6H).

2-Furfurylcyanate. (could not be obtained analytically pure).

$\nu_{max.}$ 2920 (CH), 2090 (CNO), 1690, 1500, 1220, 1020, 740 (aromatic) cm^{-1}. ^1H NMR δ, 7.4 (m, 1H); 6.3 (m, 2H); 4.55 (s, 2H) (δ, 4.5 absorption was probably an impurity of furfuryl isocyanate, though this compound was not detected in the IR).

2-Furfurylisothiouronium chloride. (see p. 79).

2-Furfurylazide. $b_{0.9} = 81.2^{o}$

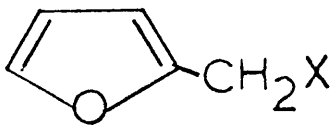
$\nu_{max.}$ 3120, 2920 (CH), 2085 (N_3, very strong), 1500, 1335, 1270, 1238, 1145, 1012, 912, 740 (aromatic) cm^{-1}.

^{1}H NMR δ, 7.4 (m, 1H), 6.35 (m, 2H); 4.25 (s, 2H).
ms 123 (p^+); 95, 67. (Found: C, 50.1; H, 3.8;
N, 34.0. $C_5H_5N_3O$ requires C, 48.8; H, 4.1; N, 34.1%).

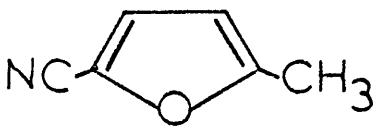
Reagent (0.06 mole)	Solvent	Products	Overall Yield
KCN (4 g.)	ether (10 ml.) water (10 ml.)	(III):(II)/1:1	80%[25,26]
KCN (4 g.)	DMSO (14 ml.)	(III)	2.4 g. (52%)
KCN (4 g.)	formamide (14 ml.)	(III):(II)/12:7	2.4 g. (52%)
KCN (4 g.)	DMF (14 ml.)	(III)	2.9 g. (63%)
KCN (4 g.)	H_2O (5 ml.) EtOH (15 ml.)	(III):(II)/7:1 (I,X=OEt) trace	1.7 g. (37%)
KCN (4 g.) KSCN (5.83 g.)	EtOH H_2O (10 ml.)	(I, X=OEt)	1.9 g. (41.5%)[33,36]
	Et_2O (10 ml.)	(I, X=SCN) trace (I, X=NCS)	5.1 g. (85%)[28,32]
NaOAc (8.2 g.)	HOAc (20 ml.)	(I, X=OAc)	3.7 g. (61.5%)

Reagent (0.06 mole)	Solvent	Products	Overall Yield
NaOAc (8.2 g.)	H_2O (10 ml.) Et_2O (10 ml.)	(I, X=OAc)	4.7 g. (78%)
Piperidine (5.1 g.)	H_2O (10 ml.)	(I, X = pip.)	2.9 g. (41%)
NaBr (6.2 g.)	Et_2O (10 ml.)	polymer	
NaCNO (3.9 g.)	H_2O (10 ml.) Et_2O (10 ml.)	(I, X = CNO)	1.3 g. (25%)
thiourea (4.56 g.)	H_2O (10 ml.) Et_2O (10 ml.)	(I, X = $SC(NH_2)_2Cl^+$)	7.9 g. (95.5%)
NaN_3	H_2O (10 ml.) Et_2O (10 ml.)	(I, X = N_3)	4.5 g. (85%)
AgCN (8.04 g.)	H_2O (10 ml.) Et_2O (10 ml.)	(III):(II)/5:2 + unidentifiable product	0.8 g. (17%)

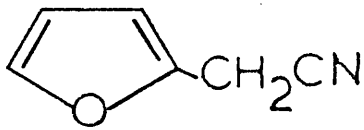
Key to table.



(I)



(II)



(III)

Variation of leaving group.

Potassium cyanide (1.3 g., 0.02 mole) was made to react with the following 2-furfuryl derivatives (0.014 mole of the furan in each case) using formamide as solvent.

1. * Furfuryl acetate at room temperature for two days gave quantitative recovery of starting material. On heating the mixture for 24 hr. at 80°, a little furfuryl alcohol was obtained, but no organic nitriles.

2. Furfurylthiocyanate gave after stirring with cyanide for 3 hr. in the cold bis furfuryldisulphide (84%) (for physical data see product of the reaction of furfurylisothiouronium chloride with cyanide (p.79).

3. * Furfurylazide did not react with cyanide at room temperature. After heating at 80° for 24 hr., oil containing furfuryl azide, furfurylnitrile, and 2-cyano-5-methyl-furan (16:3:2) (NMR analysis) was obtained (overall yield 40%) by extraction with ether. Chloroform extraction of the reaction mixture following the ether extraction gave only unidentifiable polymeric material.

Variation of temperature.

Furfuryl chloride (5 g., 0.043 mole) was reacted with potassium cyanide (4.0 g., 0.016 mole) in ether (10 ml.)/water (10 ml.) as solvent at various temperatures

* When the reactions were performed in ether/water as solvent only starting materials could be recovered.

between -20 and +80°C. The reaction mixture was extracted with ether and an oil was obtained which was analysed for 'normal' and 'abnormal' nitriles. The results were as follows.

Temperature	$\frac{\text{normal}}{\text{abnormal}}$ Product ratio	Yield of mixture
-20°	1.3	3.8 g. (83%)
0°	1.66	3.9 g. (85%)
21° (room temperature)	1.7	3.2 g. (70%)
40°	1.6	2.9 g. (63%)
60°	2.2	2.3 g. (50%)
80°	2.7	1.8 g. (39%)

BENZOTHIOPHENES

3-Chloromethylbenzo[b]thiophene

Benzo[b]thiophene (26.1 g., 0.194 mole) was chloromethylated by the method of Blicke and Sheets.[87] Pure 3-chloromethylbenzo[b]thiophene (15.2 g., 43%) as well as recovered starting material (5.3 g., 20.3%) were obtained. 3-Chloromethylbenzo[b]thiophene: b_2 = 122-4°. $\nu_{max.}$ (nujol mull) 3090, 2435 (CH), 1445, 1435, 1260, 1150, 1100, 1050, 1025, 820, 765, 740, 710, 680 (aromatic) cm^{-1}. ^1H NMR δ, 7.3 (s, 1H); 8.0 7.2 (m, 4H); 4.7 (s, 2H).

Reaction of 3-chloromethylbenzo[b]thiophene with cuprous cyanide.

Cuprous cyanide (3.3 g., 0.036 mole) was added to 3-chloromethylbenzo[b]thiophene (6.3 g., 0.035 mole). The mixture was heated at 100° for 6 hr. with stirring. The product was extracted with chloroform (5 x 50 ml.). The chloroform solution was evaporated to dryness and the yellow residue was soxhlet extracted using ether as solvent. The yellow powder obtained could not be purified further by recrystallisation or chromatographic techniques, but was shown to be a mixture of bis(benzo[b]thiopheno) [d-2,3] [d-5,6] cyclohexa-2,5-diene and tris(benzo[b]thiopheno) [d-1,2] [d-4,5] [d-7,8] cyclonona-1,4,7-triene mp. 300° (d); $\nu_{max.}$ (KBr disc) 1430, 1230, 1100 (broad), 1020, 800, 760 and 720 (aromatic) cm^{-1}. ^1H NMR δ, 7.9 - 6.7 (broad unresolved peak, 2H); 4.5 — 3.8 (broad unresolved peak, 1H). ms 438

(p^+; trimer), 292 (p^+; dimer), 146. (Found: C, 24.5; H, 4.2; S, 21.4. $(C_9H_6S)_n$ requires C, 24.0; H, 4.1; S, 21.9%).

Reaction of 3-chloromethylbenzo[b]thiophene with sodium cyanide (cf.[48])

(1) A solution of 3-chloromethylbenzo[b]thiophene (4.0 g., 0.022 mole) in dry dimethyl sulphoxide (DMSO) (10 ml.) was added slowly to sodium cyanide (1.2 g., 0.025 mole) in DMSO (20 ml.) with stirring at room temperature. The mixture was heated at 40-50° for 6 hr. and was monitored by TLC. The reaction mixture was poured into water (250 ml.) and extracted with chloroform (4 x 100 ml.). The DMSO was extracted back into water (5 x 100 ml.). The washed organic extracts were dried (Na_2SO_4) and yielded a brown oil which crystallised on cooling. The solid was recrystallised from petrol/benzene to give colourless plates (3.1 g., 82%) m.p. 60-3° (Campaigne[48] gives m.p. 65-6°) of a mixture of 3-cyanomethylbenzo[b]thiophene contaminated with ca. 1% (NMR evidence) of 2-cyano-3 methylbenzo[b]thiophene. (The mother liquors contained crude 3-cyanomethylbenzo[b]thiophene (200 mg.) with no trace of its isomer). Column chromatography on alumina did not afford separation of the isomers (see below) (Campaigne[48] isolated milligram quantities of the abnormal isomer using preparative GLC, but this was not attempted since good evidence for its presence was obtained from physical data).

(2) Experiment (1) was repeated on the same scale as above but using absolute ethanol (20 ml.) as solvent.
(3) The experiment was repeated using ethanol (10 ml.) and water (10 ml.) as solvent. In experiments (2) and (3) the mixture of sodium cyanide and chloromethyl-benzothiophene was stirred overnight at 45°.

In each of the above experiments (1), (2) and (3), 1 g. of the crude product was chromatographed on 4% deactivated alumina. The products isolated are shown in the table.

Benzo[b]thiophene derivatives isolated	R_F on alumina TLC plate (40-60 petrol)	Experiment and Eluent
3-chloromethyl (100 mg.)	0.7	(1) petrol
3-cyanomethyl (750 mg.) contaminated with 2-cyano-5-methyl (85% recovery)	0.1 (faint) 0.15	petrol/ 5% ether
3-chloromethyl (trace)	0.7	(2) petrol
3-ethoxymethyl (50 mg.)	0.45	petrol
3-cyanomethyl (800 mg.) (85% recovery)	0.1	petrol/ 5% ether
3-ethoxymethyl (30 mg.)	0.45	(3) petrol
3-cyanomethyl (400 mg.)	0.1	petrol/ 5% ether
3-hydroxymethyl (350 mg.) (78% recovery)	0	petrol/ 35% ether

3-Cyanomethylbenzo[b] thiophene:[48] m.p. 60-3°

^{1}H NMR, δ, 8—7.2 (m, 4H), 745 (t, 1H), 3.85 (d, 2H, J = 1), $\nu_{max.}$ (nujol) 2265 (CN), 1460, 860, 780, 755, 725 (aromatic) cm^{-1}.

2-Cyano-3-methylbenzo[b] thiophene:[48] 2240 (CN) cm^{-1}.

δ, 2.15 (s, 3H)-methyl group.

3-Ethoxymethylbenzo[b]thiophene:[10] colourless oil

$\nu_{max.}$ (nujol), 2875 (CH), 1430, 1260, 1105 (C-O), 1025, 850, 760, 740 (aromatic) cm^{-1}. ^{1}H NMR, δ, 8 7.5 (m, 2H); 7.5 7.05 (m, 2H); 7.2 (s, 1H); 4.7 (s, 2H); 3.55 (q, 2H, J = 6.5); 1.2 (t, 3H, J = 6.5).

3-Hydroxymethylbenzo[b]thiophene:[88,89] colourless oil

$\nu_{max.}$ 3400 (OH); 1430, 1100 (C-O), 760 (broad), 735 (aromatic) cm^{-1}. ^{1}H NMR, δ, 8—7 (m, 5H); δ, 4.2 (broad s, 3H). On addition of D_2O the peak at δ, 4.2 collapsed to a sharp singlet (2H).

2-Lithiobenzo[b]thiophene (cf.[90]).

Benzo[b]thiophene (10 g., 0.074 mole) in sodium-dried ether (30 ml.) was charged into a 100 ml. 3-neck flask. n-Butyl-lithium (32 ml. of a 2.5 N solution in hexane i.e. 0.078 mole) was added under nitrogen, while the reaction vessel was cooled in an ice/ethanol bath (-20°C). After the addition the mixture was stirred at -10° for 2 hr.

Benzo[b]thiophene-2-carboxylic acid.

The ether solution of 2-lithiobenzo[b]thiophene obtained above was poured slowly over 5 min. on to crushed solid carbon dioxide (80 g., large excess) with agitation. The resulting emulsion was suspended in ether and extracted with 2N-sodium carbonate (3 x 75 ml.). The aqueous extracts were acidified (HCl) and the white precipitate was filtered off and recrystallised from benzene to give white needles of pure benzo[b]thiophene-2-carboxylic acid (9.3 g., 70%); m.p. 239-240° (Schonberg[91] gives m.p. 236°). (On heating slowly from room temperature the needles became cubic at 129-32° and sublimed above 180°). $\nu_{max.}$ (nujol), 3000(broad OH), 1660 (CO), 1530, 1470, 1450, 1310, 770 (aromatic) cm^{-1}. ^1H NMR (d^6 acetone) δ, 8.4 (s, 1H); 8.3 7.8 (m, 2H); 7.7 7.3 (m, 2H). (The carboxylic acid proton was not observed) ms 178 (p^+), 164 (OH), 134 ($-CO_2$).

Reaction of 2-lithiobenzo[b]thiophene with formaldehyde.

2-Lithiobenzo[b]thiophene produced from 10 g. of benzo[b]thiophene (see p.94) was treated with formaldehyde generated from paraformaldehyde (10 g., 0.33 mole). The reaction mixture was poured into water (100 ml.) and work-up in the usual way yielded a solid which was recrystallised from chloroform to yield white plates of 2,2'-bibenzo[b]thienyl (1.0 g., 20%), m.p. 265°

(decomp.) Shirley[90] gives m.p. 260-1° . $\nu_{max.}$ (nujol) 1430, 825, 740, 725 (aromatic) cm^{-1}. ^1H NMR, δ, 7.65 (broad s, 2H), 7.45 7.15 (m, 8H), ms 266 (p^+), 133. (Found: C, 72.0; H, 3.7; S, 23.8. Calc. for $C_{16}H_{10}S_2$ C, 72.0; H, 3.8; S, 24.2%).

Attempted preparations of 2-hydroxymethylbenzo[b]thiophene

Attempted preparation of 2-hydroxymethylbenzo[b]-thiophene by the method of Blicke[88] from benzothiophene via its sodium salt (using sodium metal as a sand) was abortive. No reaction occurred between benzothiophene and sodium hydride in ether. Preparation via the Grignard reagent by Weissberger's method[92] was also unsuccessful. In all these cases failure was due to lack of formation of the organometallic intermediate.

2-Hydroxymethylbenzo[b]thiophene.

Lithium aluminium hydride (6.4 g., 0.17 mole) was suspended in dry ether (500 ml.) and benzo[b]thiophene-2-carboxylic acid (20 g., 0.11 mole) was added in small portions with stirring. Stirring was continued for 24 hr. when the solution was cooled to -10° and water (20 ml.) was added slowly, and then 10% sulphuric acid until just neutral. The aqueous layer (a suspension of lithium and aluminium salts) was run off and extracted with ether (2 x 150 ml.). The combined ether extracts were shaken with dilute sodium carbonate solution (2 x 200 ml.) and water (3 x 100 ml.). The ether layer

was dried (Na_2SO_4) and evaporated leaving a white solid which was recrystallised from petrol (b.p. 60-80°) to give white needles of 2-hydroxymethylbenzo[b]thiophene (15 g., 81%), m.p. 100-102° (lit.[88] 99-100°). ν_{max} (nujol), 3000(OH), 1020 (C-O), 850, 765, 750, 735 (aromatic) cm^{-1}. ^1H NMR δ, 8 – 7.5 (m, 2H); 7.5 – 7.15 (m, 2H); 7.1 (s, 1H); 4.8 (s, 1H + 2H).

2-Chloromethylbenzo[b]thiophene.

Reaction of 2-hydroxymethylbenzo[b]thiophene (8.2 g., 0.05 mole) with thionyl chloride (7.5 g., 0.63 mole) by the method of Blicke[88] gave 2-chloromethylbenzo[b]thiophene (7.2 g., 80%) b_5 = 142°, m.p. 55-6° (after recrystallisation from petrol, b.p. 60-80°). $\nu_{max.}$ 1260, 880, 855, 765, 705 (aromatic), 660 (C-Cl) cm^{-1}. ^1H NMR δ, 7.9 7.5 (m, 2H); 7.3 7.05 (m, 2H); 7.3 (s, 1H); 4.7 (s, 2H).

Reaction of cuprous cyanide with 2-chloromethylbenzo-[b]thiophene

2-Chloromethylbenzo[b]thiophene (1.5 g., 0.0082 mole) was heated with cuprous cyanide (0.85 g., 0.0096 mole) for 12 hr. The reaction mixture was cooled, hot chloroform was added and the solution filtered to remove cuprous cyanide, washing the filtrate with hot chloroform. Recrystallisation from chloroform gave a pale yellow solid (0.43 g., 29%) with physical data identical to those of the product of the reaction between 3-chloro-

methylbenzo[b]thiophene and cuprous cyanide (see p.91)*. (Found: C, 24.3; H, 4.4; S, 22.0%. $(C_9H_6S)_n$ requires C, 24.0; H, 4.1; S, 21.9%).

Reaction of 2-chloromethylbenzo[b]thiophene with sodium cyanide.

2-Chloromethylbenzo[b]thiophene (3.0 g., 0.016 mole) in dimethyl sulphoxide (7 ml.) was added to a solution of sodium cyanide (0.85 g., 0.017 mole) at room temperature. The mixture was stirred for 48 hr. After work up in the usual way, the crude organic material was applied to a 40 cm, 1.25 cm. diameter column (nylon stocking type) packed dry with alumina (6% deactivated) (cf.[93]). Two fractions were eluted with benzene.

1. Yellow crystals (100 mg., ca 3½%), m.p. 229-30° $\nu_{max.}$ (nujol) 2275 (weak CN); 1310, 1200, 945, 870, 840, 750, 730 (aromatic) cm^{-1}. ^1H NMR δ, 7.7 (m, 2nH); 7.35 (m, 2nH); 3.75 (s, nH), ms. 342, 319, 280, 258, 171, 147; (Found: C, 70.5; H, 3.4; N, 8.1, $(C_{10}H_5NS)_n$ requires C, 70.2; H, 2.9; N, 8.2).

2. 2-Cyanomethylbenzo[b]thiophene (1.8 g., 63.5%) as buff crystals, recrystallised from petrol (b.p. 40-60°) to give pale-yellow chunks m.p. and mixed m.p. 60-1° (lit.[88] 62-4°. $\nu_{max.}$ (nujol) 2285 (CN); 1415, 1100, 945,

* The solid was not as crystalline as the previous sample, however.

835, 745, 730 (aromatic) cm^{-1}. ^1H NMR, δ, 7.7 (m, 2H); 7.35 (t not resolved; 1H); 7.2 (m, 2H); 3.85 (d, 2H, J = 1).

When the above reaction was carried out using ethanol as solvent, 2-cyanomethylbenzo[b]thiophene (2.3 g., 71%) as well as recovered starting material (0.4 g., 13%) was obtained. In ethanol/water (1:1) as solvent only 2-cyanomethylbenzothiophene (2.8 g., 98%) was isolated.

BENZOFURANS

Conversion of coumarin into benzofuran.

Coumarin was converted into benzofuran by the following stages:

A.[94a] Coumarin was brominated in chloroform as solvent yielding coumarin dibromide (72%) m.p. 110-12°. $\nu_{max.}$ (nujol) 1755 (C-O); 1230, 1170, 760 (aromatic) cm^{-1}. ^1H NMR δ, 7.4 (m, 4H); 5.4 (d, 1H, J = $2\frac{1}{2}$); 5.0 (d, 1H, J = $2\frac{1}{2}$).

B.[94b] Treatment of coumarin dibromide with potassium hydroxide solution gave benzofuran-2-carboxylic acid (coumarilic acid) (90%), m.p. 194-6° (lit. 190-3°). $\nu_{max.}$ (nujol) 3500, 2500 (-OH); 1685 (C=O), 1300, 750 (aromatic) cm^{-1}. ^1H NMR δ, 7.7 (s, 1H); 7.8 7.3 (m, 4H).

C.[94b] Decarboxylation of coumarilic acid gave benzofuran (68%), b_{760} = 170-4°.

Chloromethylation of benzofuran (cf.[95])

Benzofuran was chloromethylated by a procedure modified from that of Mndzhoian . A mixture of formalin (9 g., 0.3 mole), benzene (30 ml.) and conc. HCl (40 ml.) was cooled to 0° with stirring. Benzofuran (10.8 g., 0.092 mole) was added and HCl gas was passed slowly through the reaction mixture. Stirring was continued for 12 hr. when the usual procedure (using benzene to extract the organic products) afforded 8.7 g. of crude product which was fractionated through

a Vigreux column under reduced pressure to give starting material (2 g., 18.5%), b_4 = 50-2° and impure 2-chloromethylbenzofuran (6.0 g., 39.5%), b_4 = 100-110°. Redistillation gave pure 2-chloromethylbenzofuran (3.8 g., 25%), $b_{0.9}$ = 88-90°. $\nu_{max.}$ 3050 (CH), 1660, 1580, 1460, 1250, 1190, 960, 830, 750, 715 (aromatic) 690 (C-Cl) cm^{-1}. ^1H NMR, δ, 7.5 7.0 (m, 4H); 6.4 (s, 1H); 4.4 (s, 2H).

2-Hydroxymethylbenzofuran (2-benzofuryl carbinol).

Lithium aluminium hydride reduction of coumarilic acid by the method of Gaertner[96] afforded after distillation of the crude product pure 2-hydroxymethylbenzofuran (81%) b_2 = 122-4° (lit.[96] $b_{1.1}$ = 112-3°) $\nu_{max.}$ 3360 (OH), 2970, 1465, 1265, 1020 (C-O), 950, 835, 760 (aromatic) cm^{-1}. ^1H NMR, δ, 7.75 7.1 (m, 4H), 6.7 (s, 1H), 4.6 (s + s, 2H). On addition of D_2O δ, 1.8 (s, 2H).

Alternative preparation of 2-chloromethylfuran.

Chlorination of 2-hydroxymethylbenzofuran with thionyl chloride and toluene as solvent by the method of Gaertner[96] gave pure 2-chloromethylbenzofuran (80%) $b_{1.5}$ = 120°. (For physical data see above).

Reaction of 2-chloromethylbenzofuran with sodium cyanide.

2-Chloromethylbenzofuran (5.0 g., 0.027 mole) in dimethyl sulphoxide (15 ml.) was added dropwise to a

stirred solution of potassium cyanide (2.2 g., 0.034 mole) at room temperature. The reaction mixture turned deep brown (over 5 min.) and stirring was continued for 6 hr. when the solution was poured into water (250 ml.) and worked up in the usual way to give a brown oil (6.7 g.). This crude product showed only two spots on a silica TLC plate (both in benzene and in petrol/5% ether as eluents). Column chromatography on silica using benzene as eluent afforded starting material (0.15 g., 3%) R_F (benzene) 0.36 and 2-cyanomethylbenzofuran (2.9 g., 60%) m.p. 57-8° R_F (benzene) 0.2 $b_{1.5}$ 128-130° * $\nu_{max.}$ 2265 (CN), 1600, 1460, 1250, 1180, 1905, 820, 750 cm^{-1}. ^1H NMR δ, 7.65 7.15 (m, 4H), 6.65 (t, 1H, not resolved) 3.7 (d, 2H, J = 1). (Found C, 76.4; H, 4.8; N, 8.6. $C_{10}H_7NO$ requires C, 76.5; H, 4.5; N, 8.9%). No NMR, GLC or IR evidence could be obtained for any other products.

When the reaction was repeated using ethanol/water as solvent 2-cyanomethylbenzofuran (3.6 g., 75%) was isolated as the sole product.

* Separation of the two components could also be effected by distillation.

THIAZOLES

Bromoacetone.

Bromoacetone was prepared in 43% yield by the bromination of acetone according to Organic Synthesis[97].

4-Methylthiazole.

Reaction of formamide, phosphorous pentasulphide and bromoacetone by the method of Kurkjy and Brown[98] produced pure 4-methylthiazole as a colourless oil b_{760} = 134-5° (lit.[99] b_{760} = 133-4°). $\nu_{max.}$ 3110, 3080, 2925 (CH), 1525, 1415, 1310, 935, 880, 810 cm^{-1}. ^1H NMR δ, 8.7 (d, 1H, J = 1.5); 6.85 (m, 1H); 2.4 (d, 3H, J = 0.5).

4-Methylthiazole hydrochloride.

A solution of 4-methylthiazole (0.9 g., 0.009 mole) in sodium dried ether was prepared and dry hydrogen chloride gas was passed into the solution until no more salt precipitated. The salt was filtered off, washed with ether and dried in a dessicator (over $CaCl_2$) to give pure 4-methylthiazole hydrochloride as an oil (1.12 g., 92%) $\nu_{max.}$ 3500 2300, 1600, 1430, 900, 830 (aromatic), 700 cm^{-1}. ^1H NMR δ, 100 (d, 1H, J = 2.5), 7.9 (unresolved m, 1H), 2.7 (s, 3H).

Reaction of 4-methylthiazole and N-chlorosuccinimide.

4-Methylthiazole (7.0 g., 0.07 mole) in carbon tetrachloride was treated with N-chlorosuccinimide (9.3 g., 0.07 mole). The reaction mixture was heated

on a water-bath with occasional shaking for 3 hr. The mixture was cooled, filtered (to remove succinimide) and the carbon tetrachloride removed on the rotary evaporator. The resulting oil was dissolved in ether (400 ml.) and the solution was shaken with 10% sodium carbonate solution (3 x 200 ml.), then water (2 x 200 ml.) and dried (Na_2SO_4). Removal of the sodium sulphate and evaporation of the ether gave a brown oil * (6.9 g.) which was redistilled to give pure 5-chloro-4-methylthiazole (4.7 g., 50%) as a colourless oil (b_{15} = 62-4°) $\nu_{max.}$ 3080, 2940 (CH), 1560, 1410, 1060, 935, 840 (aromatic) cm^{-1}. ^1H NMR δ, 8.7 (s, 1H), 2.35 (s, 3H).

Reaction of 4-methylthiazole with N-bromosuccinimide[100].

4-methylthiazole (2.0 g., 0.02 mole) in carbon tetrachloride (10 ml.) was treated with N-bromosuccinimide (5.1 g., 0.02 mole) under the conditions described for its reaction with N-chlorosuccinimide. A brown oil was obtained. NMR showed the presence of some 4-bromomethylthiazole (ca. 10%) (δ , 4.6 for the methylene group), but this product was lost during distillation. The oil was shown to contain one major product (R_F = 0.54) and starting material (R_F = 0.73) on alumina TLC plates using benzene as eluent. Distillation of the crude brown oil produced starting material (0.2 g., 10%)

* The crude product was shown by NMR to contain ca 3% of 4-chloromethylthiazole (δ , 4.7 for the chloromethyl group), but this product could not be isolated.

and 5-bromo-4-methylthiazole (1.3 g., 36%), b_{15} = 103° (b_7 = 91°), $\nu_{max.}$ 3060, 2920 (CH), 1710 (CS), 1535, 1425, 1380, 1050, 1025, 935, 845 cm^{-1}. ^1H NMR 8.55. (s, 1H); 2.45 (s, 3H).

2,3-Dibromo- and 2,3-dichloropropanal.

2,3-Dibromopropanal was prepared by the method of Aronstein[101] in 43% yield. In the final distillation the fraction boiling at b_{13} = 72-4° was collected.

2,3-Dichloropropanal was prepared by Moureu's[102] method in 74% yield. The fraction boiling at b_{14} = 48-50° was collected.

Thioformamide.

Thioformamide was prepared by the methods of Wilstatter[103] and Schmitz[104]. Best yields were obtained when formamide was reacted with phosphorus pentasulphide in a large volume of tetrahydrofuran (modification of Schmitz's method).

Tetrahydrofuran (THF) (400 ml.) and formamide (25 g., 0.56 mole) were placed in a 3-neck 1 l. flask fitted with an overhead stirrer and guard tube. Phosphorus pentasulphide (25 g., 0.12 mole) was added with stirring in 7 g. portions over a period of 6 hr. so that the temperature never rose above 30°. The mixture was stirred for a further 18 hr. at room temperature and the THF solution was decanted from the yellow tarry material. The THF was removed under reduced pressure

and the residue washed with petrol.

To obtain pure formamide (m.p. 28°) the crude product was recrystallised at -70° from ethyl acetate (yield of pure material 12.5 g., 36.5%). For most purposes, however, the crude product was dissolved in ethyl acetate (150 ml.), filtered and the ethyl acetate removed to give NMR pure thioformamide (22.5 g., 65.7%), m.p. ca. 15°.

In some cases where thioformamide was needed (see preparation of 4-methylthiazole p.105 for example), this compound was made in situ in the reaction using phosphorus pentasulphide and formamide.

4-Chloromethylthiazole.

4-Chloromethylthiazole hydrochloride was synthesised by the method of Hennart[105] from sym-dichloroacetone and formamide. Recrystallisation of the crude product from acetone gave pure 4-chloromethylthiazole hydrochloride (45%). $\nu_{max.}$ (nujol) 3070, 2910 (broad), 2750 2000 (hydrochloride); 1600, 1270, 1130, 990, 885, 730, 695 (aromatic) 645 cm^{-1}. ^1H NMR (D_2O) δ, 9.8 (d, 1H, J = 2.5); 8.2 (d, 1H, J = 2.5); 5.0 (s, 2H).

Attempted Preparations of 5-chloromethyl- and 5-bromomethyl and 5-chloromethyl-2-methylthiazole.

The preparations of 5-chloromethyl- and 5-bromomethylthiazole were attempted by reaction of 2,3-dichloro and 2,3-dibromopropanal (resp.) with thio-

formamide under the conditions used in the preparation of 4-chloromethylthiazole (see p.108). No thiazoles were obtained as products.

An attempt to prepare 5-chloromethyl-2-methylthiazole by the action of thioacetamide on 2,3-dichloropropanal also produced polymeric material.

2-Bromothiazole.

2-Bromothiazole was prepared from 2-aminothiazole by a modification of the procedure adopted by Ganapathi[106].

2-Aminothiazole (40 g., 0.4 mole) in 80% phosphoric acid (160 ml.) was cooled to 5°. Conc. nitric acid (240 ml.) was added slowly. At -5° to -10° (temperature was maintained with a bath containing carbon tetrachloride/solid carbon dioxide) sodium nitrite (32 g., 0.46 mole) in water (160 ml.) was added under the surface of the thiazole solution using a dropping pipette over a period of 1 hr. with stirring. After addition, the mixture was stirred for a further 30 min. at -5° and then added (over 10 min.) to a suspension of copper sulphate (66.8 g.) and sodium bromide (120 g., 1.2 mole) in water (300 ml.) previously cooled in an ice/ethanol bath. Evolution of nitrogen was immediate and subsided after 20 min. The solution was allowed to stand for 30 min. at room temperature, and was partly neutralised (to pH 7) with 10 N sodium hydroxide solution. The crude aqueous suspension was steam distilled collecting 2l. of the distillate. The product was

worked up in the usual way and the pale yellow oil obtained was redistilled to give pure 2-bromothiazole (49 g., 74%), b_{20} = 76-7°. $\nu_{max.}$ 3100, 3075 (CH), 1485, 1390, 1305, 1010, 865, 720 (aromatic) cm^{-1}. ^1H NMR δ, 7.35 (d, 1H, J = 4); 7.1 (d, 1H, J = 4).

Reaction of 4-chloromethylthiazole with potassium cyanide.

1. Potassium cyanide (2.6 g., 0.04 mole) was dissolved in dry DMSO (10 ml.) and cooled to 0°. 4-Chloromethylthiazole hydrochloride (2 g., 0.012 mole) in DMSO (10 ml.) was added dropwise with stirring. The mixture was left stirring at room temperature for 2 days. Work-up in the usual way afforded a brown oil (1.3 g.).

The experiment was repeated as follows:

2. Absolute ethanol (20 ml.) was used as solvent yielding a brown oil (1.7 g.)

3. Ethanol (10 ml.) and water (10 ml.) were used as solvent yielding a dark brown oil (1.4 g.).

The products of the above reactions were visualised by TLC (alumina plates with ether as eluent) and were separated using a 6% deactivated alumina column. The products obtained are shown in the table.

Expt.	Solvent	Products (thiazoles)	Eluent	R_F
1.	DMSO	4-cyanomethyl (0.95 g.)	ether	0.37
2.		4-chloromethyl (free base) (1.1 g.)	petrol/10% ether	0.7
	EtOH	4-cyanomethyl (trace)	ether	0.37
3.	EtOH/ H_2O	4-cyanomethyl + 5-cyano-4-methyl (1.5 g. of a 100:1 mixture-NMR)	ether	0.37 0.5

4-Chloromethylthiazole. (too unstable for analysis)

(Free base; cf. p.108 for hydrochloride). $\nu_{max.}$ 3100, 3070, 2960 (CH); 1420, 1270, 950, 880, 835, 730, 690, 645 (CCl) cm^{-1}. ^1H NMR δ, 8.7 (d, 1H, J = 2); 735 (d, 1H, J = 2); 4.7 (s, 2H). ms 133 (p^+), 98 (-Cl); 71 (-Cl; -HCN), 45 (-Cl, -HCN, -HC≡CH).

4-Cyanomethylthiazole.

$\nu_{max.}$ 3080, 3060, 2960, 2895 (CH); 2255 (CN; 1510, 1410, 1330, 950, 870, 820, 730 (aromatic) cm^{-1}. ^1H NMR δ, 8.8 (d, 1H, J = 2); 7.4 (m, 1H); 4.05 (unresolved d, 2H) ms 124 (p^+) 98 (-CN). (Found, C, 48.0; H, 3.5; N, 22.8; S, 25.5. $C_5H_4N_2S$ requires C, 48.3; H, 3.2; N, 22.6; S, 25.8%).

5-Cyano-4-methylthiazole.

$\nu_{max.}$ 2220 (CN). ^1H NMR δ, 2.85 (s) see p.113.

Ethyl 4-methylthiazole-5-carboxylic acid.

4-Methylthiazole-5-carboxylic acid was prepared using thioformamide (the thioformamide used was moderately pure; m.p. ca. 15°) and ethyl α-chloroacetoacetate as described by Harrington[107]. The crude hydrochloride was recrystallised from ethanol to give white needles of pure hydrochloride (60%), m.p. 156-7° (lit.[107] m.p. 155°). $\nu_{max.}$ (nujol), 2200 (broad); 1965 (broad; hydrochloride); 1720 (CO), 1595, 1290, 1270, 1205,

1095, 1110, 845, 760, 705 (aromatic) cm^{-1}. ^1H NMR (D_2O), δ, 9.95 (s, 1H); (q, 2H, J = 7); 2.95 (s, 3H); 1.45 (t, 3H, J = 7).

To a suspension of the hydrochloride in water an excess of dilute aqueous sodium carbonate was added. A thick white gelatinous precipitate was formed which was extracted with ether and worked up in the usual way to afford ethyl 4-methylthiazole-5-carboxylic acid quantitatively. (This sample was NMR pure and was considered sufficiently pure for conversion into the amide), m.p. 30-33° $\nu_{max.}$ (nujol), 1720 (CO); 1330, 1310, 1270, 1220, 1080, 950, 820, 760 (aromatic) cm^{-1}. ^1H NMR δ, 8.75 (s, 1H); 4.35 (q, 2H, J = 7); 2.8 (s, 2H); 1.4 (t, 3H, J = 7).

5-Amido-4-methylthiazole.

Treatment of ethyl-4-methylthiazole-5-carboxylic acid with 0.880 ammonia by the method of Harrington[107] gave after recrystallisation of the crude product from ethanol, pure 5-amido-4-methylthiazole (48%) m.p. 146-8° (lit.[107] 149°). $\nu_{max.}$ (nujol) 3320, 3250, (NH_2); 1695 (CO); 1620, 1320, 1115, 960, 860, 735, 690, 645 (aromatic) cm^{-1}. ^1H NMR (d^6 DMSO) δ, 9.0 (s, 1H); 7.6 (broad s, 2H); 2.7 (s, 3H). (Integration of this peak was not possible due to interference by the d^6 DMSO peak).

5-Cyano-4-methylthiazole.

5-Cyano-4-methylthiazole was dehydrated by heating

under reflux with phosphorus oxychloride as described by Harrington[107]. Recrystallisation of the crude product from petrol (b.p. 40-60°) gave pure 5-cyano-4-methylthiazole (55%) m.p. 33° (lit.[107] m.p. 33.5°) $\nu_{max.}$ 3080, 2090 (CH); 2220 (intense CN) 1520, 1380, 1330, 1280, 1230, 1095, 950, 850 (aromatic) cm^{-1}. ^1H NMR 9.05 (s, 1H); 2.8 (s, 3H). Thus the physical data agree well with the minor product obtained in the reaction between 4-chloromethylthiazole and cyanide (see p.112).

5-Hydroxymethyl-4-methylthiazole.

The hydrochloride of ethyl 4-methylthiazole-5-carboxylic acid (7.5 g., 0.029 mole) was added in small portions over 1 hr. to a suspension of lithium aluminium hydride (LAH) (2.4 g., 0.063 mole) in dry ether (45 ml.). The solution was stirred for 24 hr. and when the excess of LAH was destroyed cautiously with water 2N sulphuric acid was added (to pH 7). Extraction of the organic product with ether and work-up in the usual way afforded an oil (2.9 g.) which was distilled to give 2 products.

1. 4-Methylthiazole (0.61 g., 16%) b_{20} = 32-6° (physical data identical to authentic 4-methylthiazole (see p.105).

2. 5-Hydroxymethyl-4-methylthiazole (1.8 g., 32%) m.p.57-9° (after recrystallisation from benzene) $b_{1.5}$ = 122-18°

$\nu_{max.}$ 3300 (broad OH); 2960, 2920 (CH); 1410, 1015 (C-O); 900; 795 (aromatic) cm^{-1}. ^1H NMR 8.6 (s, 1H); 4.8 (s, 2H); 4.2 (broad s, 1H); 2.4 (s, 3H) ms. 129 (p^+), 111 ($-H_2O$), 84 (-HCN). A successful analysis could not be obtained.

5-Hydroxymethyl-4-methylthiazole hydrochloride.

5-Hydroxymethyl-4-methylthiazole (1.5 g., 0.012 mole) was dissolved in water (50 ml.) and the solution was filtered. 10N hydrochloric acid (10 ml.) was added and the solution was evaporated to dryness. The last traces of water were removed by azeotropic distillation with n-propanol. The hydrochloride of 5-hydroxymethyl-4-methylthiazole obtained was NMR pure. $\nu_{max.}$ 3600 2500 (broad absorption band), 1600, 1030 (C-O), 900, 800 (aromatic) cm^{-1}. ^1H NMR (D_2O) δ, 10.0 (s, 1H); 5.05 (s + s, 2H + 1H), 2.7 (s, 3H). A correct analysis could not be obtained due chiefly to the fact that the salt was hygroscopic.

5-Chloromethyl-4-methylthiazole.

5-Hydroxymethyl-4-methylthiazole hydrochloride (1.0 g., 0.006 mole) was suspended in chloroform (10 ml.); free from ethanol. Thionyl chloride ($SOCl_2$, 1.19 g., 0.01 mole) was added dropwise and the solution was stirred at room temperature overnight. The dark red solution was evaporated (to remove chloroform, $SOCl_2$ and HCl). Benzene was added and the solution evaporated

again to remove last traces of $SOCl_2$. An unstable red solid was obtained which was shown by NMR to be fairly pure (probably 90%). 5-chloro-methyl-4-methylthiazole hydrochloride (1.0 g., 95%) (too unstable for analysis), m.p. 125-35° (dec.) $\nu_{max.}$ (nujol) 2300 (broad, hydrochloride), 1970 (hydrochloride); 1600, 1265, 1000, 870, 695 (aromatic) cm^{-1}. ^1H NMR (d^6 DMSO) δ, 9.8 (s, 1H); 5.25 (s, 2H); 2.55 (s, 3H).

Reaction of 5-chloromethyl-4-methylthiazole hydrochloride with potassium cyanide.

1. 5-Chloromethyl-4-methylthiazole hydrochloride (0.5 g., 0.0027 mole) was made to react with a solution of potassium cyanide (0.5 g., 0.0078 mole) in DMSO (15 ml.) as described for 4-chloromethylthiazole. A crude brown oil (0.18 g., 48%) was obtained.

2. Reaction was carried out as above but using ethanol (7 ml.) and water (7 ml.) as solvent. The crude product was 0.2 g. (53%).

In both reactions only one product could be identified (TLC, GLC, IR, NMR). Purification of the crude oil obtained by distillation (b_7 = 84°) or column chromatography (on 6% deactivated alumina with petrol/15% ether as eluent) produced pure 5-cyanomethyl-4-methylthiazole $\nu_{max.}$ 3060, 2910 (CH); 2250 (CN); 1400, 1025, 870, 785 (aromatic) cm^{-1}. ^1H NMR δ, 8.65 (s, 1H); 3.45 (s, 2H); 2.5 (s, 3H);

(Found: C, 52.1; H, 4.0; N, 20.5; S, 22.8. $C_6H_6N_2S$ requires C, 52.2; H, 4.3(5); N, 20.3; S, 23.2%).

Attempts to prepare 2-hydroxymethylthiazole from 2-bromothiazole.

The methods of converting 2-bromothiazole (1) into 2-hydroxymethylthiazole (2) via an organometallic intermediate which were attempted are as follows:

A. 2-Thiazolyl magnesium bromide was prepared from (1) by the entrainment method of Kurkjy and Brown[108]. Formaldehyde was passed into the reaction mixture and work-up was as described[108]. Yields of compound (2) were variable, but never better than 21%.

B. Formylation of 2-thiazolyl lithium as attempted. 2-Thiazolyl lithium was prepared by the method of Gronowitz[109], using compound (1) (10.1 g., 0.06 mole) and butyl-lithium (27.1 ml. of 2.4 N., 0.065 mole). Formaldehyde gas was passed into the reaction mixture at room temperature. The formaldehyde was generated from paraformaldehyde (25 g., 0.83 mole) heated at 150-200°. After all the paraformaldehyde had been used up (ca. 1 hr.) the reaction mixture was cooled in ice and hydrolysed by slow addition of ammonium sulphate (14 g.) in water (75 ml.) with stirring. The ether layer was decanted and the aqueous phase extracted with ether (3 x 100 ml.). The thiazole (2) was extracted with 5N sulphuric acid (8 x 20 ml.). The acid extracts were treated with 0.880 ammonia (to pH8) and extracted

with ether (4 x 100 ml.), dried (Na_2SO_4), yielding a brown oil which crystallised on standing at 0° and was recrystallised from benzene to give compound (2) (1.2 g., 19%). Yields in further runs varied between 10 - 20%.

C. Thiazole-2-aldehyde was prepared from 2-thiazolyl lithium made from 2-bromothiazole (10.1 g.) and N-methylformanilide by the method of Gronowitz[109]. The product was contaminated with N-methylaniline (ca. 50%, NMR) which could not be removed by distillation or extraction with very dilute acid. When hydrochloric acid of strength greater than 0.05M was used, both the thiazole and the N-methylaniline were extracted. Impure thiazole-2-aldehyde (7.1 g.) was reduced with sodium borohydride (2.28 g., 0.06 mole, approx. 4x excess) in THF (25 ml.) to compound (2). The yield with lithium aluminium hydride was much lower. Distillation of the crude brown oil obtained gave 2-hydroxymethylthiazole (1.3 g.) still contaminated with N-methylaniline (ca. 10% NMR). A second distillation yielded pure 2-hydroxymethylthiazole (0.8 g., 13%).

In one run of the above experiment an attempt to purify thiazole-2-aldehyde via the sodium bisulphite derivative was made (cf. ref.[110]). Impure thiazole-2-aldehyde (7.5 g.) was introduced into a saturated solution of sodium metabisulphite (7.6 g. 0.04 mole ca. 1 mole excess) in water (50 ml.) and ethanol (7 ml.).

The mixture was stirred for 1 hr. at room temperature. The sodium bisulphite derivative was filtered off, washed with a little ethanol and dried to give the sodium bisulphite derivative of thiazole-2-aldehyde (7.9 g.) m.p. 181-5°(d). The sodium bisulphite derivative was shaken with 2N sodium hydroxide solution (3 x 50 ml.) and the resulting suspension was extracted with ether to give after distillation of the crude product pure 2-hydroxymethylthiazole (1.5 g., 30.5%).

Neutralisation of the aqueous layer with dil. HCl to pH6) and extraction with ether gave thiazole-2-carboxylic acid (1.1 g., 20%) m.p. 94-6° (lit.[111] m.p. 97-8°). $\nu_{max.}$ (nujol), 1705 (CO), 1600, 1240, 860, 755 (aromatic) cm^{-1}. ^1H NMR δ 7.5 (d, 1H, J = 4); 7.15 (d, 1H, J = 4).

Thiazole.

1. 2-Aminothiazole (20 g., 0.2 mole) was converted into thiazole (4.4 g., 26%) by the method of Ganapathi[106]. $\nu_{max.}$ 3110, 3075, 1480, 1380, 1315, 1240, 1120, 1040, 860, 800, 725 (aromatic) cm^{-1}. ^1H NMR δ, 8.9 (d, 1H, J = 2); δ, 7.5 (d of doublets, 1H, J = 2 and 3).

2. 2-Bromothiazole was reduced by a modification of Metzger's method[112]. These authors use a zinc/copper couple as the reducing agent. 2-Bromothiazole (16.4 g., 0.1 mole) was dissolved in glacial acetic acid (50 ml.). Zinc (20 g., 0.3 mole) was added very cautiously over a period of 1 hr. During the addition a vigorous

reaction occurred. The mixture was stirred at room temperature for 3 hr. The acetic acid was neutralised (to pH 9) with sodium carbonate powder and the product was steam distilled, extracted with ether (5 x 100 ml.) from which pure thiazole (5.6 g., 65%) was isolated. The physical data were identical to those of the thiazole obtained on deamination of 2-aminothiazole (see above).

Hydroxymethylation of thiazole.

Thiazole was hydroxymethylated according to the method of Berlin[113]. Thiazole (5 g., 0.059 mole) was heated in an autoclave with 40% formaldehyde solution (44 ml., 0.59 mole) for 6 hr. at 120°. The reaction mixture was poured into a solution of potassium carbonate (8 g.) in water (100 ml.) and extracted with ether. The organic layer was extracted with 5N HCl (4 x 50 ml.). On removal of the HCl solution a hygroscopic solid of 2-hydroxymethylthiazole hydrochloride contaminated with thiazole was obtained. Recrystallisation from isopropanol gave pure 2-hydroxymethylthiazole hydrochloride (2.2 g., 24.7%) m.p. 124-6° (lit.[113] m.p. 126-7°). $\nu_{max.}$ (nujol) 3600 2000 (hydrochloride); 1570, 1550, 1270, 1065, 1045, 870, 755 (aromatic) cm^{-1}. ^1H NMR (D_2O) δ, 9.7 (d, 1H, J = 3.5); 8.15 (d, 1H, J = 3.5); 5.25 (s, 2H).

In another experiment crude 2-hydroxymethylthiazole (4.3 g.) was synthesised from thiazole (7.5 g.) and isolated as the free base by extraction of the

crude basified product with ether. Distillation of the impure base gave starting material (0.95 g.) and 2-hydroxymethylthiazole (2.8 g., 27.6%) which was recrystallised from benzene to give pure 2-hydroxymethylthiazole (2.2 g., 20%). $\nu_{max.}$ 3230 (broad OH); 2920 (CH); 1505, 1185, 1140, 1045 (C-O), 725 (aromatic) cm^{-1}. ^1H NMR δ, 7.65 (d, 1H, J = 3); 7.25 (d, 1H, J = 3); 4.9 (s, 2H); (Found: C, 41.3; H, 4.7; N, 12.1; S, 28.1. Calc. for C_4H_5NOS C, 41.7; H, 4.3; N, 12.2; S, 27.8%).

2-Chloromethylthiazole hydrochloride.

2-Hydroxymethylthiazole hydrochloride (0.5 g., 0.003 mole) in chloroform (free from ethanol) (10 ml.) was treated dropwise with thionyl chloride (0.785 g., 0.007 mole) as described by Berlin[113]. The mixture was stirred overnight and the solvent and thionyl chloride were removed on the rotary evaporator. Last traces of thionyl chloride were removed by azeotropic distillation with benzene. The unstable brown solid (the compound deteriorated slowly over several days) could not be recrystallised but was NMR pure 2-chloromethylthiazole hydrochloride (too unstable for analysis) (0.6 g., 99.5%) m.p. 130° (dec.) $\nu_{max.}$ (nujol) 3500 2500 (hydrochloride): 1930 (hydrochloride); 1290, 980, 905, 870, 775, 750, 730 (aromatic); 625 (C-Cl) cm^{-1}. ^1H NMR (d^6 DMSO) δ, 11.65 (s, 1H); 7.9 (s, 1H); 5.2 (s, 2H).

An attempt to prepare 2-chloromethylthiazole hydrochloride by reaction of thionyl chloride (in benzene) with 2-hydroxymethylthiazole as the free base was unsuccessful, giving only unidentifiable polymeric material.

Reaction of 2-chloromethylthiazole hydrochloride with potassium cyanide.

1. 2-Chloromethylthiazole hydrochloride (0.5 g., 0.003 mole) in DMSO (5 ml.) was added dropwise at 0° to potassium cyanide (0.65 g., 0.01 mole) in DMSO (5 ml.). The mixture was stirred for 24 hr., and the usual work-up procedure afforded a brown oil (0.233 g.)

2. The same quantities as above were used except that ethanol (5 ml.) and water (5 ml.) were used as solvent. After 24 hr. the ethanol was removed under reduced pressure and work-up afforded a light brown liquid (0.3 g.).

3. The experiment was repeated using absolute ethanol (10 ml.) as solvent. A black tar containing no simple thiazoles was obtained.

The results of the above experiments are shown in the table. In each case the crude product was distilled in a sublimation tube to give in experiments 1. and 2. a colourless oil.

Experiment	Product (thiazole)	Yield
1.	2-cyanomethyl	0.223 g. (61%)
2.	2-cyanomethyl + ca.1% 5-cyano-2-methyl*	0.180 g. (49.5%)
3.	Intractable tar	-

* 5-Cyano-2-methylthiazole $\nu_{max.}$ 2225 (CN) cm^{-1}. ^1H NMR δ, 2.75 (s, methyl group). Owing to the very small amount of the abnormal product found, no attempt was made to isolate it, though some separation occurred on TLC plates (R_F = 0.55).

2-Cyanomethylthiazole. R_F (alumina; 5% ether/petrol) = 0.5 $\nu_{max.}$ 3115, 2960 (CH); 2250 (CN); 1610, 1500, 1105, 1055, 915, 730 (aromatic) cm^{-1}. ^1H NMR δ 7.75 (d, 1H, J = 3); 7.35 (d, 1H, J = 3); 4.05 (s, 2H); (Found: C, 48.0; H, 3.2; N, 22.9; S, 25.1. $C_5H_4N_2S$ requires C, 48.3; H, 3.2; N, 22.6; S, 25.8%).

FERROCENES

Conversion of Ferrocene to N,N-dimethylaminomethyl-ferrocene methiodide.

Treatment of ferrocene with N,N,N',N'-tetramethylmethylene diamine by the method of Lednicer and Hauser[114] gave N,N-dimethylaminomethyl ferrocene. The aminomethylating reagent was prepared (75%) by the method of the same authors[114]. Crude N,N-dimethylaminomethylferrocene shown to be NMR pure was not purified but converted directly into its methiodide[114] (78.5% overall yield).

N,N-dimethylaminomethylferrocene: $\nu_{max.}$ 3085, 2935, 2760 (CH); 1470, 1455, 1110, 1025, 820 (aromatic) cm^{-1}. ^1H NMR δ, 4.1 (m, 9H); 3.25 (s, 2H); 2.15 (s, 6H).

N,N-dimethylaminoferrocene methiodide: m.p. 200° (d.) (lit.[114] m.p. 200°). $\nu_{max.}$ (nujol), 1250, 1110, 885 (aromatic) cm^{-1}. ^1H NMR δ, 4.9 (s, 2H); 4.55 (m, 2H); 4.25 (m, 7H); 3.2 (s, 9H).

Cyanomethylferrocene.

Cyanomethylferrocene was prepared as described in Organic Synthesis in 70% yield, m.p. 80° (lit.[115] 81-3°). νmax. (nujol) 3100; 2240 (CN); 1100, 1035, 1025, 810 (aromatic) cm^{-1}. ^1H NMR δ, 4.2 (m, 9H); 3.4 (s, 2H).

Hydrolysis of N,N-dimethylaminomethylferrocene methiodide with sodium hydroxide.

N,N-Dimethylaminomethylferrocene methiodide was

hydrolized with aqueous sodium hydroxide as described in Organic Synthesis to give hydroxymethylferrocene (60%), m.p. 79.5 (lit.[116] m.p. 81-2°). $\nu_{max.}$ (nujol) 3230 (OH); 3090 (CH); 1235; 1105; 990 (C-O), 810 (aromatic) cm^{-1}. ^1H NMR δ, 4.3 (s, 2H); 4.15 (m, 9H); 2.6 (broad s, 1H).

During one run of the above experiment the hydrolysis was continued for 7 hr. ($3\frac{1}{2}$ hr. recommended in Organic Synthesis). Only a trace of the required alcohol was present in the product (detected by TLC). Recrystallisation of the crude product from petrol/ether gave pure diferrocenylmethylether (74.5%), m.p. 126-8° (lit.[117] m.p. 129-30°). $\nu_{max.}$ (nujol) 3090, 1235, 1105, 1030 (C-O); 820, 750 (aromatic) cm^{-1}. ^1H NMR δ, 4.35 (s, 4H); 4.3 — 4.1 (m, 18H). ms 414 (p^+); 215 ($-C_{11}H_{11}$); 199 ($-C_{11}H_{11}O$); 186 (ferrocene).

Chloromethylferrocene.[126]

Dry HCl gas was passed into a solution of hydroxymethyl ferrocene (2 g., 0.009 mole) in sodium dried ether (20 ml.) containing calcium chloride (2.5 g.) and kept at 5°. After 3 hr. the solution was filtered, the solvent removed and the green solid recrystallised from pentane (20 ml.) to give pure chloromethylferrocene (0.6 g., 27.6%), m.p. = 98-100° (d) (too unstable for analysis). $\nu_{max.}$ (nujol) 3080, 1260, 1100, 1035, 1025, 1000, 815 (aromatic), 655 (C-Cl) cm^{-1}. ^1H NMR δ, 4.45 (s, 2H); 4.1 (m, 9H).

The mother liquors from the recrystallisation contained moderately pure 2-hydroxymethylferrocene.

Attempted chloromethylation of ferrocene.

When ferrocene was treated under conditions of chloromethylation (for example see p.46), chloromethylferrocene could only be isolated in ca. 3% yield. The major product was a dark green polymeric solid insoluble in ether and chloroform, which could not be identified but was probably a polymethylene ferrocene. $\nu_{max.}$ 3075, 1105, 1000, 810 cm^{-1}.

Reaction of chloromethylferrocene with cyanide.

Chloromethylferrocene (0.5 g., 0.002 mole) was reacted with potassium cyanide (0.2 g., 0.003 mole) in various solvents. In each case the mixture was stirred for 3 days and worked up in the usual way. The results are shown in the table.

In the experiment in which DMSO was used as solvent, the two components were separated by column chromatography using 6% deactivated alumina as the stationary phase, and 7% ether/petrol (for cyanomethylferrocene) and pure ether (for hydroxymethylferrocene) as eluents.

Physical data

Cyanomethylferrocene see p.125

Hydroxymethylferrocene see p.126

Solvent(s)	Ferrocene(s) obtained	Yield	R_F(on alumina; 7% ether/petrol)
Ethanol (10 ml.)	ethoxymethyl	0.2 g., 43%	0.9
+ water (10 ml.)	cyanomethyl	trace	0.6
DMSO (10 ml.)	hydroxymethyl	0.09 g., 19.5%	0.15
	cyanomethyl	0.025 g., 5%	0.6
t-butanol (5 ml.)	cyanomethyl	trace	0.6
or dimethoxyethane (5 ml.)	polymer	0.35 g.	-

Ethoxymethylferrocene. cf. ref.[118]

Liquid melts at ca. 0°. $\nu_{max.}$ 3080, 2920 (CH), 1460, 1090 (C-O); 1000, 815 (aromatic) cm^{-1}. ^1H NMR δ, 4.4 (s, 2H); 4.35 4.15 (m, 9H); 3.55 (q, 2H, J = 6½); 1.2 (t, 3H, J = 6½). ms 244 (p^+): 200 ($-OC_2H_4$); 199 ($-OC_2H_5$); 186 (ferrocene).

TRIPHENYLMETHYLCHLORIDE

Reaction of triphenylmethylchloride with cyanide.

Trityl chloride (5.57 g.; 0.02 mole) was added to a solution of potassium cyanide (1.63 g.; 0.025 mole) in the following solvents. In each case the reaction mixture was stirred for 3 days at room temperature, poured into water (200 ml.) and the crude product was filtered off.

1. Formamide (20 ml.) was used as solvent. Recrystallisation from petrol (b.p. 60-80°) gave three fractions of pure triphenylmethylnitrile (2.9 g., 62%). The mother liquors were enriched in a minor product and were chromatographed on grade O alumina to yield 3 fractions (see table). A high amplitude NMR spectrum of the crude product showed p-cyano-phenyl-diphenyl-methane to be present to an extent of ca $2\frac{1}{2}$% (based on δ, 3.1 proton) in the crude product.

2. DMSO (20 ml.) was used as solvent. The reaction was performed on the same scale as before. The crude product was chromatographed on Grade O alumina and the fractions obtained are shown in the table, overleaf.

Experiment	Eluent	Fraction	R_F **
1.	petrol	A tritylchloride (0.1g; 2%)	0.95
	petrol/5%ether	B tritylnitrile* (0.42g; 7.8%)	0.67
	ether	C p-cyanophenyl-diphenyl-methane (0.054g; 1%)	0.56
		D tritylalcohol (trace)	0.48
2.	petrol/5%ether	A tritylnitrile (0.54g; 10%)	0.71
	petrol/50%ether	B tritylalcohol (3.0g; 58%)	0.48

** Silica gel G plates

* In addition to the pure tritylcyanide (2.9 g; 62%) obtained on recrystallisation of the crude material.

Triphenylmethylnitrile m.p. 124-6° (lit.[119] m.p. 129°) $\nu_{max.}$ (nujol) 2300 (very w. CN); 1600, 1395, 1100, 775, 720 (aromatic) cm^{-1}. ^1H NMR δ, 7.3 (m, 15H).

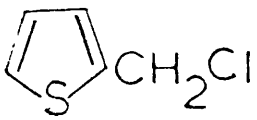
p-cyanomethyldiphenylmethane. m.p. 141-6° $\nu_{max.}$ (chloroform solution) 2280 (weak CN); 1595, 1260, 1005, 750 (aromatic) cm^{-1}. ^1H NMR δ, 7.3 (m, 14H); 2.55 (s, 1H); ms. 269, 243; (Found, C, 89.3; H, 5.9; N, 5.2. $C_{20}H_{15}N$ requires C, 89.2; H, 5.6; N, 5.2%).

Trityl alcohol: m.p. 161-3° (lit.[120] m.p. 164-5°) $\nu_{max.}$ (nujol mull) 3460 (-OH); 1598, 1445, 1154, 1009, 757, 635 (aromatic) cm^{-1}. ^1H NMR δ, 7.35 (m, 15H); 2.8 (s, 1H). On addition of D_2O the signal at δ, 2.8 disappeared.

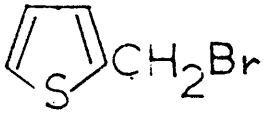
DISCUSSION

TABLE 1

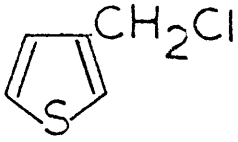
Thiophene



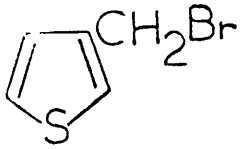
Ⓐ



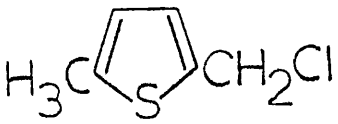
Ⓑ



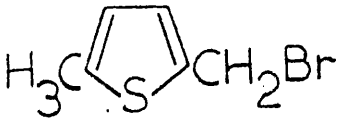
Ⓒ



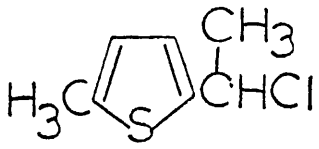
Ⓓ



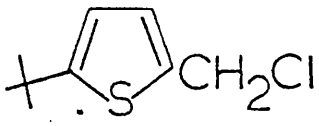
Ⓔ



Ⓕ

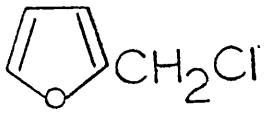


Ⓖ



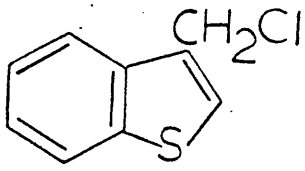
Ⓗ

Furan

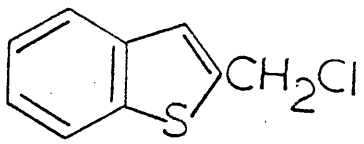


Ⓘ

Benzothiophene

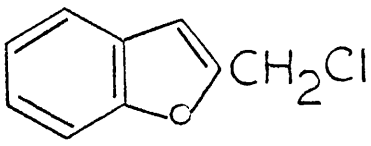


Ⓙ



Ⓚ

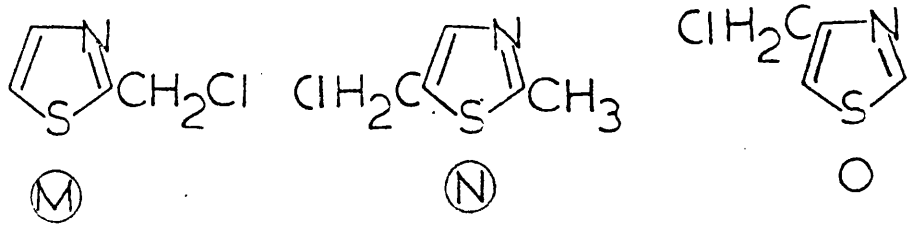
Benzofuran



Ⓛ

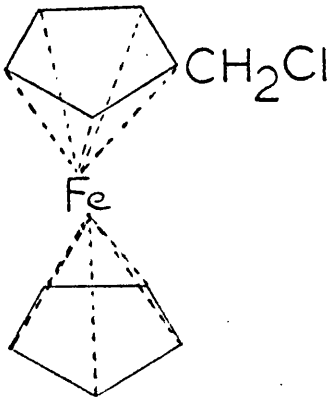
TABLE 1 (continued)

Thiazole



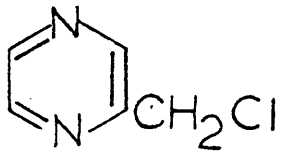
(M) (N) O

Ferrocene



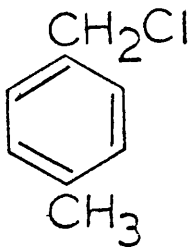
(P)

Pyrazine

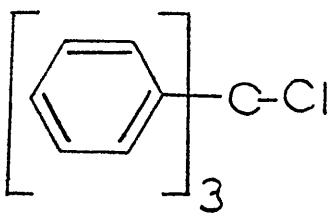


(Q)

Benzenoid



(R)

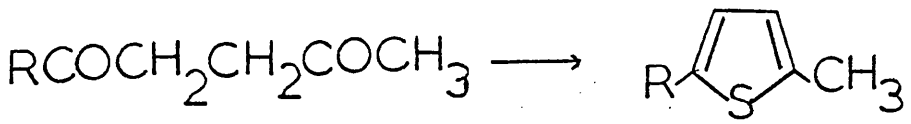


(S)

The Synthesis of α-Haloalkyl Aromatic Compounds.

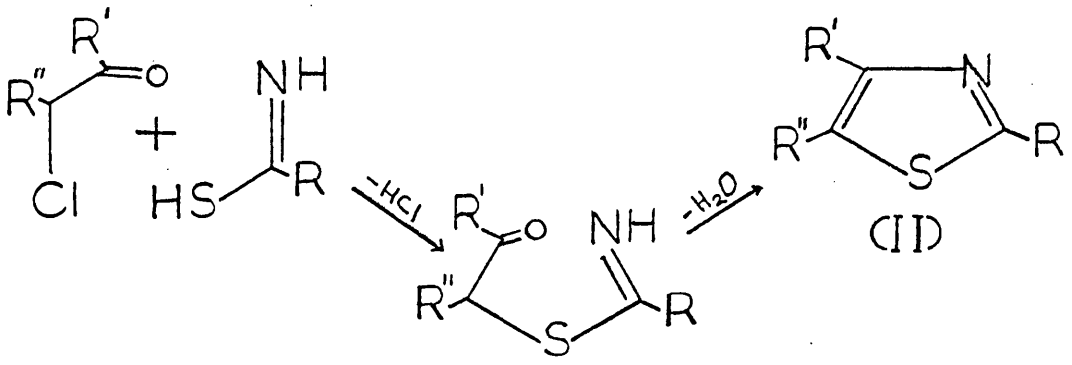
The α-haloalkyl systems investigated in the present work (A - S) are listed in Table 1. Chloromethyl heterocyclic compounds were chiefly used, but sometimes the analogous bromomethyl system was made for comparison or convenience. The only other systems not containing halomethyl groups which were studied included triphenylmethylchloride (S) and 2-α-chloroethyl-5-methylthiophene (G). The general methods for making these α-haloalkyl systems are now considered.

1. Direct Synthesis: Some heterocyclic halomethyl systems may be synthesised directly from their acyclic precursors. In most cyclisations, however, the reaction conditions are rather harsh and the reactive halomethyl groups would not survive. For example the condensation of 1,4-diketones with phosphorus pentasulphide was used to synthesise 2,5-dimethylthiophene (I, R = Me) and 2-t-butyl-5-methylthiophene (I, R = $-C(CH_3)_3$) as shown below.



(I)

For 2-chloromethyl-5-methylthiophene (I, R = CH_2Cl) this method could not be employed owing to the extreme conditions used in the reaction. However, 4-chloromethylthiazole (O)[105] was synthesised directly from sym-dichloroacetone and thioformamide because of the mild conditions used. The course of the reaction is as follows:[121]

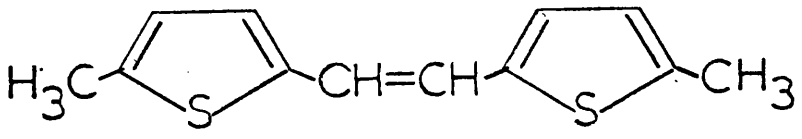


The syntheses of 5-bromomethyl (II, R=R'=H; R''=CH_2Br) 5-chloromethyl (II, R=R'=H; R''=CH_2Cl) and 5-chloromethyl-2-methylthiazole (II, R=CH_3; R'=H; R''=CH_2Cl) were unsuccessfully attempted by the above procedure. The nucleophilic attack of sulphur to displace halogen can take place on either of the two non-equivalent carbon atoms in the 2,3-dihalopropanal leading only in one case to the correct product. By contrast in sym-dichloroacetone both chlorine bearing carbon atoms are equivalent. The presence of the aldehyde group in 2,3-dichloropropanal may also be unfavourable because of a tendency to polymerise under acid conditions.

2. Halomethylation: Chloromethyl- and bromomethyl-systems are often conveniently obtained by halomethylation of the parent heterocycle with formaldehyde and the hydrogen halide. 2-Chloromethylthiophene (A) and 2-bromomethylthiophene (B) were prepared in this way. The formation of 3-chloromethylbenzothiophene (J) and 2-chloromethylbenzofuran (L) by chloromethylation is based on the unexplained observation that electrophilic substitution of benzothiophene gives 3-substituted, whereas that of benzofuran gives 2-substituted products.

Attempted chloromethylation of ferrocene gave only a trace of chloromethylferrocene. The chief product was a highly insoluble polymeric material probably polymethylene ferrocene (see for example [123]) which could not be purified.

Attempts to chloromethylate 2-methylthiophene and 3-methylthiophene were unsuccessful. The latter gave only polymeric material but the former gave a good yield of the unexpected 1,2-bis(5-methylthienyl) ethylene (III) after a basic work-up.



(III)

NMR, ms and analytical data confirmed the structure of this compound, which was unsaturated towards neutral potassium permanganate. (2-methylthiophene was used as a blank). Compound (III) appears to be cis from a comparison of IR and UV data with cis and trans-stilbene*.

Compound	ν max.	λ max.	
(III)	700 (m)	242	4,030
cis-stilbene	690 (m)	290[124]	10,000
trans-stilbene	970 (m)	280[124]	26,000

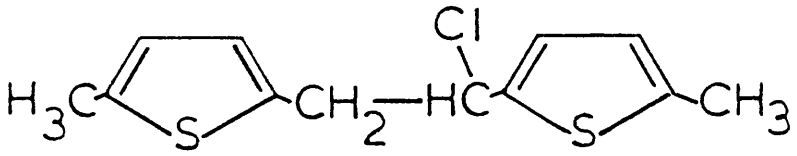
The formation of this unfavourable isomer is surprising particularly in view of the mechanism proposed below for its formation.

The above evidence for the structure of this olefin is at variance with a report that chloromethylation of 2-methylthiophene gives bis(5-methylthienyl) methane.[66]

When the chloromethylation of 2-methylthiophene was repeated, but employing an acidic work-up, a small amount of the unstable compound (IV) was isolated.

---

* A better comparison would be with the known 1,2-bisfurylethylene but no physical data are available for its geometrical isomers.

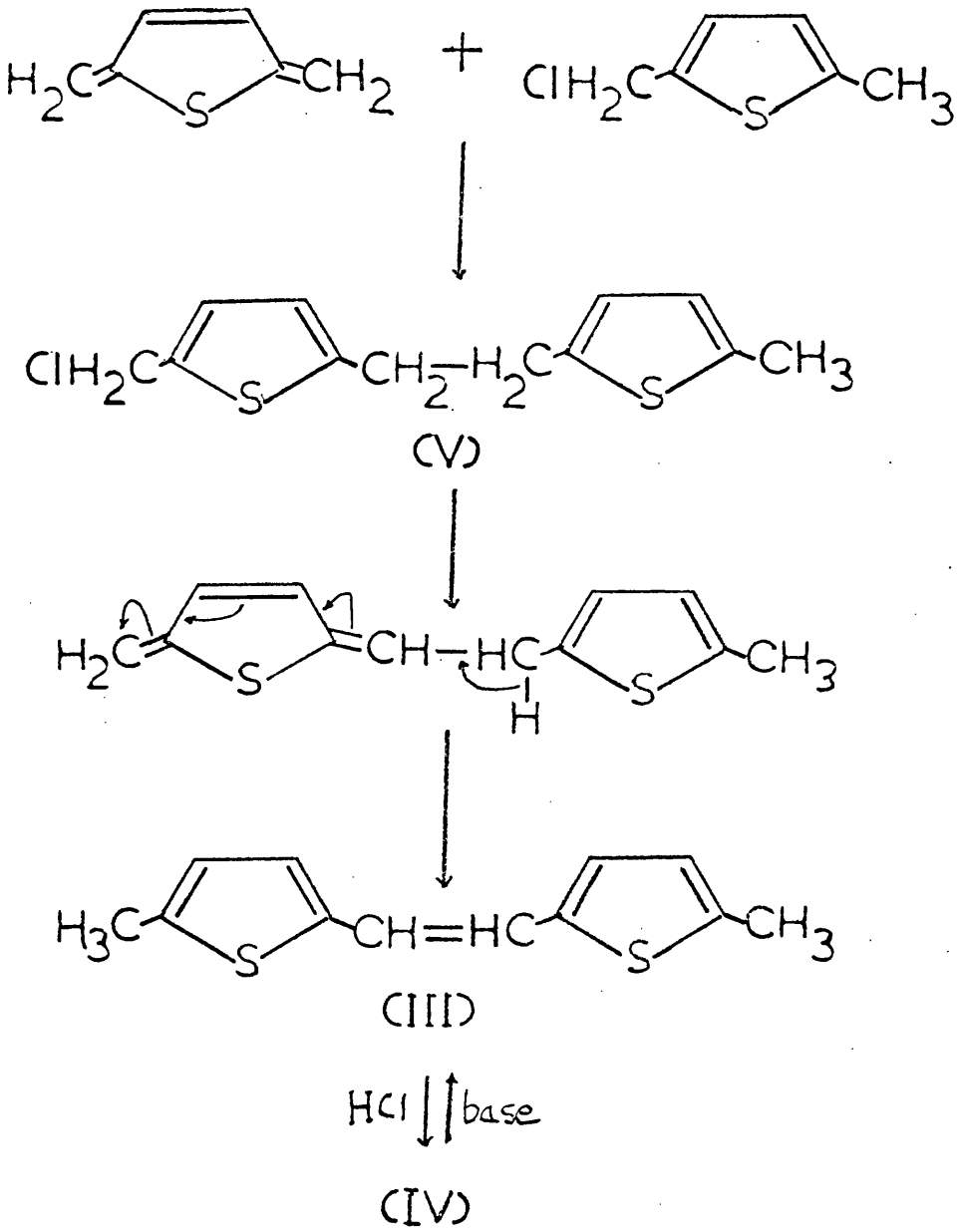


(IV)

The compound (IV) loses HCl in the mass spectrometer and the subsequent breakdown pattern corresponds well with that of the olefin (III). The addition of base would, of course, assist the loss of HCl, and only in its presence would the conversion (IV)-(III) occur rapidly. Further experiments revealed that the compound (IV) (neutral work-up) or the olefin (III) (basic work-up) were also formed when 2-chloromethyl-5-methyl-thiophene was treated with formalin under chloromethyl-ation conditions, indicating that 2-chloromethyl-5-methylthiophene may be an intermediate in the reaction. Hence it appears that the loss of HCl from one molecule of 2-chloromethyl-5-methylthiophene to form the curiously stable 2,5-dimethylene-2,5-dihydrothiophene (discussed later*) is followed by addition of a molecule of 2-chloromethyl-5-methylthiophene, which in turn loses HCl to yield the required product (III). The precursor to the olefin would probably have the structure (V),

* The presence of some 3-chloro-2,5-dimethylthiophene in the reaction products also supports this proposed mechanism.

which can lose HCl as shown below. The isolated product (IV) is probably not an intermediate in the reaction but is obtained merely as the HCl adduct of the olefin (III).



3. Halogenation of Side-chains.

The usual reagents for halogenation of a methyl group attached to an aromatic system are sulphuryl chloride, N-bromo-(NBS) and N-chlorosuccinimide (NCS) as well as some other N-bromoamides such as N-bromohydantoins and N-bromocaprolactam.[125] The N-halosuccinimides were the reagents of choice in the present work because of their specificity in allylic halogenation and their convenience. However, difficulties were encountered with NBS and NCS owing to the fact that product analysis often revealed substantial contamination of the α-haloalkyl compound with the ring-halogenated isomer. Table 2 indicates the ratio of side chain:nuclear substituted products based in most cases on NMR analysis.

The following general points were noted during a study of halogenations:

1. NCS invariably gave a greater proportion of nuclear substitution than NBS.
2. Nuclear substitution decreased markedly with the age of the N-halosuccinimide. Reaction also occured much more rapidly with an old sample of N-halosuccinimide.
3. The ratio of isomers was little influenced by factors such as light, the nature of the initiator, and the concentration of the solution. Generally nuclear substitution was favoured in dilute solution in the absence of initiator and light.

TABLE 2

System	Conditions *	NBS, side chain/ nuclear**	NCS, side chain/ nuclear
2,5-dimethylthiophene	-		1.5
	benzoyl peroxide initiator	-	0.5
	new sample of NCS	-	0
3-methylthiophene	-	0.8	0.01
	benzene solvent	1.4	-
2-methylthiophene	-	0	0
2-t-butyl-5-methyl thiophene	initiation by benzoyl peroxide***	-	0.53
4-methylthiazole	-	0.1	0.03
methyl pyrazine	-	0.28	0.25

Table 2 continued.

*** Reaction did not proceed without initiation.

** For structures of products, particularly position of nuclear substitution see Experimental Section.

* Unless otherwise stated the reaction was run in CCl_4 under reflux with no initiator using an old sample of N-halosuccinimide.

The lower yields of side-chain substituted products when NCS is used may be due to a lack of selectivity of the radical Cl. compared with Br. Old samples of NBS and NCS give faster halogenation, which may be due to the presence of small quantities of initiator (HBr and Br_2) developed on standing. However, this does not account for the fact that samples of NBS and NCS which have had a long shelf life give higher yields of side chain substituted isomers, unless some other non-selective mechanism of halogenation operates in cases where the initiators (Br_2, HBr) are not present.

4. Conversion of Alcohols into Halomethyl Compounds.

Chloromethyl aromatic compounds are frequently prepared by the action of phosphorus chlorides, thionyl chloride or hydrogen chloride on the corresponding alcohols. Thionyl chloride was preferred to the phosphorus chlorides because the reaction was cleaner and secondary products in this reaction are gaseous. This reagent in toluene or benzene was used for making 2-chloromethyl-5-methylthiophene (E), 2-α-chloroethyl-5-methylthiophene (G), 2-chloromethylfuran (I), 2-chloromethylbenzo[b]thiophene (K), 2-chloromethylbenzofuran (L), 2-chloromethylthiazole (M) and 5-chloromethyl-4-methylthiazole (N). For the very unstable 2-α-chloroethyl-5-methylthiophene (G) and 2-chloromethyl furan (I), the reaction with thionyl chloride and the

corresponding alcohols was carried out in the presence of pyridine to remove acid as it was formed. The use of this technique led in fact to the first reported synthesis of 2-chloromethyl furan[82]. Similarly the addition of a small quantity of base usually quinoline, to unstable halomethyl compounds increased their 'shelf lives' greatly.

Attempts to prepare the chloromethylthiazoles (M and N) by the action of thionyl chloride on the free bases of the corresponding alcohols led only to polymeric material. However, the conversion went in good yield if the hydrochlorides of the hydroxymethyl-thiazoles were used.

Chloromethylferrocene (P) was prepared by the action of HCl gas on an ether solution of hydroxy-methylferrocene containing anhydrous calcium chloride.[126]

Stability of Halomethyl Compounds:

Halomethyl compounds particularly those derived from π-electron-rich 5-membered heterocycles are unstable because of autocatalytic self-condensation with elimination of HCl. This mode of decomposition is confirmed by the fact that air, light and even moisture do not greatly affect the rate of polymer-isation. This autocatalysis can reach almost explosive proportions in the case of 2-chloromethylfuran which can suddenly polymerise with vigorous evolution of HCl and formation of tar. 2-α-Chloroethyl-5-methylthiophene

is even less stable decomposing in a matter of seconds and in this case polymerisation can neither be arrested by addition of base nor by cooling at -40°. Halomethyl-benzothiophenes and -benzofurans are stable for 2 - 3 weeks at 0°. The free bases of chloromethylthiazoles have not been reported and these compounds have always been isolated as their hydrochlorides which are moderately stable. The instability of the bases may be attributed to nucleophilic displacement of halogen by the ring nitrogen. However, on treatment of 4-chloromethylthiazole hydrochloride with sodium cyanide in ethanol, the free base was isolated* and found to be surprisingly stable. Significant decomposition of this compound only occurred after 24 hours at 0°. The use of cyanide to liberate unstable bases from their hydrochlorides is a promising technique.

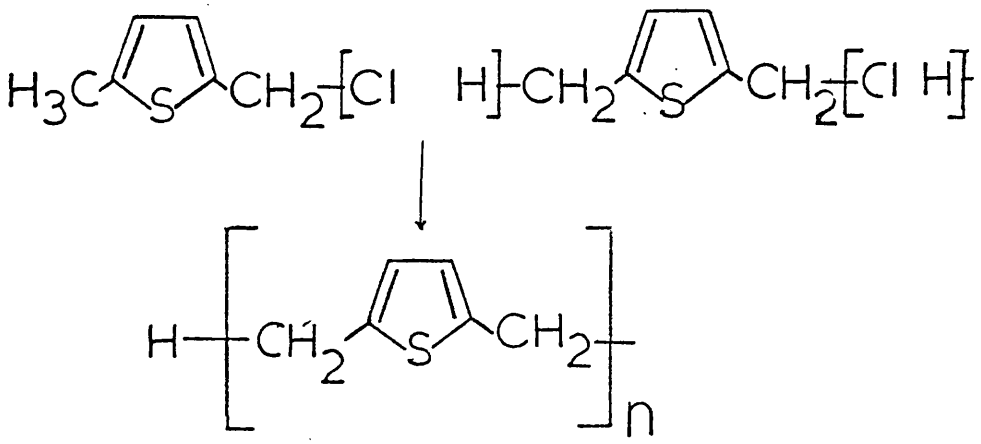
Chloromethylferrocene was found to be thermally stable but extremely sensitive to moisture. Chloromethylpyrazine is a little less stable than chloromethylbenzofuran.

Generally, the instability of halomethyl compounds is due to the readiness with which these systems condense with loss of HCl to yield polymethylene aromatic compounds. This accounts for the observed instability of the halomethyl derivatives of 5-membered

---

* The lack of cyanomethylthiazole in the product is attributed to the heterogeneity of the reaction.

π-rich heterocycles in which either a homolytic or heterolytic breakdown would be favoured. This breakdown is even more pronounced in compounds such as 2-chloromethyl-5-methylthiophene and 2-α-chloroethyl-5-methylthiophene where HCl can be eliminated between pairs of molecules to give regular chains as shown below:



This type of reaction is discussed later.

In the absence of special factors, the stability of halomethyl compounds seems to depend largely on the molecular weight of the aromatic moiety in the compound i.e. benzothiophenes > thiophenes > furans in stability. The following observed order of stability of chloromethyl compounds ties in with all the above considerations.

benzyl chloride > chloromethylferrocene > chloromethylbenzothiophene ≥ chloromethylthiazole hydrochloride > chloromethylbenzofuran > chloromethylpyrazine > 2-chloromethylthiophene > chloromethylthiazole > 2-chloromethyl-5-methylthiophene ≥ 2-chloromethylfuran.

Reaction of Halomethyl Compounds with Cyanide.

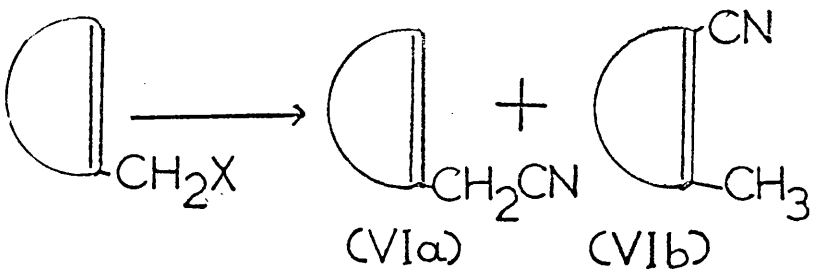
In the investigation of the reactions of the halomethyl compounds with cyanide three solvent systems were normally employed.

(i) dimethyl sulphoxide (DMSO) (dipolar aprotic)
(ii) ethanol (protic)
(iii) ethanol - water 1:1 (protic - aqueous)

DMSO was chosen as the dipolar aprotic medium because of its high dielectric constant, ready availability and the fact that both sodium and potassium cyanide are fairly soluble in it.

Ethanol was normally used as the protic medium. This solvent suffers from the disadvantages that, because of its nucleophilicity ethoxy compounds were often isolated, and the solubility of sodium and potassium cyanide is low in ethanol. For the reaction between trityl chloride and cyanide, formamide was used as solvent because of the low solubility of the halide in ethanol. α-Furfuryl chloride reacted more rapidly with ethanol than with potassium cyanide and for this system formamide was also used as the protic solvent. However, good yields of cyanides were usually obtained in ethanol. For comparison purposes an aqueous solvent system ethanol-water was also employed in most cases. Both the halide and the alkali metal cyanide are fairly soluble in this system and ethoxy compounds were only produced as minor products in ethanol-water.

The crude reaction products from the halides and cyanide were analysed carefully by physical methods to detect any products of rearrangement. If detected, separation of the 'normal' product (VIa) from the 'abnormal' product (VIb) was attempted.



(VIa) (VIb)

IR Analysis. IR was found to be a very useful tool for detecting small quantities of abnormal product. Whereas the normal product (VIa) is an alkyl cyanide, the abnormal product (VIb) is an α,β,-unsaturated, or an aromatic cyanide. The former absorbs at 2260 - 2240 cm^{-1}, α,β,-unsaturated cyanides absorb at 2235 - 2215 cm^{-1} and aryl cyanides at 2240 - 2220 cm^{-1}.[127] Thus in going from normal to abnormal isomer a shift of approximately 20 cm^{-1} to lower wave number is observed. Further, the intensity of a conjugated nitrile is much higher than that of an alkyl cyanide. For example reaction of 4-chloromethylthiazole with potassium cyanide in an aqueous medium gave a mixture of 4-cyanomethylthiazole and 5-cyano-4-methylthiazole (1%) as shown by NMR. The IR absorptions of these isomers were at 2258 and 2220 cm^{-1} respectively, the latter having an intensity of 0.36 relative to the former though 5-cyano-4-methylthiazole was only

present to an extent of 1%. This implies that the conjugated nitrile has a CN stretching frequency which is ca 36 times as intense as the cyanomethyl compound.

NMR Analysis: NMR was used to differentiate $ArCH_2CN$ from $ArCH_3$. The former group shows resonances at δ, 3.4 - 4.2 (2H) and the latter at δ, 2.1 - 2.8 (3H). Since the NMR absorption of the methyl group in the abnormal isomer is separate from any of the groups on the normal isomer, the presence of a sharp singlet in the methyl region provided good, though not conclusive evidence for the presence of the abnormal isomer.

TABLE 3

System	Methyl groups (δ)	Cyanomethyl groups (δ)
2-thenyl	2.3 *	3.9
3-thenyl	2.1 *	3.65
benzyl	2.2	3.4
3-benzothenyl	2.15	3.8
2-benzothenyl	⟝	3.85
2-benzofurfuryl	⟝	3.75
pyrazinylmethyl	2.6 *	⟝
2-furfuryl	2.3	3.7
4-thiazolylmethyl	2.8	4.05
2-thiazolylmethyl	2.7	4.2
5-thiazolylmethyl	2.7 *	4.0

Table 3 shows chemical shift values of methyl groups and corresponding cyanomethyl compounds. Where the abnormal product was not obtained and was not otherwise available (marked with an asterisk) resonances for the methyl compound unsubstituted by cyanide are given. Cyanide substitution in the ring affects the chemical shift of a methyl group only slightly e.g. 4-methylthiazole (δ , 2.5), 5-cyano-4-methylthiazole (δ , 2.8).

The halomethyl compounds whose syntheses have been

described in the previous sections were made to react with cyanide in protic and aprotic solvents and the reaction mixture analysed for 'normal' and 'abnormal' products. The results were studied for the purpose of evolving a correlation between the nature of a system and its tendency to undergo rearrangement. A detailed study of rearrangements of the α-furfuryl system was also undertaken in which the nucleophile, the leaving group, the temperature and the solvent were varied. An attempt is made to interpret these results on a rational basis.

Correlation between Structure and Ambifunctionality.

Table 4 shows all the heterocyclic systems which have been investigated for ambident electrophilic behaviour and records the percentage of rearrangement observed under optimum conditions.

For monocyclic systems we see a correlation between resonance energy and tendency to undergo rearrangement as already predicted (see p. 36). Thus furans and pyrazine (resonance stabilisations of 16 and 18 kcals/mole) rearrange readily whereas thiophene and benzene (29 and 36 kcals/mole) do not. In fused heterocyclic systems resonances energies are not quite so meaningful because we really require the contribution to the resonance stabilisation provided by the heterocyclic ring. In general this is probably a little lower than in the isolated heterocyclic system because

TABLE 4

Parent system	Position of chloromethyl substituent	% abnormal product	Resonance stabilisation of parent system	Bond* order	Bond length
benzene	-	0	36	1.50	1.39
nitrobenzene	3	16	ca 36	1.50	1.39
pyrrole	2 or 3		21[128]	1.60	1.37[129]
thiophene	2 or 3	0	29[128]	1.60	1.37[129]
furan	2	85	16[128]	1.72	1.35[129]
	3	10	16		
benzothiophene	3	2.5	29	1.84	1.34
	2	0			
benzofuran	2	0	16	1.91	1.34
pyrazine	**	100	18	1.53	1.38[129]
thiazole	4	ca 1	-	1.79(4,5)	1.347
	2	ca 1	-	1.77(2,3)	-
	5	0	-	-	-
indole	3***	0	-	1.77	1.34[129]
naphthalene	1 or 2	0	27		1.36(1,2)
					1.42(2,3)

TABLE 4 Continued

Parent system	Position of chloromethyl substituent	% abnormal product	Resonance stabilisation of parent system	Bond* order	Bond length
imidazole	2	100		1.69(2,3) 1.59(3,4) 1.74(4,5)	

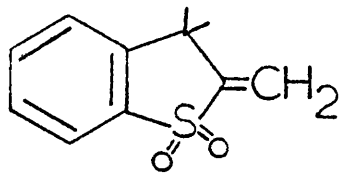
* Bond orders are normally calculated from bond lengths using Paulings equation.[130,131]

** trichloromethyl

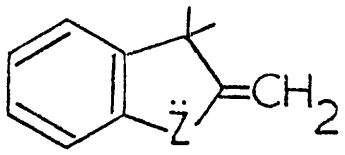
*** dimethylaminomethyl methiodide.

of the asymmetry that the benzene ring imposes on the fused systems. An indication of this stabilisation may be obtained from the orders of the 2,3-bonds in these fused systems (given in Table 4). The higher the bond order, the greater the localisation of the bond. Thus the bond orders for the 2,3-bonds in thiophene and benzothiophene are respectively 1.6 and 1.84, which might account for the small amounts of rearrangement products obtained from 3-chloromethylbenzothiophene compared with 2- or 3-chloromethylthiophene which do not behave as ambident electrophiles.

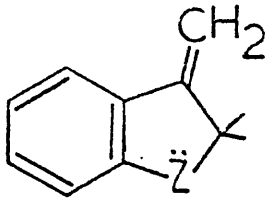
The absence of rearrangement products in 2-chloromethylbenzofuran is an anomaly in view of its extremely high bond order (1.91). It does, however, parallel the lack of ambident character of 2-chloromethylbenzothiophene-1,1-dioxide. We have already seen that 3-chloromethylbenzothiophene-1,1-dioxide readily displays ambident behaviour whereas its isomer 2-chloromethylbenzothiophene-1,1-dioxide does not. This latter case was explained in terms of the inability of the exocyclic methylene intermediate of the 2-isomer (VII) to conjugate with the polyene system due to valence saturation at sulphur.



(VII)

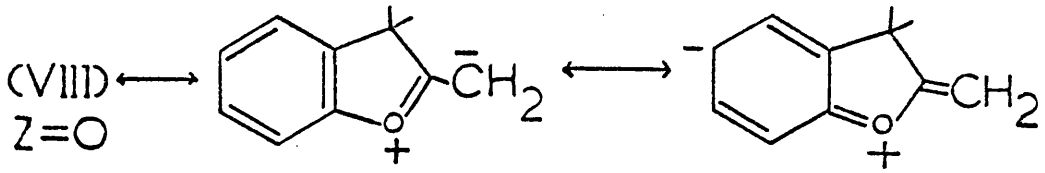


(VIII)

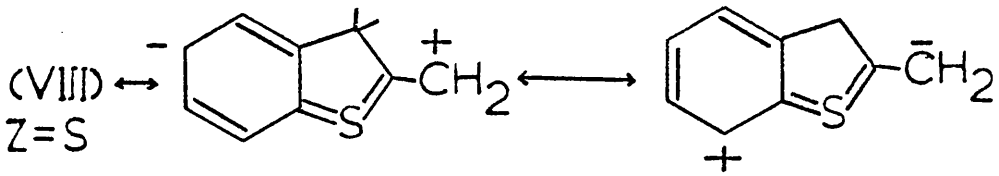


(IX)

For the two isomeric chloromethylbenzofurans the argument still applies. Conjugation cannot occur through the oxygen atom of 2-methenylbenzofuran though cross-conjugation can still occur as follows:



This would not however stabilise the species (VIII; Z=O) to any significant extent. In the compound (VIII; Z=S), conjugation of the 2-methenyl group to the benzene ring may occur to a small extent, as represented by resonance structures such as those shown below.

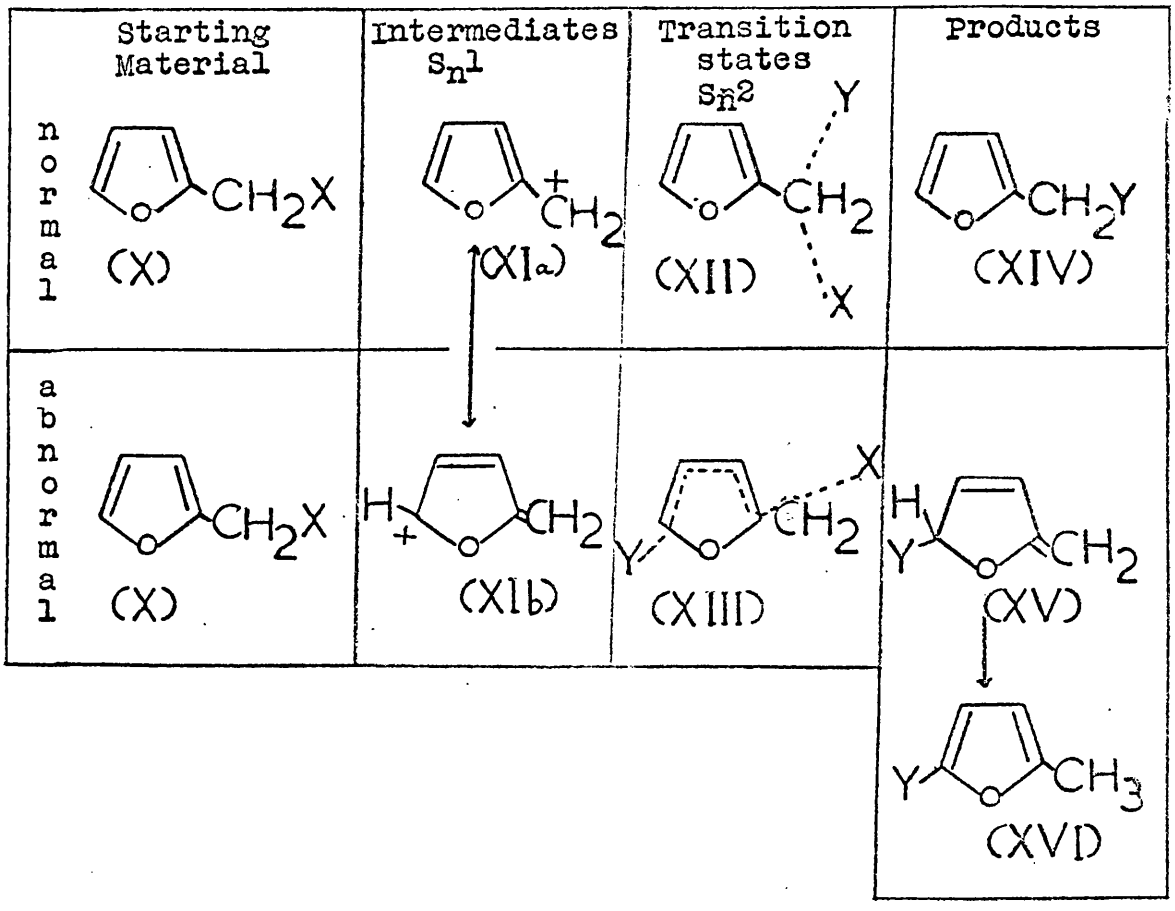


The contribution of such structures would be low and in fact controversy still exists over whether structures involving 12-coordinated sulphur can be invoked at all as canonical forms for thiophene and its derivatives (see for example[132]). It is reasonable, therefore that 3-chloromethylbenzothiophene shows weak ambident electrophilic behaviour whereas 2-chloromethylbenzothiophene does not.

Of the systems which have not been studied, it would be expected from the previous considerations that 3-chloromethylbenzofuran would show ambident electrophilic behaviour extremely readily, while the chloromethylpyrroles (resonance energy 21 kcals/mole) would be borderline cases.

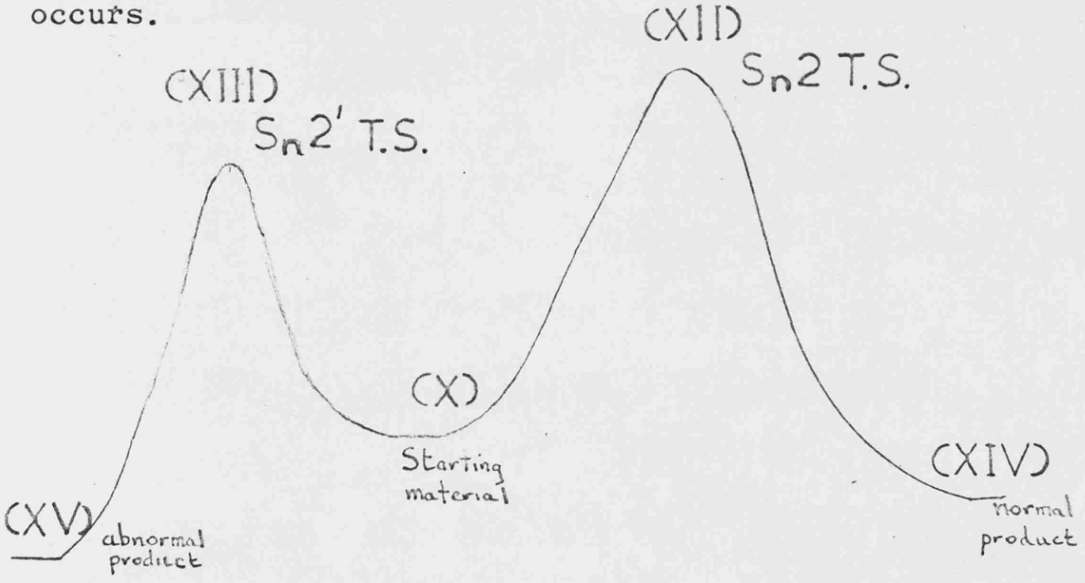
The Energy Profile.

Before considering the effects of solvent and temperature etc. on the facility of rearrangement, a qualitative picture of the energy profile leading to normal and abnormal products is required. The α-furfuryl system is used throughout this discussion for simplicity and also because most data have been obtained for it. The possible species involved along the reaction coordinate are recorded in the Table.

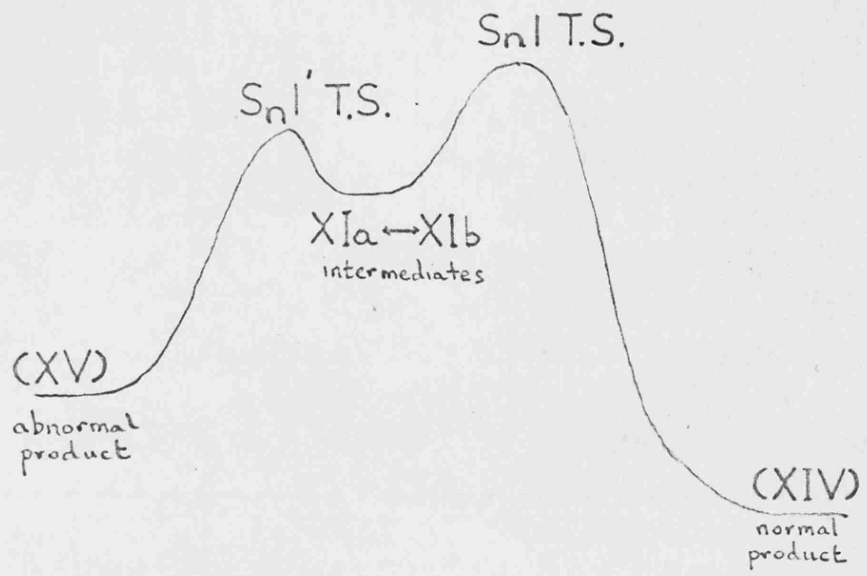


The starting material (X) is the same for both normal and abnormal reactions.

Naturally the mechanism of the reaction will determine the nature of the intermediates. If it is assumed that a nucleophilic substitution reaction is operating S_N1 or S_N2 transition states and intermediates are possible. If both the normal and abnormal reactions go by an S_N2 mechanism, the species (XII and XIII) can be visualised as transition states. The relative free energy contents of these species will determine whether normal or abnormal reaction occurs.



For a reaction in which both normal and abnormal attack occur by an S_N1 mechanism the mesomeric cation (XIa ↔ XIb) occurs as intermediate. This leads to two transition states of the S_N1 and S_N1' reactions. If these transition states resemble the intermediate mesomeric cation closely, then the product derived from the more



stable mesomer (XIa or XIb) will be formed. If, however, the transition states resemble the product, then the more stable product will be formed. The above arguments apply for kinetic control of the reaction.

The final product of the normal reaction is the furfuryl compound (XIV). For abnormal attack, though the 2-substituted-5-methylfuran (XVI) is actually isolated, the primary product of the reaction is the 2-methenyl-2,5-dihydrofuran (XV). This is supported by the isolation of some exocyclic methylene intermediates, already described in the Introduction, (see refs.[36,37]). Arguments based on thermodynamic control of the reaction must therefore be in terms of the relative stabilities of the species (XIV and XV).

Order of the reactions.

In the reaction between methoxide ion and 2-chloromethylfuran[36], Hill et. al. found that the amount of abnormal product increased from 30% (3.3M,

in MeO^-) to 67% (0.1M, MeO^-). The authors claim that this implies that the rate of abnormal product formation is independent of the nucleophile concentration i.e. is formed through an S_N1' mechanism, whereas the normal product is formed by an S_N2 mechanism. This interpretation must be treated with some scepticism, however, since the small change in yield of abnormal product (30-67%) in decreasing the MeO^- concentration 33-fold could merely be a salt - effect. Hill's interpretation does however accord with the observations in simple acyclic allylic systems, for which it has been demonstrated that an S_N1' mechanism is more common than S_N2'. In fact where primary acyclic halides react, an S_N2' mechanism is virtually unknown since normal attack is not disfavoured sterically. In 5-membered π-rich heterocyclic systems the S_N1 carbonium ion (XIa $\longleftrightarrow$ XIb) is more stable than that derived from a simple allylic system so that the S_N1 mechanism is more likely. At any rate the carbonium ion (XIa) should be favoured. This has been demonstrated by Egyed[34], who confirmed an S_N1 mechanism for the hydrolysis of furfuryl chloride*. The rate increased from $t_{\frac{1}{2}}$ = 618 minutes in THF - 10% water to $t_{\frac{1}{2}}$ = 6.39 minutes in THF - 30% water. It is perhaps surprising that an S_N2 reaction occurs at all in the methanolysis of furfuryl chloride.

---

* In this case, however, no abnormal products have been observed, probably due to the high instability of hydroxyfurans.

In contrast, 3-chloromethylbenzothiophene-1,1-dioxide reacts with various nucleophiles (see p.24);[50,51] to give abnormal products by an S_N2' mechanism. The lack of aromaticity of this system means that π-electron donation to stabilise the intermediate carbonium ion (as in acyclic allyl systems) is not possible. In fact destabilisation will occur due to the strongly electron withdrawing sulphone group.

Thermodynamic v. Kinetic Control.

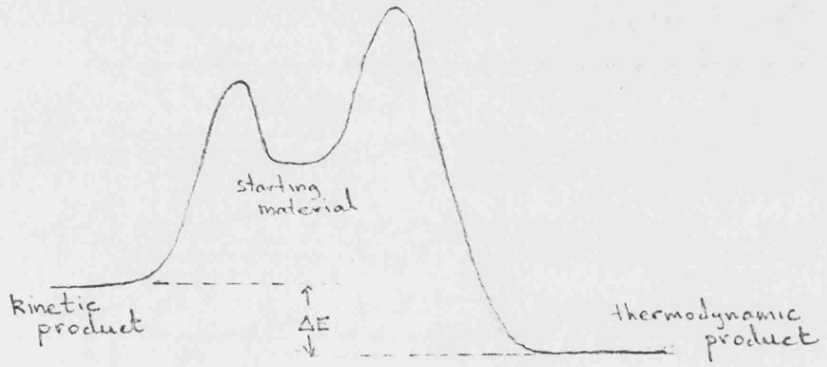
Before examining the experimental results further, the factors which operate to encourage kinetic or thermodynamic control are briefly discussed.

Thermodynamic Control: When thermodynamic control operates in a reaction, the relative amounts of starting material and product depends entirely on the free energy content of the species (the bond and resonance energies) and are given by the equation $\Delta G = - RT \log K$. For two competing reactions, to form X and Y, from the same starting material (A), the same considerations apply, provided that both products are in equilibrium with the starting material and hence with each other and also provided that the free energy content of the reactant is so small that only a small amount is present at equilibrium.

$$X \rightleftharpoons A \rightleftharpoons Y$$

The thermodynamic product will be formed when the temperature is sufficiently high for the above equilibria to be attained. Thus if the kinetic product is different from the thermodynamic product, we have the equilibria:

kinetic product $\rightleftharpoons$ starting material $\rightleftharpoons$ thermodynamic product

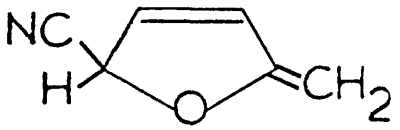


The initial rate of formation of the kinetic product will be much higher, but having been formed it may 'siphon' over to the thermodynamic product until thermodynamic equilibrium has been attained such that

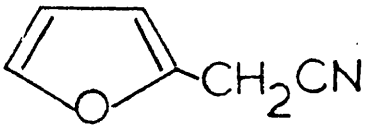
$$\Delta E = -RT \log \frac{\text{thermodynamic product}}{\text{Kinetic product}}.$$

The threshold temperature at which thermodynamic equilibrium can be attained is of course impossible to predict precisely but it will be low when (a) the leaving group is a strong nucleophile (b) the nucleophile forms a weak bond to the electrophile or (c) when the nucleophile is a stable anion. Thus for cyanide as the nucleophile and chloride as the leaving group, which are the most common moieties in ambident electrophilic rearrangement, thermodynamic control may

be expected not to operate at low temperatures, since conditions (a) and (b) are not fulfilled. (Criterion (c) is fulfilled, however, since $\bar{C}N$ is a stable anion but the large gain in energy when the C-C bond is made in the reaction should more than compensate for this). In cases where methanol or amines (such as piperidine) are nucleophiles a weaker bond is formed with the substrate and thermodynamic control may operate at room temperature. We have obtained experimental evidence to show that thermodynamic control is not operating in the reaction between 2-chloromethylfuran and cyanide. At the temperatures (25-80°) at which 2-chloromethylfuran was made to undergo rearrangement, the normal product (2-cyanomethylfuran) was not converted into its isomer (2-cyano-5-methylfuran) in the presence of cyanide. Further it is reasonable to suppose that the abnormal product 2-cyano-5-methenyl-2,5-dihydrofuran (XVII) is much less stable than the normal isomer 2-cyanomethylfuran (XVIII). Thermodynamic control of the



(XVII)



(XVIII)

reaction would, therefore, be expected to yield a much larger proportion of the normal product. This is not found. At room temperature (20°) for example the ratio of XVII:XVIII is 12:7 which would correspond to very similar energy contents in both. It may

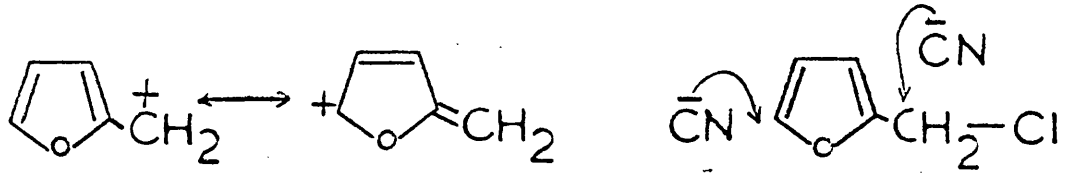
be assumed, therefore, that the reaction between 2-chloromethylfuran and cyanide is not thermodynamically controlled. This almost certainly also applies to other halomethyl heterocyclic systems which rearrange under the influence of cyanide.

Kinetic Control: The 'dynamic basicity' or 'nucleophilicity' of a nucleophile is measured by the rate constant of the reaction. The difficulty encountered if we take this statement to be axiomatic is to determine the factors (even on a qualitative basis) on which nucleophilicity depends. In fact the nucleophilicity of a given species under standard solvent conditions varies with the nature of the attacked electrophile.[133,134] A number of authors have tried to assign the most important factors which determine nucleophilicity. Streitwieser[135] has assumed that it is determined by the energy of solvation, the strength of its bond with a carbon 2p orbital, its steric effect, and the electronegativity and polarisability of the reacting atom. Edwards and Pearson[133] have named the basicity, the polarisability, and the α-effect (resulting from the presence of free electron pairs on the atom adjacent to the nucleophilic centre) as the most important factors. Hudson[136] argues that the electrostatic interaction between the nucleophile and reacting species plays an important part. A covalent bond is preferentially formed with the most

easily polarisable atom in the system.

In determining whether cyanide will attack 2-chloromethylfuran in the normal or abnormal position, the following factors must therefore be considered: 1) the strength of the furan-cyanide C-C bond, 2) steric effects, 3) the polarisability of the reactant, 4) the electrostatic attraction between the reacting species. Effects 1) and 2) probably do not play an important role here, since they are likely to be similar for abnormal and normal substitution.

For an S_N1 mechanism the intermediate mesomeric carbonium ion (XIa$\longleftrightarrow$XIb) is the species under attack. The major factor in determining the kinetic product is the relative charge densities on the primary carbonium ion (XIa) and the secondary carbonium ion (XIb). The more positive carbon atom will be more susceptible



(XIa) (XIb)

to attack, and this may well be the carbonium (XIb). Its stability and charge will depend on the mesomeric and inductive effect of the neighbouring oxygen atom. It may be said at least that if the two competing reactions are S_N1 and S_N1', it is reasonable to find a significant amount of the S_N1' product.

For an S_N2 mechanism electrostatic attractions probably play only a minor role. Thus the polarisability of the sp^3 (for normal substitution) and the sp^2 carbon atoms (for abnormal substitution) are in question. The latter has a greater s character and is probably less polarisable. Normal substitution should be favoured in this case (but see solvent effect, p.172). An explanation has, therefore, been offered for Hill's claim[36] (in the methanolysis of furfuryl chloride) that abnormal substitution is favoured by an S_N1 mechanism, while most of the normal product is formed by an S_N2 mechanism. We have seen that some non-aromatic systems react by S_N2' mechanisms. In these cases the solvent may well play a critical role in altering the nature of the transition state (see later).

The steric effect in kinetically controlled reactions may help to explain why in the reaction of furfurylchloride with cyanide no 3-cyano-2-methylfuran is formed. Similarly, rearrangement of 5-chloromethylthiazole gives only 2-cyano-5-methylthiazole and no 4-cyano-5-methylthiazole. Further, reaction of cyanide with aromatics which can only rearrange in a mono-ene system invariably give only small yields of abnormal products (3-chloromethylbenzothiophene,[48] 1%; N-methylgramine methiodide,[47] 4.3% cf. furan, ca. 50% and imidazole, 100%). As we have seen (Introduction p. 7) attack by a nucleophile on an allylic system is on

the same side as the departing group. If two double bonds intervene between the site of attack and the leaving groups, the nucleophile and leaving group will be on opposite sides*. In the former case, therefore, considerable steric hindrance can be envisaged, whereas in the latter case there can be no interference at all between nucleophile and leaving group.

Effect of temperature: Since kinetic control of a reaction helps to favour abnormal substitution, the amount of abnormal product should increase at low temperatures i.e. decrease at higher temperatures when thermodynamic control may predominate. This was in fact found when furfuryl chloride was treated with cyanide between -20 and 80°. The ratio of normal to abnormal product rose from 1.3 to 2.7 (see Experimental section). In terms of energy this is only a small difference but the trend is definite. Unfortunately under the conditions of the above temperature variation the normal product did not form any abnormal isomer, showing that thermodynamic control cannot be operating. The increase in the proportion of normal product at high temperatures may, therefore, be due to the polymerisation of the exocyclic methylene compound at such temperatures.

* by extending the argument for the mono-ene case.

Overall yields did in fact decrease from 85% (at -20^{o}) to 39% (at 80^{o}). It is conceivable that in the absence of thermal decomposition at sufficiently high temperatures, the rearranged product would cease to be formed.

Effect of the Nucleophile:

Table 5 shows all the nucleophiles which have been made to react with furfuryl chloride in the present work. The absence or presence of normal products, the exocyclic methylene compounds, and abnormal products in the reaction mixtures are shown. Egyed[34] attempted to correlate the tendency of nucleophiles to cause rearrangement with their basicity. Those derived from weak acids (high pKa) were said to cause rearrangement. This relationship was not rationally explained and it can be seen from Table 5 that in fact two nucleophiles derived from strong acids (viz. benzenesulphinic and thiosulphuric acid) do give rise to abnormal products. Conversely, weak acids (such as piperidine or thiourea) give only normal products. No firm conclusion can be drawn about phenol since only a low yield of the normal isomer was obtained. The exocyclic methylene intermediate could have been formed and polymerised during work-up.

We have already seen that abnormal products are probably formed in kinetically controlled reactions.

TABLE 5

Nucleophile	Normal product	Exocyclic methylene compound	Abnormal product	Approximate pKa of acid
$\bar{C}N$ [25,37]	+	+	+	9.14
$\bar{O}Me$ [33,36]	+	+	?	16.7
$Ph.S\bar{O}_2$ [36]	?	+	?	1.8—2 [140]
$\bar{S}CN$ [28,32]	+	-	-	high
N_3^-	+	-	-	4.72
S_2O_3Na	+	-	+	1.7 [141]
$\bar{o}Ac$	+	-	-	4.76
piperidine	+	-	-	high
Br^-	-	-	-	very low
$\bar{O}Ph$	+	?	?	9.89
$\bar{o}Ts$	+	-	-	0.7
$\bar{C}NO$	+	-	-	high
$SC(NH_2)_2$	+	-	-	high
AgCN	+	-	+	9.14

The reaction N: + RX → RN + X: should, therefore, be irreversible. The nucleophile (N) should form a bond with the electrophile (R) which is not susceptible to nucleophilic attack by the leaving group (X). It is indeed found that nucleophiles which are poor leaving groups such as $\bar{C}N$, $\bar{S}_2O_3Na$, $\bar{O}CH_3$, give rearrangement products whereas those which are good leaving groups such as $\bar{O}Ac$, $\bar{O}Ts$ and $\bar{B}r$ do not. On this basis, one might expect anions $\bar{S}CN$, $\bar{C}NO$, $\bar{N}_3$ and piperidine to give abnormal products whereas in fact they do not. No explanation for this anomaly can be given.

Silver cyanide gave no isonitrile products. The normal and abnormal nitriles were obtained in the ratio 5:3 though the yield was low.

Effect of leaving group:

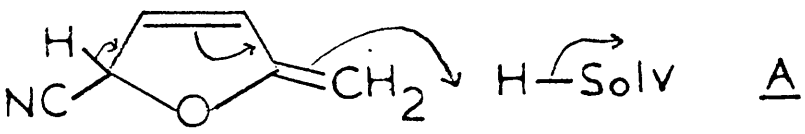
Furfuryl derivatives which ionise readily like furfuryl chloride to form the S_N1 carbonium ion should, under the influence of cyanide yield mixtures of normal and abnormal products. Of the leaving groups studied, none were as labile as halide. Cyanide (as already seen) and acetate were not displaced by cyanide even after 24 hr. at 80°. Furfurylthiocyanate reacted readily with cyanide, but attack was on the thiocyanate carbon to yield bis(furfuryl)-disulphide (see p.182). Displacement of azide by cyanide was slow even at 80°. After 24 hours a 33% conversion to

2-cyanomethyl- and 5-cyano-2-methylfuran (3:2) was effected (NMR evidence). This shows that having azide as opposed to chloride as a leaving group does not alter the reaction mechanism.

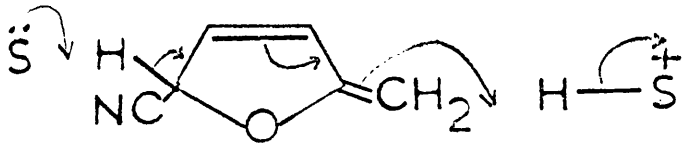
Effect of solvent.[137,138,139]

Experiments have shown that rearrangement generally occurs if protic solvents are used as media for the reactions between halides and nucleophiles, whereas dipolar aprotic solvents do not give rise to abnormal products. The notable exception is the reaction between 3-chloromethylbenzo[b]thiophene and cyanide[48] which gives a small amount of abnormal product when DMSO is used, but not in ethanol or ethanol-water. Also 3-halomethylbenzo[b]thiophene-1,1-dioxides rearrange when benzene is used as solvent.

The tendency for protic solvents to give abnormal products may be partially understood since the exocyclic methylene intermediate of abnormal product formation, can rapidly tautomerise to the more stable rearomatised product in such solvents (as shown A). In aprotic solvents tautomerism of the intermediate will presumably be much slower. If the aprotic solvent were a good hydrogen accepter (e.g. DMSO), the mechanism for prototropy would be as shown (B). In aprotic solvents, therefore, when the methylene compound is unstable, it may decompose, before it has a chance to tautomerise. In cases where a large amount



A



B

of abnormal product is formed in the protic solvent, the above effect would lead to a large lowering of the overall yield of identifiable product. This is often not the case. The total yield of 2-cyanomethylfuran by the reaction of 2-chloromethylfuran with sodium cyanide in DMSO was 60% the same as the yield of a 12:7 mixture of 2-cyanomethylfuran and 5-cyano-2-methylfuran produced when formamide was the solvent and only 7% lower than the yield from an aqueous reaction when a 1:1 mixture of isomers was formed.

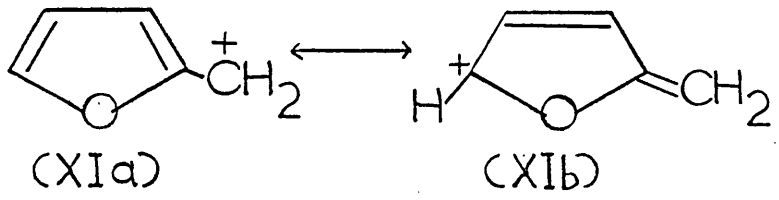
We now consider how a change in solvent can affect the ratio of products in the absence of the effect described above. For the transfer from protic to aprotic (particularly dipolar aprotic) solvents we have three possible alternatives.

Case 1: Reactions which go unimolecularly (S_N1) in all solvents.

Case 2: Reactions which go bimolecularly (S_N2) in all solvents.

Case 3: Reactions which are S_N1 in protic solvents and S_N2 in dipolar aprotic solvents. (Carbonium ion formation is favoured in protic solvents. The converse of Case 3 is, therefore, unlikely).

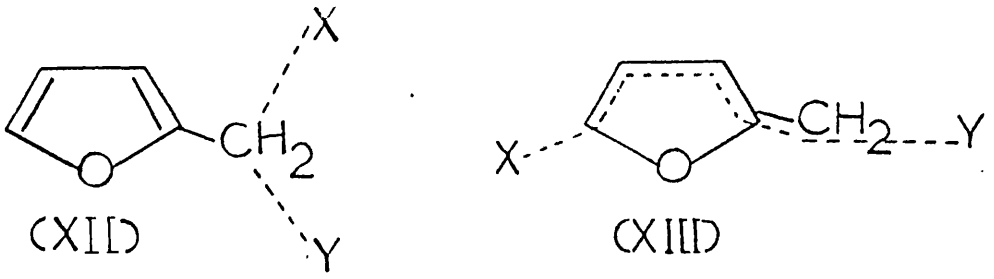
Case 1: If an S_N1 mechanism occurs in all solvents then the nature of the solvation of the intermediate carbonium ion will effect the ratio of final products. Dipolar aprotic solvents are liable to solvolyse the more polarisable carbon atom in the carbonium ion (XIa ↔ XIb). This may mean that the primary carbonium ion (XIa) may be more readily substituted by the



(XIa) (XIb)

nucleophile than the secondary carbonium ion (XIb) because of the greater solvation by the dipolar aprotic solvent at the 'abnormal' carbon atom, i.e. abnormal product formation is discouraged. However, S_N1 reactions in dipolar aprotic solvents are rare and the above case can probably be excluded.

Case 2: Large polarisable transition states are more heavily solvated by dipolar aprotic solvents owing to the ability of such solvents to give strong dipole-dipole and ion-dipole interactions. If we therefore compare the S_N2 (XII) and S_N2' transition states (XIII), the latter has its charge more dispersed and is of the



(XII) (XIII)

large, polarisable type, and is therefore more heavily solvated by solvents such as DMSO than by protic solvents. Conversely protic solvents, which solvate largely through hydrogen bond formation, stabilise transition states which have a localised negative charge viz. the S_N2 transition state (XII). In the case where a bimolecular mechanism is always present, therefore, it is conceivable that a dipolar aprotic solvent should favour abnormal product formation, whereas a protic solvent may favour normal reaction.

Case 3: In cases where an S_N1 mechanism is possible, the considerations of case 2 are over ridden and an S_N1 mechanism will always favour allylic rearrangement over an S_N2 mechanism (as already explained, p.161). Thus in the frequently visualised circumstance of a protic solvent giving rise to an S_N1 and an aprotic solvent an S_N2 reaction, for allylic systems, the protic solvent would favour rearrangement. It is indeed found that most heterocyclic ambident electrophilic systems show a preference towards the formation of abnormal products in protic solvents and give no such products in dipolar aprotic solvents.eg 2-Chloro-

methylfuran, 4-chloromethylthiazole, 2-chloromethyl-thiazole, and 2-chloromethylimidazole with cyanide ion. The systems which have been studied with regard to solvent effect are listed in Table 6. Examples cited in the literature are given a reference number, and for systems investigated in the present work the relevant page in the Experimental section is given. On the basis of the arguments presented it can be tentatively suggested that those cases which favour rearrangement in protic solvents react chiefly via an S_N1 mechanism in the protic solvent and an S_N2 mechanism in an aprotic solvent (Case 3). On the other hand if an aprotic solvent favours rearrangement the mechanism probably involves an S_N2 transition state in all solvents (Case 2).

TABLE 6

System	Nucleophile	Solvent	% Abnormal product	Reference(r) or page(p)
2-chloromethylfuran	$\bar{C}N$	$HCONH_2, H_2O, EtOH, H_2O$	50-80	p.85
2-chloromethylfuran	$\bar{C}N$	DMF, DMSO	0	p.85
3-chloromethylfuran	$\bar{C}N$	H_2O	10	r.39
2-chloromethylimidazole	$\bar{C}N$	H_2O/EtOH	100	r.43,44
2-chloromethylimidazole	$\bar{C}N$	DMF/DMSO	0	r.45,46
2-chloromethylthiazole	$\bar{C}N$	EtOH/H_2O or EtOH	1	p.123
2-chloromethylthiazole	$\bar{C}N$	DMSO	0	p.123
4-chloromethylthiazole	$\bar{C}N$	EtOH/H_2O	1	p.111
4-chloromethylthiazole	$\bar{C}N$	DMSO	0	p.111
3-chloromethylbenzothiophene-1,1-dioxide	thiourea piperidine etc.	benzene	100	r.50
1-methylgramine methiodide	$\bar{C}N$	H_2O	4.3	r.7
3-chloromethylbenzothiophene	$\bar{C}N$	EtOH/H_2O or EtOH	0	p.92

TABLE 6 Continued

System	Nucleophile	Solvent	% Abnormal product	Reference or page
3-chloromethylbenzothiophene	$\bar{C}N$	DMSO	2.5	p.92 (r.48)
Dichloromethyl and tri-chloromethylpyrazine	$\bar{O}Me$	MeOH	5—30	r. 55
1-dichloromethyl-5-nitro-2-p-toluene sulphonyl benzene	piperidine		6—16	r. 56
	$\bar{O}R$	ROH		
triphenylmethylchloride	$\bar{C}N$	$HCONH_2$	2.5	p.131
triphenylmethylchloride	$\bar{C}N$	DMSO	0	p.131

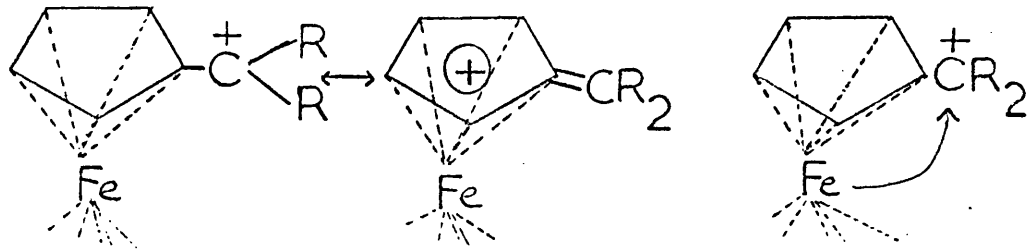
MISCELLANEOUS

1. Ferrocenes.

In the reaction between N,N-dimethylaminomethylferrocene methiodide and sodium hydroxide, as described in Organic Synthesis,[116] it was found that if heating was continued for twice the recommended time of 3.5 hr., a good yield (75%) of bis(ferrocenemethyl)ether was obtained instead of hydroxymethylferrocene. This provides the most convenient synthesis of the ether (cf. refs.[117,123,142,143])

Reaction of chloromethylferrocene with cyanide.

The stabilisation of the ferrocenyl carbonium ion by participation of iron has been established.



(XIXa) (XIXb) (XIXc)

Whether stabilisation is due to a resonance effect (XIXa ↔ XIXb) or to participation of non-bonding electrons of iron (XIXc) is not fully understood, though evidence points to the former of these two possibilities.[144-6] In this case, it was thought that halomethylferrocenes may display ambident electrophilic behaviour.

The reactions of chloromethylferrocene with sodium

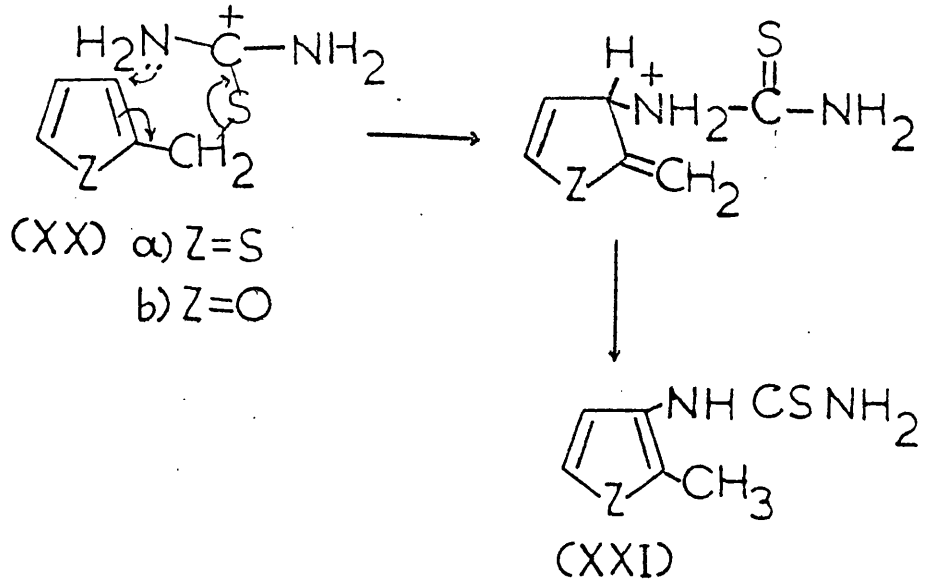
and potassium cyanides in a number of solvents were attempted. At best only small quantities of cyanomethylferrocene were obtained, the major product usually being hydroxymethylferrocene. In aqueous solvent systems this observation is not surprising, as chloromethylferrocene is extremely sensitive to moisture. However, in dry DMSO the same result was obtained. The lack of reactivity of cyanide towards the carbon atom bearing the chlorine may be due to complexing of $\bar{C}N$ with the iron atom of the ferrocene. It is realised, of course, that the electronic shell of iron is fully occupied in ferrocene and complexing by cyanide would lead to fragmentation of the ferrocene molecule.

When DMSO is used as solvent for the above reaction, an intermediate DMSO complex may be involved, which hydrolyses during aqueous work-up to the observed product:

$$FcCH_2Cl \longrightarrow FcCH_2\text{-}O\text{-}\overset{+}{S}(Me)_2\ Cl^- \longrightarrow FcCH_2OH + DMSO + HCl$$

2. Reaction of furfurylthiocyanate and isothiouronium salts with cyanide.

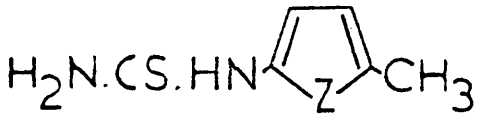
For the isothiouronium moiety as a leaving group, the possibility was considered that it might simultaneously act as a nucleophile through the nitrogen atom, as shown below.



(XX) a) Z=S
b) Z=O

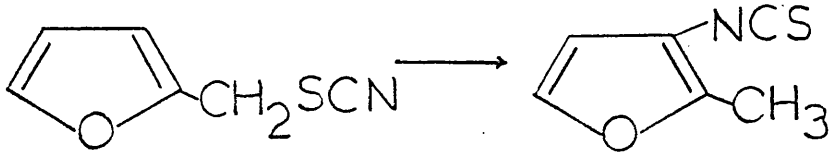
(XXI)

The final product would therefore be the substituted thiourea (XXI) and a six-membered, unstrained transition state would be involved. A similar, though less favourable mechanism could be written for nucleophilic attack by nitrogen on $C_{(5)}$ to yield the thiourea (XXII), which is therefore a possible alternative product of the above reaction.



(XXII)

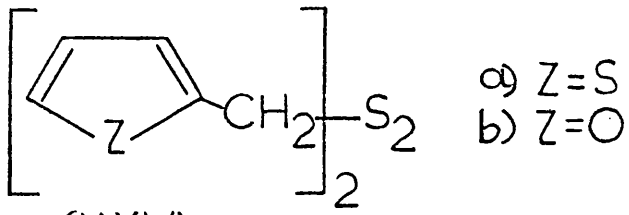
Similarly, the possibility of the transformation of furfuryl/thiocyanate (XXIII) to 3-isothiocyanato-2-methylfuran (XXIV) was considered.



(XXIII) (XXIV)

This isomerisation is less likely than the previous one, since the linearity of the S-C≡N group would disfavour close approach of the nitrogen atom to the 3-carbon atom of the furan ring.

Thermolysis of 2-furfuryl-(XXb) and 2-thenyl-isothiouronium chloride (XXa) and of furfurylthiocyanate (XXIII) at 100° in DMSO or in the absence of solvent gave no reaction (the compound (XXIII) darkened slowly at this temperature). At higher temperatures only polymeric material could be isolated. The reaction with cyanide was then attempted. Treatment of (XXa) or (XXb) with aqueous potassium cyanide, gave in each case an exothermic reaction from which bis(thenyl)disulphide (XXVa) or bis(furfuryl)disulphide (XXVb) resp. was isolated.



a) Z=S
b) Z=O

(XXV)

The reaction of furfurylthiocyanate with cyanide in ether-water also gave the disulphide (XXVb).

The above reactions are formally similar to those of aryl thiocyanates, which when treated with amines (such as trimethylamine), acetic acid and a trace of water produce aryl disulphides cleanly and in high yield.[147] The base acts as a catalyst for the reaction and the actual oxidation-reduction step is

between a mole of mercaptan and one of thiocyanate:

1.

$$ArSCN \longrightarrow Ar\text{-}S\text{-}\overset{\overset{\bar{N}}{\|}}{C}\text{-}\overset{+}{N}R_3 \longrightarrow ArSH + CO_2 + NH_3 + R_3N$$

2.

$$ArSH + ArSCN \longrightarrow ArS\text{-}SAr + HCN$$

Step 2 was independently shown to occur. The reaction between furfurylthiocyanate may be analogous:

$$ArCH_2SCN \longrightarrow ArCH_2\text{-}S\text{-}\overset{\overset{N^-}{\|}}{C}\text{-}CN \longrightarrow ArCH_2SH + CO_2 + NH_3 + \bar{C}N$$

Step 2 would then be as before

In the reaction of $ArCH_2\text{-}S\text{-}\overset{+}{C}(NH_2)_2\ \bar{Cl}$ with cyanide, the analogous intermediate would be

$$ArCH_2\text{-}\overset{\overset{NH_2}{|}}{\underset{\underset{NH_2}{|}}{C}}\text{-}CN$$

This species on hydrolysis, could break up into $ArCH_2SH$ (as before) and $HO\text{-}\overset{\overset{NH_2}{|}}{\underset{\underset{NH_2}{|}}{C}}\text{-}CN$ may be formed as the initial hydrolysis product. The unstable species could readily decompose as follows*:

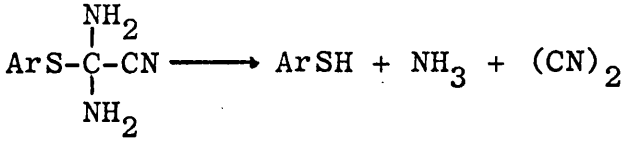
$$HO\text{-}\overset{\overset{NH_2}{|}}{\underset{\underset{NH_2}{|}}{C}}\text{-}CN \longrightarrow 2NH_3 + HCN + CO_2$$

It may be noted that the above mechanism involves

---

* The, perhaps, more likely mode of decomposition to urea and HCN is not compatible with the experimentally observed products.

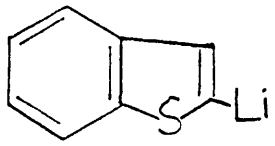
the participation of water, whereas in fact the transformation proceeds readily in dry DMSO. It may be that traces of water in the DMSO were sufficient to catalyse the reaction, or the intermediate invoked may decompose as follows:



A gaseous cyanide was evolved in the reaction, but this may have been HCN. The presence of ammonium chloride after reaction was detected, but this would have been formed from either mode of decomposition.

3. Benzothiophenes

(i) It was found that on treatment of 2-benzo[b]thienyllithium with formaldehyde (generated thermally from paraformaldehyde) the expected product 2-hydroxymethylbenzo[b]thiophene was not isolated, but instead 2,2'-bibenzo[b]thienyl was obtained in 20% yield. The surprising feature of this reaction is that CH_2O has apparently acted as an oxidising agent. However, under the conditions of the experiment air was continuously being passed into the reaction mixture. Molecular oxygen could therefore have effected the dimerisation as shown overleaf.



$$\equiv \bar{R}.\overset{+}{Li} \xrightarrow[-e]{O_2} \tfrac{1}{2}R-R + \overset{+}{Li}$$

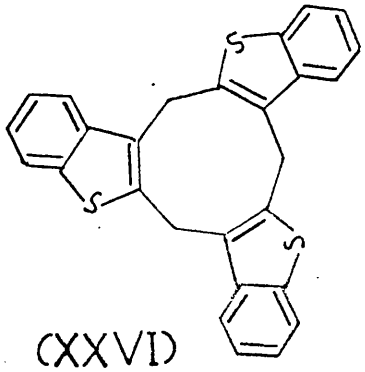
The normal course of the reaction of an alkyl- or aryl-lithium compound with molecular oxygen is via a peroxide to form the lithium alkoxide as follows:[148]

$$RLi \xrightarrow{O_2} RO\text{-}O\text{-}Li \longrightarrow 2LiOR$$

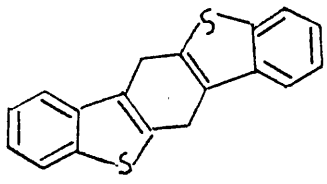
It is conceivable therefore that in the coupling of 2-benzothienyl-lithium, formaldehyde plays a reductive part in the reaction, once the peroxide is formed, i,e.

$$2RO_2Li + 3HCHO \longrightarrow 2HCO_2Li + R\text{-}R + HCOOH + H_2O$$

(ii) Treatment of 3-chloromethylbenzo[b]thiophene with cuprous cyanide gave a clean reaction at 80°, from which a mixture of the trimer (XXVI) and the dimer (XXVII) were isolated. NMR and ms evidence support these structures. Unfortunately the two compounds could not be separated by fractional crystallisation or column chromatography.

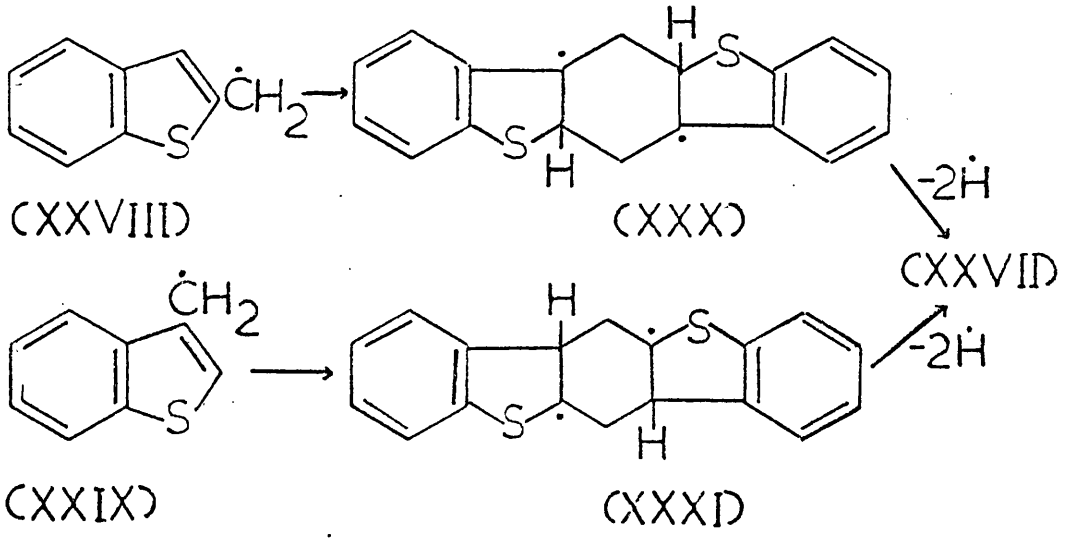


(XXVI)



(XXVII)

Further, 2-chloromethylbenzo[b]thiophene on treatment with cuprous cyanide, gave a mixture of the same dimer and trimer, but in slightly different proportions such that the relative peak heights in the mass spectra were p^+ (trimer); p^+ (dimer) = 1.10 from 3-chloromethylbenzothiophene and p^+ (trimer); p^+ (dimer) = 0.83 from 2-chloromethylbenzothiophene. This may suggest that similar, though not identical intermediates are involved in the two cases. It is not difficult to envisage, therefore, the formation and consequent dimerisation of the radicals (XXVIII) and (XXIX) to form the diradical species (XXX) and (XXXI) which may each lose two hydrogen atoms to form the required product* (XXVII). The trimer can be formed similarly.



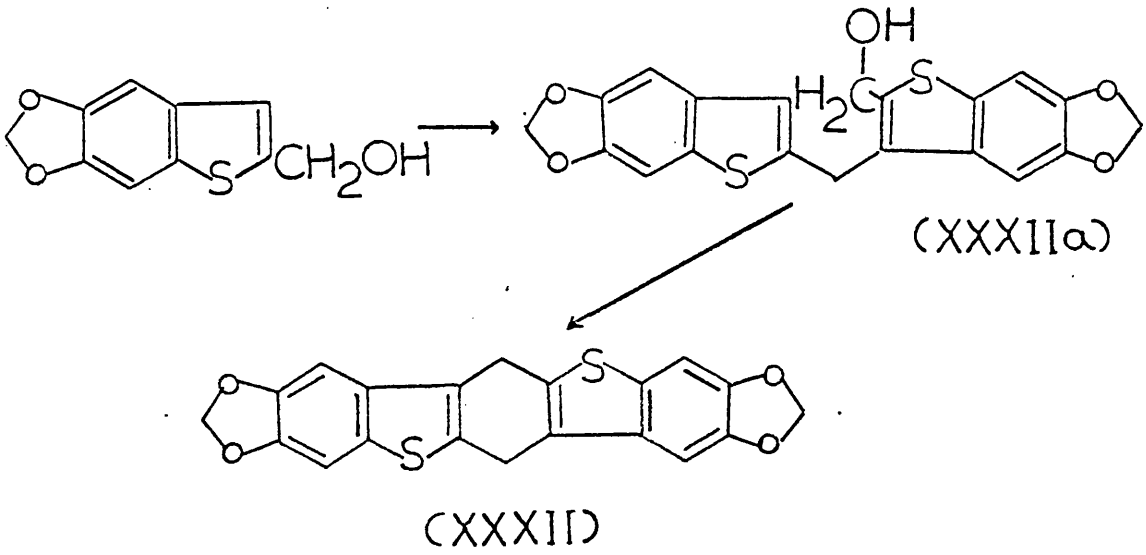
The major criticism of this proposed mechanism is that the radicals $RCH_2^{\cdot}$ (XXVIII, XXIX) would be expected to

---

* The process could be stepwise, which avoids the postulation of a diradical intermediate.

dimerise to the species $RCH_2 - CH_2R$. Such compounds could not be detected as reaction products, however,

The above reaction is reminiscent of a report[149] that 2-hydroxymethyl-5,6-methylenedioxybenzo[b]thiophene on treatment with thionyl chloride forms the dimer (XXXII).

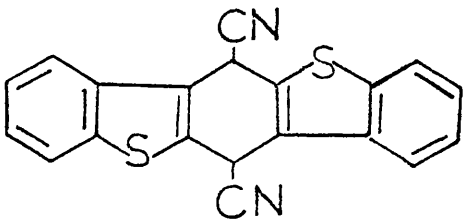


(XXXIIa)

(XXXII)

It was postulated that electrophilic attack on the hydroxymethylbenzothiophene by the benzothenyl carbonium ion led to the intermediate (XXXIIa). A further intramolecular electrophilic substitution would yield the final product. A similar mechanism was considered for dimerisation and trimerisation of 2- and 3-chloromethylbenzothiophenes, but was rejected on the grounds that conditions conducive to the formation of carbonium ions (e.g. the use of polar solvents) did not lead to the dimeric and trimeric products (but see below).

Reaction of 2-chloromethylbenzo[b]thiophene with sodium cyanide gave as a minor product, a compound whose physical data are given in the Experimental section. From the IR (which showed a cyanide peak at 2275 cm^{-1}), the mass spectrum (p^+ = 342)*, the NMR (aromatic:aliphatic protons = 4:1), and the analysis, the tentative structure (XXXIII) is put forward.



(XXXIII)

The surprising feature about this compound is that it is formally derived by oxidation of the dimers and trimer previously discussed!

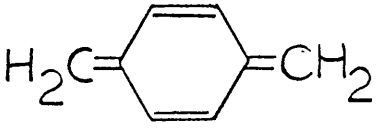
* The break-down pattern in the mass spectrum does not fit the proposed structure too well.

SOME ABNORMAL BEHAVIOUR IN THIOPHENES AND THE LECOCQ REARRANGEMENT

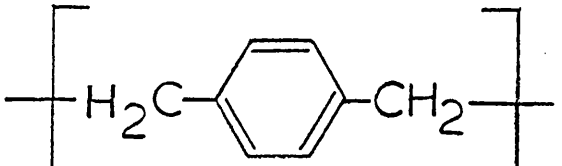
We have found several reactions displayed by the 5-methyl-2-thenyl group which are not shown by the 2-thenyl moiety. These reactions are now discussed, the first example being taken from the literature.

1. Formation of polymers related to poly-p-xylylene:

Polymers derived from the isolable p-xylylene (XXXIV) have been known for some years[150-152]. These poly-p-xylylenes (XXXV) were originally prepared by

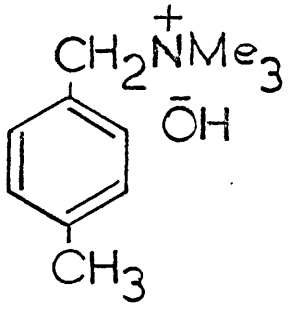


(XXXIV)

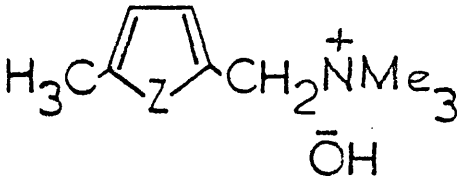


(XXXV)

the fast flow pyrolysis of p-xylene[152]. More recently Winberg[153] obtained the same polymers (XXXV) by the thermolysis of p-methylbenzyltrimethyl ammonium hydroxide (XXXVI) at 60-100° under reduced pressure.

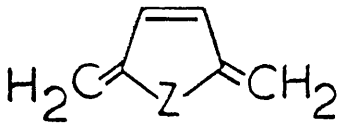


(XXXVI)



(XXXVII) a) Z=S
b) Z=O

Completely analogous reactions occurred on pyrolysis of 5-methyl-2-thenyltrimethylammonium hydroxide (XXXVIIa) or 5-methyl-2-furfuryltrimethylammonium hydroxide (XXXVIIb). The monomeric species (XXXVIII) could not be isolated in the heterocyclic cases but were assumed to be reaction intermediates by analogy with the carbocyclic case. The ready formation of the symmetrical



(XXXVIII)

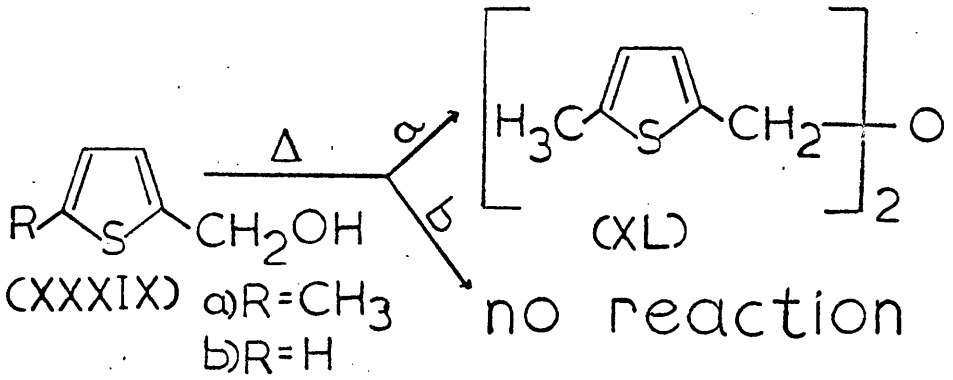
bis-methylene intermediate (XXXVIII) is postulated in the reactions described below. It must be noted, however, that the considerable modification of the chemistry of the thenyl group imposed by a 5-methyl group is not generally found in the furfuryl or benzyl systems.

2. The Instability of 2-chloromethyl-5-methylthiophene.

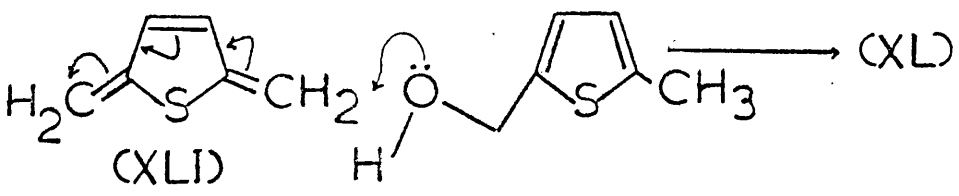
The fact that 2-chloromethyl-5-methylthiophene is much less stable thermally than 2-chloromethylthiophene has already been discussed and was attributed to an intermolecular loss of hydrogen chloride. An alternative explanation may be that the former molecule eliminates hydrogen chloride intramolecularly in 1,6-fashion to yield the unstable bis-methylene species (XXXVIII, **Z=S**), which then polymerises.

3. The ready formation of 5-methyl-2-thenylether.

We observed that 2-hydroxymethyl-5-methylthiophene (XXXIXa) was readily converted into its ether (XL) on attempted distillation whereas 2-hydroxymethylthiophene (XXXIXb) was thermally stable. The unexpected behaviour



of the former compound must presumably be due to participation of the 5-methyl group or more specifically may depend on the presence of a hydrogen atom α to the 5-carbon. Thus the alcohol (XXXIXa) may lose the elements of water by a 1,6-elimination, under thermolytic conditions yielding the unstable 2,5-bis-methylene-2,5-dihydrothiophene (XLI) as intermediate. Instead of polymerising as in the previous example α 1,6-addition of the alcohol to the intermediate (XLI) would give the desired product. Such a mechanism is not possible, of course, for 2-hydroxymethylthiophene.

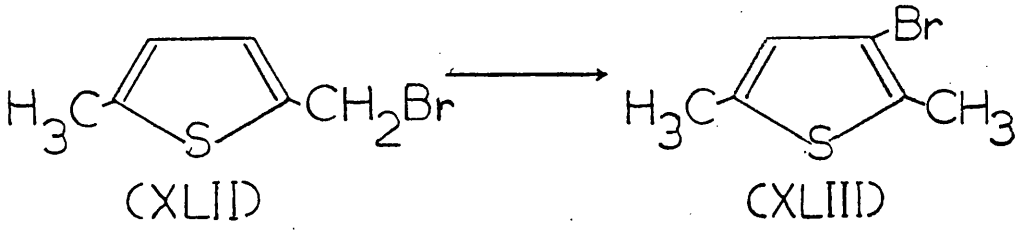


4. Chloromethylation of 2-methylthiophene.

We have already invoked the species (XLI) as an intermediate in the reaction of 2-methylthiophene under conditions of chloromethylation to explain why 1,2-bis(5-methyl-2-thienyl)ethylene is obtained. This contrasts the reaction of thiophene with formalin and HCl when 2-chloromethylthiophene is formed in good yield with none of the corresponding ethylene.

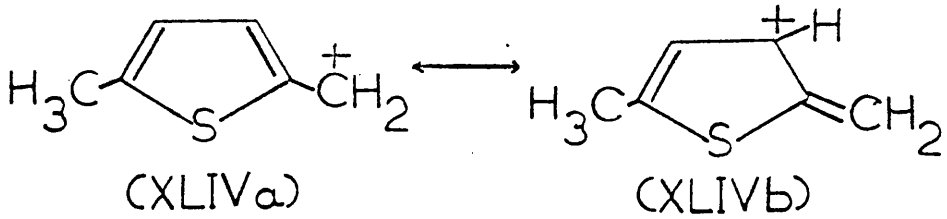
5. The 'Lecocq' Rearrangement.

The reaction of 2-bromo-5-methylthiophene (XLII) with potassium cyanide or cuprous cyanide to produce 3-bromo-2,5-dimethylthiophene (XLIII), as found by Lecocq[6,53,54], was described in the Introduction.



(XLII) (XLIII)

The present work was partly concerned with the elucidation of the mechanism of this reaction, which seemed curious in view of all the other displacements of halide by cyanide described in this thesis. In the first instance the reaction was considered to be an intramolecular ambident electrophilic transformation involving cleavage of (XLII) heterolytically into a bromide ion and the mesomeric cation (XLIVa ⟷ XLIVb).

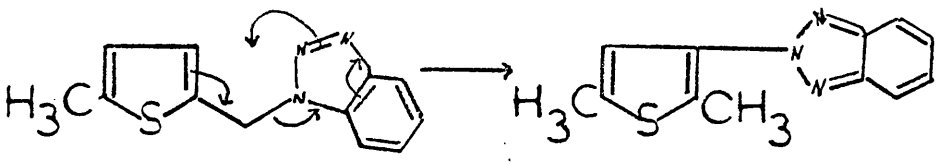


(XLIVa) (XLIVb)

If the intermediate was a tight ion pair, internal return of $B\bar{r}$ by a 'normal' attack would lead to starting material (XLII), but 'abnormal' attack would give the desired product (XLIII). This would explain the proven intramolecularity of the reaction, but is not in accord with the total absence of rearrangement of 2-chloromethylthiophene and anyway does not explain why there is no incorporation of $C\bar{N}$.

As we shall see there is now evidence that the above reaction is in fact homolytic.

Effect of System: 2-Chloromethyl-5-methylthiophene was shown to rearrange in exactly the same manner as its bromo analogue. The possibility of an intramolecular rearrangement of 5-(1-benzotriazolylmethyl)-2-methylthiophene to 3-(2-benzotriazolyl)-2,5-dimethylthiophene (cf. p.180-1) was also considered.



Unfortunately, the former compound could not be made to react with cyanide and was extremely stable to heat.

Systems in which no α-hydrogen atom was present, such as 2-chloromethylthiophene and 2-t-butyl-5-chloromethylthiophene did not undergo rearrangement. Not too surprisingly p-chloromethyltoluene did not rearrange in the presence of cuprous cyanide and only p-cyanomethyltoluene was isolated from the reaction mixture.

Variation of solvent and reagent: 2-Chloromethyl-5-methylthiophene was treated under a variety of conditions. The results are shown in the Experimental section. The following points emerge from the data obtained.

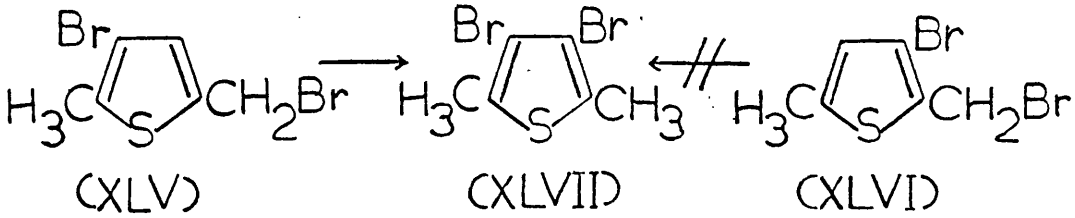
1. Rearrangement occurs very readily and cleanly in the presence of number of salts (KCN, NaCN, AgCN, CuCN, KBr), particularly the cyanides. (Cyanide ion is not necessary for the reaction to occur, however).

2. The solvent has little effect on the reaction except when it is nucleophilic in which case normal nucleophilic attack on chlorine can occur. For example, the reaction of 2-chloromethyl-5-methylthiophene with potassium cyanide in ethanol gave 3-chloro-2,5-dimethylthiophene (35%) and 2-ethoxymethyl-5-methylthiophene (46%).

3. Blank experiments using a) no solvent b) ether and c) DMSO as solvent showed that 2-chloromethyl-5-methylthiophene gives only polymeric material in the

absence of an inorganic reagent. However, an exothermic reaction occurred in the presence of acetonitrile and the rearrangement product (10%) was obtained.

4. The structural specificity of the reaction was demonstrated by Lecocq[6] who showed that 3-bromo-5-bromomethyl-2-methylthiophene (XLV) rearranged in the



(XLV) (XLVII) (XLVI)

usual way (to XLVII), but 3-bromo-2-bromomethyl-5-methylthiophene (XLVI) gave no isomeric products. Thus the halogen migrates only to an adjacent nuclear position.

Since the thiophenes, (XLV and XLVI) used by Lecocq were separated from a mixture of brominated products obtained from the reaction of N-bromosuccinimide and 3-bromo-2,5-dimethylthiophene (XLIII) the above results may have to be accepted with some caution especially since the product of the rearrangement 3,4-dibromo-2,5-dimethylthiophene (XLVII), is also a likely product in the NBS reaction.

We have also shown that when 2-chloromethyl-5-methylthiophene is treated under conditions of rearrangement in the presence of bromide ion, no bromide is incorporated into the organic compound and in particular, no 3-bromo-2,5-dimethylthiophene is obtained. Conversely

the bromomethylthiophene in the presence of chloride ion gives no organic chloride.

2-chloromethyl-5-methylthiophene was normally prepared by the action of NCS on 2,5-dimethylthiophene*. On one occasion, however, it was obtained from 2-hydroxymethyl-5-methylthiophene and thionyl chloride*. Surprisingly this sample of the thiophene [B] although identical in its physical properties to [A] showed no tendency to rearrange and in the presence of ionic cyanide gave 2-cyanomethyl-5-methylthiophene as the sole isolable product. Addition of small quantities (10%) of [A] to [B] caused some rearrangement to occur in [B] on treatment with cyanide though 2-cyanomethyl-5-methylthiophene was still isolated. Similarly addition of a catalytic quantity of NCS to a sample of [B] also induced this compound to rearrange to a small extent. It would therefore appear that the rearrangement of 2-chloromethyl-5-methylthiophene is catalysed by NCS and by some impurity in the chloromethyl compound when this is prepared with NCS. It seems likely that a free radical might therefore be involved although this does not apparently induce a chain reaction leading to rearrangement product.

The main data obtained from a study of the reaction are summarised in the following table.

---

* 2-chloromethyl-5-methylthiophene prepared by the NCS reaction is hitherto referred to as [A] and those samples prepared by the latter method (alcohol + thionyl chloride) are referred to as [B].

Thiophene	Solvent	Reagent	'normal' product	product of rearrangement	Others
2-chloromethyl or 2-bromomethyl	DMSO	NaCN	60-70%	-	-
	-	CuCN	-	-	polymer
3-bromomethyl	DMSO	KCN	64%	-	-
2-t-butyl-5-chloro methyl	DMSO	KCN	68%	-	-
	-	CuCN	-	-	polymer
2- α-chloroethyl	-	CuCN or KCN	-	-	polymer
2-bromomethyl-5-methyl	-	CuCN	-	88%	-
	DMSO	KCN	-	40%	-
	DMSO	KCL	-	15%***	-
2-chloromethyl-5-methyl	-	CuCN	-	75%	-
	DMSO	NaCN	-	67%	-
	DMSO	KBr	-	23%**	-
	-	CuCN (catalytic)	-	70%	-
	MeCN	-	-	7%	polymer

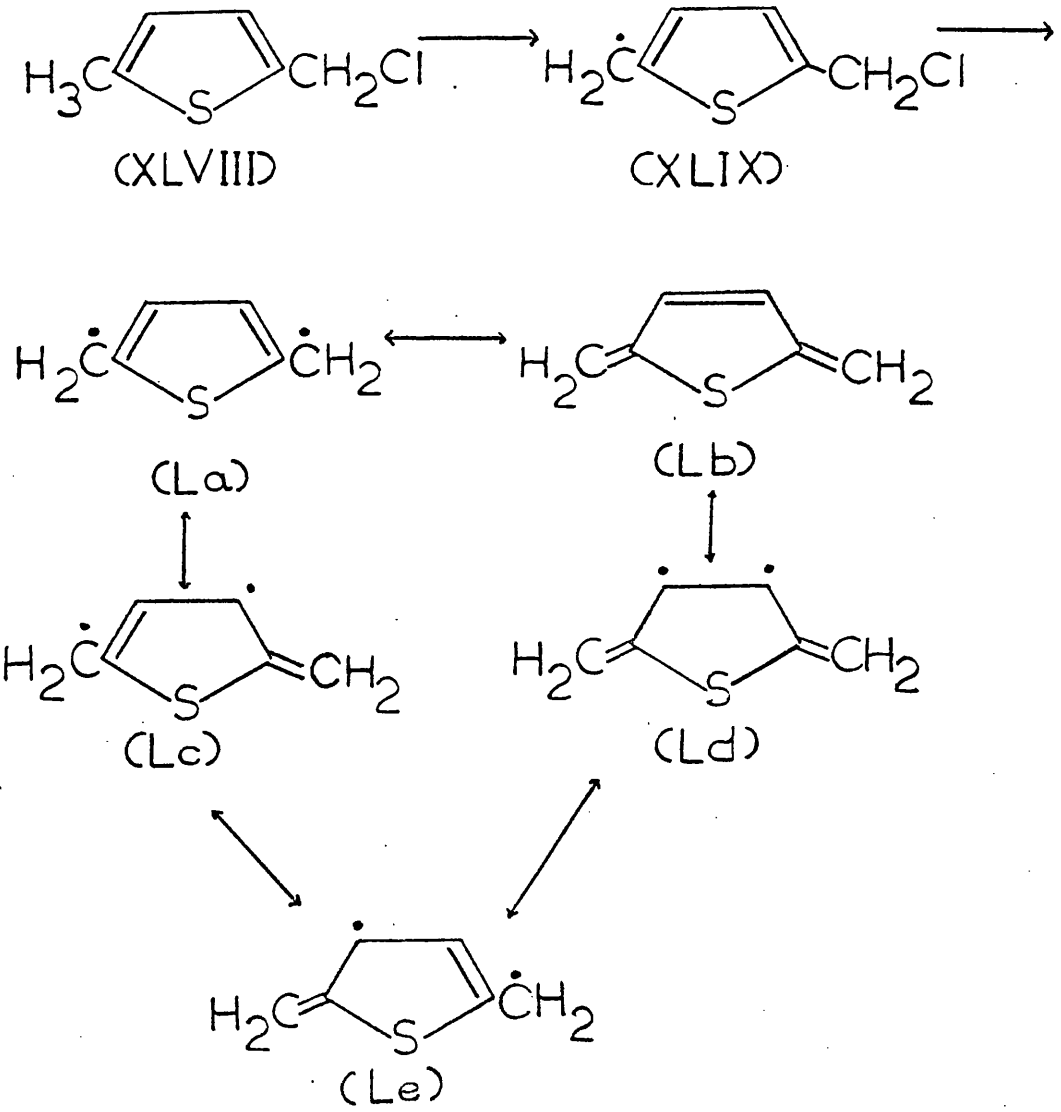
Thiophene	Solvent	Reagent	'normal' product	product of rearrangement	Others
	Ether, DMSO or no solvent	-	-	-	polymer
	-	AgCN	-	80%	-

* 2-ethoxymethyl-5-methylthiophene

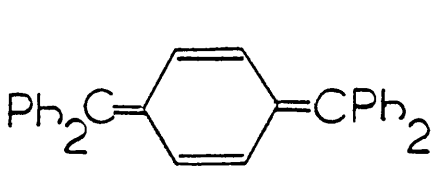
** 3-chloro-2,5-dimethylthiophene only

*** 3-bromo-2,5-dimethylthiophene only

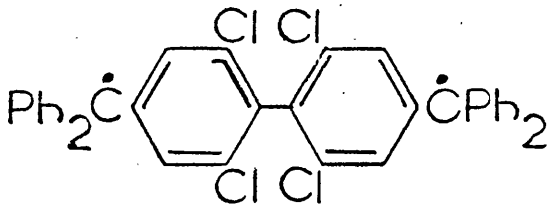
In view of the above results, it may be said that any mechanism proposed for the rearrangement must explain i) the intramolecularity 2) the necessity for an α-hydrogen atom in the 5-position of the ring 3) the lack of solvent effect 4) the apparent radical initiation of the reaction and 5) the catalysis of the reaction by ionic species or cuprous cyanide. It is not easy to propose a mechanism compatible with all these factors and a number of variants could be visualised.



A possible mechanism for the reaction is as follows: initial loss of H· from the methyl group of 2-chloromethyl-5-methylthiophene (XLVIII) to form the radical species (XLIX). This latter compound could perhaps lose Cl more readily than (XLVIII) to form the curiously stable p-xylylene type of structure (Lb). The structures (L a - e) are all mesomeric. In fact the diradical paramagnetic structures (eg. La) have been shown for p-xylylene to be comparable in energy to the bismethylene species (XXXIV) cf. (Lb). In cases of more extended conjugation (Chichibabin hydrocarbons eg. LI), when



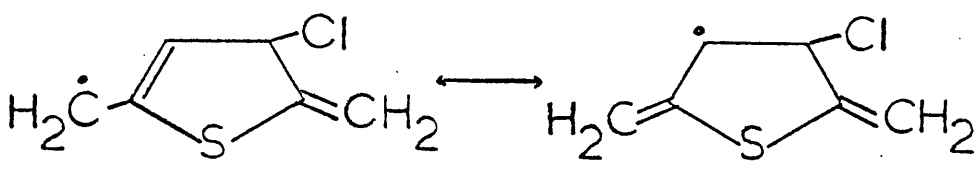
(LI)



(LII)

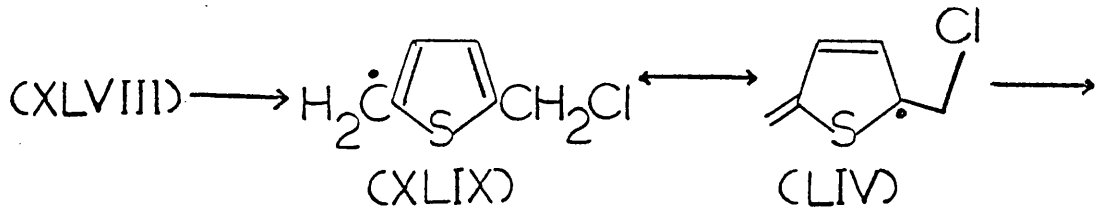
the planar configuration is disfavoured by steric strain the compounds are often paramagnetic eg. (LII)[154].

Recombination of Cl with the diradical species (Lc), (Ld), or (Le) would lead to the intermediates. (LIIIa), (LIIIb), and (LIIIa) respectively, which on picking up an H atom and rearomatising would lead to the desired product.

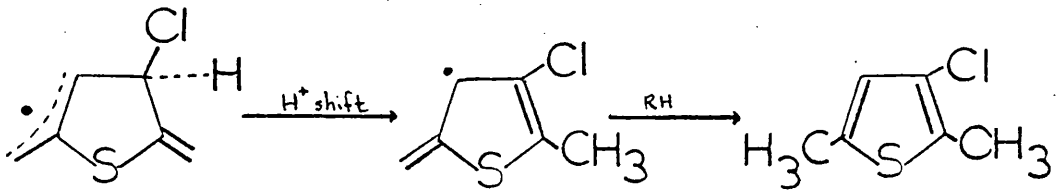


(LIIIa) (LIIIb)

The intramolecularity of the reaction could be explained in terms of a tight radical pair formed between Cl and the diradical structures (La, c, d, and e). The following reaction scheme eliminates the need to involve a diradical species and explains the intramolecularity and structural specificity of the reaction.



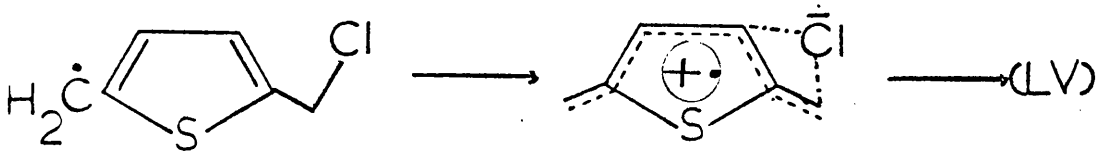
(XLIX) (LIV)



(LV) (LVI) (LVII)

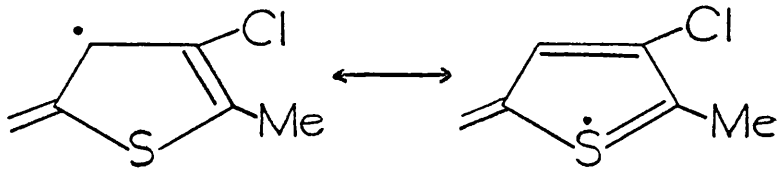
The radical (XLIX) is formed as before and is mesomeric with (LIV). The change from sp^2 (120^o) to sp^3 (109^o) of the α-carbon atom enables somewhat closer approach of chlorine to the β-carbon atom. Homolytic cleavage of the C-Cl bond with the formation of an exocyclic methylene group and the simultaneous addition of the developing Cl to the diene system may occur to form the radical (LV). The tautomerism of this species to (LVI) followed by abstraction of H· would lead to the required product (LVII).

The catalysis of the reaction by ionic species may merely aid the tautomerism step (LV) - (LVI) or else the breakage of the C-Cl bond may occur heterolytically to a radical ion.



Mechanisms in which cyanide actually participates in the reaction (either as $C\bar{N}$ or $\dot{C}N$) were ruled out on the basis that a thiophene - cyanide C-C bond, once formed would probably not break up at a later stage along the reaction pathway.

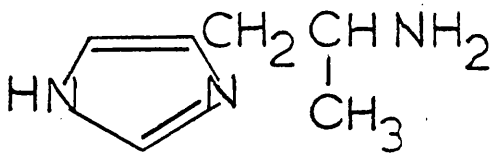
The uniqueness of thiophene in showing the Lecocq rearrangement may be due to the additional stability a sulphur atom can impart to a thenyl radical viz.



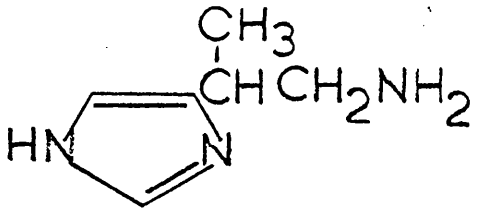
METHYLHISTAMINES

DISCUSSION

The seven monomethylhistamines have been synthesised and their biological properties in various tests have been examined[155]. From the available pharmacological data it is evident that in their role as histamine agonists these compounds are extremely demanding stereochemically. 4(5)-(2-Aminopropyl)imidazole (α-methylhistamine) (I) and 4(5)-(2-amino-1-methylethyl)imidazole (β-methylhistamine) (II) are particularly interesting in this context since they can display optical isomerism. There is a possibility, therefore, that the enantiomers of these two compounds may show different activity towards one or more biochemical systems. If this were so, information on the stereochemical requirements of histamine receptors might be obtained.



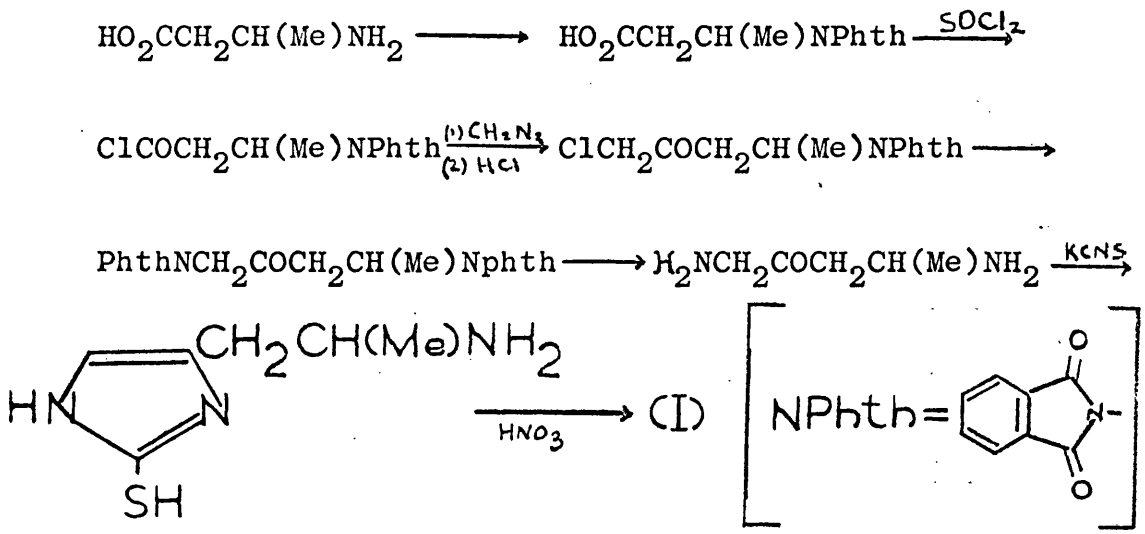
(I)



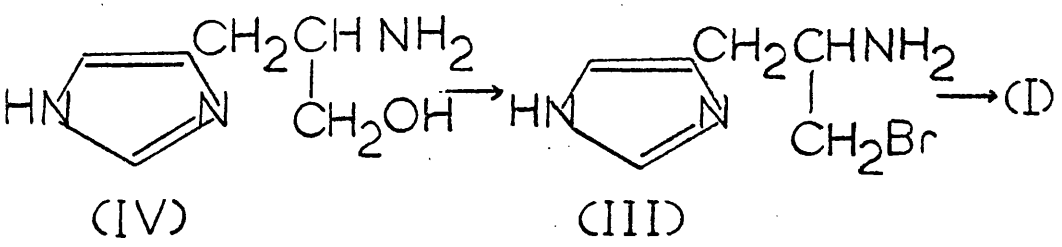
(II)

α-Methylhistamine: α-Methylhistamine has been synthesised by Alles[156] (see Scheme A below).

Scheme A



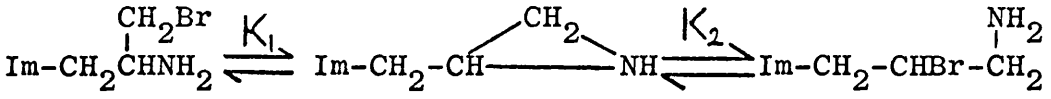
Since this synthesis was rather tedious[155], it was proposed to obtain α-methylhistamine by an alternative route. L - histidinol (IV) is commercially available and has been converted into α-bromomethylhistamine (III)[157]. If this bromo-compound (III) could be reduced to α-methylhistamine (I), this would provide a more attractive route to (I). Further, the synthesis should lead to optically active (possibly optically pure) α-methylhistamine since the starting material L-histidinol is optically pure and the reaction scheme does not involve attack at the asymmetric carbon atom.



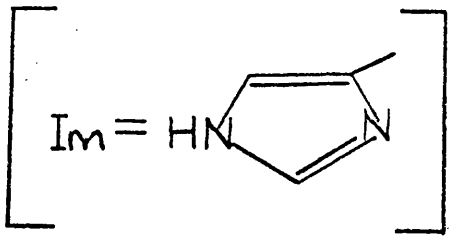
(IV) (III)

It may be noted that α-bromomethylhistamine is only stable under acidic conditions[157]. As the pH is raised, the equilibrium (K_1) shown in Scheme B shifts to the right with the formation of the aziridine (IIIa). Though this reaction is reversible, it was not advisable to handle α-bromomethylhistamine under basic conditions, since acid cleavage of the aziridine may also involve the equilibrium (K_2) in which 4(5)-(3-amino-2-bromopropyl)imidazole (IIIb) would be formed.

Scheme B



(III) (IIIa) (IIIb)



L-Histidinol (IV) was converted into α-bromomethylhistamine (III) by the method of Usher[157]. The base (III) was isolated as the dihydrobromide. Reduction of the dihydrobromide was attempted in methanol using 10% palladium-charcoal (Pd/C) as catalyst and a slight excess of HBr. Pd/C was used as it appears to be the

catalyst least poisoned under acidic conditions see for example Augustine[158] and Baltzly[159]. Conversion into α-methylhistamine dihydrobromide increased to 80% (NMR analysis of crude product) if hydrogenation was continued for 4 days, with the addition of more Pd/C after 2 days. This product was isolated as the dipicrate (47%).

The dipicrate was acidified and α-methylhistamine dihydrochloride was obtained. The product appeared to be pure (TLC) and its physical data corresponded with those of authentic dl-α-methylhistamine but it could not be obtained in the crystalline state, not even on seeding with the authentic material. Rotation measurements $[\alpha]_D^{26} = 2.66 \pm 0.13$ (C, 3.5; H_2O) showed the compound to be optically active, confirming that at least partial retention of configuration had occurred.

β-Methylhistamine: 4(5)-(2-amino-1-methylethyl) imidazole (II) has been prepared according to Scheme C[155].

Scheme C

$HO_2CCH(Me)CH_2NH_2 \longrightarrow HO_2CCH(Me)CH_2NPhth \longrightarrow$

$ClCOCH(Me)CH_2NPhth \longrightarrow BrCH_2COCH(Me)CH_2NPhth \longrightarrow$

$Im\text{-}CH(Me)CH_2NPhth \longrightarrow (II)$

The above reaction scheme was repeated. 1-Bromo-3-methyl-4-phthalimidobutan-2-one was cyclised using formamide at 180° (Bredereck reaction[160]). The formamide in the reaction should not be too dry as this gives low yields. In practice BDH formamide from an unopened bottle gave the highest yields. Dr. R.A. Slater[155] has found that addition of water to the formamide leads to virtual arrest of the reaction. The product of the reaction, N-phthalimido-β-methylhistamine (VI), was not isolated but hydrolysed with ION HCL directly to β-methylhistamine dihydrochloride. Purification was effected by conversion of the dihydrochloride into the free base by ion exchange chromatography, followed by synthesis, isolation, and purification of the dipicrate. This dipicrate was converted quantitatively into the dihydrochloride.

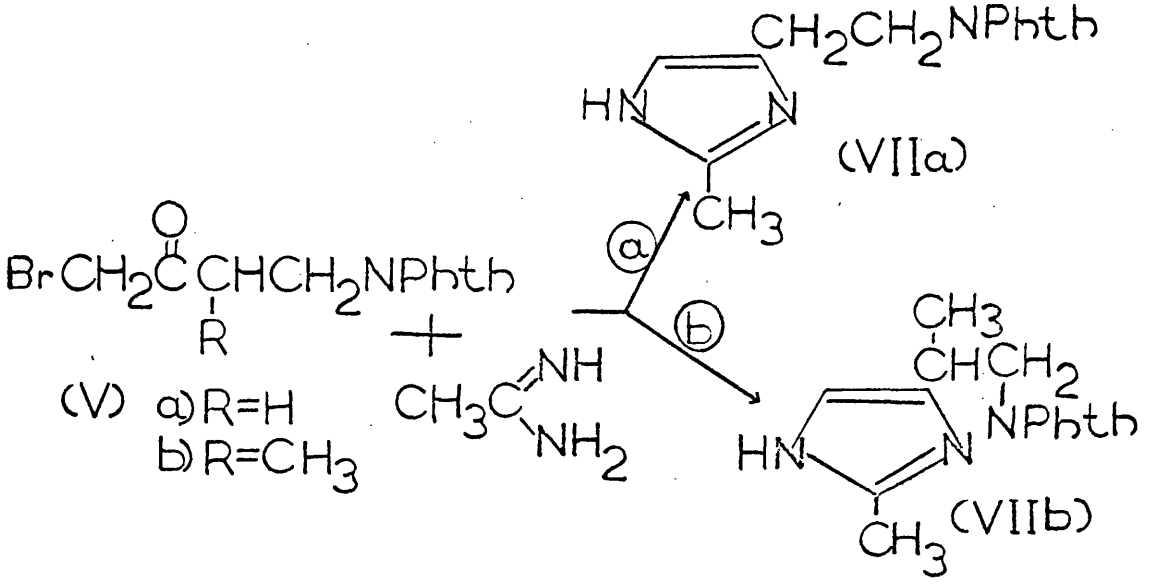
Attempted Resolution of β-Methylhistamine.

Attempts to resolve β-methylhistamine through its L-tartrate were unsuccessful, due chiefly to the fact that the diastereoisomer mixture was highly deliquescent. The mono-D-camphor-10-sulphonate of β-methylhistamine was not crystallisable.

Finally, a highly crystalline sample of β-methylhistamine di-D-camphor-10-sulphonate was obtained on treatment of β-methylhistamine (free base) with two moles of D-camphor-10 -sulphonate. Details of the

manipulation of the diastereoisomers to yield a pure sample of β-methylhistamine dihydrochloride of $[\alpha]_D^{26}$ = 1.4° (C, 5; H_2O) are given in the Experimental section.

Attempted Preparation of 4(5)-(2-amino-1-methylethyl)-2-methyl imidazole.

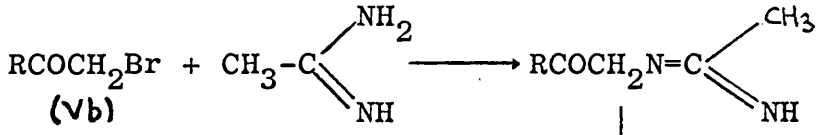


The bromomethylketone (Vb), already used in the synthesis of β-methylhistamine, was thought to be a precursor of the new dimethylhistamine (VIIb) by analogy with the known cyclisation of 1-bromo-4-phthalimido-butan-2-one with acetamidine to form 2-methylhistamine (VIIa).

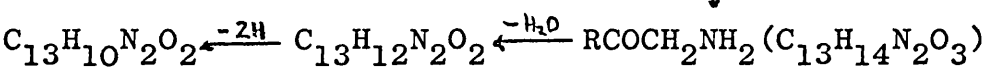
The synthesis of N-phthalimido-2-methylhistamine (VIIa) was repeated successfully by the method of Dr. J.C. Emmett[155]. Under identical conditions 1-bromo-3-methyl-4-phthalimidobutan-2-one (Vb) was reacted with acetamidine. The expected N-phthalimido derivate of 4(5)-(2-amino-1-methylethyl)-2-methylimidazole (VIIb)

was not obtained but instead a compound (VIII) was formed with a molecular formula $C_{13}H_{10}N_2O_2$ as shown by high resolution ms and analysis and formed a monohydrochloride ($C_{13}H_{11}ClN_2O_2$). IR showed the compound to have a carbonyl group, but probably not an N-phthalimido group. NMR showed the presence of 4H (aromatics); 1H (-OH or -NHR); 2H ($-NH_2$); 3H ($-CH_3$). The compound (VIII) could not be hydrolysed even with ION HCL.

A number of possible structures for the compound (VIII) can be visualised. The general pathway of the reaction may be as follows:



$RCOCH_2Br$ (Vb) + $CH_3-C(NH_2)=NH$ → $RCOCH_2N=C(CH_3)-NH$

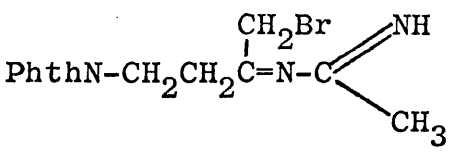


$C_{13}H_{10}N_2O_2$ ←(-2H)— $C_{13}H_{12}N_2O_2$ ←($-H_2O$)— $RCOCH_2NH_2$ ($C_{13}H_{14}N_2O_3$)

(VIII) (IX)

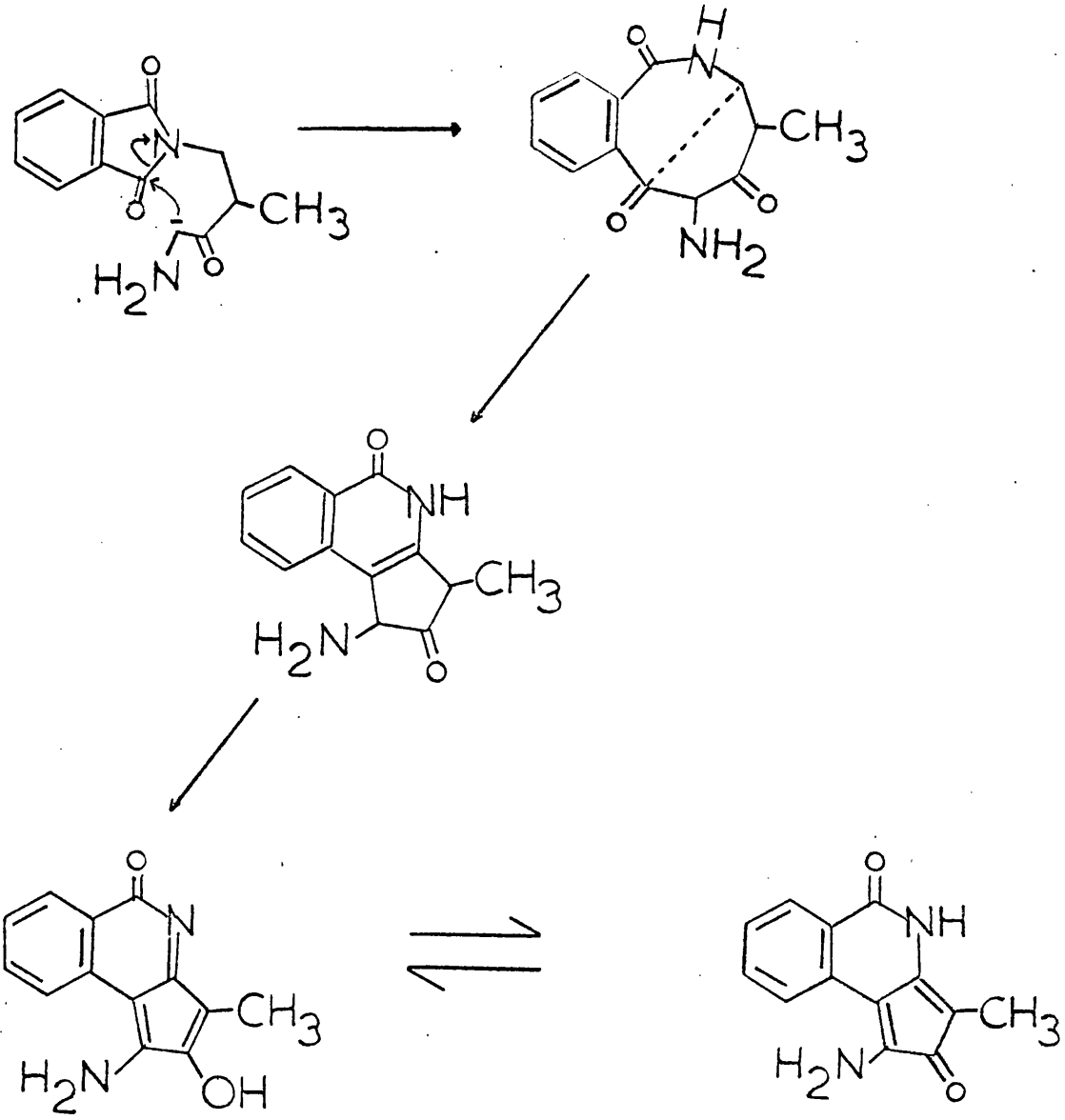
R = PhthN-CH_2CH(Me)-

In the reaction of PhN-$CH_2CH_2COCH_2Br$ (Và) with acetamidine to produce N-phthalimido-2-methylhistamine (VIIa), the initial step probably involves the condensation of the ketone with acetamidine to form



PhthN-CH_2CH_2-$C(CH_2Br)$=N-$C(NH)-CH_3$

The presence of the methyl group in the homologous bromomethylketone (Vb) may impart sufficient steric hindrance to the carbonyl function for the first step of Scheme D to occur more readily than condensation of $>C=O$ with NH_2. Hydrolysis of the imine so formed would lead to the amine (IX). One possible structure (which fits all available physical data) is given below with its mode of formation from the amine (IX).



(VIII)?

Pharmacological Testing.

The samples of the optically active methylhistamines α-methylhistamine, $[\alpha]_D^{26} = -2.66^\circ$, and β-methylhistamine, $[\alpha]_D^{26} = +1.4^\circ$, obtained in the present work have been submitted for pharmacological testing. No data are available at this time, however.

EXPERIMENTAL

4,(5)-(2-Amino-3-bromopropyl)imidazole.

L-Histidinol dihydrochloride* (5.35 g; 0.025 mole) was converted into 4(5)-(2-amino-3-bromopropyl)imidazole using 48% aqueous hydrobromic acid (125 ml.) by the method of Usher[157]. Recrystallisation of the crude salt from methanol-ether yielded pure 4(5)-(2-amino-3-bromopropyl)imidazole dihydrobromide, (8.04 g; 88%), m.p. 214-16° (Lit.[157] m.p. 211-13°). $[\alpha]_D^{26}$ = + 15.4° (C,4; H_2O) (lit[157] $[\alpha]_D^{25}$ + 16.1°), $\nu_{max.}$ (nujol) 1940 (hydrobromide), 1610, 1500, 1370, 905, 785 (aromatic) cm^{-1}. ^1H NMR (D_2O) δ, 8.78 (d, 1H, J=1.5), 7.52 (m, 1H), 3.9-3.6 (m, 3H), 3.3-3.1 (m, 2H) (Found C, 20.4; H, 3.5; N, 11.7; Calc. for $C_6H_{12}Br_3N_3$ C, 19.7; H, 3.3; N, 11.5%).

4(5)-2-Aminopropylimidazole (α-Methylhistamine).

10% Palladium-charcoal (1.75 g.) was suspended in methanol (100 ml.) and treated with hydrogen at room temperature. 4(5)-(2-Amino-3-bromopropyl)imidazole dihydrobromide (1.75 g; 0.0048 mole) in methanol (75 ml.) and conc. HBr (1 drop) was added. The mixture was hydrogenated with vigorous shaking for 2 days, when about half of the theoretical volume (50 ml.) had been

---

* Purchased from the Cyclo Chemical Corporation.

taken up. 10% Palladium/charcoal (1.0 g.) in methanol (70 ml.) was added and hydrogenation was continued for 2 further days when a total of 88 ml. of hydrogen had been absorbed (theoretical 115 ml. at 27°C).

The reaction mixture was filtered through kieselguhr and the filtrate was evaporated to dryness yielding a yellow oil (1.7 g.) the NMR of which showed it to contain approximately 80% of α-methylhistamine, 20% starting material, and traces of unidentifiable products.

The impure α-methylhistamine was converted into its free base (0.625 g; 82%) by application to an IRA-401 amberlite resin column to give the impure base. Treatment of the base with picric acid in absolute ethanol gave fractions of moderately pure dipicrate, which were combined and recrystallised from ethanol-water to yield pure α-methylhistamine dipicrate (1.3 g. 46.6% overall yield), m.p. 173-6° (lit.[156] m.p. of the dipicrate of dl-α-methylhistamine 202-4°). R_F (MeOH:NH_3, 20:1) 0.4 on precoated silica gel plates.

The dipicrate (1.3 g.) was converted into the dihydrochloride by partition between nitrobenzene and 5N hydrochloric acid (50 ml.). The aqueous layer was extracted with chloroform (3 x 50 ml.) boiled with decolourising charcoal and filtered. On removal of the water and drying the product by azeotropic distillation with isopropanol, a colourless oil was obtained shown to be homogeneous on TLC. The oil could not be

crystallised, but was shown to be TLC pure α-methylhistamine, $[\alpha]_D^{26} = -2.66 \pm 0.13$ (C, 3.5; H_2O), $\nu_{max.}$ (nujol) 2000 (hydrochloride); 1620; 1150; 955; 780 cm^{-1}. ^1H NMR (D_2O) δ, 7.77 (d, 1H, J = 1.5); 6.52 (m, 1H); 2.73 (q of triplets, 1H, J = 6.5); 3.25-3.05 (m, 2H); 1.37 (d, 3H, J = 6.5). TLC R_F = 0.41 on precoated silica gel plates using methanol: ammonia (20:1) as eluent. Except for its lack of crystallisability the physical properties of the α-methylhistamine dihydrochloride were similar to those of a sample of dl-α-methylhistamine dihydrochloride provided by Smith Kline and French Laboratories. Dr. R.A. Slater[155] has obtained a hygroscopic sample of the dl-dihydrochloride of m.p. 169-70°. On seeding the optically active material produced above with this racemic dihydrochloride, crystallisation could not be induced.

2-Methyl-3-phthalimidopropionic acid.

Treatment of 3-aminoisobutyric acid (70 g; 0.7 mole) with phthalic anhydride (109.2 g; 0.73 mole) by the method of Balenovic[161] gave, after recrystallisation of the crude product from 96% ethanol, pure 2-methyl-3-phthalimidopropionic acid (125.6 g; 86%), m.p. 163°, (lit.[161] m.p. 161°) $\nu_{max.}$ (nujol) 1770 (phthalimido); 1710 (C=O) 1460, 1238, 1030, 933, 722, (aromatic) cm^{-1}. ^1H NMR δ, 7.9-7.8 (m, 4H); 3.9 (m, 2H); 3.15 (m, 1H); 1.25 (d, 3H, J=7.5).

2-Methyl-3-phthalimidopropionyl chloride.

Reaction of 2-methyl-3-phthalimidopropionic acid (116.5; 0.5 mole) with thionyl chloride by the method of Balenovic[161], gave a white waxy solid of 2-methyl-3-phthalimidopropionyl chloride (125.5 g; 100%), m.p. 47.5-49° (lit. m.p. not given). ν_{max} (nujol) 1770, 1705, 1030, 912, 714 cm^{-1}. ^1H NMR δ, 7.8 (m, 4H); 4.4-3.25 (m,3H); 1.4 (d, 3H, J = 6.5). This material was used for the next reaction without further purification.

1-Bromo-3-methyl-4-phthalimidobutan-2-one.

2-Methyl-3-phthalimidopropionyl chloride (4.5 g; 0.18 mole) was treated with diazomethane as described by Balenovic[161]. The diazoketone so formed was treated cautiously in situ with an excess of concentrated aqueous HBr (120 ml.). Recrystallisation from ethanol gave pure 1-bromo-3-methyl-4-phthalimidobutan-2-one (49.7 g; 94%) m.p. 97-9°, $\nu_{max.}$ (nujol) 1770 (phthalimido); 1715 (c=O), 1195, 1050, 940, 743, 730 (aromatic) cm^{-1}. The conversion of the diazoketone to the bromomethyl-ketone has been previously conducted by Dr. R.A. Slater[155] (m.p. = 97-8°).

4(5)-(2-Amino-1-methylethyl)imidazole (β-methylhistamine)

1-Bromo-3-methyl-4-phthalimidobutan-2-one (12.4 g; 0.04 mole) and formamide (72 ml.) were heated together for 24 hr. at 180-5°. During this period the solution

turned red and a white sublimate appeared in the condenser.

The formamide was removed on the rotary evaporator at 0.3 mm the residue was treated with water (200 ml.) and the mixture was heated on a steam bath for 10 min. and then cooled to 0^{o}. The red-brown precipitate of phthalimide (ca. 2g.) was filtered off, ION HCl (175 ml.) was added to the filtrate and the resulting solution was heated under reflux overnight to convert the N-phthalimido derivative of β-methylhistamine into the dihydrochloride of the base. The red solution was evaporated to dryness. On trituration with water (35 ml.) a pale brown solid (ca. 1.5 g.) was obtained, and shown to be moderately pure phthalic acid. The filtered solution was again evaporated to dryness and the residue extracted with hot ethanol (5 x 100 ml.). After the solution had cooled to room temperature, the white inorganic solid was filtered off, and the filtrate was partially decolourised with charcoal.

The ethanolic solution was evaporated to dryness, the residue was dissolved in water and the resulting solution applied to a column of Amberlite resin IRA-401 in the hydroxy-form . Deionised water (3L), eluted a colourless oil (2.6 g.), which was shown by TLC to contain one main component (R_F = 0.44 - brown) and two minor components (R_F = 0.10 - grey and 0.78 - blue) by

TLC on precoated silica with methanol:0.880 ammonia (20:1) as eluting agent. The spots were visualised with potassium iodoplatinate (KIP) spray.

The crude β-methylhistamine (2.6 g.) was dissolved in absolute ethanol (25 ml.) and added to a hot solution of ethanolic picric acid (10.4 g. in 75 ml.). On cooling, the solution deposited yellow crystals, shown to be moderately pure β-methylhistamine dipicrate, contamminated only with a small amount of picric acid (TLC). This sample was normally converted into the dihydrochloride. Recrystallisation of the impure dipicrate from methanol-water yielded pure 4(5)-(1-methyl-2-amino-ethyl)imidazole dipicrate (β-methylhistamine dipicrate) (11.3 g; 48.5%) m.p. 214-15°. $\nu_{max.}$ (nujol) 1640-1430 (multiplet, picric acid), 1160, 1080, 920, 835, 790, 740 710 (aromatic) cm^{-1}. The physical data for this dipicrate were the same as those of a sample prepared by Dr. R.A. Slater[155].

β-Methylhistamine dipicrate was converted into its dihydrochloride as described for α-methylhistamine. Trituration caused the colourless oil to crystallise. Recrystallisation from ethanol or methanol-isopropanol yielded pure 4(5)-(1-methyl-2-aminoethyl)imidazole dihydrochloride as colourless prisms (3.5 g; 45%) m.p. 203° (S.K.& F[155] m.p. 204°), $\nu_{max.}$ (nujol) 1615, 1372, 1081, 840 (aromatic) cm^{-1}. ^1H NMR (D_2O) δ, 8.67 (d, 1H, J = 2); 7.51 (m, 1H); 3.40 (m, 3H); 1.41 (d, 3H J = 7). TLC R_F = 0.44 using precoated silica plates in

methanol:0.880 ammonia (20:1). The component was visualised as a brown spot with KIP as developer. Physical data including TLC corresponded well with a sample of the dihydrochloride prepared by Dr. R.A. Slater[155].

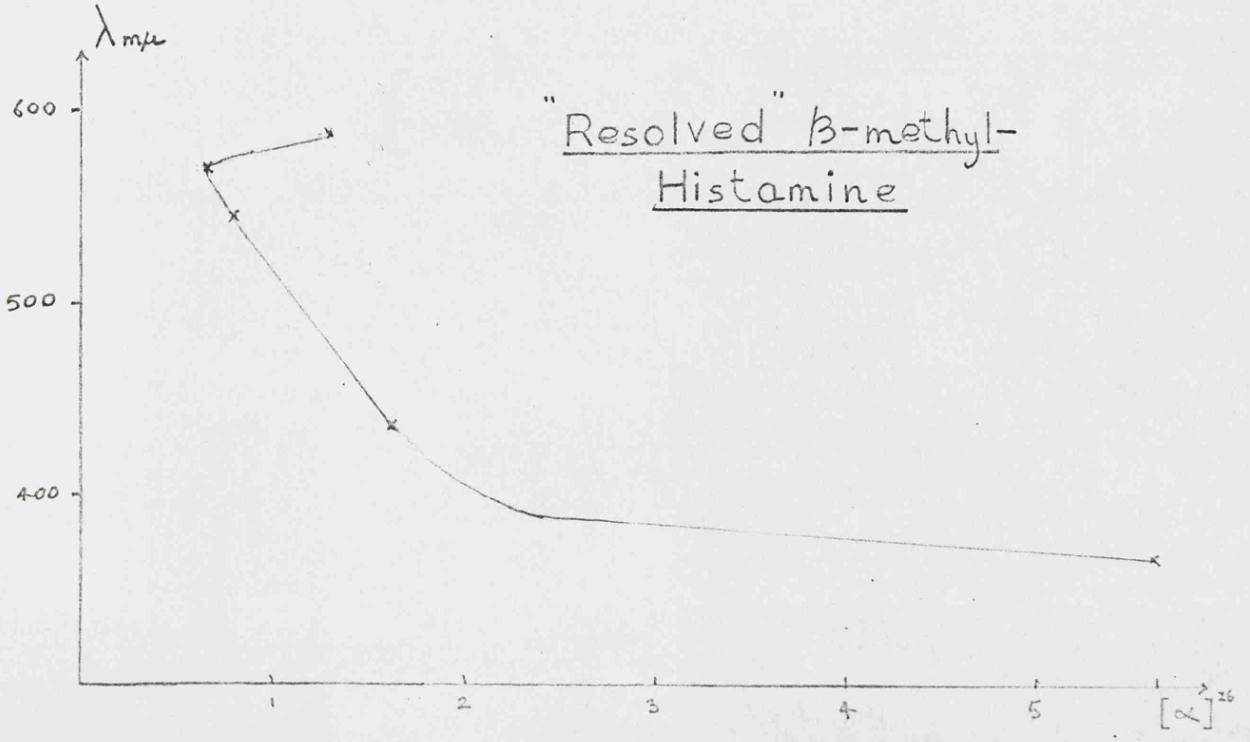
Attempted Resolution of β-Methylhistamine via its di-D-camphor-10-sulphonate.

β-Methylhistamine dihydrochloride (4.65 g; 0.0235 mole) was converted into its free base using ion exchange chromatography as previously described. β-Methylhistamine (2.775 g; 0.0222 mole) was obtained and was added to a solution of D-camphor-10-sulphonic acid (11.1 g; 0.044 mole) in ethanol (40 ml.). The solution was boiled for 5 min. Recrystallisation from nitromethane of the white solid obtained gave a diastereoisomeric mixture of β-methylhistamine di-D-camphor-10-sulphonate m.p. 193-196.5° $\nu_{max.}$ (nujol) 1742 (C=O), 1625, 1220-1165, 1058, 815, 655 (aromatic) cm^{-1}. ^1H NMR (D_2O) δ, 7.5 (d, 1H, J = 1.3); 8.8 (d, 1H, J = 1.3); 3.5 1.4 (24H); 1.08 (s, 6H); 0.85 (s, 6H). (Found C, 53.5; H, 7.3; N, 7.3; S, 10.8. $C_{26}H_{43}N_3O_8S_2$ requires C, 53.0; H, 7.4; N, 7.1; S, 10.9%).

Repeated recrystallisation of the mixture of diastereoisomers, gave a material, which when reconverted into its dihydrochloride had $[\alpha]_D^{26} = 1.8°$ (c, 5; H_2O). No fractions with $[\alpha]_D > 1.8°$ could be obtained. At λ = 365mu, $[\alpha]^{26}$ rose to + 5.63°. A plot of wavelength is shown overleaf .

All fractions with $[\alpha]_D > +1.5^o$ were combined and recrystallised from isopropanol to give β-methyl-histamine dihydrochloride (400 mg.); $[\alpha]_D = 1.4^o$, m.p. = 195-7°. The mother liquors contained a material with $[\alpha]_D^{26} = 1.6^o$, but the solid was impure (TLC).

No other solvents or solvent systems were as effective as nitromethane for resolution. Only tetrahydrofuran chloroform could be used for recrystallisation of the diastereoisomers. Resolution did occur in this case, but less effectively than with nitromethane. The diastereoisomeric mixture was found to be too soluble in methanol, ethanol, n-butanol, dichloromethane, and chloroform and it was insoluble in ethyl acetate, diethyl ether, benzene, dioxan, tetrahydrofuran, and acetonitrile. No criteria for the optical purity of the "resolved" salt can be given other than the fact that the mixture of diastereoisomers was recrystallised to constant rotation. NMR (in D_2O or $CDCl_3$) failed to differentiate the diastereoisomers.



2-Methylhistamine[155]

Sodium (6.9 g; 0.3 mole) was dissolved in dry ethanol (600 ml.) and this solution was added to acetamidine hydrochloride (28.4 g; 0.3 mole) in ethanol (200 ml.). The solution was heated to reflux with stirring and a solution of 1-bromo-4-phthalimido-butan-2-one (29.6 g; 0.1 mole) in ethanol (500 ml.) and DMF (100 ml.) was added over 3 hr. During the addition of the ketone the solution turned bright yellow, gradually becoming orange. The reaction mixture was heated under reflux for a further 2 hr. and left to stand at room temperature for 2 days, when it was filtered. The filtrate was evaporated, the residue was dissolved in ethanol and treated with charcoal. The solution was acidified (ethanolic HCl) and ethyl acetate was added. Slow crystallisation occurred and four crops were obtained. The first three crops, which were rich in phthalimido residues (as shown by IR) were combined, dissolved in water and basicified with sodium bicarbonate solution to pH9. Pink plates of the free base were obtained, filtered, and recrystallised from ethyl acetate to give moderately pure N-phthalimido-2-methylhistamine as colourless plates (2.5 g; 9.8%) m.p. 292-5° (S.K &F. m.p. 292-5°) $\nu_{max.}$ (nujol) 1770 (phthalimido); 1720 (doublet, C=O), 1583, 1420, 1390, 1030, 998, 739 (aromatic) cm^{-1}. ^1H NMR δ, 7.88 (s, 4H); 7.80 (broad s, 1H); 6.74 (broad s, 1H); 3.83

(t, 2H, J = 8); 2.82 (t, 2H, J = 8); 2.26 (s, 3H). ms 255 (p^+), 160, 108, 133, 104, 95, 76, 67, 54, 50. (Found C, 64.8; H, 5.2; N, 16.4. $C_{14}H_{13}N_3O_2$ requires C, 65.9; H, 5.1; N, 16.5%).

The N-phthalimido compound was heated under reflux with 5N HCl (40 ml.) overnight. Pure 2-methylhistamine dihydrochloride was obtained. m.p. 223-6° (S.K & F.[155] m.p. 222-4°).

Attempted Preparation of 2, β -Dimethylhistamine.

1-Bromo-3-methyl-4-phthalimidobutan-2-one (31.0 g; 0.1 mole) was treated with acetamidine exactly as described in the previous preparation (of 2-methylhistamine).

A hydrochloride was obtained which was converted into its free base and recrystallised from isopropanol to give a compound (1.6 g.) m.p. 208-9°. $\nu_{max.}$ (nujol) 3620 (weak OH) 1720 (C=O); 1655, 1480, 1260, 1095, 808, 770, 705 (aromatic) cm^{-1}. ^1H NMR δ, 8.5-7.5 (m, 5H); 2.4 (s, 3H); 6.0 (broad s, 2H). (Found C, 67.9; H, 4.4; N, 12.4(5). $C_{13}H_{10}N_2O_2$ requires C, 69.0; H, 4.4; N, 12.4%). ms. 226, 211, 198, 170, (high resolution ms showed p^+ = 226.0724326 corresponding to $C_{13}H_{10}N_2O_2$, p^+ = 226.074222).

On heating the base under reflux with concentrated aqueous HCl, the monohydrochloride of the base was regenerated. It had m.p. 325° (d). $\nu_{max.}$ (nujol) 1758 (C=O), 1718, 1698 (C=O), 1398, 1250, 1085, 889, 770, 700 (aromatic) cm^{-1}. ^1H NMR (TFA) δ, 8.85-7.89 (m, 5H); 2.52 (s, 3H). (Found C, 59.2; H, 4.1; Cl, 13.2; N, 10.5. $C_{13}H_{11}ClN_2O_2$ requires C, 59.4; H, 4.2; Cl, 13.5; N, 10.7%).

BIBLIOGRAPHY

1. R. Gompper Angew.Chem. (Intern.Ed.Engl.) 3 560 (1964).

2. B. Cardillo, G. Casnati, A. Pochini and A. Ricca Tet. 23 3771 (1967).

3. H. Gilman and J.E. Kirby J.Amer.Chem.Soc. 54 345 (1932).

4. P.R. Austin and J.R. Johnson J.Amer.Chem.Soc. 54 647 (1932).

5. T. Reichstein and H. Zschokke Helv.Chim.Acta. 15 249 (1932).

6. J. Lecocq and N.P. Buu-Hoi Compt.Rend. 222 1441 (1946).

7. E. Campaigne and W.M. Le Suer J.Amer.Chem.Soc. 70 1555 (1948).

8. R. Gaertner J.Amer.Chem.Soc. 73 3934 (1951).

9. R. Gaertner J.Amer.Chem.Soc. 74 766 (1952).

10. R. Gaertner J Amer.Chem.Soc. 74 2185 (1952).

11. S. Huenig Angew.Chem. (Intern.Ed.Engl.) 3 548 (1964).

12. R.H. Dewolfe and W.G. Young Chem.Rev. 56 753 (1956).

13. W.G. Young J.Chem.Ed. 39 455 (1962).

14. de la Mare in deMayo Molecular Rearrangements Vol.I p.27. Interscience Inc. New York (1963).

15. S. Patai The Chemistry of Alkenes. Interscience Inc. New York. Mackenzie pp. 436-453 and R.H. de Wolfe and W.G. Young pp. 681-738.

16. L.J. Andrews and W.G. Young J.Amer.Chem.Soc. 66 421 (1944).

17. G. Beutter and J. Meisenheimer Ann. 508 58 (1933).

18. J. Roberts, W.G. Young, and S. Winstein J.Amer.Chem. Soc. 64 2157 (1942).

19. H.L. Goering, S. Winstein, and W.G. Young J.Amer. Chem.Soc. 73 1958 (1951).

20. A. Fry Pure Appl.Chem. 8 409 (1964).

21. G. Stork and W.N. White J.Amer.Chem.Soc. 78 4609 (1956).

22. Y.R. Bhatia, P.D. Landor, and S.R. Landor J.Chem.Soc. 1959 24. R.J.D. Evans, S.R. Landor, and R.T. Smith J.Chem.Soc. 1963 1506.

23. M. Hanack and K. Goerler Chem.Ber. 96 2121 (1963).

24. H. Balli Angew.Chem. (Intern.Ed.Engl.) 9 80 (1970).

25. T. Reichstein Chem.Ber. 63 749 (1930).

26. E.W. Scott and J.R. Johnson J.Amer.Chem.Soc. 54 2549 (1932).

27. M.M. Runde, E.W. Scott, and J.R. Johnson J.Amer. Chem.Soc. 52 1284 (1930).

28. O. Moldenhauer, G. Trautmann, and R. Pflueger Ann. 583 61 (1953).

29. Y. Oshiro, H. Tanisake, and S. Komori J.Soc.Chem. Synth.Japan 24 950 (1966).

30. K.Yu Novitskii, Kh Gresl, and Yu K. Yur'ev Zh.Organ. Chim. 1 539 (1965). Chem.Abs. 63 1761f

31. K. Yu. Novitskii, Kh. Gresl, and Yu. K. Yur'ev Khim.Geterotsikl Soedin 1966 829. Chem. Abs. 67/32529d

32. R.G. Fayter and L.A. Spurlock J. Org.Chem. 34 4035 (1969).

33. C.J. Benning Ph.D. Thesis, Ohio State University 1953. Diss.Abstr. 18 1612 (1958)

34. J. Egyed and A. Gerecs Acta.Chim.Acad.Sci.Hung. 29 91 (1961).

35. K. Yu. Novitskii, Yu. K. Yur'ev, and V.N. Zhingareva Zh.Obshch Khim. 22 3303 (1962) Chem.Abs. 58 11301g .

36. E.A. Hill, M.B. Hughes, and M. Stasiewicz, Abstract of Papers, 155th National Meeting of the A.C.S., San Francisco 1968 p.121.

37. S. Divald, M.C. Chun, and M.M. Joullie Tet.Letts. 10 777 (1970).

38. K. Yu. Novitskii, Kh. Gresl, and Yu. K. Yur'ev Khim. Geterotsikl Soedin 1966 832. Chem.Abs. 67 32530x

39. E. Sherman and E.D. Amstutz J.Amer.Chem.Soc. 72 2195 (1950).

40. B.B. Greene and K.G. Lewis Austr.J.Chem. 21 1845 (1968)

A.A. Bothner-By and D. Jung J.Amer.Chem.Soc. 90 2432 (1968)

A.A. Bothner-By and D.F. Kossner J.Amer.Chem.Soc. 90 2351 (1968)

J.B. Butler and R.D. Laundon J.Chem.Soc.(C) 1969 173

R.T. Hobgood and J.H. Goldstein J.Mol.Spectr. 12 76 (1969).

41. R.G. Jones J.Amer.Chem.Soc. 71 383 (1949).

42. H.M. Lee and R.G. Jones J.Pharmacol.Exp.Therap. 95 71 (1949). P.C. Jocelyn (Arch.Int.Pharmacodyn. 113 251 (1958). "Handbook of Experimental Pharmacology" Vol. XVIII/I. "Histamine and Antihistamines",

Part I, ed. M. Rocha, New York, 1966 (a) R.G. Jones p.34 (b) M. Rocha and Silva p.234.

43. C.D. Gutsche and H. Voges J.Org.Chem. 32 2685 (1967).

44. G.J. Durant, M.E. Foottit, C.R. Ganellin, J.M. Loynes, E.S. Pepper, and A.M. Roe Chem.Commun. 1968 108.

45. Personal Communication M.E. Foottit and A.M. Roe, Smith, Kline, and French Laboratories, Welwyn Garden City, Herts, England.

46. E.C. Kornfeld, L. Wolf, T.M. Lin, and I.H. Slater J.Med.Chem. 11 1028 (1968).

47. H.R. Snyder and E.L. Eliel J.Amer.Chem.Soc. 70 1703, 1857 (1948).

48. E. Campaigne and E.S. Neiss J. Het.Chem. 2 231 (1965).

49. E. Campaigne, E.S. Neiss and T. Bosin J.Med.Chem. 10 270 (1967).

50. F.G. Bordwell, F. Ross, and J. Weinstock J.Amer.Chem. Soc. 82 2878 (1960).

51. F.G. Bordwell, P.E. Sokol, and J.D. Spainhour J.Amer. Chem.Soc. 82 288 (1960).

52. F.G. Bordwell, R.W. Hemwall, and D.A. Shexnayder J.Amer.Chem.Soc. 89 7144 (1967)
J.Org.Chem. 33 3226, 3233 (1968)
F.G. Bordwell and D.A. Shexnayder J.Org.Chem. 33 3236, 3240 (1968).

53. J. Lecocq Ann.Chim. 3 62 (1948).

54. N.P. Buu-Hoi and J. Lecocq Compt.Rend. 224 658 (1947).

55. E.J.J. Grabowski, E.W. Tristram, R. Tull, and P.I. Pollak Tet.Lett. 56 5931 (1968).

56. J.D. Loudon and D.M. Smith Proc.Chem.Soc. 1963 182.

57. J.D. Loudon and D.M. Smith J.Chem.Soc.(C) 1964 2806.

58. A. Kliegl and W. Hoelle Chem.Ber. 59 901 (1926).

59. F. Asinger and G. Lock Monatsch. 62 323 (1933).

60. C. Paal Chem.Ber. 18, 2240 (1885).

61. M.W. Farrar and R. Levine J.Amer.Chem.Soc. 72 4433 (1950).

62. W.H. Hensley and J.A. Lambrech Chem.Abs. 63 p.7018b.

63. K.B. Wiberg and H.F. McShane Org.Synth.Col.Vol.III 197.

64. Y. Inaba, G. Kimmra and M. Kineone Chem.Abs. 59 p.3896b (1963).

65. E. Campaigne and B.F. Tullar Org.Synth.Coll.Vol.IV 921.

66. W.S. Emerson and T.M. Patrick J.Org.Chem. 14 790 (1949).

67. C.W. Rees and R.C. Storr J.Chem.Soc.(C) 1969 1474.

68. I.J. Rinkes Rec.Trav.Chim. 52 546 (1933).

69. H.D. Hartough and A.I. Kosak J.Amer.Chem.Soc. 69 3093 (1947).

70. M.S. Newman and H.L. Holmes Org.Synth.Coll.Vol.II 428 (1943).

71. A. Vogel "Practical Organic Chemistry" Third Edition p.189.

72. J.H. Bayer and D. Straw J.Amer.Chem.Soc. 74 4506-8 (1952).

73. G.A. Hill and E.L. Kropa J.Amer.Chem.Soc. 55 2509 (1933).

74. H. Adkins, N. Isbell and B. Wajak Org.Synth.Coll. Vol.II 262.

75. N. Messina and E.V. Brown J.Amer.Chem.Soc. 74 920 (1952).

76. F.F. Blicke Chem.Abs. 42 613g. U.S. Patent 2,425,721.

77. P. Cagniant Bull.Soc.Chim.Fr. 1949 847.

78. H. Rupe and F. Wiederkehr Helv.Chim.Acta 7 654 (1924).

79. E.E. Campaigne and W.C. McCarthy J.Amer.Chem.Soc. 76 4466 (1954).

80. T.L. Cairns and B.C. McKusick J.Org.Chem. 15 790 (1950).

81. F. Kipris and J. Ornfelt J.Amer.Chem.Soc. 71 2271 (1949).

82. N.R. Kirner J.Amer.Chem.Soc. 50 1955 (1928).

83. H. Kofod Org.Synth.Coll.Vol.IV 491

84. T.B. Johnson and J.M. Sprague J.Amer.Chem.Soc. 69 2439 (1937).

85. H. Staudiger & T. Reichstein Chem.Abs. 22 4537 Can. Pat. 283,765.

86. E.L. Eliel and P.E. Peckham J. Amer.Chem.Soc. 72 1209 (1950).

87. F.F. Blicke and D.G. Sheets J.Amer.Chem.Soc. 70 3768 (1948).

88. F.F. Blicke and D.G. Sheets J.Amer.Chem.Soc. 71 2856 (1949).

89. E. Campaigne and E.S. Neiss J.Het.Chem. 3 46 (1966).

90. D.A. Shirley and M.D. Cameron J.Amer.Chem.Soc. 74 664 (1952).

91. A. Schonberg, E. Peterson, and H. Kaltschmitt Chem.Ber. 66 233 (1933).

92. R. Weissberger and O. Kruber Chem.Ber. 53 1558 (1920).

93. B. Loer and M.M. Goodman Chem and Ind. 1967 2026.

94. A.L. Mndzhoian "Syntheses of Heterocyclic Compounds" Chapman Hall Ltd. London 1959 Vol. 4
a) p.108 b) p.83

95. A.L. Mndzhoian and A.A. Arayon Izv.Aked.Nauk.Arm.SSR. Khim.Nauk. 14 591 [Chem.Abs. 58 5607a]

96. R. Gaertner J.Amer.Chem.Soc. 73 4400 (1951).

97. P.A. Levene Org.Synth. Coll.Vol.II p.88.

98. R.P. Kurkjy and E.V. Brown J.Amer.Chem.Soc. 74 5778 (1952).

99. A. Arapides Ann. 249 7 (1888).
A. Hantzsch Ann. 250 257 (1889).

100. B.M. Mikhailou and V.P. Bronovitskaya Zhur. Obshchei. Khim. 27 26 (1957) Chem.Abs. 16436h.

101. L. Aronstein Suppl.Bd.III 185 (1864).

102. C. Moureu Ann.Chim. 15 158 (1921).

103. R. Willstatter and T. Wirth Chem.Ber. 42 1908 (1909).

104. W.R. Schmitz U.S. Patent 2,682,558 (1954) [Chem. Abs. 49 90293]

105. C. Hennart Bull.Soc.Chim.Fr. 1966 2093.

106. K. Ganapathi and A. Venkataramon. Proc.Ind.Acad.Sci. 22A 370 (1945).

107. C.R. Harrington and R.C.G. Moggrige J.Chem.Soc.(C) 1939 443.

108. R.P. Kurkjy and E.V. Brown J.Amer.Chem.Soc. 74 6260 (1952).

109. G. Borgen and S. Gronowitz Acta.Chem.Scand. 20 2593 (1966).

110. A. Vogel "Practical Organic Chemistry" (3rd Edition) p.342.

111. H.C. Beyerman, P.M. Berben and J.S. Bantekoe Rec. Trav.Chim. 73 325 (1954).

112. M. Azzaro, R. Hardley, E.F.G. Herington and J. Metzger Bull.Soc.Chim.France 1963 1904.

113. A.Y. Berlin and V.P. Bronovitskaya Zhur.Obshchei. Khim 31 1356 (1961) [Chem.Abs. 55 24719]

114. D. Lednicer and C.R. Hauser Org.Synth 40 p.31.

115. D. Lednicer and C.R. Hauser Org.Synth. 40 p.45.

116. D. Lednicer and T.A. Mashburn Org.Synth 40 p.52.

117. R.V. Lindsey, G.W. Parshall, M.L. Peterson and G.M. Whitman J.Amer.Chem.Soc. 79 3416 (1957).

118. A.N. Nesmeyanov, E.G. Perevalova, L.S. Shilovtseva and Y.A. Ustynyuk. Izvest.Akad.Nauk.SSSR Otdel.Khim. Nauk. 1960 554 [Chem.Abs. 54 22540i]

119. H. Wieland and B. Rosenfeld Ann. 484 236 (1930)

120. A.A. Morton and J.R. Stevens J.Amer.Chem.Soc. 53 4030 (1931).

121. R.H. Wiley, D.C. England and L.C. Behr Organic Reactions VI p.367.

123. K. Schlogl and A. Mohar Naturwissenshaften 48 376 (1961).

124. G.P. Muller and D. Pickens J.Amer.Chem.Soc. 72 3636 (1950).

125. H. Taub and T. Hino J.Org.Chem. 25 263 (1960).

126. T.T. Tidwell and T.G. Traylor J.Amer.Chem.Soc. 88 3442 (1966).

127. L.J. Bellamy "Infrared Spectra of Complete Molecules" p.223.

128. G.W. Wheland "Resonance in Organic Chemistry" John Wiley and Sons, Inc., New York (1955).

129. M.M. Palmer "The Structure and Reactions of Heterocyclic compounds". E. Arnold Ltd., London (1967).

130. L. Pauling, L.O. Brockway and J.Y. Beach J.Amer.Chem. Soc. 57 2705 (1935).

131. L. Pauling and L.O. Brockway J.Amer.Chem.Soc. 59 1223 (1937).

132. W.G. Salmond Quarterly Reviews 22 253 (1968).

133. J.O. Edwards and R.G. Pearson J.Amer.Chem.Soc. 84 16 (1962).

134. Th.C. Bruice, J.J. Bruno and Wei-Shin Chou J.Amer. Chem.Soc. 85 1659 (1963).

135. A. Streitwieser Chem.Reviews 56 581 (1956).

136. R.F. Hudson and G. Klopman J.Chem.Soc.(B) 1964 5.

137. A.J. Parker The Effects of Solvation on the Properties of Anions in Dipolar Aprotic Solvents. Quarterly Reviews 16 163 (1962).

138. R. Alexander, E.C.F. Ko, A.J. Parker and T.J. Braxton J.Amer.Chem.Soc. 90 5049 (1968).

139. A.J. Parker Chem.Rev. 69 1 (1969).

140. R.K. Durkhard, D.E. Sellers, F. DeCou and J.L. Lambert J.Org.Chem. 24 767 (1959).

141. F.M. Page J.Chem.Soc.(B) 1953 1719.

142. K. Schlogl Monatsch Chem. 88 601 (1957).

143. K. Schlogl and A. Mohar Monatsch Chem. 92 219 (1961).

144. T.G. Traylor and J.C. Ware J.Amer.Chem.Soc. 89 2304 (1967).

145. J.C. Ware and T.G. Traylor Tet.Lett. 1965 1295.

146. M. Cais Organometal.Chem.Rev. 1 435 (1966).

147. E. Hoggarth and W.A. Sexton J.Chem.Soc. 1947 815.

148. D.C. Ayres "Carbanions in Synthesis" Oldbourne Press, London p.23 (1966).

149. E. Campaigne and E.S. Neiss J.Het.Chem. 2 100 (1965).

150. M. Szwarc Discuss.Faraday Soc. 2 46 (1947).

151. L.A. Errede and M. Szwarc Quarterly Rev. 12 301 (1958).

152. L.A. Errede and B.F. Landrum J.Amer.Chem.Soc. 79 4952 (1957).

153. H.E. Winberg, F.S. Fawcett, W.E. Mochel and C.W. Theobald J.Amer.Chem.Soc. 82 1428 (1960).

154. E. Muller and E. Tietz Chem.Ber. 74 807 (1941).

155. Unpublished work; Smith Kline, and French Laboratories.

156. G.A. Alles, B.B. Wisegarver, N.B. Chapman and A.J. Thompsett, J.Org.Chem. 22 221 (1957).

157. D.A. Usher J.Amer.Chem.Soc. 90 363 (1968).

158. R.L. Augustine Catalytic Hydrogenations

159. R. Baltzly and A.P. Phillips J.Amer.Chem.Soc. 68 261 (1946).

160. H. Bredereck, R. Gompper, H.G.V. Schuk and G.Theilig Newer Preparative Methods of Organic Chemistry Ed W. Foerst III p.241 (1964).

161. K. Balenovic and N. Bregant Tet 5 44 (1959).