ELECTROPHILIC SUBSTITUTION
IN
AROMATIC SYSTEMS

A thesis submitted
by
BRIAN JONES

to the University of Wales
in candidature for the degree of
Philosophiae Doctor

School of Physical and Molecular Science,
University College of North Wales,
Bangor.

BEST COPY AVAILABLE.
For my parents.
The nitrodecarboxylation of 2-acetamidothiophene-3-carboxylic acid was investigated in an attempt to improve the yield of 2-acetamido-3,5-dinitrothiophene obtained as product. The latter compound is valuable as an intermediate in the dyestuffs industry. It was found that both 2-acetamido-5-nitrothiophene-3-carboxylic acid and 2-acetamido-3,5-dinitrothiophene are susceptible to hydrolysis to unstable amines in the nitrating medium, a mixture of sulphuric and nitric acid.

The rates of nitrodecarboxylation of a variety of substituted thiophenes were determined as a function of sulphuric acid concentration. The characteristics of the reaction were found to be similar to those of conventional nitrodeprotonation, although the latter reaction is considerably faster, (the ipso factor, $i_f^{CO_2H}$ for nitrodecarboxylation was found to be $5.6 \times 10^{-4}$). Ring systems in which the carbon atom containing the carboxyl group is activated towards electrophilic attack are particularly susceptible to nitrodecarboxylation. A Hammett reaction constant, $p^+$, of $-4.8$ was obtained for the nitrodecarboxylation reaction, the reaction constant for the corresponding nitrodeprotonation reaction being $-3.4$. A concerted mechanism, similar to that for conventional nitration, is favoured for the nitrodecarboxylation reaction.

The rates of hydrolysis of a variety of amido-thiophenes were also determined as a function of sulphuric acid concentration. In concentrated acid most amides were hydrolysed by the unimolecular A1 mechanism whereas in more dilute acid the bimolecular A2 mechanism of hydrolysis predominated. The amino-thiophenes produced were particularly unstable in presence of nitric acid. This hydrolysis to an unstable amine partially accounts for the unsatisfactory yield of 2-acetamido-3,5-dinitrothiophene-3-carboxylic acid in sulphuric-nitric acid. Indeed, the stability of the corresponding
formamido derivatives to hydrolysis is reflected in the improved yield of 2-formamido-3,5-dinitrothiophene obtained by a similar nitration process (70.3% compared with 46.2% for the acetamido derivative).

Unsuccessful attempts were made to isolate oxidation products of unstable thiophene derivatives and the rates of oxidation were determined in sulphuric-nitric acid mixtures.
ACKNOWLEDGEMENTS

I wish to express my sincere thanks to Prof. C.J.M. Stirling and Dr. D.R. Marshall, of U.C.N.W., Bangor, and Dr. B.R. Fishwick of I.C.I., Manchester for their help, guidance and encouragement throughout the course of this work.

I should also like to thank the technical staff at U.C.N.W. and I.C.I. for their ready assistance and co-operation, especially Mr. E. Lewis for the provision of the micro-analysis service. I am also grateful to Mrs. Pat Pritchard and my wife for their assistance in producing the manuscript.

Finally I wish to express my gratitude to the Science Research Council and I.C.I. Organics Division for providing me with a research grant.
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PART 1

INTRODUCTION
CHAPTER 1

THE INDUSTRIAL PROCESS
THE INDUSTRIAL PROCESS \textsuperscript{1,2}

A recent I.C.I. invention relates to a process for manufacturing heterocyclic thiophene compounds. The process involves the synthesis of compounds of general formula:-

\begin{array}{c}
\begin{array}{c}
\text{R} \\
\text{S}
\end{array} \\
\begin{array}{c}
\text{NO}_2 \\
\text{NH}_2
\end{array}
\end{array}

(A)

where R is a hydrogen atom or alkyl group.

Compounds of this general formula are prepared by decarboxylating and dinitrating compounds of formula:-

\begin{array}{c}
\begin{array}{c}
\text{R} \\
\text{S}
\end{array} \\
\begin{array}{c}
\text{CO}_2\text{H} \\
\text{NHAcyl}
\end{array}
\end{array}

(B)

The acyl group is finally hydrolysed to give the dinitro amine. Typical acyl groups for use in this way are formyl, acetyl, propionyl, benzoyl, chloracetyl etc.

The conversion of (B) to (A) can be accomplished in a variety of ways:-

(1) Compounds of type (B) can be converted to type (A) by decarboxylation prior to dinitration. The decarboxylation can be effected by heating the compound to a temperature above its melting point or by heating in
a basic solvent, such as dimethylaniline or quinoline at ~ 200°C. The subsequent dinitration can be accomplished with nitric acid in sulphuric acid.

(2) One nitro group can be introduced into the 5-position of the thiophene ring followed by decarboxylation and introduction of the second nitro group into the 3-position. The 5-nitro derivative can be prepared by nitration in acetic anhydride, although a sulphuric acid medium is preferred. One mole of nitric acid per mole of substrate is used, the temperature being kept below 0°C. The resulting compound can then be decarboxylated by heat followed by nitration with a mixture of nitric acid and sulphuric acid.

(3) The dinitration can be carried out under such conditions that simultaneous decarboxylation takes place. This can be accomplished by stirring the compound in a mixture of nitric acid and sulphuric acid (containing at least 2 moles of nitric acid per mole of compound). The temperature is maintained below 0°C.

Hydrolysis of the Amide Group

The removal of the acyl group is accomplished by treatment of the dinitro amide with an aqueous or alcoholic solution of a mineral acid, such as sulphuric acid, at ~ 100°C. It is not essential to isolate the dinitro compound prior to hydrolysis. This reaction can be effected by diluting the nitration mixture with the necessary amount of water and heating to remove the acyl group. The resulting amine can then be isolated by further dilution with water and filtration of the solid which is thus precipitated. When the hydrolysis is carried out in this
way a substance such as sulphamic acid is added to destroy any nitrous acid or other oxidising agents present.

A specific example of a synthesis of the general type discussed above is the industrial preparation of 2-amino-3,5-dinitrothiophene. This is the process which is particularly relevant to this investigation.

2-Amino-3,5-Dinitrothiophene

This heterocyclic compound is valuable as a diazotisable amine in the manufacture of disperse monoazo dyestuffs. The method for preparation of this thiophene derivative is shown in scheme 1.

Scheme 1: Industrial preparation of 2-amino-3,5-dinitrothiophene.
2-Acetamidothiophene-3-carboxylic acid

Mercaptoacetaldehyde, one of the starting materials, is prepared as a dimer by reaction of chloroacetaldehyde with sodium hydrosulphide, NaSH, in aqueous medium:

\[
2\text{CH}_2\text{CHO} + 2\text{NaSH} \rightarrow 2(\text{HSC} \text{H}_2\text{CHO})
\]

If desired, the subsequent reaction with cyanoacetic acid can be carried out without isolating the dimer. This reaction is carried out in an aqueous solution of sodium hydroxide, and the product acylated in situ with, for example, acetic anhydride. The mixture is acidified and the 2-acetamidothiophene-3-carboxylic acid is isolated (scheme 1).

Nitration of 2-Acetamidothiophene-3-carboxylic acid

The simultaneous dinitration and decarboxylation of 2-acetamidothiophene-3-carboxylic acid is accomplished by nitrating the compound in sulphuric acid (98%) with a mixture of 100% nitric acid and 100% sulphuric acid in the proportions 33 : 67, < 0°.

The nitration is found to occur only in moderate yield to give the bis-nitroderivative which results from nitration at C₅ being accompanied
by nitro-decarboxylation at C₃. The occurrence of nitrodecarboxylation is a helpful feature of the industrial process, since it obviates the necessity of a separate decarboxylation stage. However, loss of groups from aromatic substrates during electrophilic substitution is a well known type of process although mechanistic and kinetic work on this type of decarbonylation have received only scattered attention, mainly in homocyclic aromatic systems. The reaction appears to be prevalent mainly in systems activated towards electrophilic attack.

2-Acetamidothiophene-3-carboxylic acid can be mononitrated in the 5-position under the appropriate conditions in 88% yield. The second nitrodecarboxylation step proceeds in only 53% yield. Thus, the overall yield for the simultaneous dinitration and decarboxylation of 2-acetamidothiophene-3-carboxylic acid, under industrial conditions, is 47%.

One part of this investigation has been concerned with a study of nitrodecarboxylation in heterocyclic aromatic acids with particular reference to substituted thiophenes activated towards electrophilic attack. The sequence of reactions involved in nitrodecarboxylation has been examined and attempts made to obtain rate constants for the competing processes involved in the industrial reaction. It was hoped, in this way, to determine the cause of yield loss and, in the case of commercial interest to improve the overall yield. No systematic study of nitrodecarboxylation in heterocyclic systems has been reported in the literature.

The final step in the industrial synthesis of 2-amino-3,5-dinitrothiophene involves the hydrolysis of the acetamido derivative. This is accomplished by refluxing the amide with dilute sulphuric acid
for several hours. In fact, the significance of such hydrolysis reactions in all concentrations of sulphuric acid was later to become apparent in a detailed study of the industrial process.
CHAPTER 2

THIOPHENE CHEMISTRY
THIOPHENE CHEMISTRY

Much of the early work on thiophene chemistry was carried out by Wilhelm Steinkopf. In particular, Steinkopf carried out a great deal of work on the preparation of the different isomers of simple thiophenes. He contributed prolifically to the mercuration of thiophene, the halogenation and synthesis of many new thiophene derivatives.

A commercial process for the synthesis of thiophene was developed in the early 1940's. This arose from the discovery of the synthesis of thiophene from butane and sulphur. Reduced and unreduced thiophenes are present in shale oil and reduced thiophenes in petroleum. Commercial outlets for thiophene are relatively few, but it is used in the synthesis of some drugs and as a constituent of some copolymers. The important nutritional factor, biotin, is a derivative of tetrahydrothiophene.

Structure

![Structure Diagram]

It has been suggested that thiophene is not well represented by the classical structure shown above. A state of resonance exists and the major contributing resonance structures are as shown below:
If account is taken of the s and d contribution to the p bonding, then additional structures with a negative charge on sulphur may contribute to the resonance form of thiophene. The fact that thiophene can be alkylated on the sulphur atom supports the idea that the resonance structures with a negative charge on sulphur have significance:

![Resonance Structures of Thiophene]

Thiophene is best made on the small scale by heating sodium succinate with phosphorus 'trisulphide'. It is a colourless liquid b.p 84.12°C.

**Chemical Properties**

The thiophene ring shows typically aromatic behaviour and since the time of the classic investigations it has been well known that thiophene reacts with electrophilic reagents much more easily and rapidly than benzene. It can for instance be brominated, acetylated, formylated and mercurated under conditions under which benzene does not react.

The unreduced nucleus is stable to alkalis, moderately stable to acids and fairly resistant to oxidation whereby thiophene homologues give carboxylic acids in modest yield.

It is well known that substitution takes place with very few exceptions, predominantly in the 2- or α- position of thiophene. Substitution occurs much more easily in thiophene than in the benzene ring and the ratio of nitration rates has been reported as 850 : 1.
However, it is apparent that the selectivity of a reagent toward thiophene and benzene can differ appreciably, and this difference in selectivity is also strongly noticeable in the proportions of 2- and 3- isomers formed. Although in certain reactions no 3- isomer has been detected, small amounts have been found in other reactions\textsuperscript{14,15}.

The preferential \( \alpha \)-substitution of thiophene is probably not related to excess negative charge at the \( \alpha \)-carbon in the ground state but is best understood by considering the localization energies of the transition states for 2- and 3- substitution\textsuperscript{16,17}.

For 2- substitution:

\[
\begin{align*}
\text{S} & \quad \text{H} \\
+ & \quad + \quad + \\
\text{X} & \quad \text{H} \\
\text{S} & \quad \text{X}
\end{align*}
\]

For 3- substitution:

\[
\begin{align*}
\text{S} & \quad \text{H} \\
\text{X} & \quad \text{H} \\
\text{S} & \quad \text{E}
\end{align*}
\]

The resonance stabilisation or delocalization of positive charge in the intermediate cation is obviously greater in the cation derived by \( \alpha \)-addition.
Directive Effects of Substituents

The point of attack is determined primarily by the fact that α-positions are more easily substituted than β, and also by the usual ortho, para or meta-directive effect of an existing substituent. A substituent may reinforce the 2,5-activation or reduce it by selective deactivation. Identification of the product obtained in these substitution reactions has been achieved by proton magnetic resonance spectroscopy and isomer ratios determined by spectroscopy and gas chromatography.

SOME THIOPHENE DERIVATIVES OF INDUSTRIAL SIGNIFICANCE

(A) Nitro-Thiophenes

The mono-nitration of thiophene is best performed in acetic anhydride\(^1\), giving mainly 2-nitrothiophene. Thiophene reacts violently, sometimes explosively after an induction period, with usual nitrating mixtures. This is considered to be due to an autocatalytic nitrosation. The product of nitration is always a mixture of 2- and 3-nitro derivatives, the 2-isomer predominating. 2-Nitrothiophene is much less reactive and can be smoothly nitrated with fuming nitric acid, to yield a mixture of 2,4- and 2,5-disubstituted products. 2,4-Dinitrothiophene is the main product (80%)\(^1\).

3-Nitrothiophene is prepared by hydrolysing the product of nitration of thiophene-2-sulphonyl chloride\(^1\), or of 2-cyanothiophene\(^2\). Further nitration of 3-nitrothiophene gives only 2,4-dinitrothiophene. Nitration of substituted thiophenes occasionally leads to displacement of halogen, carboxyl or acyl groups (see later).

(B) Amino-Thiophenes

Amino-thiophenes can be prepared by reducing nitrothiophenes with tin
and hydrochloric acid. The free bases are oils which resinify rapidly in the air. They are best stored as the stannic-chloride double salts and also give stable acetyl derivatives. From a study of U.V. and I.R. spectra of nitro-substituted aminothiophenes, Hurd and Kreuz\textsuperscript{21} concluded that these amines exist as mixtures of amino and imino forms. Very little is known of the chemistry of these bases, the only simple reaction being the diazotization of 2-aminothiophene and the azo coupling of the resulting diazonium ion \textsuperscript{22,23}. However, the reactivity of the 5- position of 2-aminothiophene in diazo coupling which is present also in the acylated derivatives\textsuperscript{24,25}, complicates the formation of a diazonium salt from 2-aminothiophene. The thiophene ring is so strongly activated by an amino group that even 3-acetamidothiophene couples with p-nitrobenzene diazonium ion\textsuperscript{25}:

\[
\begin{align*}
\text{HAc} & \rightarrow \text{N=N-C}_6\text{H}_4\text{NO}_2 \quad 80\% \\
\text{NHAc} & \quad \text{p-NO}_2\text{C}_6\text{H}_4\text{N}_2 \\
\end{align*}
\]

2-Acetamidothiophene gives mainly 5- substituted derivatives\textsuperscript{24,26}, while 3-acetamidothiophene undergoes substitution first in the 2-position and then in the 5- position. The substitution reactions of 3-acetamidothiophene have been extensively studied\textsuperscript{25}.

(H) Thiophenecarboxylic acids

The most general route to thiophene-carboxylic acids is the carbonation of thienyl Grignard compounds. Thiophene-2-carboxylic acid is prepared by treatment of 2-thienyl magnesium bromide in tetrahydrofuran with carbon dioxide\textsuperscript{27}. Another general method is by oxidation of
2-acetylthiophene\textsuperscript{28}.

A very general synthesis of thiophenecarboxylic acids (or esters) is that of Hinsberg:\textsuperscript{29}

\[ X \text{O} \quad Y \] + \[ \text{EtO}_2\text{C} \quad \text{S} \quad \text{CO}_2\text{Et} \] \[ \text{R.T.} \] \[ \text{tBuO}^- \] \[ X \text{CO}_2\text{Et} \quad Y \text{CO}_2\text{Et} \]

The Hinsberg Synthesis involves two consecutive aldol condensations between a 1,2 dicarbonyl compound and diethyl thiodiacetate. \( X \) and \( Y \) can be hydrogen, alkyl, aryl, hydroxyl, or carboxyl. Oxalic acid will undergo this reaction. Subsequent decarboxylation provides a route to 3,4 disubstituted thiophenes.

Thiophene-2-carboxylic acid resembles benzoic acid in most of its properties, although it is a stronger acid (pKa 3.53). It is, however, nitrated much more readily, the product consisting of a mixture of 4- and 5- nitro derivatives\textsuperscript{30}. 2-Nitrothiophene is also a minor product\textsuperscript{31}. The 5-isomer is obtained upon bromination and chlorination of thiophene-2-carboxylic acid\textsuperscript{32}. In general, the directing effect of the carboxyl group does not overcome that of the ring.

Thiophene carboxylic acids can be decarboxylated by boiling with copper in quinoline, by copper bronze, or by a mercuriacetate group and subsequent removal of the latter. This reluctance to decarboxylate readily is surprising in view of the ease of displacement of a carboxyl group from the \( \alpha \)-position by, for example, a nitro group\textsuperscript{33}.

Thiophene-3-carboxylic acid (pKa 4.10) has been obtained from the 3-aldehyde\textsuperscript{34} and in good yield by the oxidation of 3-methylthiophene with aqueous sodium dichromate at 225 - 250°\textsuperscript{35}. Campagne\textsuperscript{36} has made an
extensive study of the substitution reactions of thiophene-3-carboxylic acid. Monosubstitution occurs exclusively in the 5-position in the case of chlorination, bromination and nitration. Upon further treatment, a second halogen could be introduced in the 2-position. Further nitration however could not be achieved:

There was no evidence for displacement of carboxyl by nitro and the 5-nitrothiophene-3-carboxylic acid was recoverable in good yield.

**Nucleophilic Substitution in Thiophene Derivatives**

The halogens of halothiophenes are more labile than those of the corresponding benzene derivatives. Halogen substituents in the 2-position are more reactive than those in the 3-position, and undergo nucleophilic substitutions more rapidly than benzene derivatives. Hurd and Kreuz found that in qualitative experiments 2-chloro-3,5-dinitrothiophene was more reactive toward piperidine and methanolic potassium hydroxide than 2,4-dinitrochlorobenzene. A quantitative study of the reaction of six isomeric bromonitrothiophenes with piperidine showed that the thiophenes react about one thousand times faster than the corresponding benzenes.

Nucleophilic substitution has been used in the preparation of many thiophenes. Nitrothienols and derivatives of them have been obtained from halogenated nitrothiophenes. Allyl ethers have been prepared by the reaction of 5-chloro-4 nitro-2-acetylthiophene, 3-nitro-2-chlorothiophene and 2-nitro-3-bromothiophene with sodium allyloxide.
Halothiophenes which are not activated through the presence of an electron-withdrawing substituent undergo substitution under more forcing conditions with copper salts in pyridine or quinoline. Both 3-cyanothiophene and 5-methyl-2-cyanothiophene have been obtained from the corresponding bromo compounds

**Substitution with Elimination of Substituents**

In the reactions of 2,5-disubstituted thiophenes elimination of an α-substituent occurs to a much greater extent than in the benzene series. The Friedel-Crafts acetylation of 2-ethyl-5-bromothiophene yields 2-ethyl-5-acetylthiophene. Several other examples of displacement of substituents appear in the literature. Replacement of halogen, carboxyl, alkyl, etc. are all known reactions. The presence of substituents which lower the electron density at the reaction centre prevent substitution occurring. Elimination of β-substituents is less common. Very little is known about the mechanism of reactions of this sort and the whole concept is discussed in greater detail in chapter 4.

**Summary**

In general, thiophene resembles benzene, rather than furan or pyrroles, in most of its reactions. It is, however, more reactive and less stable than benzene. Thiophene possesses very few properties which could be attributed to an enol ether or a 1,3-diene type of structure. Thiophene reacts with electrophilic reagents and substitution at the reactive 2- and 5-positions of the molecule usually appears to be direct, i.e. conventional electrophilic aromatic substitution. No intermediate 2,5-addition compounds have been isolated (c.f. furan). Various other non-substitution reactions are discussed in chapter 8, (e.g. addition reactions, oxidation etc.).
A.R. Butler\textsuperscript{43-47} has recently studied electrophilic substitution of the thiophene ring, and concluded that in most cases the mechanism is the same as that for substitution of the benzene ring. A study of the halogenation of substituted thiophenes\textsuperscript{45} showed that the 'characteristics of these reactions are similar to those for the corresponding benzene compounds and Hammett $\sigma^+$ constants are equally successful in correlating data for electrophilic substitutions in thiophenes'. Butler\textsuperscript{43} studied the dissociation constants for a number of substituted thiophene-5-carboxylic acids and used these values to evaluate $\sigma$-constants for the thiophene molecule. The results indicate that the sulphur atom has very little effect upon the transmission of substituent effects across the ring. In general electrophilic substitutions at the thiophene ring exhibit a selectivity which is always somewhat lower than that of corresponding reactions of the benzene ring\textsuperscript{48}. The values of $\rho$-constants for bromination, chlorination\textsuperscript{45}, protodetritation\textsuperscript{49} and acetylation\textsuperscript{50} of 2-substituted thiophenes are somewhat smaller than the $\rho$-values for the corresponding substitutions of benzene derivatives. These differences in $\rho$-values have been attributed to a smaller positive charge on the thiophene ring in the transition state, i.e. the occurrence of 'earlier' transition states. The limited study of substituent effects in the thiophene ring suggests a good correlation with the Hammett equation, as based on the dissociation of benzoic acid in water at 25$^\circ$. Molecular Orbital calculations and dipole moment measurements suggest that the ortho, meta and para positions of benzene correspond to the 3, 4 and 5- positions in 2-substituted thiophenes\textsuperscript{51}.

Finally, there is a much larger tendency for existing substituents to be displaced by incoming groups than in the benzene series. The reactivity of the $\alpha$- position in thiophenes is sufficiently great that
a highly reactive electrophile will displace a substituent in certain instances. The present investigation provides the first quantitative investigation of substituent effects in 'ipso' substitutions of this sort.
CHAPTER 3

REACTIONS IN SULPHURIC ACID
Sulphuric Acid/Water Mixtures

One of the earliest methods for determination of the composition of sulphuric acid/water mixtures involved a study of the vapour pressure above such mixtures. This vapour pressure is due almost entirely to water owing to the low volatility of sulphuric acid. The more recent measurements of Shankman and Gordon\textsuperscript{52}, who studied the concentration range 16-70\% acid at 25\degree C, are at present the best available. At higher concentrations of sulphuric acid direct vapour pressure measurements became difficult and therefore Giauque et al.\textsuperscript{53} used a freezing point method to obtain activities of water at concentrations > 70\%. The activities of water at 25\degree C based on all such measurements are reported by Giauque\textsuperscript{54}.

The freezing points of sulphuric acid solutions are very sensitive to the amount of water present. This sensitivity provides a means of determining sulphuric acid concentrations with a great deal of accuracy. The variation of freezing point with sulphuric acid concentration is shown in fig. 1 and, indeed, use was made of this variation in the present investigation.

It has been shown\textsuperscript{54} that the vapour pressure of sulphur trioxide becomes noticeable only at concentrations > 90\%. The existence of an equilibrium is well established in the 100\% acid:

\[ 2\text{H}_2\text{SO}_4 \rightleftharpoons \text{H}_2\text{SO}_4\cdot\text{H}_2\text{O} + \text{SO}_3 \]
Acidity Functions

The most important property of sulphuric acid/water mixtures, from the point of view of their application as reaction media, is their acidity. This acidity is measurable in terms of an acidity function. This concept was first introduced by Hammett\textsuperscript{55,56} and his acidity function was defined as a measure of the ability of the medium to protonate simple bases. Other acidity functions have since been defined which measure the ability of the acid media to effect ionizations of other kinds. The applications of acidity functions to kinetic problems often stem from the fact that substances undergoing acid-catalysed reactions are protonated in acid media prior to reaction.

The $H_0$ Acidity Function

In concentrated acid media in which the concept of pH cannot be defined with any degree of accuracy, a new measure of acidity is necessary. The $H_0$ acidity relates to indicators ionizing according to the scheme:

\[
\begin{align*}
B + H^+ &\leftrightarrow BH^+
\end{align*}
\]

The reference point for the acidity scale is chosen so that in very dilute acid solution $H_0 = -\log (H^+)$. Hammett and Deyrup\textsuperscript{55} then studied the protonation equilibria of simple basic indicators which ionize as shown above. The $H_0$ function, therefore, refers to the protonation of simple base indicators.

The $H_A$ Acidity Function

A striking deviation from the Hammett acidity function was observed in the protonation of amides\textsuperscript{57}. A new acidity function for the
protonation of primary amides was determined and termed $H_A$. The values of this acidity function coincide with $H_0$ values up to about 15% sulphuric acid but diverge from them increasingly at higher concentrations. The function has been evaluated up to 81.8% sulphuric acid. This acidity function is also based on dilute aqueous solution as the standard state (see later).

The $H_R$ Acidity Function

Certain basic molecules ionize in acid solutions in a more complex manner which may be regarded as a protonation accompanied by dehydration:

$$
\text{ROH} + H^+ \rightleftharpoons R^+ + H_2O
$$

The bases which behave in this manner are often termed secondary bases, and the water molecule may be regarded as their conjugate acid. The $H_R$ acidity scale was determined from the ionization of tri-aryl carbinols according to the above scheme\textsuperscript{58-59}. The standard state for this acidity function is also an infinitely dilute solution in water and for dilute acid solutions $H_R$ becomes equal to $pH$. Also, as the activity of water approaches unity, $H_R$ becomes equal to $H_0$. The procedure for determining $H_R$ values is the same as for the $H_0$ function, namely the stepwise extension of the scale into more and more concentrated acid solutions by means of a series of overlapping indicators. The $H_R$ acidity function has been determined by Deno\textsuperscript{58} by means of a series of eighteen substituted arylmethanols.

A plot of some acidity functions against weight per cent of sulphuric acid in sulphuric acid/water mixtures is shown in fig. 2.
Fig. 2: Acidity functions for sulphuric acid/water mixtures
NITRATION IN SULPHURIC ACID

Nitration is an important electrophilic aromatic substitution reaction which has played a prominent part in the determination of substituent effects in aromatic systems. Nitration is an irreversible second-order reaction and nitric acid in sulphuric acid/water mixtures is a most effective nitrating medium. The nitrating agent has been well established as the nitronium ion, NO₂⁺. Nitric acid is converted into nitronium ions in concentrated sulphuric acid:

\[ \text{HNO}_3 + 2\text{H}_2\text{SO}_4 \rightleftharpoons \text{NO}_2^+ + \text{H}_3\text{O}^+ + 2\text{HSO}_4^- \]

The range of sulphuric acid/water concentrations in which the conversions of nitric acid to NO₂⁺ occurs has been established by U.V. spectrophotometry. The spectra indicate that HNO₃ still predominates in 85% sulphuric acid. At higher concentrations marked changes occur in the absorption spectrum, corresponding to an increase in the concentration of NO₂⁺. On the basis of Raman spectroscopic data it is estimated that nitric acid is almost completely converted into NO₂⁺ in about 90% sulphuric acid. Nitronium ions are present in spectroscopically detectable amounts only in solutions of nitric acid in > 85% sulphuric acid.

Kinetics and Mechanism of Nitration

A simple kinetic order for the nitration of aromatic compounds was first established by Martinsen for nitration in sulphuric acid. The rate of nitration of nitrobenzene was found to obey a second-order rate law, first order in the concentration of the aromatic and of nitric acid.

Variation of Nitration Rates with Sulphuric Acid Concentration

The variation with acidity of the second-order rate constants for
nitration of a number of substrates is shown in fig. 3. The rates of nitration of aromatic substrates in sulphuric acid/water mixtures are extremely sensitive to the concentration of sulphuric acid. They have been shown to parallel the ionization of triarylcarbinols in such acid mixtures, i.e. to follow the $H_R$ acidity function. This represents kinetic evidence for the nitronium ion as the nitrating agent since the rates of nitration for the second-order reaction are given by:

$$\text{Rate} = k_{2\text{obs}} [\text{ArH}] [\text{HNO}_3]$$

The rate can only depend on acidity if the concentration of one of the effective reactants depends on acidity. This is the case with the nitronium ion, owing to the existence of the equilibrium:

$$\text{HNO}_3 + 2\text{H}_2\text{SO}_4 \rightleftharpoons \text{NO}_2^+ + \text{H}_3\text{O}^+ + 2\text{HSO}_4^-$$

The ionizing characteristics of nitric acid are similar to those of the organic indicators used to define the $H_R$ scale of acidity:

$$\text{ROH} + \text{H}^+ \rightleftharpoons \text{R}^+ + \text{H}_2\text{O}$$

The increase in nitration rate with sulphuric acid concentration in the range 80-90% sulphuric acid is attributed to an increase in the nitronium ion concentration. The slopes of the plots of log. $k_2$ against $H_R$ are, however, not always close to unity. A better correlation, up to nearly 89% sulphuric acid is obtained with plots of log. $k_2$ against $- (H_R + \log a_{\text{H}_2\text{O}}')$. Moodie$^{63}$ found that such plots gave straight lines of near unit slope for a wide range of substrates. However, slopes of plots against $-H_R$ are usually greater. This is because of the difference in activity coefficient behaviour of species involved in the sulphuric - nitric acid equilibrium and in the triarylcarbinol indicators.
Fig. 3: Rate profiles for nitration in 80-100% sulphuric acid.
The correlations of rates with acidity functions provide a convenient basis for comparison of the reactivities of various substrates.

**Rate Maximum and Higher Acidities**

Since nitric acid is fully converted to nitronium ions in about 90% sulphuric acid the rates of nitration should become independent of acidity at approximately this acid concentration. However, rather than a levelling off in the rate, maxima in the rate-acidity profiles are observed for a wide variety of substrates at about 87-92% sulphuric acid (fig. 3)\(^64\). No entirely satisfactory explanation of these maxima has been produced. If the maxima were associated exclusively with the state of the nitrating agent in solution they would be expected to occur at precisely the same acid concentration for all substrates. The small variation in the position of the maxima for various substrates rules out this possibility. The possibility that progressive protonation of the substrate leads to deactivation and a consequent fall in rate cannot be ignored. However, rate maxima have also been observed in cases where protonation of the substrate is highly unlikely\(^65\). In an earlier hypothesis the decrease in rate above 90% acid was ascribed to the diminution of the concentration of bisulphate ions. It was assumed that these ions catalysed the reaction by assisting the proton transfer from the aromatic compound\(^66\). This hypothesis was disproved by Melander, who showed that in nitration the loss of the proton was kinetically insignificant. The variation in the rate has also been attributed to a change in activity coefficients which is known to occur in strongly acidic solutions. The activity coefficients in sulphuric acid of a series of aromatic compounds have been determined\(^67\). It has been shown that if the rates of nitration were corrected for the decrease of the activity coefficients, the corrected rate constant varied only slightly between 90% and 100% sulphuric acid\(^68\).
Mechanism of Nitration

As a second order reaction between the aromatic substrate and the nitronium ion nitration could occur either as a single-step displacement of a proton by the nitronium ion or via the formation of an intermediate in a two-step process as shown in scheme 1:-

\[
\begin{align*}
\text{ArH} + \text{NO}_2^+ & \xrightleftharpoons[k_1]{k_{-1}} \text{Ar}^+\text{H} \rightarrow \text{Ar}\text{NO}_2 \\
\text{Ar}^-\text{H} & \xrightarrow[k_2]{\text{NO}_2^-} \text{ArNO}_2^- + \text{H}^+
\end{align*}
\]

Scheme 1: Mechanism of Aromatic Nitration

The mechanism of scheme 1 is widely accepted. The absence of kinetic isotope effects\(^{69}\) suggests that the reaction occurs by a slow rate-determining step involving formation of a bond between the nitronium ion and the aromatic ring, followed by the fast loss of a proton.

Substituent Effects in Nitration

Nitration in sulphuric acid is particularly useful as a means of studying the reactivities of aromatic compounds towards electrophiles. Nitration in aqueous sulphuric acid can provide data for compounds covering a large span of reactivities since the second-order rate constant decreases by a factor of about \(10^4\) for each decrease of 10% in the acid concentration (below 90% sulphuric acid). Nitration in sulphuric acid is particularly suited to the study of strongly deactivated compounds. Direct comparisons with benzene can be made in solutions up to 82% sulphuric acid\(^{70}\). However, with strongly activating substituents, nitration in sulphuric acid is of limited value because
of the early onset of diffusion control. Coombes et al.\textsuperscript{70} investigated
the nitration of benzene and other reactive compounds in aqueous sulphuric
cacid. A limit was reached beyond which the introduction of further
activating substituents did not increase the rate of nitration. This
limit was identified as the rate of encounter of the nitronium ions
and the aromatic molecules. The rates of reaction of compounds such as
phenol and 1-naphthol are equal to the encounter rate. Indeed,
nitration in sulphuric acid cannot differentiate between compounds more
than about 38 times more reactive than benzene. At this point,
differentiation disappears because reactions occur at the encounter rate.
Indeed for very reactive substrates the rate-determining step can even
be the formation of nitronium ion in the sulphuric/nitric acid equilibrium.
For deactivated compounds this limitation does not exist, and nitration
in sulphuric acid is a useful method for comparing the reactivities
of such compounds. However, there is a practical difficulty in
following such reactions because secondary processes, e.g. oxidation,
might become important. The limited solubilities of aromatic compounds
in sulphuric acid has also been a problem, and much of the work on the
orientation of nitration relates to reaction under heterogeneous
conditions.

\textbf{Linear Free Energy Relationships}

The problem of correlating substituent effects in electrophilic
substitution by a Hammett-type equation has been examined by Brown et al.\textsuperscript{71}
The treatment of aromatic substitution in terms of a linear free energy
relationship with $\sigma^+$ constants was suggested\textsuperscript{72}, where

$$\sigma^+ = \log_{10} \frac{k_R}{k_H}$$

where $k_R$ is the rate of solvolysis of the phenyl-dimethylcarbinyl chlorides,
$\text{R}_6\text{C}_{\text{H}}\text{Me}_2\text{Cl}$. A new set of substituent parameters, $\sigma^+$, were thus derived.
These substituent constants can be used for inter-relating the rates of other similar reactions e.g. electrophilic substitutions:

\[ \log_{10} \frac{k^R}{k^H} = \rho^+ \sigma^+ \]

In this equation \( k^R \) is the rate coefficient for the reaction of a derivative of benzene, \( k^H \) is the corresponding rate for the unsubstituted compound. The \( \rho^+ \) term is a parameter independent of \( R \), but characteristic of the reaction and the conditions. It is a measure of the sensitivity of a given reaction series to substituent effects and is termed the reaction constant. The \( \sigma^+ \) term is a substituent parameter independent of the reaction, but characteristic of the substituent \( R \). The applicability of the two-parameter equation and the constants devised by Brown\(^1\) to electrophilic aromatic substitutions was tested by plotting values of the partial rate factors for a reaction against the appropriate substituent constants. The correlation of \( \sigma^+ \)-parameters and the aromatic reactivity was quite good\(^2\). The slopes of the linear correlations give the values of the reaction constants. However, there is still some dispute as to whether the effect of a substituent can be represented by a constant or whether its nature depends on a specific reaction.

As regards nitration quantitative linear correlations of aromatic reactivity using the \( \rho^+ \sigma^+ \) relation have been obtained. However, because of the practical difficulties involved with nitration in sulphuric acid, which were mentioned earlier, correlations for nitration have most often been obtained with other solvents\(^3\)-\(^7\). Stock and Brown\(^7\) studied the relationship between \( \sigma^+ \) constants and rates of nitration in various organic solvents and obtained a reaction constant of \( \rho = -6.0 \). A reaction constant of \( \rho = -6.53 \) has also been reported.
for nitration in nitromethane and acetic anhydride. Inclusion of further substituents gave $\rho = -6.22$.

Coombes et al. obtained partial rate factors for nitration of benzene derivatives in sulphuric acid. The data are plotted against $G^+$ constants in fig. 4. Coombes states that correlation is 'very poor' but as can be seen from fig. 4 a reasonable straight line plot is obtained. From this plot the reaction constant is calculated as $\rho = -11.6$. However, Coombes believes that Brown's treatment of substituent effects would receive its severest test with strongly activating substituents. The basic assumption in the $\rho + G^+$ relation is that the direct resonance effects of substituents can be represented by a constant. Substituents such as $p - \text{OMe}$ and $p - \text{NH}_2$, which by the mesomeric effect activate electrophilic substitution, would test the validity of this assumption. Nitration in sulphuric acid is useless for this purpose because of the early onset of diffusion control. Thus, the data of fig. 4 refer mainly to deactivating substituents. In conclusion, it might be said that quantitative linear correlations of aromatic reactivity towards nitration in sulphuric acid, using the $\rho + G^+$ relation, have been achieved to a limited degree. However, correlations are not entirely satisfactory because of the restrictions and problems involved with nitration in sulphuric acid. Only a limited number of substituents (mostly deactivating) have been studied.

**Heterocyclic Systems**

No quantitative interpretation of substituent effects upon rates of nitration of thiophene derivatives has been reported. However, a study of the halogenation of substituted thiophenes showed that the characteristics of these reactions are similar to those for the
Fig. 4: Correlation of partial rate factors for nitration of benzene derivatives with $\sigma^+$ constants

$\rho = -11.6$
corresponding benzene compounds. Butler found that $6^+$ constants are equally successful in correlating data for electrophilic substitution in thiophenes. The sulphur atom appears to have little effect upon the mechanism except to make the molecule more reactive. The nitration of thiophene itself in sulphuric acid has been studied and the mechanism confirmed as being similar to that of benzene. A linear relationship was shown to exist between the logarithm of the observed second-order rate constant and $- (H_R + \log_ e a_{H_2O})$, with a slope of unity up to 90% sulphuric acid. Thiophene is more reactive than benzene towards nitration and so, again, it is not possible to study the effect of any activating substituents because of the early onset of diffusion control. Solubility problems arise with more dilute acid but thiophene itself polymerises at high concentrations of sulphuric acid.

Protonation of Substituents

Many aromatic compounds are sufficiently basic to be protonated in concentrated sulphuric acid. If nitration occurs substantially through the free base, then the reactivity of the conjugate acid will generally be negligible. Thus, increasing the acidity of the medium will, by depleting the concentration of the free base, reduce the rate of reaction. However, nitration may or may not involve the predominant form of the substrate. If the predominant form is the conjugate acid and the reaction still proceeds through the unprotonated form then the observed second-order rate constant must be corrected to give one appropriate to the reacting free base. The fall in the concentration of the active species can be calculated from a knowledge of the ionization ratio. The ionization ratio is obtained from a knowledge of the $pK_a$ of the conjugate acid and the acidity function which, for the particular compound, gives the best measure of the acidity of the medium. Several criteria have been used in identifying the reacting species in reactions of this kind.
The study of the variation of the observed second-order rate constant with acidity has been particularly important.

As discussed earlier, for neutral compounds plots of the logarithm of the observed second-order rate constant for nitration at 25°C against the percentage of sulphuric acid have similar slopes. It has also been shown that plots of $\log_{10} k_{obs}$ against $-\left[H_R^- + \log a_{H_2O}\right]$ are usually linear, with slopes close to unity. For basic compounds which are predominantly protonated in the media in which nitration is conducted, similar slopes are to be expected if the conjugate acid is the species undergoing nitration. For example, nitration of the anilinium ion at 25°C gave a slope of unity for

$$\frac{d \log_{10} k_Z}{d \left[-\left(H_R^- + \log a_{H_2O}\right)\right]}$$

The unprotonated form of the base will generally be the more reactive toward nitration, and it is possible that nitration will occur through the free base, even when its concentration is very small compared with that of the conjugate acid. In such cases substantially lower slopes are to be expected because the proportion of free base falls with increasing acidity. The observed second-order rate constants can be corrected to give values relevant to the free base by determining the ionization ratio. Ideally, the corrected rate profile should have a slope similar to those given by substrates which are nitrated via the dominant species. One difficulty here arises from the fact that the acidity function followed by the compound under study is known in only a few cases (so it is not possible to determine the ionization ratio). Examples of compounds exhibiting low slopes which are attributable to nitration through the minority free base are acetophenone (slope = 0.76) and benzoic acid (0.80).
The way in which the rate of nitration of some non-basic compounds depends upon acidity in the region above that of maximum rate (~ 90% sulphuric acid) has been discussed earlier. Protonation partly accounts for the particularly marked fall in rate which occurs in the nitration of anthraquinone, benzoic acid, benzenesulphonic acid and some nitroanilines.

The orientation of substitution is an important factor to be considered in recognising both changes in the effective electrophile and in the nature of the aromatic substrate. For example, the anilinium ion is meta directing whereas aniline itself is ortho-para directing. Orientation in the nitration of p-nitroaniline agrees with other evidence in indicating that nitration occurs through the free base.

DECARBOXYLATIONS IN SULPHURIC ACID

Numerous quantitative studies on aromatic decarboxylation have been reported. Verhoek studied the decarboxylation of trinitrobenzoic acid and established that for aromatic acids with electron-withdrawing substituents, the loss of CO₂ occurs via a unimolecular reaction of the anion:

\[
\text{RCO}_2^- \quad \text{slow} \quad \rightarrow \quad \text{R}^- + \text{CO}_2
\]

\[
\text{R}^- + \text{H}_2\text{O} \quad \text{fast} \quad \rightarrow \quad \text{RH} + \text{CH}^-
\]

Support for the proposed slow step comes from the observation of a \(^{13}\text{C}\) isotope effect and the absence of a \(\text{D}_2\text{O}\) solvent isotope effect.

A different mechanism for decarboxylation has been proposed for aromatic carboxylic acids containing electron-releasing substituents. Schubert and Willi found a dependence of rate on acidity and suggested a mechanism of \(A - SE2\) type:
The proposed mechanism involves a rate-determining attack of $H^+$ on the carbon of the aromatic ring. Evidence for this mechanism again comes from solvent isotope effects. Few substituent effects have been examined in the protodecarboxylation reaction, but the results available are consistent with the view that the reaction is electrophilic.

For substituted salicylic acids, Willi proposed a mechanism involving the anion, rather than the acid:

$$\text{ArCO}_2^- + H^+ \leftrightarrow \text{ArH}^+ \rightarrow \text{ArH} + \text{CO}_2^-$$

Dunn proposed a mechanism for the decarboxylation of 4-methyl and 4-methoxyanthranilic acids in terms of three possible intermediates:

Dunn concluded that the decarboxylation path probably went exclusively through the intermediate B but because of the complex nature of the system decarboxylation via species A and C could not be excluded.
Los et al.\textsuperscript{95} reported data for a large number of 4-aminobenzoic acids with different substituents at the 2 and 6 positions. In order to rationalize their observations the authors proposed the general reaction mechanism shown below:

\[
\begin{align*}
RCO_2H + H_3O^+ & \rightleftharpoons RH + CO_2H + H_2O \\
RCO_2^- + H_3O^+ & \rightleftharpoons RH + CO_2^- + H_2O \\
RH^+CO_2H + H_2O & \rightleftharpoons RH + CO_2^- + H_3O^+ \\
RH^+CO_2^- & \rightarrow RH + CO_2 \\
\end{align*}
\]

The species $RH^+CO_2H$ and $RH^+CO_2^-$ involve protonation at the 1-carbon of the ring and are both assumed to be reaction intermediates present in small concentration. Some indirect support for the proposal that the reaction proceeds via an intermediate of the type $RH^+CO_2^-$ came from the data on the bromodecarboxylation of aromatic acids\textsuperscript{96}. The kinetics of this reaction are consistent with a mechanism proceeding via an intermediate formed by electrophile attack on the anion of the acid.

Longridge and Long\textsuperscript{97} studied the decarboxylation of aromatic carboxylic acids in acidic solution and concluded that the existence of a species with a strongly basic site such as $RH^+CO_2^-$ seems unlikely in concentrated acid. Indeed under highly acidic conditions one might expect appreciable protonation of the carboxylic acid itself\textsuperscript{88}. Whilst evidence suggests that this type of species is frequently involved in reactions it is doubtful whether it is an essential intermediate for all aromatic decarboxylations. The ionization of $RH^+CO_2H$ may not be necessary for decarboxylation to proceed in all cases.
Attempts to determine the $pK_{BH^+}$ values of amides in concentrated acid have been made relatively recently. The basicities of substituted benzamides were studied by U.V. spectroscopy and were subsequently recalculated to the $H_A$ acidity function scale. Benzamide has a $pK_{BH^+}$ value on this scale of -1.74 and $pK_{BH^+}$ values of substituted benzamides correlate with the $\sigma$-substituent constants, with $\rho = 0.92$. This was interpreted by Edward et al. as indicating that amides are N-protonated because the dissociation of the conjugate acids of amides is closely similar to that of carboxylic acids (used to define $\sigma$-constants).

The question of O- vs. N-protonation has been a subject of controversy for many years. Indeed several authors have indicated that the acid catalysed hydrolysis of amides may go via either of two mechanisms, depending on whether the oxygen or nitrogen atom of the amide has been protonated. The usual justification for considering oxygen protonation is that amides are mesomeric. The proton addition would then occur at the atom carrying the partial negative charge. The resulting O-protonated amide ions are themselves mesomeric, unlike the N-protonated cations. Those who favour nitrogen protonation have argued that the mesomeric stabilities would not be important enough to overcome the greater basicity of nitrogen over oxygen.

The most convincing evidence in favour of O-protonation, comes from n.m.r. studies in concentrated acids. Gillespie and Birchall slowed down the rate of exchange of protons of acetamide, N,N-dimethylacetamide, formamide and dimethylformamide with the solvent by lowering the temperature. They assigned the spectra to the $C=OH^+$ group. The spectrum of pure liquid dimethylformamide shows two peaks for the two
methyl groups, due to restricted rotation about the C-N bond, resulting in different environments for the methyl protons. These peaks remain unchanged in aqueous strong acids\textsuperscript{104}, indicating that O-protonation predominates, retaining the partial double-bond character of the carbon-nitrogen bond:

\[ \text{OH} \]

\[ \text{H} \quad \text{C} \quad \text{\_} \quad \overset{\text{\_}}{\text{N}} \quad \text{CH}_3 \]

The NHMe\textsubscript{2} group produced by N-protonation would be free to rotate, producing a different spectrum. Similar results have been obtained with other amides\textsuperscript{105}.

Infrared and Raman-spectra evidence e.g. shifts in frequency, has generally been interpreted in terms of N-protonation but Katritzky and Jones\textsuperscript{106} do not consider that the evidence negates the possibility of O-protonation. Hantzsch\textsuperscript{107} used the similarities in U.V. spectra of benzamide and ethylbenzamido-ether to suggest O-protonation. Edward et al.\textsuperscript{99}, however, showed that the evidence was also compatible with N-protonation. Huisgen and Brade\textsuperscript{108} presented evidence for O-protonation from basicity studies. They found that N-substituents have less effect on the basicities of amides than on those of corresponding amines. This suggests that the basic centre of amides is further from the nitrogen atom than in amines. However, as mentioned earlier, application of the Hammett equation to basicities of substituted benzamides led to a better correlation of pK\textsubscript{BH+} with \( \sigma \) than with \( \sigma^+ \) (correlation with \( \sigma^+ \) is required for protonation of the carbonyl oxygen\textsuperscript{109}). This suggests that amides protonate on nitrogen. However, the concept that all reactions comply with a set of unique \( \sigma \) or \( \sigma^+ \) values has been criticised\textsuperscript{110}. 

Much of the chemical evidence available at present favours the O-protonated form.

From the available evidence it would appear that the O-protonated form predominates but N-protonation cannot be excluded. Thus, it is reasonable to postulate hydrolysis mechanisms involving a rapid protonation pre-equilibrium on either the oxygen or nitrogen atom. The importance of O- and/or N-protonation with regard to acid hydrolysis of amides is apparent in Chapter 5.

**Amide Acidity Function**

Yates\(^{57}\) extended the idea of having a specific acidity function for a particular structural type of base to amides. He produced the \(H_A\) function which is analogous to \(H_A\), but applicable to the ionization of amides by proton addition. \(H_A\) is based on a series of primary substituted benzanilides, except in dilute acids where there is no substituted benzanilide basic enough to be appreciably protonated. \(H_A\) is, therefore, initially based on p-nitroaniline as the primary indicator. This acidity function has been used to determine \(pK_{BH^+}\) values of amides. The values have been measured in sulphuric acid\(^{57}\) and hydrochloric acid\(^{113}\), and the function tested\(^{100}\) for several amides other than those used originally, with generally good agreement.

The most general method for determining pKa values involves determination of the ratio of conjugate acid to free base at varying acid concentrations. However, for the weakly basic amides, the region of observable protonation occurs in strong acid. Since the stoichiometric concentration of hydrogen ions, conjugate acid and free base is no longer accurately equatable to the activities of the species the \(H_A\) acidity function of amides is of fundamental importance in the determination of ionization ratios.
PART 2.

ELECTROPHILIC DISPLACEMENT REACTIONS.
CHAPTER 4

INTRODUCTION -
ELECTROPHILIC SUBSTITUTION
ELECTROPHILIC SUBSTITUTION REACTIONS

The aromatic substitution reaction that has received the closest study is nitration. The kinetics and mechanisms of reactions in which benzen and other aromatic compounds undergo substitution have been studied extensively. Nitration

Nitration has been shown to be an irreversible second-order reaction and takes place with a variety of nitrating agents in a variety of media. Despite the fact that the rate of nitration of a given compound depends on the conditions, the mechanism is essentially the same. Nitric acid in sulphuric acid/water mixtures is a common nitrating medium, in which the nitrating agent has been well established as the nitronium ion, \( \text{NO}_2^+ \). In concentrated sulphuric acid the reaction which produces the nitronium ion is:

\[
\text{HNO}_3 + 2\text{H}_2\text{SO}_4 \rightleftharpoons \text{NO}_2^+ + \text{H}_3\text{O}^+ + 2\text{HSO}_4^-
\]

Evidence for the existence of nitronium ions in solutions of nitric acid in sulphuric acid came from freezing point depression data and Raman spectra. Nitronium ions are present in spectroscopically detectable amounts only in solutions of nitric acid in > 85% sulphuric acid. The conversion of nitric acid to nitronium ions is complete in about 90% sulphuric acid. The rates of nitration of aromatic substrates in sulphuric acid/water mixtures are extremely sensitive to the concentration of sulphuric acid. Westheimer and Kharasch demonstrated a linear relationship between nitronium ion concentration and the rate of nitration in media containing sulphuric acid < 90%. Rates of nitration have been shown to parallel the ionization of triarylcarbinols, i.e. to follow the \( H_R \) acidity function. Triarylcarbinols ionize in the same
way as nitric acid:

\[ R_3COH + 2H_2SO_4 \rightleftharpoons H_3O^+ + R_3C^+ + 2HSO_4^- \]

The slopes of the plots of \( \log k \) vs. \( H_R \) are, however, not always close to unity. Moodie\textsuperscript{119} found that plots of \( \log k \) vs. \(-\left(H_R + \log a_{H_2O}\right)\) are straight lines of near unit slope for a wide range of substrates. The water activity term compensates for activity coefficient differences between species involved in the sulphuric/nitric acid equilibrium and species involved in the triarylcarbinol equilibrium.

**Mechanism of Nitration**

The mechanism of aromatic nitration was discussed by Ridd\textsuperscript{120} in 1971. He showed that the major mechanism of nitration in solutions of nitric acid in sulphuric acid and inert organic solvents is as follows:

\[ ArH + NO_2^+ \xrightleftharpoons[k_1]{k_2} ArH + NO_2 \]

Scheme 1: Mechanism of aromatic nitration

It is believed that the nitronium ion and the aromatic diffuse together to give an "encounter pair", of undefined structure. The encounter pair produces a Wheland intermediate, shown above, which by loss of a proton generates a nitro compound. Depending on the conditions and the aromatic substrate any of the steps may be rate determining. Indeed, for very reactive substrates which combine with the nitronium ions as fast as they are formed, the rate-determining step is then the formation of the nitronium ion.
The mechanism of scheme 1 has been accepted for nitration since Melander\textsuperscript{121} demonstrated that the rate of displacement of tritium is about the same as that of protium. This could not be so if the aryl-hydrogen bond were broken in the transition state. If it is broken in the second, fast step, no isotope effect would be observed. The high rate of breakdown of the intermediate and the irreversibility of the reaction imply a free energy-reaction co-ordinate diagram of the type shown in fig. 1.

![Free energy diagram for the nitration of aromatic compounds](image)

**Fig. 1:** Free energy diagram for the nitration of aromatic compounds

**Kinetics**

Except in certain circumstances in which formation of the nitronium...
ion provides the rate-determining step, the kinetics are usually second-order. Many nitrations have been shown to follow the kinetic law of the form:

$$\text{Rate} \propto (\text{Ar-H})(\text{NO}_2^+)$$

Thus, in the majority of cases the rate-determining step is the initial attack by \(\text{NO}_2^+\). This has been confirmed by the absence of kinetic isotope effects in most nitrations \(^{69,122}\).

**ANOMALOUS SUBSTITUTION REACTIONS**

**General Reaction**

The general features of electrophilic aromatic substitutions are now well understood and can be explained in terms of the two-step \(S_\text{E2}\) mechanism which involves a relatively unstable \(S\)-complex (Wheland intermediate).

$$\text{ArX} + E^+ \rightleftharpoons \text{Ar}^+ \underset{E}{\text{X}} \rightarrow \text{ArE} + X^+$$

Until recently, most attention was given to those nuclear substitutions in which \(X = H\), i.e. conventional electrophilic substitutions. There is now a growing interest in other types of electrophilic reaction particularly those in which \(X\) is a group other than hydrogen. Many electrophilic substitutions in which the leaving group is other than hydrogen have been reviewed \(^{123}\).

**Directive Effects**

An enormous amount of data exists concerning directive effects in electrophilic aromatic substitution. Substituents have been classed as activating or deactivating, ortho-para directing or meta directing and quantitative measures of these effects have been determined. The
directive effects of a substituent $R$ are expressed by the partial rate factors, $Q_f^R$, $M_f^R$, and $P_f^R$. These factors represent the rates of electrophilic attack at a single position ortho, meta or para to the substituent, relative to the rate of attack at a single position of benzene. However, this situation has been complicated by recognition of the importance of ipso attack. The term "ipso" was introduced by Perrin and Skinner\textsuperscript{124} to denote attack by a reagent at a substituted position. Very little information exists concerning the directive effect of a substituent for attack directly at the ipso position. Perrin expressed such a directive effect quantitatively by means of an ipso partial rate factor:

$$I_f^R = \frac{K_{ArR} \times \% \text{attack at ipso position in ArR}}{K_{ArH} \times \% \text{attack at corresponding position in ArH}}$$

In this expression $K_{ArR}$ represents the rate constant for total reaction of ArR, the system of interest. $K_{ArH}$ is the rate constant for the corresponding system in which the substituent $R$ is replaced by hydrogen. The choice of name for the term $I_f^R$ is unfortunate since partial rate factors are generally understood to be measures of reactivity relative to a position in benzene. The definition of $I_f^R$, however, means that these factors do not express reactivities relative to benzene, or indeed, to any single reference compound.

In common with other partial rate factors, the ipso factor, $I_f^R$ is characteristic not only of the substituent $R$ but also of the aromatic substrate, the attacking electrophile and the reaction conditions.

**Determination of Ipso Factors**

The general form of a reaction involving attack at a substituted position of benzene can be represented:
The ipso factor of the substituent $E_2$ is given by the value of $k_1$, divided by the value of $k_1$ for the reaction in which $E_2$ is hydrogen. In order that the measured rate of reaction be simply $k_1$, it is necessary that $k_{-1}$ be sufficiently small, so that the attack of $E_1^+$ is effectively irreversible. Several ipso factors are shown in table 1.

<table>
<thead>
<tr>
<th>REACTION</th>
<th>$R$</th>
<th>$i_f^R$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protodesilylation</td>
<td>$\text{Me}_3\text{Si}$</td>
<td>$\sim 10^5$</td>
</tr>
<tr>
<td>Bromodesilylation</td>
<td>$\text{Me}_3\text{Si}$</td>
<td>$\sim 10^8$</td>
</tr>
<tr>
<td>Diazodesilylation</td>
<td>$\text{Me}_3\text{Si}$</td>
<td>$&lt; 1$</td>
</tr>
<tr>
<td>Protodeboronation</td>
<td>$\text{B(OH)}_2$</td>
<td>$\sim 4$</td>
</tr>
<tr>
<td>Bromodemethylation</td>
<td>Me</td>
<td>0.29</td>
</tr>
<tr>
<td>Bromine exchange</td>
<td>Br</td>
<td>$&lt; 2 \times 10^{-7}$</td>
</tr>
<tr>
<td>Protodecarboxylation</td>
<td>$\text{CO}_2\text{H}$</td>
<td>$2 \times 10^{-3}$</td>
</tr>
<tr>
<td>Nitrodehalogenation</td>
<td>I</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>Br</td>
<td>0.079</td>
</tr>
<tr>
<td></td>
<td>Cl</td>
<td>0.061</td>
</tr>
<tr>
<td>Diazodehalogenation</td>
<td>I</td>
<td>0.149</td>
</tr>
<tr>
<td></td>
<td>Br</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>Cl</td>
<td>0.007</td>
</tr>
</tbody>
</table>

**TABLE 1: Ipso Rate Factors ($i_f^R$) for some electrophilic substitutions**

From the few available data it is not possible to develop a complete theory of such substituent effects. Ipso factors cannot be predicted from well-understood ortho, meta and para directive effects, and the values observed in table 1 cannot be rationalized at present.
Other Ipso Substitutions

Many ipso substitutions occur in aromatics which are strongly activated toward electrophilic attack. Protodecarboxylation\textsuperscript{129} and protodehalogenation\textsuperscript{130} are familiar reactions but other processes such as nitrodealkylation\textsuperscript{131}, halodecarbonylation\textsuperscript{132}, halodesulphonation\textsuperscript{133} and sulphodesilylation\textsuperscript{134} are less familiar. Nitrations, in particular, are noted for 'anomalous reaction products'\textsuperscript{135} and a few examples are now discussed.

Nitrodealkylations

Demethylation occurs upon nitration of polymethylbenzenes and is often accompanied by side-chain substitution\textsuperscript{135}. Secondary and tertiary alkyl groups are more easily displaced, and numerous examples of deiso-propylation and de - tert - butylation are known\textsuperscript{136}. The electrophilic nature of the reaction is indicated by the fact that the process has not been observed in the nitration of monoalkylbenzenes. In general, the more highly branched alkyl groups are replaced, presumably due to the stability of the leaving carbonium ion.

The nitration of p-cymene has been extensively studied in an effort to minimize side reactions and to improve the yield and purity of the 2-nitro- and 2,6-dinitro - p-cymenes\textsuperscript{136,137}. A 10\% yield of p-nitro toluene was obtained under most reaction conditions. In most cases nitrodealkylation is a comparatively minor side-reaction accompanying nitrodeprotonation. However, in certain circumstances it can be the predominant reaction. For example, the nitration of 1,2,4,5-tetra-iso-propylbenzene with nitric acid in acetic anhydride gives entirely the nitrodealkylated product:-
Nitration of the ring positions containing hydrogen is subject to the steric hindrance of two iso-propyl groups.\textsuperscript{131}

Nitrodecarboxylation

Nitration and halogenation of amino, hydroxy, or alkoxy- benzoic acids are often accompanied by decarboxylation\textsuperscript{138-140}. However, it is possible to show that the nuclear hydrogen atoms ortho and para to the activating group are displaced in preference to the carboxyl group. By careful control of the reaction conditions the reaction can be arrested before the latter has been removed. The reaction occurs less readily than nitrodeprotonation, either because the step in which the carbon-carbon bond is ruptured is slow (and rate-determining) or because the electron-withdrawing nature of the carboxyl group retards the initial attack of electrophile.

The nitration of anisic acid with sulphuric acid and absolute nitric acid yields three products\textsuperscript{139}:

\[
\begin{align*}
\text{CH}_3\text{O} & \quad \text{HNO}_3 \\
\text{CO}_2\text{H} & \quad \text{H}_2\text{SO}_4
\end{align*}
\]

It is interesting to note that although a carboxyl group ortho or para to -OH or -OR is usually readily replaced, 2,3,4-trimethoxy-benzoic acid
does not undergo nitrodecarboxylation whereas 3,4,5-trimethoxybenzoic
does: 141

In the latter compound nitrodeprotonation is more strongly sterically
hindered than in the former, and this suffices to favour replacement of
the carboxyl group. Some other examples of nitrodecarboxylation and
related reactions are shown below:

Nitrodesulphonation

The nitration of sulphonic acids may give either the normal products
of substitution or those of replacement of the sulphonic acid group,
depending upon the conditions and on the substituents present in the
molecule. Nitrodesulphonation is particularly well documented among the
phenol sulphonic acids. 143 Halodesulphonations are also well known. 133

Nitrodehalogenation is a common reaction and as discussed earlier,
has been used to determine ipso factors for the halogens. 124
The mechanism of less familiar reactions such as nitrodesilylation have also been studied.  

**Heterocyclic Compounds**

The reactivity of the α-positions in pyrroles, furans and thiophenes is sufficiently great that a highly reactive electrophile will displace a substituent in some cases. Substituents which are readily removed from the 2-position are halogens, carboxyl groups and sulphonic acid groups.

Steinkopf and Muller studied the nitration of thiophene-2-carboxylic acid and found a small amount of 2-nitrothiophene in the nitration product. This was considered to have been formed by the decomposition of 5-nitrothiophene-2-carboxylic acid. Rinkes confirmed this formation of 2-nitrothiophene but found that 5-nitrothiophene-2-carboxylic acid failed to split off carbon dioxide even at its melting point. Rinkes concluded that 2-nitrothiophene was formed by displacement of the carboxyl group by nitro:—

![Chemical diagram]

\[
\text{CH}_2\text{C}_2\text{H}_2\text{(CO}_2\text{H}\rarrow_{\text{HNO}_3, \text{Ac}_2\text{O}}^\downarrow\text{NO}_2\text{C}_2\text{H}_2\text{S}\text{CO}_2\text{H} + \text{NO}_2\text{C}_2\text{H}_2\text{S}\text{CO}_2\text{H} \sim 45\% + \text{S}\text{NO}_2\text{C}_2\text{H}_2\text{S} \sim 10\%}
\]
2-Methylthiophene-5-carboxylic acid was nitrated by Rinkes using acetic anhydride and fuming nitric acid to give as the main product 4-nitro-5-methyl thiophene-2-carboxylic acid. However, Rinkes also isolated 5-nitro-2-methylthiophene and 3,5-dinitro-2-methylthiophene from the reaction products. This reaction was further investigated by Campagne and Grose:

\[
\begin{align*}
\text{HN}_3O + \text{Ac}_2O & \rightarrow \text{NO}_2 - \text{S}^\circ_2 \text{H} \\
\text{S}^\circ_2 - \text{S} & \rightarrow \text{TRACE} & \approx 40\% \\
\text{CH}_3 & \rightarrow \text{NO}_2 & \approx 15\%
\end{align*}
\]

In the reactions of 2,5-disubstituted thiophenes, such as that shown above, the displacement of an \(\alpha\)-substituent occurs to a much greater extent than in the benzene series. However, the presence of substituents which lower the electron density at the 2-position, or esterification of the carboxyl group, prevents decarboxylative nitration. Nitration of halogenated 2-acetamidothiophenes leads to replacement of halogen by the nitro group, and elimination of alkyl groups is also known. Elimination of an \(\alpha\)-substituent occurs in the furan and pyrrole series in similar circumstances.

Elimination of \(\beta\)-substituents is less common. Campagne and Bourgeois studied the substitution reactions of thiophene-3-carboxylic acid. This
acid was nitrated readily in cold sulphuric-nitric acid to give 5-nitrothiophene-3-carboxylic acid. Campagne and Bourgeois found this nitro acid to be 'remarkably stable for a thiophene compound, and could be recovered after treatment in nitrating mixture at 140° for two hours'. This behaviour contrasts sharply with the nitration of 2-acetamido-thiophene-3-carboxylic acid, the initial subject of this research:

The electrophilic nature of the process is thus indicated by the fact that replacement only occurs if the ring position with the carboxyl group attached is strongly activated towards electrophilic substitution.

Since ipso substitution involves leaving groups other than hydrogen there is a growing interest in establishing an order for the leaving abilities of the electrophiles.

Leaving Group Ability

Perrin\textsuperscript{147} investigated the relative leaving abilities of electrophiles in electrophilic aromatic substitution. The general case involves the decomposition of an intermediate: -

The question of interest is which of the two electrophiles, $E_1^+$ or $E_2^+$, is lost more readily and why? When one of the electrophiles is $H^+$ hydrogen isotope effects provide the answer\textsuperscript{148}. 

\[ \text{Leaving Group Ability} \]
If \( k_2 \gg k_1 \) then no isotope effect is observed, i.e. ArD will react at the same rate as ArH. However, if \( k_1 \gg k_2 \) then loss of \( H^+ \) (or \( D^+ \)) competes with loss of \( E^+ \). The second step then becomes rate determining and a deuterium isotope effect will be observed. Thus if electrophilic substitution of an electrophile, \( E^+ \), for a proton \( H^+ \), shows an isotope effect appreciably greater than unity, then \( E^+ \) is a better leaving group than \( H^+ \). Iodinations, nitrosations and mercurations all proceed with appreciable isotope effects and so \( I^+ \), \( NO^+ \) and \( Hg^{2+} \) are all lost at least as readily as \( H^+ \). In contrast nitrations, chlorinations and alkylations rarely show appreciable isotope effects suggesting that \( NO_2^+ \), \( Cl^+ \) and \( R^+ \) are lost much less readily than \( H^+ \). It is assumed that if \( E_1 ArH^+ \) loses \( E_1^+ \) much less readily than it loses \( H^+ \) and if \( E_2 ArH^+ \) loses \( E_2^+ \) about as readily as it loses \( H^+ \) then \( E_2^+ \) is a better leaving group than \( E_1^+ \).

If one takes the magnitude of the hydrogen isotope effect as a quantitative reflection of the ratio \( \frac{k_1}{k_2} \) then an approximate order of increasing leaving ability can be obtained:

\[
Cl^+ \sim NO_2^+ \sim R^+ < Br^+ < D^+ < ArN_2^+ \sim SO_3^+ < RCO^+ < NO^+ \sim H^+ \sim I^+ < Hg^{2+}
\]

Perrin considered the order for those electrophiles which are readily lost to be reliable since it is based on isotope effects (\( \frac{k_H}{k_D} \)) ranging from 3 to 7. However the relative leaving abilities of those electrophiles that are lost much less readily cannot be easily predicted since in general, \( \frac{k_H}{k_D} < 2 \). Steric problems are also encountered in considering these isotope effects quantitatively. Aromatic substitutions by electrophiles such as \( ArN_2^+ \), \( Br^+ \), \( SO_3 \) and \( RCO^+ \), which are usually lost less readily than \( H^+ \), show higher isotope effects in certain circumstances.
This is due to a steric effect which hinders the formation of a coplanar structure involving the substituent and aromatic, and thereby decreases $k_2$ relative to $k_1$.

Perrin decided, therefore, that a direct comparison of the relative leaving abilities of the poorer leaving groups was necessary. The relative leaving abilities of $\text{Cl}^+$, $\text{Br}^+$ and $\text{NO}_2^+$ in acetic acid - acetic anhydride mixtures was considered. The model for an intermediate having two of these substituents was the conjugate acid of 1-halo-1-nitro-2-keto-1,2-dihydronaphthalenes:

When $X = \text{Cl}$, the above intermediate decomposes by loss and migration of $\text{NO}_2^+$ rather than $\text{Cl}^+$, in mixtures of acetic acid and acetic anhydride:

The 1-chloro-6-nitro-2-naphthol arises by migration of $\text{NO}_2^+$, and not by an intermolecular process. This is an example of the rare migration of a nitro group. Other products which were isolated included 2-hydroxy-1,4-naphthoquinone, which arises via 1,2 naphthoquinone. A small amount of 1-chloro-2-naphthol was also detected. No 1-nitro-2-naphthol or 1,6-dinitro-2-naphthol was found - the loss of $\text{Cl}^+$ does not compete with loss and migration of $\text{NO}_2^+$. 
In contrast, the bromo analogue, 1-bromo-1-nitro-2-keto-1,2-
dihydronaphthalene, upon treatment with an acetic acid - acetic anhydride
mixture yielded 1-nitro-2-naphthol. This was produced by loss of Br+ and so loss or migration of NO2+ does not compete with SN2 displacement
on bromine by acetic acid or chloride (a small quantity of hydrochloric
acid was present in the reaction solution):

$$\text{Br} \quad \text{NO}_2 \quad \text{H}^+ \quad \text{Br} \quad \text{NO}_2 \quad \text{Cl}^-$$

Fries \textsuperscript{151} studied the rearrangement of 1-chloro-1-methyl-2-keto-1,2-
dihydronaphthalene in acetic acid and found that Cl+ is a better leaving
group than CH$_3$+. Fischer \textsuperscript{128} has also studied the diazodehalogenation of
1-halogeno-2-naphthol-6-sulphonic acids. The ease of displacement of
halogen was found to be Cl+ < Br+ < I+ < H+. A complete sequence of
leaving abilities for these 'poor leaving groups' can thus be postulated:

\[ \text{CH}_3^+ < \text{Cl}^+ < \text{NO}_2^+ < \text{Br}^+ < \text{I}^+ < \text{H}^+ \]

It is also possible to include other electrophiles whose relative
leaving abilities have been determined. From kinetic studies and/or
isotope effects in protodecarboxylation \textsuperscript{97}, protodeboronation \textsuperscript{126} and
protodesilylation \textsuperscript{125} it is obvious that H+ is a poorer leaving group
than CO$_2$, B(\text{OH})$_3$ and Me$_3$Si+. Since H+ is a better leaving group than
Br+ and I+ then this sequence is consistent with the kinetics of bromodecarboxylation \textsuperscript{96} and halodeboronation \textsuperscript{152}.

Simple considerations of relative leaving abilities have clarified
some previously puzzling features of aromatic reactivity. For example,
the variations in the mechanism of protodecarboxylation\textsuperscript{97,153} are readily understood in terms of the variations in the relative leaving abilities of \( H^+ \) and \( \text{CO}_2 \):-

\[ \text{Products} \]

In dilute acid the above intermediate loses \( \text{CO}_2 \) more readily than \( \text{H}_2\text{O} \) removes \( H^+ \). In buffer solutions, general base catalysis increases the rate of proton removal, but does not affect the rate of \( \text{CO}_2 \) loss. In strong acid the intermediate is present as a species almost entirely protonated on oxygen. This readily loses \( H^+ \) but cannot lose \( \text{CO}_2 \). It is believed that similar phenomena are involved in protodecarboxylation\textsuperscript{129}, protodeformylation\textsuperscript{154} and protodesulphonation\textsuperscript{155}.

\textbf{\( S_N1 \) and \( S_N2 \) Processes}

The relative leaving abilities are not intrinsic properties of the electrophiles. Proton loss can be regarded as an \( S_N2 \) displacement on hydrogen, whereas loss of \( \text{NO}_2^+ \) or \( \text{NO}^+ \) is an \( S_N1 \) process. Whether loss of some other electrophile is by an \( S_N1 \) or \( S_N2 \) process may be determined on the basis of the mechanism of attack by that electrophile. Thus the halogens, \( I^+ \), \( \text{Br}^+ \) and \( \text{Cl}^+ \) are never lost as such, but are removed by nucleophiles. Relative leaving abilities might therefore show some variation with reaction conditions, depending upon the mechanism by which the electrophile is removed from the \( S \)-complex. Perrin\textsuperscript{147} decided that a single order of leaving abilities was inappropriate. He considered the information obtained from isotope effects from reactions of model compounds, and from other kinetic studies, and then listed those electrophiles that ionize in an \( S_N1 \) process separately from those that are cleaved in an \( S_N2 \) process:
(A) \( \text{NO}_2^+ < \text{i-Pr}^+ \sim \text{SO}_3^- < \text{t-Bu}^+ \sim \text{ArN}_2^+ < \text{ArCHOH}^+ < \text{NO}^+ < \text{CO}_2 < \text{B(OH)}_3^- \)

(B) \( \text{CH}_3^+ < \text{Cl}^+ < \text{Br}^+ < \text{I}^+ \sim \text{RCO}^- < \text{H}^+ \sim \text{I}^- < \text{Hg}^{2+} < \text{Me}_3\text{Si}^- \)

**TABLE 2: Relative leaving abilities of electrophiles**

(A) ionized in \( S_N^1 \) process \hspace{1cm} (B) cleaved in \( S_N^2 \) process.

Although the reaction conditions can have a considerable effect on the leaving abilities of species that react by an \( S_N^2 \) process, it is possible to compare the two processes. For example, it was shown earlier that a frequent order is \( \text{Cl}^+ < \text{NO}_2^+ < \text{Br}^+ \).

**Factors Affecting Leaving Abilities**

(A) **Carbon-Electrophile Bond**

The above order of leaving abilities is a reasonable one for the relative rates of breaking the carbon-electrophile bond. Thus, \( \text{NO}_2^+ \) is an extremely powerful electrophile, forming a strong C-N bond which is difficult to cleave. In contrast, good leaving groups such as \( \text{Hg}^{2+}, \text{H}^+ \) and \( \text{NO}^+ \) are particularly stable species, of low electrophilicity. The C-Hg⁺, C-H, and C-NO bonds are, therefore, readily cleaved.

Ionization of \( R^+ \) from the intermediate would not be expected to be a fast reaction unless \( R^+ \) were a very stable carbonium ion.

(B) **Reaction Conditions**

Electrophiles such as \( \text{Cl}^+, \text{Br}^+, \text{I}^+, \text{H}^+, \text{Hg}^{2+} \) and \( \text{CH}_3^+ \) are removed in an \( S_N^2 \) type process. The relative leaving abilities of these species depend on the nature and concentration of the nucleophiles present. A striking example of this occurs in the nitration of anthracene in acetonitrile, for which \( k^H/k^D = 6.1 \). In such a weakly basic
the proton becomes a very poor leaving group, in this case even poorer than \( \text{NO}_2^+ \), which needs no nucleophile for removal.

For those substituents that are removed in an \( S_N^2 \) process, it is necessary to consider the strengths of both the bond to be broken and the bond to be made.

(C) Steric Effects

Large, bulky substituents close to the reaction centre will hinder the approach of a bulky electrophile. This will effectively decrease the rate of the second step of the reaction:

\[
Ar - H + E^+ \xleftrightarrow{k_1} Ar^+ \xrightarrow{k_2} ArE + H^+;
\]

The overall effect of such steric hindrance is to decrease the ratio \( k_2/k_{-1} \). The leaving ability of the proton is thus decreased relative to that of the electrophile. Reversal of the initial electrophilic attack thus competes with loss of the proton, resulting in a hydrogen isotope effect.

Aromatic substitutions by electrophiles such as \( \text{ArN}_2^+ \), \( \text{Br}^+ \), \( \text{SO}_3^+ \) and \( \text{RCO}^+ \), which are usually lost less readily than \( H^+ \), show higher isotope effects under special circumstances. This usually occurs when steric effects hinder the overall substitution process.

(D) Stability of Leaving Group

Reaction conditions can have a considerable effect on the leaving abilities of species involved in \( S_N^2 \) type processes. However, the stability of the leaving group is an important factor in considering the relative leaving abilities of species which ionize in an \( S_N^1 \) type process. Ionization of \( R^+ \) from an intermediate is only a fast reaction when \( R^+ \) is
a stable carbonium ion e.g. t-Bu⁺. Good leaving groups, such as NO₂⁻, are particularly stable species, of low electrophilicity.

However, for those substituents which are removed in an SN₂ type process comparisons of leaving ability cannot be absolute but are applicable only under the conditions specified.

(E) Selectivity of Reaction

Since reactions involving powerful electrophiles show no isotope effect it has been suggested that the selectivity of the reaction is important. A powerful electrophile has a poor leaving ability, so that proton loss is always favoured and no isotope effect is observed. However, mercuration, although a rather unselective reaction, does show an appreciable isotope effect.

Other Consequences of Ipso Attack

Although ipso substitution is the most common result of attack by an electrophile at a substituted nuclear position, other consequences are also known.

a) Nucleophilic Addition

The stereoisomers shown below have been isolated during the nitration of o-xylene by nitric acid in acetic anhydride.

Similarly the acetoxylation that accompanies the nitration of many
methyl-benzenes in acetic anhydride occurs by an addition-elimination pathway.\textsuperscript{159}

b) **Rearrangement by Migration of Substituent**

A common type of rearrangement that can occur involves the migration of the electrophile from the nuclear position initially attacked to another nuclear position or to a side-chain. Many examples of 1,2-migration of the nitro group have been reported.\textsuperscript{160-162}

The existence of a pathway involving rearrangement of the electrophile to another ring position may be overlooked, particularly if the final product can also be formed directly by a conventional substitution. The demonstration of 1,2-migration of the nitro group makes uncertain the extent to which ortho-substituted products arise by direct ortho attack.

The trapping of ipso-intermediates by solvent molecules e.g. acetic anhydride, is being investigated.\textsuperscript{163} There is no evidence, at present, for the migration of the ipso substituent itself.

c) **Formation of Dienones and Quinones**

This is another possible consequence of ipso attack. Phenols give stable cyclohexadienones when the ipso position or the hydroxyl group is flanked by bulky groups.\textsuperscript{164} Demethylation of methoxyl occurs in the nitration of p-methoxytoluene in aqueous sulphuric acid and also in the nitration of p-chloroanisole.\textsuperscript{124}

d) **Return to Starting Materials**

The intermediate, believed to be produced by ipso attack, could return to starting materials but this unproductive pathway is seldom detectable.
Summary

Electrophilic attack upon an aromatic system does not always yield the products expected for a conventional substitution. The fact that reactions of this sort exist has important implications concerning quantitative studies of aromatic reactivity. It has been shown that the products of conventional ring substitution can be formed by 1,2 shifts. This suggests that care is needed when interpreting results of seemingly 'simple' substitutions.

Ipso attack at aromatic ring carbons bearing various substituents is known to occur and the longest recognised consequence is ipso substitution. Although ipso factors have been determined for several reactions further research is necessary for an understanding of them to develop. Attempts have been made to obtain an order of leaving abilities of electrophiles, but often the relative leaving abilities show some variation with reaction conditions depending upon the mechanism of removal of the electrophile. However, very little work has been done on the kinetics and mechanism of ipso substitutions. In general, a system strongly activated toward electrophilic attack is required, but no quantitative interpretation of this activating effect has ever been attempted.

The sensitivity of the nitrodecarboxylation reaction to substituent effects and reaction conditions, in a series of thiophene derivatives, has been investigated during the course of this work.
CHAPTER 5

NITRODECARBOXYLATION OF THIOPHENE DERIVATIVES
A step in the synthesis of 2-amino-3,5-dinitrothiophene involves nitration of 2-acetamidothiophene-3-carboxylic acid. Nitration is found to occur in only moderate yield to give a bis-nitroderivative, which results from nitration at \( C_5 \) being accompanied by nitro-decarboxylation at \( C_3 \):

\[
\text{NHAc} \quad \text{CO}_2\text{H} \quad \overset{\text{HNO}_3, \text{H}_2\text{SO}_4}{\longrightarrow} \quad \text{NO}_2 \quad \text{NO}_2 \quad \text{NHAc}
\]

Occurrence of nitrodecarboxylation, while being a helpful feature of the industrial process, since it obviates the necessity of a separate decarboxylation step, presents a fundamental problem in mechanistic organic chemistry. Loss of groups from aromatic substrates during electrophilic substitution is a well known type of process but most attention has been focussed on reactions such as protodesilylation which occur readily in simple systems. Nitrodecarboxylation and the related reaction of decarbonylation have received only scattered attention. The reaction appears to be prevalent in systems activated towards electrophiles but although nitrodecarboxylation has been observed in the thiophene series no systematic study in heterocyclic systems has been reported.

Nitrodecarboxylation of 2-acetamido-5-nitrothiophene-3-carboxylic acid

The nitrodecarboxylation step of the industrial process was accomplished by treatment of the mono-nitro carboxylic acid with a sulphuric-nitric acid mixture. Industrially it has been found that the most suitable
quantity of nitric acid for optimum quality and quantity of product is 1.5 moles of nitric acid per mole of substrate. However, the best yield of 2-acetamido-3,5-dinitrothiophene obtained was 56.3% and the yield under industrial conditions is only 53%. The poor yield of product can be partly accounted for by considering the A1 hydrolysis of both starting material and product in concentrated sulphuric acid (see Chapter 7).

Variation of Rate with Acidity

Rates of nitration of 2-acetamido-5-nitrothiophene-3-carboxylic acid in concentrated sulphuric acid solutions were determined by U.V. spectroscopy. The observed second-order rate constants for nitrodecarboxylation of 2-acetamido-5-nitrothiophene-3-carboxylic acid are shown in Table 1. The rate constants are average values obtained over a number of kinetic runs, since both starting material and product are rather unstable in sulphuric-nitric acid mixtures. This is especially true in the more concentrated acid where hydrolysis to an unstable amine occurs at an appreciable rate. However, in all cases, the rate of nitration (nitrodecarboxylation) was greater than the rate of degradation.

<table>
<thead>
<tr>
<th>$H_2SO_4$ CONCENTRATION (W/W)</th>
<th>MEAN $k_{2obs}$ $(1 \text{ mol}^{-1} \text{sec}^{-1})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>80.9%</td>
<td>5.5x10^{-4}</td>
</tr>
<tr>
<td>82.4%</td>
<td>2.6x10^{-3}</td>
</tr>
<tr>
<td>83.5%</td>
<td>8.7x10^{-3}</td>
</tr>
<tr>
<td>86.1%</td>
<td>3.5x10^{-2}</td>
</tr>
<tr>
<td>88.2%</td>
<td>6.5x10^{-2}</td>
</tr>
<tr>
<td>89.9%</td>
<td>1.3x10^{-1}</td>
</tr>
<tr>
<td>92.3%</td>
<td>7.9x10^{-2}</td>
</tr>
<tr>
<td>94.7%</td>
<td>4.4x10^{-2}</td>
</tr>
</tbody>
</table>

TABLE 1: Observed rate constants for nitration of 2-acetamido-5-nitrothiophene-3-carboxylic acid in nitric-sulphuric acid solutions at 25°C.
The solubility of the weakly basic amide 2-acetamido-5-nitrothiophene-3-carboxylic acid was very sensitive to changes in sulphuric acid concentration. The compound was barely soluble below 80% sulphuric acid and so nitration rates were restricted to the more concentrated acid media.

A rate profile for the nitrodecarboxylation reaction in 80-95% sulphuric acid is shown in fig. 1, and is very similar in form to a conventional rate profile for a nitrodeprotonation reaction e.g. nitration of nitrobenzene. In both cases, the increase in nitration rate up to ~90% sulphuric acid can be attributed to the increase in the degree of conversion of nitric acid to nitronium ions:

\[
\text{HNO}_3 + 2\text{H}_2\text{SO}_4 \rightleftharpoons \text{NO}_2^+ + \text{H}_2\text{O}^+ + 2\text{HSO}_4^-
\]

The decrease in rate above ~90% sulphuric acid can be attributed to rather complex solvent effects.

A first-order dependence upon nitric acid concentration has been demonstrated for the nitrodecarboxylation reaction (see experimental section):

\[
\text{Rate} = k_{\text{obs}} [\text{substrate}] (\text{HNO}_3)
\]

Since the rate of nitration of a second-order reaction can only depend on acidity if the concentration of one or other of the effective reactants depends upon acidity, then the rate profile of fig. 1 represents kinetic evidence for the nitronium ion as the nitrating agent (since the nitronium ion concentration does, indeed, depend upon acidity - see Chapter 3).

The rates of nitration (nitrodeprotonation) of aromatic substrates in sulphuric acid/water mixtures have been shown to parallel, fairly closely, the ionization of triarylcarbinols in sulphuric acid/water.
Fig. 1: Plot of nitrodecarboxylation rates for 2-acetamido-5-nitrothiophene-3-carboxylic acid vs. sulphuric acid concentration (c.f. plot for nitrodeprotonation of nitrobenzene).
mixtures \(^6,117\) i.e. to follow the \(H_R\) acidity function \(^118\). Moodie et al. \(^119\) found that plots of \(\log k\) vs. \(-\left(H_R + \log a_{H_2O}\right)\) are straight lines of near unit slope for a wide range of substrates (in media up to \(\sim90\%\) sulphuric acid). The water activity term, \(a_{H_2O}\), suggests that an additional molecule of water may be present in the sulphuric-nitric acid equilibrium (relative to the triarylcarbinol-sulphuric acid equilibrium). Slopes of plots of \(\log k\) vs. \(-H_R\) are usually > 1.

The data presented in table 1 are plotted in fig. 2 against \(-\left(H_R + \log a_{H_2O}\right)\), the latter values being derived from published data \(^52,58\). As shown, a straight line of unit slope is observed up to approximately 83% sulphuric acid. Thereafter the slope is markedly reduced, however. This effect can be explained in terms of amide protonation in concentrated acid. The unprotonated form of the base is the more reactive toward nitration and so the unit slope below \(\sim83\%\) sulphuric acid is due to nitration of the free base. However, the decrease in slope at higher concentrations can be understood in terms of a decrease in concentration of the reactive substrate, the free amide. The concentration of the less reactive, protonated amide increases with sulphuric acid concentration and so the slope of \(\log k\) vs. \(-\left(H_R + \log a_{H_2O}\right)\) is less than unity. Despite this restriction, the overall effect of increasing the acid concentration is to increase the rate of reaction owing to the predominant increase in nitronium ion concentration, i.e. \(-\left(H_R + \log a_{H_2O}\right)\) increases more rapidly with increase of \(\left(H_2SO_4\right)\) than does \(-H_A\), the amide protonation acidity function. Substantially lower slopes have also been observed by Moodie \(^167\) and Brignell \(^168\) due to the proportion of reactive free base falling with increasing acidity.

The plot shown in fig. 2 suggests an onset of protonation of 2-acetamido-5-nitrothiophene-3-carboxylic acid in \(\sim83\%\) sulphuric acid. This is further supported by the fact that below 80% sulphuric acid the
Fig. 2: Plot of $\log k_{2\text{obs}}$ against $-(H_R + \log a_{H_2O})$ for nitrodecarboxylation of 2-acetamido-5-nitrothiophene-3-carboxylic acid in sulphuric acid/water mixtures, at 25$^\circ$. 

SLOPE = 1.0 

7+Log $K_{2\text{obs}}$. 

- (H$_R$ + Log a$_{H_2O}$)
compound is not sufficiently soluble for even U.V. analysis ($10^{-4} - 10^{-5}$ M). Above ~82% acid the solubility increases markedly with increasing acid concentration, the thiophene derivative being quite soluble in 90% sulphuric acid.

**Nitration of 2-acetamido-5-nitrothiophene**

2-Acetamido-5-nitrothiophene was prepared by decarboxylation of the corresponding 3-carboxylic acid. The rates of nitration of this compound in sulphuric acid/water mixtures were determined, again, by U.V. spectroscopy. The observed second-order rate constants, $k_{2\text{obs}}$, for the nitrodeprotonation reaction are shown in table 2:

For reaction:-

![Chemical structure diagram]

<table>
<thead>
<tr>
<th>$H_2SO_4$ CONCENTRATION (w/w)</th>
<th>MEAN $k_{2\text{obs}}$ (1 mol$^{-1}$ sec$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>73.5%</td>
<td>4.3x10$^{-3}$</td>
</tr>
<tr>
<td>75.5%</td>
<td>2.6x10$^{-2}$</td>
</tr>
<tr>
<td>77.6%</td>
<td>1.0x10$^{-1}$</td>
</tr>
<tr>
<td>79.2%</td>
<td>2.9x10$^{-1}$</td>
</tr>
<tr>
<td>83.5%</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**TABLE 2**: Observed second-order rate constants for nitration of 2-acetamido-5-nitrothiophene in sulphuric-nitric acid mixtures at 25°C.

A plot of $\log k_{2\text{obs}}$, where $k_{2\text{obs}}$ is the observed second-order rate constant against $-(H_R + \log a_{H_2O})$ is shown in fig. 3 and is very similar
Fig. 3: Plot of log $k_{2\,\text{obs}}$ against $-(H_R + \log a_{H_2O})$ for nitration of 2-acetamido-5-nitrothiophene in sulphuric acid/water mixtures, at 25°C.
in form to that obtained for the corresponding nitrodecarboxylation reaction. The unit slope up to ~78% sulphuric acid is due to nitration of the base, which is present almost completely in the unprotonated form. Above ~78% sulphuric acid the slope decreases due to the increasing degree of amide protonation. Again, the more reactive free base is the species undergoing nitration but its concentration decreases with increasing sulphuric acid concentration.

Fig. 3 suggests an onset of protonation of 2-acetamido-5-nitrothiophene in ~78% sulphuric acid, a lower acid concentration than for the corresponding carboxylic acid (83%). This is to be expected since the carboxylic acid should be the weaker base. Similar solubility effects were observed for 2-acetamido-5-nitrothiophene as for the carboxylic acid i.e. it was practically insoluble below 80% sulphuric acid but fairly soluble in stronger sulphuric acid solutions.

The yield of 2-acetamido-3,5-dinitrothiophene obtained by nitration of 2-acetamido-5-nitrothiophene under similar conditions to the industrial process for the nitrodecarboxylation reaction was 82.6%. This contrasts with the 56.3% yield obtained by means of the latter process. However, only an equimolar quantity of nitric acid was required for the nitrodeprotonation reaction and the reaction was complete a few minutes after completion of the addition. The nitrodecarboxylation reaction required 1½ moles of nitric acid for complete reaction and the mixture was stirred for 2 hrs before drounout. Thus, competitive degradation of both starting material and product (via amide or the hydrolysis product, amine) is more likely during the slower nitrodecarboxylation reaction, leading to a reduced yield of product.
An ipso partial rate factor has been defined as:-

\[ i_f^R = \frac{k_{ArR} \times \% \text{ attack at ipso position in } ArR}{k_{ArH} \times \% \text{ attack at corresponding position in } ArH} \]

Since all other positions are effectively unreactive in the systems studied above, an ipso partial rate factor for the nitrodecarboxylation reaction can be defined:-

\[ i_f^{CO_2H} = \frac{\text{Rate of nitrodecarboxylation}}{\text{Rate of nitrodeprotonation}} \]

Extrapolation of the unit slope portion of the nitration plot in fig. 3 enables a direct comparison with the rate of nitrodecarboxylation in the same range of sulphuric acid concentration (c.f. fig. 2). Thus the vertical separation in log k units of the unit slope portions of figs. 2 and 3 represents (irrespective of protonation effects) \( \log i_f^{CO_2H} \).

Thus:

\[ \log i_f^{CO_2H} = -3.25 \]
\[ \text{i.e. } i_f^{CO_2H} = 5.6 \times 10^{-4} \]

This ipso factor for nitrodecarboxylation of \( 5.6 \times 10^{-4} \) is comparable with an ipso factor of \( 2 \times 10^{-3} \) obtained for a protodecarboxylation reaction\(^9\). However, direct comparison of ipso factors must be viewed with some caution because they are characteristic not only of the substituent (the carboxyl group) but also of the aromatic substrate, the attacking electrophile and the reaction conditions.

**OTHER 2-ACYLAMINO-5-NITROTHIOPHENE-3-CARBOXYLIC ACIDS**

Because of the poor yield of product obtained in the industrial nitration of 2-acetamido-5-nitrothiophene-3-carboxylic acid, a series
of alternative amides were prepared. The amides were subjected to identical industrial nitration conditions and the yields of 2-acylamino-3,5-dinitrothiophene determined in each case. The rates of nitrodecarboxylation of these amides were also determined by U.V. spectroscopy and the results are presented in table 3.

For the reaction:

\[
\begin{align*}
RCH_2CH_2Cl & \quad CH_3CH_2CH(CH_3)\_2C(CH_3)\_3 \\
H & \quad 10^{k_{\text{obs}}} \\
\text{(1 mol}^{-1}\text{ sec}\^{-1}) & \quad \text{Yield of dinitro amide} \\
H & \quad 3.9 \quad 72.7\% \\
CH_3 & \quad 1.3 \quad 56.3\% \\
CH_3CH_2Cl & \quad 8.5 \quad 81.3\% \\
CH_3CH_2CH(CH_3)\_2 & \quad 1.1 \quad 49.8\% \\
CH(CH_3)\_2 & \quad 6.4 \quad 51.4\% \\
C(CH_3)\_3 & \quad 2.3 \quad 42.1\% \\
\end{align*}
\]

TABLE 3: Rates of nitrodecarboxylation of 2-acylamino-5-nitrothiophene-3-carboxylic acids in \textasciitilde 90\% sulphuric acid at 25\(^\circ\)C, together with yields of nitrated product obtained under industrial nitration conditions.

It can be seen from table 3 that the improved yield obtained with the formamido and chloroacetamido derivatives is not due to any substantial increase in rate and therefore shorter reaction time. The improved yield can be accounted for by considering the A1 hydrolysis of amides
in concentrated sulphuric acid (see later). All of the amides, other than the formamido and chloroacetamido derivatives, are readily hydrolysed in concentrated acid to unstable amines. These amines are not isolable from the reaction mixtures because of their great instability in presence of nitric acid.

When 2-formamidothiophene-3-carboxylic acid was nitrated with 2½ moles of nitric acid per mole of substrate (as in the industrial nitration of 2-acetamidothiophene-3-carboxylic acid) the yield of 2-formamido-3,5-dinitrothiophene was 70.3%. This is a considerable improvement on the 46.2% yield of 2-acetamido-3,5-dinitrothiophene.

The variations in the rates of nitrodecarboxylation of the 2-acylamino-5-nitrothiophene-3-carboxylic acid derivatives with sulphuric acid concentration are shown in table 4. Plots of log k²obs against -(H⁺ + log a H₂O) are shown in fig. 4 and it can be seen that the behaviour is very similar to that of the corresponding 2-acetamido derivative i.e. an initial slope of unity, with a subsequent reduced slope due to the increased protonation of substrate. This protonation reduces the concentration of the more reactive species, the unprotonated amide.

For reaction:

\[ \text{CO}_2\text{H} \quad \text{H}_2\text{SO}_4 \quad \text{NO}_2 \quad \text{HNO}_3 \]
Fig. 4: Plots of log $k_{2\text{obs}}$ against $-(H_R + \log a_{H_2O})$ for nitrodecarboxylation of 2-acylamino-5-nitrothiophene-3-carboxylic acids in sulphuric acid/water mixtures at 25°.
TABLE 4: Rates of nitrodecarboxylation of 2-acylamino-5-nitrothiophene-3-carboxylic acids in sulphuric acid/water mixtures at 25°.

<table>
<thead>
<tr>
<th>% H₂SO₄</th>
<th>R = H, CH₂Cl, CH₂CH₃, CH(CH₃)₂, C(CH₃)₃</th>
<th>k₂obs (1 mol⁻¹ sec⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90.2</td>
<td>8.5x10⁻¹, 6.4x10⁻¹, 2.3x10⁻¹</td>
<td></td>
</tr>
<tr>
<td>88.2</td>
<td>1.9x10⁻¹, 2.3x10⁻¹, 2.9x10⁻¹, 4.5x10⁻²</td>
<td></td>
</tr>
<tr>
<td>86.1</td>
<td>2.1x10⁻¹, 7.7x10⁻³, 4.0x10⁻², 1.3x10⁻²</td>
<td></td>
</tr>
<tr>
<td>83.5</td>
<td>4.7x10⁻², 2.9x10⁻³, 4.0x10⁻², 4.5x10⁻²</td>
<td></td>
</tr>
<tr>
<td>80.9</td>
<td>3.2x10⁻³, 5.3x10⁻⁴, 1.9x10⁻³, 1.1x10⁻³</td>
<td></td>
</tr>
</tbody>
</table>

A further study of the nature and mechanism of the nitrodecarboxylation reaction was performed by studying a variety of thiophene ring systems.

(A) 3-Amidothiophene-2-carboxylic acids

Compounds of this type provide an interesting comparison with those of industrial interest since the positions of activating group and the reaction site are reversed.

When 3-acetamidothiophene-2-carboxylic acid was treated with an equimolar quantity of nitric acid in concentrated sulphuric acid only the 4-nitro isomer was isolated. This behaviour was similar to that of the corresponding 2-acetamidothiophene-3-carboxylic acid i.e. the favoured nitrodeprotonation reaction occurring exclusively, with no evidence of any nitrodecarboxylation.

The fact that the nitro group enters the 4-position in the case of the 3-acetamido derivative was demonstrated by hydrolysing the amide to amine and subsequent deamination:
Scheme 1:— Proof of structure of product of nitration of 3-acetamido-thiophene-2-carboxylic acid.

The final product, 4-nitrothiophene-2-carboxylic acid, is a known compound with a melting-point different from the 5-nitro isomer\textsuperscript{31}.

When 3-acetamido-4-nitrothiophene-2-carboxylic acid was treated with a sulphuric acid-nitric acid mixture (in an identical manner to that used preparatively for nitrodecarboxylation of 2-acetamido-5-nitrothiophene-3-carboxylic acid) there was no evidence of carbon dioxide evolution either during the addition of mixed acid or on drown-out. The starting material was recovered in 96% yield. Nitrodecarboxylation was eventually detected in 90% sulphuric acid at room temperature. However, treatment with nitric acid for 4 hrs was required for complete reaction; the product, 3-acetamido-2,4-dinitrothiophene, being isolated in only 32% yield. This reluctance to nitrodecarboxylate is in contrast to the corresponding 2-amido-3-carboxylic acid. Thiophene derivatives containing a carboxyl group in the \( \alpha \)-position are usually much more susceptible to nitrodecarboxylation due to the greater electron-density at the \( \alpha \)-position relative to the 3- or 8-position. Rinkes\textsuperscript{31} obtained
some 2-nitrothiophene during the nitration of thiophene-2-carboxylic acid in sulphuric-nitric acid, whereas Campagne\textsuperscript{36} found that the only product of nitration of thiophene-3-carboxylic acid was the 5-nitro isomer. Thus the reluctance of 3-acetamido-4-nitrothiophene-2-carboxylic acid to nitrodecarboxylate cannot be readily rationalized. The presence of the nitro group would certainly deactivate the system towards electrophilic attack, both 5-nitro and 4-nitro thiophene-2-carboxylic acid being stable to nitrodecarboxylation\textsuperscript{31}. 3-Formamidothiophene-2-carboxylic acid behaved in a similar manner to the corresponding acetamido derivative i.e. mono-nitration in the 4-position and only a slow subsequent nitrodecarboxylation reaction.

(B) 2-Amido-4,5-Substituted Thiophene-3-Carboxylic Acids

An attempt was made to study the nitrodecarboxylation reaction in thiophene ring systems in which the 4- and 5-positions were suitably blocked, in order to eliminate the possibility of unwanted nitrodeprotonation reactions. 2-Amino-4,5-dimethylthiophene-3-carboxylic acid was prepared as a possible starting point for a variety of activated thiophene-3-carboxylic acids, by treatment of methyl ethyl ketone with ethyl cyanoacetate and sulphur in presence of base. However, attempts to replace the amino group with a variety of substituents proved unsuccessful. The Sandmeyer reaction was attempted by treatment of a solution of the diazonium salt with cuprous chloride in hydrochloric acid, but no 2-chloro-3-carboxylic acid derivative was isolable from the reaction mixture. Similarly efforts to replace the diazonium group with cyano, hydroxy, bromo etc. were equally unsuccessful. The products were black, tarry solids with an unpleasant smell, from which none of the desired products were isolable.

Methyl-2-amino-4,5-dimethylthiophene-3-carboxylate was deaminated by
warming a solution of the diazonium salt with copper acetate in ethanol. However all attempts to substitute in the 2-position of 4,5-dimethyl-thiophene-3-carboxylic acid by conventional electrophilic substitution reactions e.g. halogenation, alkylation etc., were unsuccessful.

A further attempt to prepare 2-hydroxy-4,5-dimethylthiophene-3-carboxylic acid involved a variation upon the rearrangement reaction proposed by Gewald:

\[
\text{NaOEt} \quad \xrightarrow{\text{EtOH}} \quad \text{[Reagents]} \quad \xrightarrow{\text{EtOH}}
\]

Scheme 2: Mechanism proposed by Gewald for rearrangement of ethyl-2-amino-4-methylthiophene-3-carboxylate to 2-hydroxy-3-cyano-4-methylthiophene.

When methyl-2-amino-4,5-dimethylthiophene-3-carboxylate was treated with sodium ethoxide in this way an 86% recovery of starting material was obtained after refluxing for 4 hrs. There was no evidence for formation of a cyano or hydroxy- compound. Gewald does state that "the reaction proceeds smoothly only if position 5 is free or substituted
by an electron withdrawing group".

2-Amino-4-methylthiophene-3-carboxylic acid was similarly prepared and the rearrangement reaction with sodium ethoxide proceeded quite smoothly to yield 2-hydroxy-3-cyano-4-methylthiophene as in scheme 2. A sharp carbonyl peak in the infra-red spectrum of the product indicates that the hydroxy-cyano-thiophene exists predominantly in the keto form:

\[
\text{Me} \quad \text{CN} \quad \text{OH} \quad \text{S} \quad \text{Me}
\]

The 2-hydroxy derivative was methylated to give the more stable 2-methoxy compound but all attempts to convert the cyano group to a carboxyl group were unsuccessful. Hydrolysis to an amide was possible in concentrated sulphuric acid but 2-methoxy-4-methylthiophene-3-carboxylic acid could not be prepared. Refluxing for several hours in concentrated hydrochloric acid, under a nitrogen atmosphere, led only to re-appearance of the hydroxyl group in the 2-position.

A variation upon the rearrangement reaction of scheme 2 was attempted in the hope of avoiding the undesirable isolation of a cyano compound.

Scheme 3: Proposed scheme for preparation of ethyl-2-hydroxythiophene-3-carboxylate
The intermediate proposed for the rearrangement reaction to a 2-hydroxy-3-cyano derivative in scheme 2 is very similar to the intermediate proposed for a conventional sulphur insertion reaction for preparation of thiophene derivatives (see experimental section). Thus, an attempt was made to prepare a 2-hydroxy thiophene derivative from simple starting materials e.g. mercaptoacetaldehyde dimer and diethyl malonate (c.f. the starting materials for preparation of the 2-amino derivative are mercaptoacetaldehyde dimer and ethylcyanoacetate). The proposed scheme is illustrated in scheme 3. However, upon treatment of mercaptoacetaldehyde dimer with diethyl malonate in presence of sodium ethoxide the only isolable product was a black tarry substance with a strong, unpleasant smell. No identifiable thiophene derivatives were detectable. Similarly, further attempts to prepare 2-hydroxy-3-cyano thiophene derivatives from simple starting materials were equally unsuccessful. For example, treatment of acetyl acetone and ethyl cyanoacetate with sodium ethoxide and sulphur led to recovery of sulphur but no detectable thiophene products. When the same reagents were mixed in presence of triethylamine as base, rather than ethoxide, the product was that of conventional sulphur insertion, ethyl-2-amino-4-methyl-5-acetylthiophene-3-carboxylate. Hydroxythiophenes are, in fact, generally unstable and have been known to decompose rapidly in air to unstable tars. This characteristic may be due, in part, to the ability of compounds of this class to undergo a rearrangement to a keto-form, i.e. to exist in two tautomeric forms.

Despite several difficulties encountered in the preparation of 2-substituted 4,5-dimethylthiophene-3-carboxylic acids and the corresponding 2-substituted-4-methylthiophene-3-carboxylic acids, the 2-amido derivatives were readily available. The nitrodecarboxylation of 2-acetamido-4,5-dimethylthiophene-3-carboxylic acid proceeded readily in a 98% sulphuric
acid-nitric acid mixture at $0^\circ$. The yield of 2-acetamido-3-nitro-4,5-dimethylthiophene obtained was 52.4%.

\[ \text{CH}_3\text{C}_\text{O}_2\text{H} \quad \text{HNO}_3 \quad \text{H}_2\text{SO}_4 \quad \text{CH}_3\text{S} \text{NHCOCCH}_3 \]

The reaction product was susceptible to hydrolysis to an unstable amine in concentrated sulphuric acid. This would partly account for the unsatisfactory yield of nitro amide obtained from the nitrodecarboxylation reaction.

When 2-acetamido-4-methylthiophene-3-carboxylic acid was nitrated in 98% sulphuric acid with an equimolar quantity of nitric acid at $0^\circ$ the 5-nitro isomer was isolable. Further treatment with nitric acid led to a nitrodecarboxylation reaction, the overall yield of 2-acetamido-4-methyl-3,5-dinitrothiophene being 44.0%:

\[ \text{CH}_3\text{C}_\text{O}_2\text{H} \quad \text{HNO}_3 \quad \text{H}_2\text{SO}_4 \quad \text{CH}_3\text{S} \text{NHCOCCH}_3 \]

Again, the reaction product was hydrolysed to an unstable amine in concentrated sulphuric acid, and this was reflected in the rather poor yield of 2-acetamido-4-methyl-3,5-dinitrothiophene obtained.

(C) 2-Substituted-3-Nitrothiophene-5-Carboxylic Acids

1) Synthesis:

A series of 'para'-substituted thiophene-carboxylic acids were prepared with a view to studying the effect of such substituents upon the
rate of nitrodecarboxylation for the process:

\[
\text{HN}_3O \rightarrow \text{HNO}_3
\]

\[
\text{S}_2\text{SO}_4 \rightarrow \text{H}_2\text{SO}_4
\]

This system possesses several advantages over the systems considered previously. Firstly, the variable substituent, X, is effectively para to the reactive site, containing the carboxyl group. This should eliminate any ortho steric effects. Secondly, the carboxyl group should be quite reactive since thiophene-2-carboxylic acid itself, upon nitration, yields a mixture of products, one of which is 2-nitrothiophene\textsuperscript{31}. Further examples of nitrodecarboxylation of substituted thiophene-2-carboxylic acids are known\textsuperscript{3,31,33}. Finally, the presence of the nitro group, ortho to X, should increase the stability of the thiophene nucleus itself to oxidative attack by nitric acid.

\textit{2-Methyl-3-nitrothiophene-5-carboxylic acid}

Campagne\textsuperscript{33} found that 2-methyl-3-nitrothiophene-5-carboxylic acid underwent a nitrodecarboxylation reaction with nitric acid in both acetic anhydride and concentrated sulphuric acid as solvent. Upon nitration of 2-methylthiophene-5-carboxylic acid in 98% sulphuric acid at 20\textdegree, Campagne obtained a 41% yield of 2-methyl-3-nitrothiophene-5-carboxylic acid and a 12.5% yield of 2-methyl-3,5-dinitrothiophene. When the same reaction was performed at -5\textdegree a 61% yield of the 3-nitro acid was obtained and only a small amount of nitrodecarboxylated product was detectable. Indeed, Campagne\textsuperscript{33} reports a quantitative recovery of 2-methyl-3-nitrothiophene-5-carboxylic acid from a sulphuric-nitric acid mixture at -5\textdegree. Upon increasing the temperature to -1\textdegree, a vigorous evolution of carbon dioxide was observed, and when a weighed sample was
nitrated by this procedure at 20\(^\circ\)C, a 96\% yield of 2-methyl-3,5-dinitrothiophene was obtained.

2-Methylthiophene-5-carboxylic acid was prepared by acetylation of 2-methylthiophene and oxidation of the 5-acetyl derivative. Nitration with an excess of nitric acid in sulphuric acid at -10\(^\circ\)C yielded 2-methyl-3-nitrothiophene-5-carboxylic acid as the only product. The rate of nitrodecarboxylation of this methyl activated carboxylic acid was studied as a function of sulphuric acid concentration.

2-Ethyl-3-nitrothiophene-5-carboxylic acid was prepared in a similar manner and its rate of nitrodecarboxylation similarly studied.

2-Halogeno-3-nitrothiophene-5-carboxylic acids

2-Halogeno-3-nitrothiophene-5-carboxylic acids were prepared by halogenation of thiophene-5-carboxylic acid and subsequent mono-nitration in the 3-position with a sulphuric-nitric acid mixture at -20\(^\circ\)C. Nitration of 2-chlorothiophene-5-carboxylic acid at -20\(^\circ\)C led to a 62.5\% yield of 2-chloro-3-nitrothiophene-5-carboxylic acid and a 22\% yield of the nitrodecarboxylated product, 2-chloro-3,5-dinitrothiophene. A similar mixture of products was obtained with the corresponding 2-bromo derivative. The rates of nitrodecarboxylation of the 2-halogeno-3-nitrothiophene-5-carboxylic acids were studied as a function of sulphuric acid concentration.

2-Methoxy-3-nitrothiophene-5-carboxylic acid

1) Nucleophilic Substitution

The halogens of halo-nitrothiophenes are more labile than those of the corresponding benzene derivatives. Hurd and Kreuz\(^{21}\) found that 2-chloro-3,5-dinitrothiophene was more reactive towards piperidine and
methanolic potassium hydroxide than 2,4-dinitrochlorobenzene. Nucleophilic substitutions of this sort have been used in the preparation of many substituted thiophenes. Aminonitrothiophenes, nitrothienols and allyl ether derivatives have all been obtained from the appropriate halogenated nitrothiophenes.\textsuperscript{21,172}

2-Methoxy-3-nitrothiophene-5-carboxylic acid was prepared by treatment of the corresponding 2-bromo derivative with methanolic potassium hydroxide. An 80\% yield of the 2-methoxy-activated carboxylic acid was obtained:

\[
\text{NO}_2 \quad \text{Br} \quad \text{CO}_2\text{H(Me)} \quad \text{OMe} \quad \rightarrow \quad \text{NO}_2 \quad \text{OMe} \quad \text{CO}_2\text{H(Me)}
\]

2-Methylthio-3-nitrothiophene-5-carboxylic acid

This derivative was prepared in a similar manner to the corresponding 2-methoxy derivative, i.e. treatment of 2-bromo-3-nitrothiophene-5-carboxylic acid with methane thiol in a methanolic potassium hydroxide solution. An 88.5\% yield of the 2-methylthio derivative was obtained:

\[
\text{NO}_2 \quad \text{CO}_2\text{Me} \quad \text{Br} \quad \text{MeSH} \quad \text{OH}^- \quad \rightarrow \quad \text{NO}_2 \quad \text{CO}_2\text{Me} \quad \text{SMe} \quad \text{OH}^- / \text{MeOH} \]
\]

\[
\text{NO}_2 \quad \text{CO}_2\text{H} \quad \text{SMe}
\]
No nitrodecarboxylation was detectable upon treatment of 2-methylthio-3-nitrothiophene-5-carboxylic acid with nitric acid in 98% sulphuric acid. Instead, a sulphone was isolated from the reaction mixture, presumably due to an oxidation in presence of nitric acid:

![Chemical Structure](image)

The sulphone substituted thiophene-carboxylic acid showed no tendency to nitrodecarboxylate, even at room temperature with a ten-fold excess of nitric acid.

2-Acetamido-3-nitrothiophene-5-carboxylic acid

All attempts to prepare 2-acetamido-3-nitrothiophene-5-carboxylic acid failed. Upon treatment of methyl-2-bromo-3-nitrothiophene-5-carboxylate with ammonium hydroxide in methanol a 68% yield of the corresponding 2-amino derivative was obtained. Subsequent acetylation gave the 2-acetamido derivative but all attempts to convert this acetamido ester to the corresponding acetamido acid resulted in preferential amide hydrolysis to the 2-amino compound. The product of prolonged alkaline hydrolysis was 2-amino-3-nitrothiophene-5-carboxylic acid but attempts to re-acetylate this compound were unsuccessful. The proposed method of preparation is shown in scheme 4:–
Scheme 4: Attempted preparation of 2-acetamido-3-nitrothiophene-5-carboxylic acid.

All attempts to replace the bromine atom of 2-bromo-3-nitrothiophene-5-carboxylic acid with the acetamido group directly, by nucleophilic displacement of bromide with acetamide, were unsuccessful. There was no evidence of substitution upon refluxing the bromo acid with acetamide in methanol for 48 hrs. Attempts to prepare the acetamide anion in situ were also unsuccessful.

An alternative approach involved nitration of thiophene-2-carboxylic acid. Separation of the 5-nitro isomer and reduction of the methyl ester (followed by acetylation) gave methyl-2-acetamidothiophene-5-carboxylate. Nitration gave the 3-nitro isomer but, again, all attempts to hydrolyse methyl-2-acetamido-3-nitrothiophene-5-carboxylate were unsuccessful. The amido group was preferentially hydrolysed to the amine under basic conditions and this amine was rather unstable in presence of excess base. Attempts to hydrolyse the ester group at the methyl-2-acetamidothiophene-5-carboxylate stage were equally unsuccessful.
Scheme 5:- Attempted preparation of 2-acetamido-3-nitrothiophene-5-carboxylic acid.

3-Nitrothiophene-5-carboxylic acid was obtained as a by-product in the nitration of thiophene-5-carboxylic acid. Treatment of a solution of 3-nitrothiophene-5-carboxylic acid in sulphuric acid with excess nitric acid at room temperature failed to produce any nitrodecarboxylated product. The starting material was recoverable after 48 hrs standing at room temperature (55% yield). Attempted nitrodecarboxylation at higher temperatures led to degradation of the starting material. 2-Nitrothiophene-5-carboxylic acid was similarly stable to any further nitration reaction. The lack of reactivity of 3-nitrothiophene-5-carboxylic acid is especially surprising in view of the fact that nitrodecarboxylation of the corresponding 2-halogeno derivative occurs at a measurable rate. Rinkes'
did not obtain any 3,5-dinitrothiophene as product in the nitration of thiophene-5-carboxylic acid, thus supporting the lack of reactivity of 3-nitrothiophene-5-carboxylic acid (which Rinkes did isolate as a reaction product).

2-N-Methylamino-3-nitrothiophene-5-carboxylic acid was prepared in a similar manner to the 2-amino derivative i.e. by treatment of the 2-bromo ester with methylamine in methanol. Acetylation gave the N-methylacetamido derivative. However, as in the case of the corresponding 2-acetamido derivative, attempts to prepare 2-N-methylacetamido-3-nitrothiophene-5-carboxylic acid by hydrolysis of the ester were hindered by the extremely labile amido group, which was hydrolysed preferentially under basic conditions.

**Decarboxylation of 2-substituted-3-nitrothiophene-5-carboxylic acids**

2-Substituted-3-nitrothiophenes were prepared by decarboxylation of the corresponding 5-carboxylic acids. The nitrodecarboxylation of the latter derivatives could then be directly compared with the corresponding nitrodeprotonation reactions:

![Reaction diagram](image)

Both 2-methyl-3-nitrothiophene and 2-ethyl-3-nitrothiophene were prepared by decarboxylation of the 5-carboxylic acid with copper-quinoline\textsuperscript{172}. 2-Chloro and 2-bromo-3-nitrothiophenes were prepared by decarboxylation of the 5-carboxylic acids with mercuric oxide and glacial acetic acid\textsuperscript{21}.
The variation in rate of nitrodeprotonation with sulphuric acid concentration was determined for the decarboxylated products.

ii) Kinetics

(a) Nitrodecarboxylation

For reaction:

\[
\begin{align*}
\text{NO}_2 & \quad \text{HNO}_3 \\
\text{S} & \quad \text{H}_2\text{SO}_4 \\
\text{CO}_2\text{H} & \quad \text{NO}_2
\end{align*}
\]

\(X = \text{CH}_3, \text{CH}_2\text{CH}_3, \text{Cl, Br, OCH}_3\)

The rate of nitrodecarboxylation of each of the 2-substituted-3-nitrothiophene-5-carboxylic acids was studied as a function of sulphuric acid concentration. The observed second-order rate constants, obtained by U.V. spectroscopy, are plotted against \(-\left(H_R + \log a_{H_2O}\right)\) in fig. 5 (for each substrate).

For the 2-methyl, 2-ethyl, 2-chloro and 2-bromo derivatives the plots of \(\log k_{2obs}\) against \(-\left(H_R + \log a_{H_2O}\right)\) revealed straight lines of approximately unit slope in the range of sulphuric acid concentration which was studied. This suggests that in each case the nitrodecarboxylation proceeds via a single reactive species, presumably the unprotonated 2-substituted-3-nitrothiophene-5-carboxylic acid. The observed variation in rate with sulphuric acid concentration is in accordance with nitronium ion nitration.

However, in the case of 2-methoxy-3-nitrothiophene-5-carboxylic acid a plot of \(\log k_{2obs}\) against \(-\left(H_R + \log a_{H_2O}\right)\) revealed a straight line plot of approximately unit slope up to ~80% sulphuric acid and thereafter the slope decreases to ~0.35. This suggests that above 80%
Fig. 5: Plots of $\log k_{2 \text{obs}}$ against $-(H_P + \log a_{H_2O})$ for nitrodecarboxylation of 2-substituted-3-nitrothiophene-5-carboxylic acids in sulphuric acid/water mixtures at 25°C.
sulphuric acid extensive protonation of the methoxy group occurs thereby decreasing the concentration of the reactive (unprotonated) substrate. The protonated methoxy group is a much less effective activating group for attack by nitronium ion and hence the increase in rate above 80% sulphuric acid is less than anticipated from considerations of the nitronium ion concentration only. However, the overall plot shown in fig. 5 is again in accordance with nitronium ion nitration.

(b) Nitrodeprotonation

For reaction:

\[
\begin{align*}
\text{NO}_2 & \text{X} \text{S} \\
\rightarrow & \text{HNO}_3 \\
\text{H}_2\text{SO}_4 & \rightarrow \text{NO}_2 \text{X} \text{S}
\end{align*}
\]

\(X = \text{CH}_3, \text{CH}_2\text{CH}_3, \text{Cl}, \text{Br}\)

The rate of nitrodeprotonation of each of the 2-substituted-3-nitrothiophenes was studied as a function of sulphuric acid concentration. The logarithms of the observed second-order rate constants, obtained by U.V. spectroscopy, are plotted against \(-\text{H}_R + \log a_{\text{H}_2\text{O}}\) in fig. 6. In each case, straight lines of unit slope were obtained for the range of acid concentration studied (73% - 83% sulphuric acid). The reactions are, therefore, presumably conventional nitrations, the reactive species being the unprotonated 2-substituted-3-nitrothiophene in each case. The plots shown in fig. 6 are indicative of nitronium ion nitration.

iii) Product Analysis

(a) Nitrodecarboxylation

When the nitrodecarboxylation of the 2-substituted-3-nitrothiophene-
Fig. 6: Plots of log $k_2$ obs against $-(H_R + \log a_{H_2O})$ for nitrodeprotonation of 2-substituted-3-nitrothiophenes in sulphuric acid/water mixtures at 25°C.
5-carboxylic acids was performed on a preparative scale, with $1\frac{1}{2}$ moles of nitric acid per mole of thiophene derivative at $0 - 5^\circ$, 2-substituted-3,5-dinitrothiophenes were obtained. The 2-halogeno-3-nitrothiophene-5-carboxylic acids required stirring for two hours at $0 - 5^\circ$ for complete reaction of the starting material, the 2-halogeno-3,5-dinitrothiophenes being isolated in ~85% yield. When 2-methoxy-3-nitrothiophene-5-carboxylic acid was similarly nitrated with nitric acid in 98% sulphuric acid at $0 - 5^\circ$ a 90% yield of 2-methoxy-3,5-dinitrothiophene was obtained after only 20 minutes reaction time.

(b) Nitrodeprotonation

A 93% yield of 2-methyl-3,5-dinitrothiophene was obtained upon nitration of 2-methyl-3-nitrothiophene with an equimolar quantity of nitric acid, in concentrated sulphuric acid. Under similar conditions 2-ethyl-3-nitrothiophene, upon nitration, yielded 89% of the dinitro derivative. Similarly the 2-halogeno-3-nitrothiophenes were nitrated, at $0 - 5^\circ$, in 90% yield, the reaction time being < 20 minutes (compared with the 2 hours reaction time required for the corresponding nitro-decarboxylation reaction).

Hammett Plots

It is believed that quantitative linear correlations of aromatic reactivity using the $\sigma^+ \rho^+$ relation can be drawn to a limited extent only. Generally, the precisions of the correlations are not as good as those given by the Hammett equation for reactions in which direct resonance effects are not important. The use of Brown's equation for electrophilic substitutions has, in general, been fully discussed$^{3,71}$:

$$\log_{10} \frac{k}{k_0} = \rho^+ \sigma^+$$
where \( k \) is rate constant for the substituted compound

\[ k_0 \] is rate constant for the unsubstituted compound

\( \rho^+ \) is the reaction constant

\( \sigma^+ \) is the substituent constant

The reaction constant, \( \rho^+ \) is a parameter which is independent of the substituent but characteristic of the particular reaction and the conditions. It is a measure of the sensitivity of a given reaction series to substituent effects. The \( \sigma^+ \) term is a substituent parameter independent of the reaction, but characteristic of the substituent. The applicability of the two-parameter equation and the constants devised by Brown\textsuperscript{71,73} for electrophilic aromatic substitutions has been confirmed by plotting values of the partial rate factors for a reaction against the appropriate substituent constants\textsuperscript{65}. The slopes of the linear correlations give the values of the reaction constants.

**Nitrodecarboxylation**

There is no report in the literature of any reaction constant for an ipso substitution reaction. The rates of nitrodecarboxylation of a variety of 2-substituted thiophene-5-carboxylic acids in 89.9% sulphuric acid are shown in table 5.

For reaction:

\[
\begin{array}{c}
\text{NO}_2 \quad \text{X} \\
\text{S} \quad \text{CO}_2\text{H}
\end{array}
\xrightarrow{\text{HNO}_3} \begin{array}{c}
\text{NO}_2 \quad \text{X} \\
\text{S} \quad \text{NO}_2
\end{array}
\]
TABLE 5: Rates of nitrodecarboxylation of 2-substituted-3-nitrothiophene-5-carboxylic acids in 89.9% sulphuric acid at 25°.

* - the rate constant for the 2-methoxy compound is that for the unprotonated species, calculated by extrapolation of the straight line (slope unity) obtained by plotting log k_{2obs} against -(H_R + log a_{H_2O}).

A plot of log k_{2obs} against σ⁺ values is shown in fig. 7 and it can be seen that a reasonable straight line is obtained. The slope is -4.6 and this value represents the sensitivity of the nitrodecarboxylation reaction to substituent effects. The negative value implies that electron-releasing substituents accelerate the reaction rate, thus confirming the electrophilic nature of the process.

Nitrodeprotonation

The rates of nitration (nitrodeprotonation) of a variety of 2-substituted-3-nitrothiophenes in 83.5% sulphuric acid are shown in table 6:-

<table>
<thead>
<tr>
<th>Substituent, X</th>
<th>σ⁺</th>
<th>k_{2obs} in 89.9% H₂SO₄ (1 mol⁻¹ sec⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl</td>
<td>+0.114</td>
<td>7.2x10⁻⁴</td>
</tr>
<tr>
<td>Br</td>
<td>+0.150</td>
<td>4.7x10⁻⁴</td>
</tr>
<tr>
<td>CH₂CH₃</td>
<td>-0.295</td>
<td>5.1x10⁻²</td>
</tr>
<tr>
<td>CH₃</td>
<td>-0.311</td>
<td>6.3x10⁻²</td>
</tr>
<tr>
<td>OCH₃</td>
<td>-0.778</td>
<td>9.1*</td>
</tr>
</tbody>
</table>
Fig. 7: Plot of $7 + \log k_{2\,obs}$ against $\sigma^+$ values for nitrodecarboxylation of 2-substituted-3-nitrothiophene-5-carboxylic acids in 89.8% sulphuric acid at 25°.
For reaction:

\[
\begin{array}{c}
\text{NO}_2 \quad \text{HNO}_3 \\
\text{H}_2\text{SO}_4 \\
\text{H}_2\text{SO}_4
\end{array}
\]

<table>
<thead>
<tr>
<th>Substituent, X</th>
<th>( \sigma^+ )</th>
<th>( k_{2\text{obs}} ) in 83.5% H\text{2SO}_4 (1 \text{ mol}^{-1} \text{ sec}^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl</td>
<td>+0.114</td>
<td>4.8x10^{-3}</td>
</tr>
<tr>
<td>Br</td>
<td>+0.150</td>
<td>3.7x10^{-3}</td>
</tr>
<tr>
<td>CH_2CH_3</td>
<td>-0.295</td>
<td>1.0x10^{-1}</td>
</tr>
<tr>
<td>CH_3</td>
<td>-0.311</td>
<td>1.4x10^{-1}</td>
</tr>
</tbody>
</table>

TABLE 6: Rates of nitration of 2-substituted-3-nitrothiophenes in 83.5\% sulphuric acid at 25\°.

A plot of \( \log k_{2\text{obs}} \) against \( \sigma^+ \) values is shown in fig. 8. A straight line of slope -3.4 is obtained; this value representing the sensitivity of the nitration reaction to substituent effects. Again the negative value is to be expected for an electrophilic process of this sort.

Comparison of Nitrodecarboxylation and Nitrodeprotonation

\[
\begin{align*}
p^+_{\text{de-CO}_2\text{H}} & = -4.6 \\
p^+_{\text{d-H}} & = -3.4
\end{align*}
\]

A comparison of the reaction constants obtained for the nitrodecarboxylation and nitrodeprotonation reactions reveals that the former is rather more sensitive to substituent effects.

In general, nitration in aqueous sulphuric acid can provide data for compounds covering a large span of reactivities since the second-order
Fig. 8: Plot of $7 + \log K_{2obs}$ against $\sigma^*$ values for nitration of 2-substituted-3-nitrothiophenes in 83.5% sulphuric acid at 25°.
rate constant decreases by a factor of about $10^4$ for each decrease of 10% in the sulphuric acid concentration. Direct comparisons with benzene can be made in solutions up to 82% sulphuric acid. However, with strongly activating substituents, nitration in sulphuric acid is of limited value because of the early onset of diffusion control. Coombes et al.\textsuperscript{79} obtained partial rate factors for nitration of benzene derivatives in sulphuric acid. A plot of the data against $\sigma^+$ constants gave a straight line of slope -11.6. No such nitration reaction constant has been obtained for thiophene derivatives. Coombes' data refers primarily to deactivating substituents because of the practical difficulties involved with highly activated systems (diffusion control etc.). Correlations for nitration have most often been obtained with other solvents e.g. for nitration, $\rho = -6.0$ in nitromethane\textsuperscript{73} and $\rho = -6.5$ in acetic anhydride.

Comparison of the reaction constants obtained in the current investigation with those for nitration of substituted benzenes reveals that the thiophene derivatives are considerably less sensitive to substituent effects. This implies a smaller positive charge on the thiophene ring in the transition state i.e. an 'earlier' transition state. A similar effect has been observed by Butler\textsuperscript{44,45} for the halogenation of substituted thiophenes. A linear correlation with $\sigma^+$ values was obtained with a $\rho$ value of -6.5 for chlorination. This is lower than the value (-9.8) for the chlorination of substituted benzenes in acetic acid. Clementi and Marino\textsuperscript{48} also report that 'electrophilic substitutions at the thiophene ring exhibit a selectivity which is always somewhat lower than that of corresponding reactions at the benzene ring'. However, no quantitative interpretation of substituent effects upon rates of nitration of thiophene derivatives has been reported.
Summary and Conclusions

The current investigation represents one of the few kinetic and mechanistic studies of an 'ipso' substitution reaction. The nitrodecarboxylation reaction has been shown to possess many of the characteristics of the conventional nitrodeprotonation reaction.

(A) Electrophilic

The electrophilic nature of the process has been demonstrated by the necessity for activation of the reaction site by electron release. The reaction constant, $p^+$, for nitrodecarboxylation of 2-substituted-3-nitrothiophene-5-carboxylic acids, was -4.6, confirming earlier observations that electron-releasing substituents facilitate nitrodecarboxylation. The ease of nitrodecarboxylation of 2-acetamido-5-nitrothiophene-3-carboxylic acid contrasts sharply with the stability of 5-nitrothiophene-3-carboxylic acid to nitrating media.

(B) Nitronium Ion Nitration

The nitronium ion is believed to be the attacking electrophile, because of the variation in rate of nitrodecarboxylation with sulphuric acid concentration. This variation in rate is very similar to that observed for conventional nitrodeprotonation reactions where the nitronium ion has been confirmed as the effective electrophile. The nitrodecarboxylation reaction was first-order with respect to both thiophene derivative and nitric acid.

Butler studied the nitration of thiophene and some substituted thiophenes in sulphuric acid and concluded that the mechanism was the same as that for benzene compounds. The variation of $k_{2obs}$, the observed second-order rate constant, with acid concentration was measured and a linear relationship, with a slope of unity, was demonstrated between
log \( k_{2obs} \) and \(- (H_R + \log a_{H_2O})\).

The current investigation has demonstrated a similar effect for the nitrodecarboxylation reaction i.e. a slope of unity between \( \log k_{2obs} \) and \(- (H_R + \log a_{H_2O})\). Schofield and Williamson have shown that a similar relationship exists for a number of benzene compounds.

Nitrous acid is known to interfere in aromatic nitration, particularly with highly activated compounds, where an important route to the nitro-compound has been shown to be nitrosation followed by oxidation. However, the rates of nitrodecarboxylation of 2-substituted-3-nitrothiophene-5-carboxylic acids were unaffected by the addition of small quantities of urea, which would destroy any nitrous acid present. Similarly, the yield of 2-acetamido-3,5-dinitrothiophene obtained industrially was unaffected by the addition of urea to the reaction mixtures. Butler has found some evidence of nitrosation in the thiophene series, but only where diffusion-controlled nitration is predominant.

(C) Substituent Effects

The nitrodecarboxylation reaction has been shown to be rather more sensitive to substituent effects than the corresponding nitrodeprotonation reaction. However these thiophene derivatives are considerably less sensitive to substituent effects than the benzene series. This suggests an 'earlier' transition state i.e. less positive charge on the thiophene ring. The characteristics of the nitration reactions are similar to those of the corresponding benzene compounds. Hammett's \( \sigma^+ \) constants are equally successful in correlating data for electrophilic substitutions (nitrodecarboxylation and nitrodeprotonation) in thiophene compounds. Thus, the sulphur atom in thiophene appears to have little influence upon the relative transmissions of substituent effects in electrophilic substitutions.
(D) **Ipso Factors**

The nitrodecarboxylation reaction has been shown to be considerably slower than the corresponding nitrodeprotonation reaction. An ipso factor of $5.6 \times 10^{-4}$ was obtained by comparing the rate of nitration of 2-acetamido-5-nitrothiophene-3-carboxylic acid with that of 2-acetamido-5-nitrothiophene. This relative reluctance to nitrodecarboxylate can be partially explained in terms of the decrease in electron-density at the reaction site due to the electron-withdrawing carboxyl group. There is obviously a greater steric hindrance to electrophilic attack in the case of the nitrodecarboxylation reaction. Ipso substitutions are, in general, considerably slower than the corresponding deprotonation reactions.

(E) **Mechanism**

The possibility that the nitrodecarboxylation reaction consists of a two stage process, protodecarboxylation followed by conventional nitrodeprotonation, has been discarded.

i) A fast protodecarboxylation followed by slow nitrodeprotonation would not account for the considerable ipso factor i.e. the large rate difference between the nitrodecarboxylation and corresponding nitrodeprotonation reaction. This mechanism would require an ipso factor of unity.

ii) A slow protodecarboxylation followed by fast nitration would not account for the variation in nitration rate with nitronium ion concentration. This mechanism would require the reaction to be zero order in nitric acid. Also, the carboxylic acids show no tendency to decarboxylate in sulphuric acid alone under the appropriate reaction conditions.

A concerted mechanism, similar to that for conventional nitration, is a possibility:
It is not possible to state, at this stage, which of the two steps in the proposed mechanism is slower. However, the $p^+$ value of -4.6 for the nitrodecarboxylation reaction suggests a slow first step, which involves the initial attack of electrophile. This is comparable with conventional nitrodeprotonation:

$$\text{ArH} + \text{NO}_2^+ \overset{k_1}{\underset{k_{-1}}{\rightleftharpoons}} \text{Ar}^+ + \text{H}^+$$

Evidence for the above mechanism arises from a study of isotope effects. If the rate-determining step involved the breaking of the C-H bond i.e. the second step above, then deuterated substrates should undergo substitution more slowly than non-deuterated compounds. In most aromatic substitutions, and especially in the case of conventional nitrations, there is no isotope effect. This is in accordance with the mechanism proposed, the initial attack by electrophile being rate-determining.

A study of isotope effects would similarly provide valuable information regarding the mechanism of nitrodecarboxylation. The replacement of the $^{12}\text{C}$ carbon atom of the carboxyl group with a heavier carbon isotope e.g. $^{13}\text{C}$, and the subsequent effect upon the rate of nitrodecarboxylation, would
be most informative.

\[
\begin{align*}
\text{Ar} - \text{CO}_2\text{H} + \text{NO}_2^+ & \quad \overset{k_1}{\rightleftharpoons} \quad \text{Ar} - \text{CO}_2\text{H} - \text{NO}_2 \\
& \quad \overset{k_2}{\rightarrow} \quad \text{ArNO}_2 + \text{CO}_2 + \text{H}^+ \\
\end{align*}
\]

The absence of any carbon isotope effect would be in accordance with the two-step mechanism postulated above, the initial attack of nitronium ion again being rate-determining. However, if a measurable isotope effect were observed then a slow second step, involving the carbon-carbon bond breaking, would be favoured\textsuperscript{96,175}. Many conventional protodecarboxylation reactions are believed to proceed by the mechanism - for electrophilic substitutions, with H\textsuperscript{+} as the electrophile and COOH\textsuperscript{+} as the leaving group\textsuperscript{176}. Evidence for this mechanism is that these reactions are first-order both in H\textsuperscript{+} and in ArCO\textsubscript{2}H, and the reaction is subject to general acid catalysis\textsuperscript{177}. Also no \textsuperscript{13}COOH isotope effect has been observed, indicating that cleavage does not occur in the rate-determining step\textsuperscript{153}.

Finally, the possibility of a 1-step mechanism cannot be completely ruled out at this stage:

\[
\begin{align*}
\begin{array}{c}
\text{NO}_2 \\
\end{array} & \rightarrow \\
\begin{array}{c}
\text{TS} \\
\downarrow \\
\text{Products.}
\end{array}
\end{align*}
\]
PART 3

HYDROLYSIS OF THIOPHENE-AMIDES.
CHAPTER 6

GENERAL AMIDE HYDROLYSIS
HYDROLYSIS OF AMIDES

Amides hydrolyse under suitable conditions to regenerate the parent carboxylic acid and an amine:–

\[
\text{RC} \equiv \text{NR}_2 + \text{H}_2\text{O} \xrightarrow{H^+ \text{ or } OH^-} \text{RCO}_2\text{H} + \text{R}_2\text{NH}
\]

The initial step involves nucleophilic addition to the carbonyl function but water itself, a poor nucleophile, is virtually inert. Indeed, many amides are recrystallizable from this solvent. Hydrolysis can be effected, however, with the assistance of either basic or acidic catalysts. In basic conditions, the more powerful \( \text{OH}^- \) nucleophile is available, whereas protonation of the amide in acidic solutions renders the carbonyl carbon more susceptible to nucleophilic attack by water itself.

Amides also react with nucleophilic solvents other than water, e.g. amines, carboxylic acids etc. Alcohols form esters in the presence of either base or acid catalysts:–

\[
\text{RC} \equiv \text{NR}_2 + \text{R}^2\text{OH} \xrightarrow{H^+ \text{ or } OH^-} \text{RCO}_2\text{R}^2 + \text{R}_2\text{NH}
\]

BASIC HYDROLYSIS

The base catalysed hydrolysis of amides is usually less facile than that of esters. This is due to the less favoured nucleophilic addition to the carbonyl group in the former case. Indeed, basic hydrolysis of simple alkylamides require relatively high temperatures. Reid\textsuperscript{178,179} showed that the alkaline hydrolysis was a second order reaction:

\[
\text{Rate} = k (\text{Amide}) (\text{OH}^-)
\]

This suggested attack by the hydroxide ion on the polarized carbonyl
group of the neutral amide. A bimolecular mechanism was proposed:

\[
\begin{align*}
(1) \quad RCONR_2^+ + OH^- & \quad \overset{k_1}{\underset{k_{-1}}{\rightleftharpoons}} R-C-NR_2^+ + H_2O \quad \overset{k_2}{\rightarrow} RCO_2H + OH^- \\
& \quad + \text{P}_2\text{NH}
\end{align*}
\]

This is a two-step mechanism and involves the formation of a tetrahedral intermediate.

The same mechanism can be represented in an alternative way as an 'SN2' type process:

\[
\begin{align*}
(2) \quad RCONR_2^+ + OH^- & \quad \overset{k_1}{\underset{k_{-1}}{\rightleftharpoons}} R-C-NR_2^+ + H_2O \quad \overset{k_2}{\rightarrow} RCO_2H + OH^- \\
& \quad + \text{P}_2\text{NH}
\end{align*}
\]

Bender\textsuperscript{180,181} has shown that the favoured intermediate state in the basic hydrolysis of an amide is a molecular rather than a transition state. The evidence is that an amide undergoing alkaline hydrolysis in water containing \textsuperscript{18}O will incorporate a certain proportion of this isotope before it becomes hydrolysed. This shows that the reaction intermediate is sufficiently long-lived to survive the proton shift required to bring its two oxygen atoms into equivalence. Thus, either might split off to regenerate the amide and so incorporate a certain amount of \textsuperscript{18}O in the latter. Extensive investigations have established the importance of tetrahedral intermediates in nucleophilic displacements at carbonyl carbon\textsuperscript{182,183}, and in a few instances it has been possible to isolate such species\textsuperscript{184}. Although similar intermediates have not been isolated from the alkaline hydrolysis of amides, there is now little doubt that the reaction does proceed via the mechanism outlined in scheme 1\textsuperscript{185-187}.
Structural Effects

Since the intermediate complex of scheme (1) is negatively charged one would expect electropositive substituents to retard and electronegative substituents to accelerate the hydrolysis of amides by this mechanism. Furthermore, since the rate controlling process is bimolecular, one would expect steric effects from substituents close to the reaction centre.

Reid investigated the rates of hydrolysis of substituted benzamides with aqueous barium hydroxide. He found that electron attracting meta- and para-substituents do, indeed, accelerate the rate of hydrolysis. Electron releasing substituents retard hydrolysis. Reid also showed that all ortho substituents retard the rate of hydrolysis. This is consistent with a strong steric effect. In general electron attracting groups lower the activation energy of substituted benzamide hydrolyses, while electron-repelling groups raise it.

Bender measured substituent effects for both exchange and alkaline hydrolysis rates of para-substituted acetanilides.

<table>
<thead>
<tr>
<th>Process</th>
<th>( \rho )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall hydrolysis (ph)</td>
<td>0.1</td>
</tr>
<tr>
<td>Formation of intermediate (p1)</td>
<td>1.0</td>
</tr>
<tr>
<td>Partitioning of intermediate (p2/p-1)</td>
<td>-0.9</td>
</tr>
</tbody>
</table>

TABLE 1: Hammett \( \rho \) values for alkaline hydrolysis of para-substituted acetanilides.

It is clear from table 1 that substituent effects are quite small for the overall rate of hydrolysis, but electron-withdrawing groups facilitate addition of hydroxide ion to the carbonyl group. The negative sign for \( p2/p-1 \) implies that electron attracting substituents in the aniline fragment favour exchange over hydrolysis. Anilides are generally stable.
towards basic hydrolysis but compounds containing strongly electron-withdrawing groups in the carboxyl fragment are hydrolysed fairly rapidly. Substituent effects in the amino fragment are more complex.

In relatively strong solutions of aqueous hydroxide (\(> 0.1\text{M}\)) the hydrolysis rate of acetanilides follows an expression containing first- and second-order terms in hydroxide ion concentration\(^{190}\). Orders either greater or less than unity have been observed when the amide itself was sufficiently acidic to be partially ionised, e.g. trifluoroacetanilide\(^ {186,191}\).

**ACID HYDROLYSIS**

Strong mineral acids are often effective reagents for the hydrolysis of amides. The products are usually a mixture of the amine and carboxylic acid, consistent with fission of the N-acyl bond:-

\[
\text{RCONR}_2 + \text{H}_3\text{O}^+ \rightarrow \text{RCO}_2\text{H} + \text{R}_2\text{NH}_2^+
\]

Examples of N-alkyl bond fission have also been reported\(^{192,193}\). The rates of acid catalysed reactions depend on acid concentration. Most reactions are accelerated, some rates reach a maximum, while others pass through a maximum and then decrease\(^ {194}\). The situation is further complicated as some reactions which have a rate maximum at intermediate acid concentrations may decrease to a minimum and then increase in rate at higher acid concentrations\(^ {195-197}\).

In dilute acid, reaction rates have a first-order dependence on the hydronium ion concentration:-

\[
\text{Rate} = k_2 \text{[Amide]} \text{[H}_3\text{O}^+)\]

Kinetic indications that water is involved in the nucleophilic attack on the conjugate acid of the amide were obtained by Reid\(^ {178}\). The mechanism
generally accepted for the hydrolysis of amides in dilute acid solution involves attack by a water molecule on the conjugate acid of the amide as the rate-determining step:-

\[
\text{RCONR}_2^+ + \text{H}_3\text{O}^+ \leftrightharpoons \text{R} - \text{C} - \text{NR}_2^+ + \text{H}_2\text{O}
\]

Scheme 3:- A2-mechanism for hydrolysis of amides in dilute acid.

**Structural Effects**

Bender\textsuperscript{180} showed that the complex formed in such an A2 mechanism is a molecule, and not merely a transition state. Reid\textsuperscript{178,179} investigated the effect of substituents on the hydrolysis rates of substituted benzamides. He showed that in dilute acid, where only small concentrations of the conjugate acid are present, polar substituent effects on the hydrolysis of benzamides are very small. Conversely steric effects are large (e.g. for nitrobenzamides \( \frac{k_{\text{ortho}}}{k_{\text{para}}} = 0.03 \)). Small polar effects are accounted for by the A2 mechanism. An electron-releasing substituent, which favours protonation, and thus increases the concentration of the conjugate acid, decreases however its reactivity to nucleophilic attack by water. The reverse is true for electron-withdrawing substituents. Large steric effects are expected if steric hindrance to the attack by
water in the second, rate-determining step, is involved. The basicities of substituted benzamides are now well established \((p = 0.92)^{198}\), and Leisten\(^{199}\) showed that if hydrolysis is studied in acid solutions sufficiently concentrated for complete protonation of amides then hydrolysis rates show the expected polar effects. In concentrated perchloric acid, electron-withdrawing groups accelerate the rate of hydrolysis of substituted benzamides:

<table>
<thead>
<tr>
<th>Process</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall hydrolysis (conc. acid)</td>
<td>1.08</td>
</tr>
<tr>
<td>Basicities of substituted benzamides</td>
<td>-0.92</td>
</tr>
<tr>
<td>Overall hydrolysis (dilute acid)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

**TABLE 2:** Hammett \(p\) values for acid hydrolysis of \(m^-\) and \(p^-\) substituted benzamides\(^{199}\).

The \(\rho_{obs.}\) value for overall hydrolysis in dilute acid is calculated in table 2 as 0.16 and is in satisfactory agreement with the value of 0.12 obtained from Reid's results\(^{200}\). This is consistent with a small polar substituent effect and shows that the effect on the rate-determining step is slightly dominant. Aliphatic amides generally hydrolyse faster than benzamide, and this is reflected in the lower energies of activation for their hydrolysis\(^{201}\). The order of decreasing reactivity is formamide, propionamide and acetamide, the difference between the latter two being small. As both formamide and propionamide are weaker bases than acetamide\(^{202}\), their faster hydrolysis must be due to enhanced nucleophilic attack in the rate-determining step. Bolton\(^{203,204}\) studied the hydrolysis of primary aliphatic amides in dilute acids and found that the hydrolysis was governed by a combination of steric and conjugative substituent effects.
The effect of N-substituents on the rates of hydrolysis of amides has been studied less systematically\textsuperscript{205,206}. Bolton\textsuperscript{204} found that hydrolysis was again governed by a combination of steric and conjugative effects:

<table>
<thead>
<tr>
<th>Amide</th>
<th>$10^4 k \text{ (1 mol}^{-1} \text{ sec}^{-1})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetamide</td>
<td>10.3</td>
</tr>
<tr>
<td>N-Methylacetamide</td>
<td>0.58</td>
</tr>
<tr>
<td>N,N-Dimethylacetamide</td>
<td>0.65</td>
</tr>
</tbody>
</table>

TABLE 3: Acid-catalysed hydrolysis of amides at 75°.

The apparently anomalous reactivity of secondary amides, NH$_2$ $\gg$ NMe$_2$ $\gg$ NHMe, is due to the combined but opposite, steric and polar effects. If only the steric factor were important, then the tertiary amide should be the least reactive. A similar effect is observed for derivatives of benzamide\textsuperscript{207}.

Rate Maximum

Benrath\textsuperscript{208} showed that as the acid concentration is increased the hydrolysis rate increases to a maximum and then decreases. Subsequent workers\textsuperscript{209-211} have indicated that this is a general phenomenon. The position of the maximum differs with respect to hydrogen ion concentration both with different amides and different mineral acids\textsuperscript{210}. The rate maximum is usually in the region of 2M to 5M for sulphuric acid. This result was at one time explained in terms of the hypothesis that at high acid concentrations the protonated amide combined with the anion of the acid, forming an unhydrolyzable complex\textsuperscript{208}. Taylor\textsuperscript{209} showed this to be incorrect since the position of the maximum rate was independent of amide concentration. Krieble\textsuperscript{210} suggested that the decrease in rate at higher acid concentrations was due to the decreased activity of water.
The rate of hydrolysis of amides by the A2-mechanism shows a dependence on acidity and on water activity (scheme 3). Thus below the rate maximum increasing acidity raises the concentration of the reactive intermediate, whereas beyond the rate maximum the chief effect of increasing acidity is to decrease the activity of water. Accordingly, these two effects account qualitatively for the rate maxima:

\[
\begin{array}{c|c|c|c}
\text{AMIDE} & -pK_a & \text{ACIDITY (M)} & -H_0 \\
\hline
\text{Formamide} & 4.75 & \text{H}_2\text{SO}_4 & 2.16 \\
\text{Acetamide} & 0.6 & 2.5 & 1.12 \\
\text{Propionamide} & 0.8 & 2.4 & 1.07 \\
\text{Benzamide} & 1.74 & 3.5 & 1.62 \\
\text{p-Nitrobenzamide} & 2.70 & 4.5 & 2.05 \\
\text{o-Nitroacetanilide} & 3.72 & 6.1 & 2.79 \\
\end{array}
\]

**TABLE 4**: Rate maxima for the acid-catalysed hydrolysis of amides as a function of $H_0$.

Edwards and Meacock extended this explanation to provide a satisfactory quantitative treatment of the rate maxima. The situation may be formulated in terms of the general A2 mechanism:

\[
\begin{align*}
\text{H}_3\text{O}^+ + A & \rightleftharpoons \text{AH}^+ + \text{H}_2\text{O} \\
\text{AH}^+ + \text{H}_2\text{O} & \rightleftharpoons X^+ \rightarrow \text{Products}
\end{align*}
\]

Application of the steady-state treatment leads to the following relationship:

\[
k_{\text{obs}} = \frac{k_2 K_{\text{AH}^+} [\text{H}_3\text{O}^+]}{K_{\text{AH}^+} + h_0} \quad \text{[1]}
\]
where $k_{1 \text{obs}}$ = experimentally determined pseudo first-order rate constant

$k_2$ = second-order rate constant

$K_{AH^+}$ = acid dissociation constant

$h_o$ = Hammett's acidity function, $h_o = K_{AH^+} \cdot \frac{(AH^+)}{(A)}$

The special cases of this equation are:

(1) When the acid concentration is sufficiently small

$$h_o \ll K_{AH^+}$$

Then,

$$k_{1 \text{obs}} = k_2 \cdot (H_3O^+)$$

This applies to amides at low acid concentrations and in fact, is the situation in ester hydrolysis in most acid concentrations investigated. This is due to the fact that esters are very weak bases and so $K_{AH^+} \gg h_o$ in all cases.

(2) When the acid concentration is sufficiently high

$$h_o \gg K_{AH^+}$$

Then,

$$k_{1 \text{obs}} = \frac{k_2 \cdot K_{AH^+} \cdot (H_3O^+)}{h_o}$$

At acid concentrations greater than about 2M, $h_o$ increases much more rapidly than $(H_3O^+)$, with the result that $k_{1 \text{obs}}$ decreases with increasing acid concentration.

Equation (1) gives, therefore, satisfactory theoretical rate-acidity profiles. Edward and Meacock regarded the hydrolysis of amides as a bimolecular process with the equation for the rate of the limiting step including the ionised form of the reactant, and water. They also suggested that the intermediate could be either O- or N-protonated (see
Isotope Effects

In contrast to alkaline hydrolysis, no measurable $^{18}O$ exchange between the carbonyl group and the solvent is observed during the acid catalysed hydrolysis of amides. This implies that steps subsequent to the attack of water on the protonated amide are rapid, and the formation of the tetrahedral intermediate is the rate-determining step (scheme 3). This intermediate is only short-lived, unstable and rapidly converts to hydrolysed product. A change from rate-determining decomposition to the rate-determining formation of the tetrahedral intermediate is therefore apparent in going from alkaline to acidic conditions.

Several workers have studied the deuterium isotope effect on the acid hydrolysis of acetamide and benzamide in protium and deuterium oxide. These investigations showed that the overall effect was to shift the entire rate profile so that the maximum occurred at lower acid concentration in $D_2O$ than in $H_2O$.

<table>
<thead>
<tr>
<th>SUBSTRATE</th>
<th>ACIDITY</th>
<th>$k_{D_2O}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$k_{D_2O}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$k_{H_2O}$</td>
</tr>
<tr>
<td>Acetamide</td>
<td>0.1M</td>
<td>1.45</td>
</tr>
<tr>
<td></td>
<td>4.0M</td>
<td>0.88</td>
</tr>
<tr>
<td>Benzamide</td>
<td>1M</td>
<td>1.15</td>
</tr>
<tr>
<td></td>
<td>6M</td>
<td>0.90</td>
</tr>
</tbody>
</table>

TABLE 5: Solvent isotope effects for the hydrolysis of amides catalysed by hydrochloric acid.207,215
Values of $k_{D_2O}/k_{H_2O}$, > 1 in dilute acid reflect the higher concentration of protonated amide in heavy water. This is due to the fact that $D_2O$ is a weaker base than $H_2O$. Thus at low acid concentration the initial protonation equilibrium controls the isotope effect and $k_{D_2O}/k_{H_2O} > 1$. At higher acid concentration the amide is largely in the form of the conjugate acid in both solvents. Here the reaction of the protonated substrate becomes important. Since $D_2O$ is a weaker nucleophile than $H_2O$ the isotope effect is reversed and $k_{D_2O}/k_{H_2O} < 1$. These observations and Arrhenius parameter work are in accord with the A2-bimolecular mechanism.

**Water Activity**

Various attempts have been made to specify in a more exact way the role of water in the transition state of acid-catalysed reactions such as the hydrolysis of amides. The significance of linear free-energy relationships between observed rate coefficients and various combinations of water activity and acidity function data has been noted. In 1961 Bunnett presented the Hydration Parameter Treatment, which attempted to overcome the problem of disentangling the roles of proton and water molecule. Yates and Stevens criticised Bunnett's relationship and devised a modification using $H_A$, rather than $H_0$, to calculate the fraction of protonated substrate. The equation derived by Yates and his colleagues was:

$$\log k_{obs} + H_A = r \log a_{H_2O} + \text{constant} \quad \text{-------(2)}$$

where $k_{obs}$ = experimental first-order rate constant

$H_A$ = acidity function (measured from equilibrium protonation of amides)

$a_{H_2O}$ = water activity
The number of water molecules required to convert protonated amide to the transition state structure.

This equation is similar to that devised earlier by Bunnett but the $H_A$ acidity function is an improvement since it refers specifically to amide substrates. This allowed the water dependence of the second and rate-determining step of the mechanism to be studied. This treatment was applied by Yates and Stevens to hydrolysis data on benzamide and p-nitrobenzamide in sulphuric acid, and by Yates and Riordan to literature data on the hydrolysis of acetamide, propionamide, and benzamide. For the more weakly basic heterocyclic amides, nicotinamide, picolinamide and isonicotinamide log $k_{1obs} + H_A$ vs. log $a_{H_2O}$ was plotted. In all cases slopes greater than unity were found, mostly in the range 3 ± 0.4. This has led to the suggestion that the transition state for hydrolysis be represented as below:

In view of this result, water taking part in the transition state should be regarded as hydrogen bonded to two further water molecules. This hydrogen bonding enhances the negative charge on the attacking oxygen atom and hence facilitates the reaction. A similar conclusion for this aspect of the transition state has been reached by both Moodie, using a more direct relationship involving the water activity but not acidity function data, and by Bunnett and Olsen, using acidity function data but not the water activity. However, despite the unanimous agreement between these apparently independent treatments the real significance of the hydration parameter, $r$, is questionable. Bunnett and Olsen proposed an improved linear free energy relationship for a
more general treatment of reaction rates. Bunton formulated a new reaction scheme involving two transition states, arising from two distinct mechanistic pathways involving protonation on both oxygen and nitrogen. However, although this treatment correlated well with known data, criticism came from Moodie and collaborators. There is no doubt that water is involved in a rate-determining nucleophilic attack on the protonated amide, and the hydrolysis is therefore of the A2 type.

The A1 Mechanism

Since the rates of the A2 hydrolyses of amides decrease at sufficiently high acid concentrations, Duffy and Leisten examined the question of whether unimolecular amide hydrolysis may occur under anhydrous acid conditions. During the hydrolysis of nitro-derivatives of acetanilide in sulphuric acid a more complex dependence of the pseudo first-order rate constant on acid concentration was observed. The rate maximum at intermediate acidities was followed by a minimum and a subsequent increase in rate at high acid concentration. Similar rate profiles have been observed for esters.

![Graph](image)

---

Fig. 1: Rates of hydrolysis of p-nitroacetanilide (A) and 3,5 dinitroacetanilide (B) in sulphuric acid-water mixtures at 85°C.
Duffy and Leisten \textsuperscript{196} discuss their results in terms of a change in mechanism from A2 to A1. Amides are strong bases in anhydrous sulphuric acid \textsuperscript{229} and in a unimolecular mechanism the position of protonation is important because dissociation of the oxygen protonated form cannot seriously be considered to explain the reaction in highly acidic media:

\[ + \]

\[ \text{Scheme 4: A1 mechanism for hydrolysis of amides in concentrated acid.} \]

The fact that the reaction proceeds via the less stable N-protonated form is discussed by Duffy and Leisten \textsuperscript{196}. They assume that the heterolytic electron-shift occurs towards the added proton and in the stable O-protonated form of the conjugate acid this would produce the unlikely fragments RCOH and R'\textsubscript{2}N\textsuperscript{+}. The polar effects observed are in contrast with those associated with such a mechanism. Reaction must proceed via the N-protonated form and the fact that even the very weakly basic amides are protonated in anhydrous sulphuric acid was demonstrated by considering freezing point depressions.

If an amide is to be hydrolysed in anhydrous sulphuric acid the hydrolytic water must necessarily come from the sulphuric acid itself, affording SO\textsubscript{3} which combines with hydrogen sulphate ion to form the hydrogen disulphate ion, HS\textsubscript{2}O\textsubscript{7}. Carboxylic acids are believed to exist as acidium ions in this medium. The complete reaction is thus:
Such reactions should lead to a change in the number of solute particles \((i = 2 \rightarrow 4)\) and can thus be followed using cryoscopic methods.

**Structural Effects**

Duffy and Leisten\(^{196}\) studied a number of N-substituted amides, with N-substituents containing strongly electron-withdrawing groups, which would favour a heterolytic acyl-nitrogen bond fission:

\[
\begin{align*}
\text{O} \\
R & \quad \overset{\text{N}}{\text{C}} \quad \overset{\text{R'}}{\text{H}} & \longrightarrow & \quad R'\text{CO} + R'_2\text{NH} \\
\end{align*}
\]

However an electron-withdrawing group in \(R'\) would also drive the equilibrium below to the left-hand side by reducing the proton-affinity of the adjacent nitrogen atom. The effect upon the basicity of the oxygen atom is obviously less.

This explains why, in fig. 1 the rate of hydrolysis of p-nitro-acetanilide can be greater or less than that of 3,5 dinitroacetanilide, depending upon the acid concentration (between 80-100% sulphuric acid). The extent to which the two possible polar effects in \(R'\) oppose each other is difficult to predict.
<table>
<thead>
<tr>
<th>AMIDE</th>
<th>RCONHR'</th>
<th>H₂SO₄ (%)</th>
<th>TEMP (°C)</th>
<th>K (10⁻³ min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃</td>
<td>3,5-(NO₂)₂C₆H₃</td>
<td>100.0</td>
<td>80.0</td>
<td>8.56</td>
</tr>
<tr>
<td>CH₃CH₂</td>
<td>&quot;</td>
<td>100.0</td>
<td>60.0</td>
<td>22.2</td>
</tr>
<tr>
<td>CH₂Cl</td>
<td>&quot;</td>
<td>100.0</td>
<td>90.0</td>
<td>&lt;0.2</td>
</tr>
<tr>
<td>Ph</td>
<td>2,4-(NO₂)₂C₆H₃</td>
<td>100.0</td>
<td>13.3</td>
<td>22.0</td>
</tr>
<tr>
<td>p-NO₂C₆H₄</td>
<td>&quot;</td>
<td>100.0</td>
<td>13.3</td>
<td>0.46</td>
</tr>
<tr>
<td>o-NO₂C₆H₄</td>
<td>&quot;</td>
<td>100.0</td>
<td>13.3</td>
<td>20.7</td>
</tr>
<tr>
<td>Ph</td>
<td>p-NO₂C₆H₄</td>
<td>98.1</td>
<td>48.1</td>
<td>3.91</td>
</tr>
<tr>
<td>p-CH₃C₆H₄</td>
<td>&quot;</td>
<td>98.1</td>
<td>48.1</td>
<td>13.3</td>
</tr>
<tr>
<td>o-CH₃C₆H₄</td>
<td>&quot;</td>
<td>98.1</td>
<td>48.1</td>
<td>380</td>
</tr>
<tr>
<td>CH₃</td>
<td>&quot;</td>
<td>100.0</td>
<td>63.7</td>
<td>44.1</td>
</tr>
<tr>
<td>CH₃</td>
<td>&quot;</td>
<td>100.0</td>
<td>55.0</td>
<td>14.8</td>
</tr>
<tr>
<td>CH₃</td>
<td>&quot;</td>
<td>100.0</td>
<td>45.0</td>
<td>3.94</td>
</tr>
</tbody>
</table>

**TABLE 6: Structural effects on the hydrolysis of amides in concentrated sulphuric acid.**

A comparison of series B and C in table 6, shows that an increase in the number of nitro groups in the N-substituent considerably accelerates the reaction. However, this is not true for series A and D where p-nitroacetanilide is seen to react faster than 3,5 dintroacetanilide. This illustrates the difficulty in predicting N-substituent effects.

Substituent effects in the 'acyl fragment' are easier to predict. It can be seen from series A that electron-releasing substituents in R accelerate the reaction considerably, whereas electron-withdrawing substituents cause a sharp fall in rate. The same effect is observed in series C where
methyl substitution in the phenyl ring increases the rate, especially effectively when in the ortho position. The introduction of a nitro group into the phenyl ring in series B causes a fall in rate, but not as effectively when in the ortho position as when in the para position. This is probably due to steric hindrance to coplanarity of this bulky group. The polar effects are as expected for the A1 mechanism since electron-releasing substituents in R would favour the heterolysis:

\[ \text{R-CONR}_2^+ + \text{H}_2\text{O} \rightarrow \text{R-CO}^- + \text{R}_2^+\text{NH} \]

Polar groups in R would not be expected to greatly affect the position of the protonation equilibrium due to the relative remoteness from the reaction site. Thus the overall polar effect of substituents in the acyl fragment is such that electron-withdrawing substituents inhibit hydrolysis whereas electron-releasing substituents favour hydrolysis.

Duffy and Leisten obtained a reaction constant \( \rho \) for substitution in the R group. The constant was obtained from series B and C by plotting the logarithms of the rate constants against \( \sigma^+ \) constants (to take account of the developing carbonium ion in the transition state). The reaction constant, \( \rho \), obtained was -3.1, which contrasts sharply with the value of +1.08 obtained for the A2 hydrolysis step for substituted benzamides (see table 2). The \( \rho \) value of -3.1 for the A1 hydrolysis is of the same sign and similar magnitude to that obtained for the A1 hydrolysis of esters.

Arrhenius Parameters

Duffy and Leisten obtained Arrhenius parameters for the A1 hydrolysis of a series of substituted benzamides. They found that the energies of activation for hydrolysis of substituted benzamides are in the
range 114-133 kJ mol\(^{-1}\). This is considerably higher than for the A2 hydrolysis of the same substrates at lower acid concentrations which are in the range 94.1-98.7 kJ mol\(^{-1}\). The lower energies in the latter case indicate that nucleophilic attack by water molecules on the carbonyl carbon facilitates hydrolysis.

**Steric Effects**

It can be seen from table 6 that ortho substituents in the acyl fragment have a greater accelerating effect upon the rate than the corresponding para substituents, regardless of polarity. These results again contrast sharply with those obtained for the A2 mechanism, but are comparable with those observed for ester hydrolysis in anhydrous sulphuric acid. It is also evident that ortho groups in the amine-fragment exert a large accelerative steric effect. Such ortho steric effects are also reflected in enthalpy-entropy relationships for substituted benzanilides.

**Medium Effects**

The A1 mechanism of scheme 4 would predict only small changes of rate with solvent composition. This is due to the fact that the change in solvent from anhydrous to aqueous sulphuric acid should have little effect upon the O- and N-protonated equilibrium. Similarly the acyl cleavage step should be insensitive to medium changes since there is no change in the total electrical charge from reactant to transition state. However, it can be seen from fig. 1 that the rates of hydrolysis of p-nitro and 3,5 dinitroacetanilide depend considerably, and to different extents, on the composition of the solvent. Addition of other acids into sulphuric acid should produce no change in rate for the fully protonated amides. However, a change in hydrolysis rate was found for 3,5-dinitroacetanilide following the order of acidity:
In all mixtures of sulphuric acid with stronger acids the rate of hydrolysis was greater than in 100% sulphuric acid alone. In mixtures with weaker acids, the rate is lower, but in both cases the effects are not proportional to the acidity functions. This dependence of rate upon acid composition suggests, therefore, general acid catalysis. The fact that the reaction rate varies almost linearly with the mole fraction of the stronger acid in the solvent supports this theory. Duffy and Leisten therefore proposed that the A1 mechanism of amide hydrolysis should be modified by assuming a proton transfer synchronous with the heterolysis of the CO-N bond i.e. they suggest that proton addition to the nitrogen to form the ammonium ion commences before the transition state is fully formed (scheme 4). This modification not only accounts for general acid-catalysis but also explains why the rate of hydrolysis of p-nitroacetanilide is more sharply dependent upon acidity than that of 3,5-dinitroacetanilide. This is because the extent of catalysis depends not only upon the strength of the acid, but also upon the basic strength of the amine formed, and p-nitroaniline is a stronger base than 3,5-dinitroaniline (fig. 1).

It is clear from fig. 1 that below ~78% sulphuric acid the rate of hydrolysis rises with decreasing acid concentration. This is, of course, due to the increasing concentration of free water available for nucleophilic attack by the A2 mechanism. The curves for p-nitro and 3,5-dinitroacetanilide are parallel in this region, indicating that the rate variation is associated with the solvent and not with the particular amide. In general, the regions of hydrolysis by the A1 and the A2 mechanism are separated by a minimum in the rate-acidity profiles.

Vinnik agreed that the mechanism changes from bimolecular to unimolecular in concentrated sulphuric acid but differed in his explanation of the increasing rate of hydrolysis. He suggested that in...
concentrated solutions of sulphuric acid the protonated amide, and molecules of undissociated sulphuric acid react. The activated complex thus incorporates the protonated amide and sulphuric acid molecule, whereas in the bimolecular mechanism at low acidities it incorporates the amide, water molecule, and a proton.

Evidence for a changeover in mechanism has been found for substituted acetanilides in many cases. Giffney and O'Connor studied the hydrolysis of twelve substituted acetanilides over a wide range of acidity in sulphuric acid. In dilute acid (< 75%) the data fitted well with the Bunnett and Bunnett-Olsen criteria of an A2 mechanism. In more concentrated acid Arrhenius parameters indicated a change to an A1 mechanism, the rate increasing with increasing acidity. The rate profiles of all the acetanilides studied had a minimum in concentrated sulphuric acid, with a subsequent increase in rate with acidity. Barnett and O'Connor suggested that for some substituted acetanilides, in the region 70-80% sulphuric acid, there are two mechanisms occurring in parallel and at comparable rates - both A1 and A2 hydrolysis. In the case of acetanilide itself there is evidence that in sulphuric acid > 80% sulphonation occurs in preference to hydrolysis. Acetanilides with electron-donating substituents in the 4-position are sulphonated in concentrated sulphuric acid, and these substituted intermediates are hydrolysed by an A1 mechanism.

Giffney and O'Connor obtained Hammett plots for 4-substituted acetanilides hydrolysing by an A1 mechanism. Since their substrates were fully protonated in 90% sulphuric acid the $\rho$ value of +4.39 obtained by correlation with $\sigma^+$ values is as anticipated by Duffy and Leisten. Electron-withdrawing substituents in the amino fragment favour the acyl-nitrogen bond fission. It was also confirmed that the A2 mechanism in dilute acid is favoured by electron withdrawal ($\rho > + 1.0$) but it is
significant that the mechanism in highly acidic media is much more dependent on electron withdrawal. Giffney and O'Connor believe that their kinetic results are consistent with an A1 reaction occurring through the O-protonated form, and not the minor N-protonated form in concentrated sulphuric acid. For the A2 mechanism in dilute acid they favour water attack on the N-protonated conjugate acid in the rate-determining step. Speculation as to whether A1 and/or A2 hydrolysis proceed via the O or N protonated forms, or even both, is still very much in evidence.
CHAPTER 7

HYDROLYSIS OF THIOPHENE AMIDES
HYDROLYSIS OF THIOPHENE AMIDES

The experimental procedure for determination of the rate of nitro-decarboxylation of 2-acetamido-5-nitrothiophene-3-carboxylic acid involved dissolving the compound in a sulphuric acid solution, addition of a nitric acid/sulphuric acid solution and observation of the change in U.V. absorbance. However, prior to addition of nitric acid an increase in absorbance at $\lambda = 440$ nm was observed. This change in spectrum was initially observed in 98% sulphuric acid but was subsequently found to occur at other acid concentrations.

$^{13}$C Spectra

In an attempt to discover the nature of the observed change in U.V. spectrum $^{13}$C spectra of three thiophene derivatives were examined in some detail.

(A) 2-Acetamido-3,5-dinitrothiophene

This is the final product of nitration of 2-acetamidothiophene-3-carboxylic acid. This $^{13}$C spectrum in 98% sulphuric acid revealed changes in spectrum as shown in fig. 1. The 'change' was virtually complete after 3 hrs. Further changes to this spectrum were relatively slow and complex. Assignment of the aromatic carbon peaks is difficult but the peaks at 181.6 and 22.6 (originally) correspond to the carbonyl carbon and methyl carbon, respectively, of the amide group. Upon drounout of the sulphuric acid solution, which after 3 hrs was black and rather viscous, a dark solid was obtained which had only a weak carbonyl absorption in the infra-red. This material was identified as 2-amino-3,5-dinitrothiophene by comparison with an authentic sample of the amine, prepared by dilute acid hydrolysis of the original amide. A $^{13}$C spectrum of authentic 2-amino-3,5-dinitrothiophene corresponded to the third spectrum of fig. 1 without the peaks at 194.0 and 21.1.
Fig. 1: $^{13}$C spectral changes of 2-acetamido-3,5-dinitrothiophene in 98% sulphuric acid (chemical shifts are p.p.m. from T.M.S. as external standard).
The changes in the $^{13}$C spectra, as shown in fig. 1, can therefore be interpreted in terms of a hydrolysis of amide to amine in concentrated sulphuric acid. The change in U.V. spectrum which occurs in sulphuric acid is confirmed as being due to the longer wavelength absorption of amine. Both $^{13}$C and U.V. spectroscopy confirm the hydrolysis to amine and whilst the latter is isolable in poor yield, it is not stable for long periods in concentrated sulphuric acid. No amine was recoverable after 48 hrs.

(B) 2-Acetamido-5-nitrothiophene-3-carboxylic acid

This is an intermediate 'product' of nitration of 2-acetamidothiophene-3-carboxylic acid. The $^{13}$C spectral changes which occur upon dissolving this compound in concentrated sulphuric acid are illustrated in fig. 2. The change in spectrum is analogous to that for the dinitroamide but the rate of hydrolysis is greater for the mono-nitro acid. The conversion to amine is complete inside 2 hrs but this amine is less stable in concentrated sulphuric acid than the dinitro amine. The sulphuric acid solution became dark and viscous and no 2-amino-5-nitrothiophene-3-carboxylic acid was recoverable from the reaction after 8 hrs.

The $^{13}$C spectrum of hydrolysed 2-acetamido-5-nitrothiophene-3-carboxylic acid shows the two peaks at 194.0 and 21.1 ppm which were also observed in the final spectrum (fig. 1) for hydrolysis of 2-acetamido-3,5-dinitrothiophene. A $^{13}$C spectrum of acetic acid in concentrated sulphuric acid shows two peaks at 194.0 and 21.0 ppm believed to be due to the species, $\text{CH}_3\text{CO}_2\text{H}^+$, i.e. protonated acetic acid. This further supports the previous evidence confirming that hydrolysis of the thiophene amides occurs in concentrated sulphuric acid producing the corresponding amines and protonated acetic acid (for acetamides).
Fig. 2: $^{13}$C spectral changes of 2-acetamido-5-nitrothiophene-3-carboxylic acid in 98% sulphuric acid (chemical shifts are ppm from T.M.S. as external standard).
This compound is the starting material which is dinitrated to produce 2-acetamido-3,5-dinitrothiophene. The $^{13}$C changes which were observed upon dissolving this compound in concentrated sulphuric acid are shown in fig. 3. Two distinct changes were observed producing the second and third spectra but intermediate spectra were extremely complex, often containing in excess of twenty peaks. The spectrum which appeared after 6-8 hrs was unchanged after 24 hrs and, indeed, only a small decrease in intensity of the aromatic carbon peaks was detectable after 5 days. This is in direct contrast to the other amides studied (figs. 1 and 2) in which the amines were rather unstable in concentrated sulphuric acid. The initial change is believed to correspond to an intramolecular dehydration:

\[
\begin{align*}
\text{CO}_2\text{H} \\
\text{NHCOCH}_3 \\
\end{align*}
\]

The anhydro cyclic structure shown above was prepared from 2-acetamidothiophene-3-carboxylic acid and then dissolved in 98% sulphuric acid. A $^{13}$C spectrum revealed a complex series of peaks, very similar to an intermediate spectrum obtained when 2-acetamidothiophene-3-carboxylic acid was dissolved in sulphuric acid. After 3-4 hrs the $^{13}$C spectrum was identical to the final spectrum of fig. 3. By comparison of the individual $^{13}$C spectra at certain time intervals it was concluded that the cyclic structure shown above is present as an intermediate during the reaction of 2-acetamidothiophene-3-carboxylic acid with concentrated sulphuric acid. However, all attempts to isolate this compound from the sulphuric acid solution were unsuccessful. A $^{13}$C spectral analysis of ethyl-2-acetamidothiophene-3-carboxylate in 98% sulphuric acid revealed a simple, slow hydrolysis reaction with no evidence of any complex
Fig. 3: Simplified $^{13}$C spectral changes of 2-acetamidothiophene-3-carboxylic acid in 98% sulphuric acid (chemical shifts are ppm from T.M.S. as external standard).
intermediate. Formation of a cyclic anhydro derivative, as for the amido-
carboxylic acid, is not possible for the amido-ester.

The final spectrum of fig. 3 contains the carbonyl and methyl carbon
peaks at 194.0 and 21.1 ppm respectively i.e. the chemical shifts
corresponding to protonated acetic acid\(^{243}\). The overall change would
therefore seem to involve hydrolysis of the original amido-acid to a
relatively stable amine. It would seem unlikely that hydrolysis proceeds
via the anhydro cyclic structure and so an equilibrium is proposed:

\[
\begin{align*}
\text{NHCOCH}_3 & \xrightarrow{H_3O^+} \text{CO}_2H \\
\text{H}_3\text{CO}_2\text{H}^+ & \quad \text{NH}_2
\end{align*}
\]

The regeneration to amido-acid is necessary for hydrolysis to occur
and since there is a high equilibrium conversion to the cyclic structure,
the regeneration step could be rate-determining. This would account for
the relatively slow rate of hydrolysis. The final product of hydrolysis,
although quite stable in concentrated sulphuric acid was not isolable
from solution. Drown-out into ice-water gave no recognisable products.
The amine is protonated in concentrated acid and the possibility of
sulphonation of either the original amide or final amine in the 5-position
cannot be ignored\(^{245}\). \(^1\)H N.M.R. evidence on this point was inconclusive
but no sulphonic acid or amine was isolable from the reaction solution.

**Hydrolysis in Concentrated Sulphuric Acid**

2-Aacetamido-3,5-dinitrothiophene is converted to the corresponding
2-amino derivative by refluxing with dilute sulphuric acid, on a preparative scale. However, the hydrolysis in concentrated acid is faster and much less desirable. The amine, produced in this way, is extremely unstable in presence of nitric acid and rather unstable in sulphuric acid alone. Thus, hydrolysis is an undesirable side reaction during the nitration of thiophene amides in sulphuric/nitric acid. In order to improve the yield of nitrations of this sort an attempt was made to minimise the hydrolysis rate of both 2-acetamido-5-nitrothiophene-3-carboxylic acid and the dinitro derivative.

**Variation of Hydrolysis Rate with Sulphuric Acid Concentration**

Rates of hydrolysis of 2-acetamido-3,5-dinitrothiophene in concentrated sulphuric acid solutions were determined by U.V. spectroscopy. The rate of formation of the amine, which absorbs at a longer wavelength, was determined. Two methods were used for standardisation of sulphuric acid solutions - freezing-point determination and titrimetry. The freezing-point of sulphuric acid solutions is extremely sensitive to small changes in concentration but disadvantages of this method include supercooling effects and the fact that there are often two (or even three) possible concentrations of acid for each freezing-point (see chapter 3). The more dilute sulphuric acid solutions were standardised by titration with standard sodium hydroxide.

The first-order rate constants for the hydrolysis of 2-acetamido-3,5-dinitrothiophene in sulphuric acid-water mixtures are shown in table 1. The values of \( k_{obs} \), the first-order rate constant, are average values over a number of kinetic runs since the reaction product, the amine, is rather unstable in concentrated acid. However, in all cases, the rate of hydrolysis was greater than the rate of decomposition of amine.
TABLE 1: First-order rate constants for hydrolysis of 2-acetamido-3,5-dinitrothiophene in sulphuric acid-water mixtures at 25°C. 

\[
\text{(Substrate)} = 10^{-4} - 10^{-5} \text{M}
\]

<table>
<thead>
<tr>
<th>H\textsubscript{2}SO\textsubscript{4} CONCENTRATION (W/W)</th>
<th>AV. ( k_{\text{obs}} ) (sec\textsuperscript{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>99.6%</td>
<td>( 44 \times 10^{-5} )</td>
</tr>
<tr>
<td>98.6%</td>
<td>( 31 \times 10^{-5} )</td>
</tr>
<tr>
<td>93.5%</td>
<td>( 5.9 \times 10^{-5} )</td>
</tr>
<tr>
<td>92.1%</td>
<td>( 3.3 \times 10^{-5} )</td>
</tr>
<tr>
<td>89.1%</td>
<td>( 1.1 \times 10^{-5} )</td>
</tr>
<tr>
<td>86.7%</td>
<td>( 0.83 \times 10^{-5} )</td>
</tr>
<tr>
<td>82.7%</td>
<td>( 0.63 \times 10^{-5} )</td>
</tr>
<tr>
<td>75.3%</td>
<td>( 0.85 \times 10^{-5} )</td>
</tr>
<tr>
<td>69.4%</td>
<td>( 1.1 \times 10^{-5} )</td>
</tr>
</tbody>
</table>

The solubility of the weakly basic amide, 2-acetamido-3,5-dinitrothiophene was very sensitive to changes in sulphuric acid concentration. The compound was barely soluble below 88% sulphuric acid and below 82% acid was not even sufficiently soluble for U.V. spectral analysis. Rates of hydrolysis below 82% acid are therefore, only approximate and were obtained by aliquoting in aqueous methanol from a heterogeneous mixture of amide and dilute sulphuric acid. Subsequent U.V. analysis of the methanol aliquots enabled the rate of formation of amine to be determined.

A plot of log \( k_{\text{obs}} \) vs. sulphuric acid concentration is shown in fig. 4, and shows a minimum at approximately 82% sulphuric acid. Above 82% acid the rate of hydrolysis increases quite rapidly with increasing acidity whereas below 82% the rate of increase is less rapid. A similar effect was observed for 2-acetamido-5-nitrothiophene-3-carboxylic acid.

**Mechanism**

Above 82% sulphuric acid the unimolecular mechanism for hydrolysis of amides is proposed:
The unimolecular A1 mechanism proposed for the hydrolysis of 2-acetamido-3,5-dinitrothiophene is shown in scheme 1. This mechanism would account for the facile hydrolysis in concentrated acid despite the absence of an appreciable amount of water (which is usually associated with the hydrolysis of amides and esters). This complex dependence of the pseudo first-order rate constant on acid concentration was observed during the hydrolysis of the nitro-derivatives of acetanilide in sulphuric acid\textsuperscript{196,218,232}. Duffy and Leisten\textsuperscript{196} discussed their results in terms of a change in mechanism in concentrated sulphuric acid.

The reason for the increase in hydrolysis rate above 82% sulphuric acid is not immediately obvious from scheme 1. Any change in acid
Fig. 4: Plot of hydrolysis rates for 2-acetamido-3,5-dinitrothiophene vs. sulphuric acid concentration.
concentration should have little effect upon the O- and N-protonated equilibrium (step 1). The second slow step of scheme 1 should also be insensitive to increasing acid concentration since there is no change in the total electrical charge from reactant to transition state. Duffy and Leisten further demonstrated a dependence of the hydrolysis rate upon acidity and suggested general acid-catalysis. To account for their results Duffy and Leisten proposed a modification of the A1-mechanism. They suggested that step 3 of scheme 1 occurs synchronously with the heterolysis (step 2), i.e. that proton addition to the nitrogen atom commences before the transition state of the heterolysis is fully formed. This modification is applicable to the hydrolysis of 2-acetamido-3,5-dinitrothiophene in concentrated sulphuric acid (in scheme 1), and accounts for general acid-catalysis in scheme 1. However, it has been shown that 2-acetamido-3,5-dinitrothiophene is a relatively weak base which will be only partially protonated below ~92% sulphuric acid. Thus the increase in the rate of hydrolysis can also be accounted for in terms of an increase in the degree of protonation, as the concentration of acid increases.

**Oleum Solutions**

All attempts to determine hydrolysis rates in solutions > 100% sulphuric acid were unsuccessful. A $^{13}$C spectrum of a solution of 2-acetamido-3,5-dinitrothiophene in 10% oleum revealed a complex series of peaks after ~20 mins. After a few hours the spectrum contained a large number of carbonyl carbon peaks. Two particularly predominant peaks were present at 21.1 and 194.0 ppm (from T.M.S.), i.e. the positions corresponding to protonated acetic acid. Although hydrolysis of amides is not unknown in anhydrous sulphuric acid, it was not possible to detect hydrolysis prior to oxidation of the amine in the oleum solution. Indeed the peaks at 21.1 and 194.0 could have arisen from direct oxidation of the amide in the reaction solution. A similar effect was observed upon
dissolving 2-acetamido-3,5-dinitrothiophene in other oleum solutions. The protonated acetic acid, \( \text{CH}_3\text{CO}_2\text{H}^+ \) was present, and stable in all cases. The fact that this species and not the acylium ion, \( \text{CH}_3\text{CO}^+ \), is present indicates that water is either an oxidation product or has come from the dissociation of sulphuric acid, affording sulphur trioxide. The latter combines with hydrogen sulphate to form the hydrogen disulphate ion, \( \text{HS}_2\text{O}_7^- \).

\[
2\text{H}_2\text{SO}_4 \rightleftharpoons \text{H}_3\text{O}^+ + \text{HS}_2\text{O}_7^- 
\]

**Position of Protonation**

The A-1 mechanism for hydrolysis of amides is believed to proceed via the less stable N-protonated form. This is due to the fact that a heterolytic acyl-nitrogen bond fission, via the O-protonated form would yield \( \text{RNH}^+ \) as one of the products, which is extremely unlikely. Similarly the A-1 mechanism via the N-protonated form is favoured for the hydrolysis of 2-acetamido-3,5-dinitrothiophene in concentrated sulphuric acid.

**Structural Effects**

(A) **The Acyl Group**

A variety of N-Acyl substituted thiophenes were synthesised and their behaviour in concentrated sulphuric acid examined. 2-Amino-3,5-dinitrothiophene, a weakly basic amine, could only be acylated under vigorous conditions often leading to poor yields of impure products. The more strongly basic amine, 2-amino-5-nitrothiophene-3-carboxylic acid was therefore acylated with a variety of acylating agents to yield the amides:
Subsequent nitrodecarboxylation of the amides gave the 2-acylamino-3,5-dinitrothiophenes as products:

\[
\text{NHCOX} \quad \xrightarrow{\text{HNO}_3, \ \text{H}_2\text{SO}_4} \quad \text{NHCOX}
\]

The rates of hydrolysis in concentrated sulphuric acid of both the 2-acylamino-5-nitrothiophene-3-carboxylic acids and the 2-acylamino-3,5-dinitrothiophenes are shown in tables 2 and 3 respectively.

**FOR REACTION:**

\[
\text{NHCOX} \quad \xrightarrow{\text{H}_2\text{SO}_4} \quad \text{NH}_2
\]

<table>
<thead>
<tr>
<th>R</th>
<th>( k_{\text{obs}} (98% \text{H}_2\text{SO}_4) ) (sec(^{-1}))</th>
<th>( k_{\text{obs}} (90% \text{H}_2\text{SO}_4) ) (sec(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>-H</td>
<td>(&lt; 10^{-8})</td>
<td>(&lt; 10^{-8})</td>
</tr>
<tr>
<td>-CH(_3)</td>
<td>(8.1 \times 10^{-4})</td>
<td>(1.2 \times 10^{-4})</td>
</tr>
<tr>
<td>-CH(_2)Cl</td>
<td>(&lt; 10^{-8})</td>
<td>(&lt; 10^{-8})</td>
</tr>
<tr>
<td>-CH(_2)CH(_3)</td>
<td>(9.3 \times 10^{-4})</td>
<td>(2.4 \times 10^{-4})</td>
</tr>
<tr>
<td>-CH((CH_3))</td>
<td>(9.8 \times 10^{-4})</td>
<td>(3.1 \times 10^{-4})</td>
</tr>
<tr>
<td>-C((CH_3))_2</td>
<td>(77 \times 10^{-4})</td>
<td>(21 \times 10^{-4})</td>
</tr>
</tbody>
</table>

**TABLE 2:** Rates of hydrolysis of 2-acylamino-5-nitrothiophene-3-carboxylic acids in concentrated sulphuric acid.
TABLE 3: Rates of hydrolysis of 2-acylamino-3,5-dinitrothiophenes in concentrated sulphuric acid.

The hydrolysis of most of the amides in tables 2 and 3 was confirmed by $^{13}$C spectroscopy in sulphuric acid. The free amines were recoverable from concentrated sulphuric acid. 2-Amino-5-nitrothiophene-3-carboxylic acid was less stable in strongly acidic solutions than the dinitro amine and was only recoverable in poor yield. No hydrolysis of the formamido or chloroacetamido derivatives was detectable in 98% or 90% sulphuric acid either by U.V. or $^{13}$C spectroscopy. Both amides were stable for a period of days in concentrated sulphuric acid and were recoverable in good yield.

The rates of hydrolysis of the other amides were determined by measuring the rate of formation of the amine. The rate of formation of amine was always greater than the rate of degradation of amine in concentrated sulphuric acid. However, this was an obvious source of error in the rate measurements, particularly for those amides which produced the less stable 2-amino-5-nitrothiophene-3-carboxylic acid.

The substituent effects in the acyl group can be understood in terms
of the A1 mechanism of scheme 1. The slow step here is the heterolysis:

\[
\begin{align*}
\text{NO}_2 & \quad \text{N}_2 \quad + \text{RCO}^+ \\
\text{NO}_2 & \quad \text{N}_2 \quad \text{NH}_2 \text{COR}
\end{align*}
\]

If the effect of changing the R group is largely confined to the above step then one would expect electron-releasing groups in R to accelerate and electron-attracting groups to retard hydrolysis. The observed results in tables 2 and 3 are in accordance with this. The difference in rate between the acetamido and formamido derivatives is particularly marked. The chloroacetamido derivatives are further deactivated towards hydrolysis. Only small increases in the rate of hydrolysis are observed for most of the other amides i.e. \( \text{NHCOCH}(\text{CH}_3)_2 > \text{NHCOCH}_2\text{CH}_3 > \text{NHCOCH}_3 \). However, in the case of the N-t-butyl amide there is a pronounced increase in the reaction rate. A steric accelerating effect has also been observed during the hydrolysis of ortho substituted benzamides in concentrated sulphuric acid\(^{136}\).

(B) The Amino Group

The effect of polar groups in the amino 'fragment' upon the rate of hydrolysis is more complex. The results in tables 2 and 3 indicate that the 2-acylamino-5-nitrothiophene-3-carboxylic acids are hydrolysed faster than the corresponding dinitro derivatives. This is not what one would expect if one considers the heterolytic acyl-nitrogen bond fission:

\[
\begin{align*}
\text{Y} & \quad \text{S} \quad \text{NH}_2\text{COCH}_3 \\
\text{X} & \quad \text{S} \quad \text{NH}_2
\end{align*}
\]

- \( \text{CH}_3\text{CO}^+ \)
N-substituents containing strongly electron-withdrawing groups should enhance the rate of this reaction. This is illustrated by the ease of hydrolysis of the nitroacetanilides and also most of the nitrothiopheneamides of tables 2 and 3. However the effect of such substituents upon the protonation equilibrium must also be considered:

\[
\begin{align*}
X & \quad \text{enriched nitrogen atom} \\
Y & \quad \text{strongly electron-withdrawing group}
\end{align*}
\]

The more electron-withdrawing are the X and Y groups the greater will be the tendency for the above equilibrium to lie on the left-hand side. This is because there will be a greater reduction in the proton-affinity of the adjacent nitrogen atom than that of the oxygen atom. Thus, if hydrolysis proceeds via the N-protonated form, as seems likely, then the rate is decreased as the number of electron-withdrawing substituents is increased. This is illustrated by the increased rate of hydrolysis when a nitro substituent is replaced by a carboxyl group (tables 2 and 3). The behaviour of several other acetamidothiophenes in concentrated sulphuric acid was examined by $^{13}$C spectroscopy and the results are summarized in table 4.

Results for compounds (A) and (B) illustrate the sensitivity of the A1-hydrolysis reaction to substituent effects in the amino fragment. In general N-substituents containing strongly electron withdrawing groups are required for hydrolysis in order to facilitate the acyl-nitrogen bond fission. However, electron-withdrawing substituents decrease the basicity of the nitrogen atom and this not only decreases the basicity of the amide as a whole but also decreases the equilibrium concentration of N-protonated amide relative to O-protonated amide. Thus, these two effects of substituents on the thiophene ring will oppose each other to an unknown
TABLE 4: Behaviour of some substituted acetamidothiophenes in 98% sulphuric acid at 25°C.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Behaviour in 98% sulphuric acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) <img src="image" alt="Chemical Structure" /></td>
<td>Rapid hydrolysis to amine which is rather unstable in conc. acid.</td>
</tr>
<tr>
<td>(B) <img src="image" alt="Chemical Structure" /></td>
<td>Only a very slow hydrolysis reaction - amide recoverable in good yield after 24 hrs.</td>
</tr>
<tr>
<td>(C) <img src="image" alt="Chemical Structure" /></td>
<td>Rapid hydrolysis producing an unstable amine.</td>
</tr>
<tr>
<td>(D) <img src="image" alt="Chemical Structure" /></td>
<td>No evidence of hydrolysis - amide recoverable in good yield.</td>
</tr>
<tr>
<td>(E) <img src="image" alt="Chemical Structure" /></td>
<td>No evidence of rapid hydrolysis but series of 13C changes and poor recovery suggest further reaction e.g. sulphonation.</td>
</tr>
</tbody>
</table>

extent. Electron-releasing groups in the acyl part of the molecule facilitate hydrolysis by the A1 mechanism and so acetamido-thiophene derivatives always hydrolyse faster than the corresponding chloroacetamido-thiophene derivatives.

**THE A-2 MECHANISM**

The final step in the industrial preparation of 2-amino-3,5-dinitrothiophene involves hydrolysis of the corresponding 2-acetamido-thiophene derivative by refluxing with dilute sulphuric acid (2M). The
mechanism proposed for hydrolysis in dilute acid is the A2 mechanism of scheme 2. A study of the variation of the rate of hydrolysis of 2-acetamido-3,5-dinitrothiophene with acid concentration (fig. 4) revealed a minimum in the rate profile at ~82% sulphuric acid.

Scheme 2: Bimolecular (A2) mechanism of hydrolysis of 2-acetamido-3,5-dinitrothiophene.

Above 82% acid the A1 mechanism is in operation resulting in an increased reaction rate. Below 82% sulphuric acid the increase in the reaction rate can be understood in terms of the A2 mechanism. The slow step of scheme 2 is the attack of water at the protonated amide group (step 2).
As the acid concentration decreases below 82% so too does the activity of water, required for A2 hydrolysis, increase. Thus, although the degree of protonation of the rather weakly basic nitrothiopheneamides decreases, the overall effect is an increase in the rate of hydrolysis due to an increase in the concentration of free water. This increase in rate would be expected to continue down to ~4M sulphuric acid whereupon the equilibrium concentration of protonated amide would be so small that any further decrease in acid concentration would result in a slower rate of hydrolysis. A quantitative study of this effect was not performed for the thiophene amides due to practical problems of solubility etc. However, this trend towards maximum A2 hydrolysis at ~4M sulphuric acid was demonstrated qualitatively for 2-acetamido-3,5-dinitrothiophene.

Structural Effects

(A) Acyl Group

Although 2-acetamido-3,5-dinitrothiophene can be readily hydrolysed in dilute sulphuric acid the rate of hydrolysis is not comparable with that in concentrated acid by the A1 mechanism. Conversely the corresponding 2-formamido derivative was hydrolysed much more readily in dilute acid than in concentrated acid. This trend was further illustrated by the ease of hydrolysis of the 2-chloroacetamido derivative in dilute sulphuric acid:

For the reaction:-
TABLE 5: Conditions required for hydrolysis of 2-acylamino-3,5-dinitrothiophenes in dilute sulphuric acid.

The observed acyl structural effects (table 5) can be understood in terms of the A2-mechanism of scheme 2. The slow step is the attack by water:

Electron-withdrawing groups in R decrease the electron-density at the carbonyl carbon and thereby increase its reactivity to nucleophilic attack by water. Since chloroacetamido derivatives are hydrolysed more readily than acetamido derivatives then this effect obviously overcomes that of reducing the basicity of the amide by electron withdrawal. This is in direct contrast to the acyl structural effects observed by A1 hydrolysis in concentrated acid.

(B) The Amino Group

The effect of substituents (on the thiophene ring) upon the rate of hydrolysis in dilute sulphuric acid was not studied in any great detail.
Electron-withdrawing groups would be expected to favour attack by water but would also decrease the equilibrium concentration of protonated amide. 2-Acetamido-5-nitrothiophene-3-carboxylic acid was hydrolysed at a very similar rate to the corresponding dinitro derivative in dilute acid.

**BASIC HYDROLYSIS OF AMIDO ThiOPHENES**

A step in the attempted synthesis of 2-acetamido-3-nitrothiophene-5-carboxylic acid involves the hydrolysis of the corresponding methyl ester:-

![Chemical structure](image)

The final product of hydrolysis is thus the amino-acid and not the desired amido acid. It is also possible to isolate the amino ester from the reaction solution which indicates that the basic hydrolysis of the amido group is extremely facile; even more so than the ester group in this particular example. The mechanism for the basic hydrolysis of amido-thiophenes is shown in scheme 3. Great care is required when this amide hydrolysis is used preparatively since the amine is unstable in presence of excess hydroxide ions. This is especially true when the thiophene ring contains strongly electron-withdrawing substituents which presumably activate the ring towards nucleophilic attack and thereby ring-opening.
Scheme 3: Mechanism for the basic hydrolysis of methyl-2-acetamido-3-nitrothiophene-5-carboxylate.

Structural Effects

(A) The Acyl Group

The basic hydrolysis of the ester group in methyl-2-formamido-4,5-dimethylthiophene-3-carboxylate was accompanied by hydrolysis of the amide:

Under identical reaction conditions only the acetamido acid was obtained for the corresponding acetamido derivative. Thus, the formamido group is more susceptible to basic hydrolysis than the acetamido group. The first step of scheme 3 involves a nucleophilic attack at the carbonyl carbon. Electron-releasing groups in the acyl group will decrease the reactivity of this carbon towards nucleophilic attack. The expected order of reactivity is therefore chloroacetamido > formamido > acetamido and this was verified experimentally.
The Amino Group

The examples mentioned above involve the basic hydrolysis of the amides:-

\[
\begin{align*}
\text{(A)} & \quad \text{Compound (A) was found to undergo basic amide hydrolysis much more readily than compound (B). In the former case the amide group was more susceptible to hydrolysis than the ester group whereas the converse is true for (B). Again this can be understood in terms of a decrease in the electron density at the carbonyl carbon (of amide), the decrease being greater in (B) than in (A) due to the two electron withdrawing substituents. Nucleophilic attack by OH}^{-} \text{ is thus favoured in compound B and so hydrolysis is enhanced. 2-Acetamido-3,5-dinitrothiophene is extremely susceptible to hydrolysis in basic media, the subsequent amine being unstable in presence of excess OH}^{-} \text{ ions.}
\end{align*}
\]

Summary

Most of the amidothiophenes involved in this investigation are susceptible to either basic or acidic hydrolysis, or both. Basic hydrolysis is favoured by electron-withdrawing groups in both the thiophene ring and the acyl group. However, when the thiophene ring contains strongly electron-withdrawing substituents the subsequent amine is often unstable - the ring being highly activated towards nucleophilic attack.

In dilute acid the amidothiophenes are hydrolysed only with some difficulty, especially those containing electron-withdrawing substituents.
in the thiophene ring. This is due to the small equilibrium concentration of protonated amide, necessary for hydrolysis. However, electron-withdrawing groups in the acyl fragment do favour hydrolysis by the A2 mechanism in this way by increasing the reactivity towards attack by water. Thiophene substituent effects (the amino fragment) are more complex.

In concentrated acid where the activity of water is low, hydrolysis proceeds by the A1 mechanism. Electron-withdrawing substituents in the thiophene ring favour this mechanism, which involves a heterolytic acyl-nitrogen bond fission. However, this effect is complicated by equilibrium protonation effects etc. Electron-withdrawing groups in the acyl fragment hinder hydrolysis by the A1 mechanism. The great sensitivity of this reaction to changes in the acyl group is illustrated by the difference in behaviour of 2-acetamido-3,5-dinitrothiophene and the corresponding formamido derivative. The former is rapidly hydrolysed in concentrated sulphuric acid at room temperature whereas the latter amide is recoverable after a period of days in concentrated acid.

The significance of the hydrolysis in concentrated sulphuric acid is particularly important in the current investigation. During the nitration of 2-acetamido-5-nitrothiophene-3-carboxylic acid in sulphuric/nitric acids a side-reaction is occurring:
The amine, produced by hydrolysis in concentrated sulphuric acid, is extremely unstable in presence of oxidising agents such as nitric acid and is degraded. Thus, hydrolysis is an unwanted side-reaction resulting in yield loss. It is significant that the desired product, 2-acetamido-3,5-dinitrothiophene is also susceptible to hydrolysis in concentrated sulphuric acid. The amine produced in this way is again extremely unstable in presence of nitric acid and is not isolable from the reaction mixture. The hydrolysis of the reaction product is thus another source of yield loss.

As shown earlier, 2-formamido thiophene derivatives are less susceptible to hydrolysis than the corresponding acetamido derivatives. Therefore, one might anticipate an improved yield for the nitration of 2-formamido-5-nitrothiophene-3-carboxylic acid:

\[
\text{HNO}_3 \quad \text{H}_2\text{SO}_4
\]

This has been verified experimentally (see chapter 5), the yield being improved from 56% (for acetamido) to 72% (for formamido). A similar increase in yield was obtained for nitrodecarboxylation of 2-chloroacetamido-5-nitrothiophene-3-carboxylic acid.
PART 4.

DEGRADATION OF

THIOPHENE DERIVATIVES
CHAPTER 8

INTRODUCTION TO REACTIONS INVOLVING DESTRUCTION OF THE THIOPHENE NUCLEUS
DEGRADATION OF THIOPHENES

INTRODUCTION

The thiophene ring shows typical aromatic behaviour. The nucleus is stable to alkalis, moderately stable to acids and fairly resistant to oxidation.

Polymerisation

Polymerisation of thiophene by 100% orthophosphoric acid gives a trimer:

\[
\begin{array}{c}
\text{S} \\
\text{S} \\
\text{S} \\
\text{S} \\
\text{S} \\
\text{S}
\end{array}
\]

Polymerisation can also be effected with concentrated sulphuric acid and the sulphonation of thiophene, by sulphuric acid is often conducted in ligroin to minimise resinification.

Reduction

The usually stable thiophene ring can sometimes be opened smoothly by reduction. Non-catalytic reduction of thiophenes by sodium or lithium in liquid ammonia leads to complete destruction of the ring system, ultimately giving butenethiols and alkenes. Hydrodesulphurisation of thiophene to butane and hydrogen sulphide over various catalysts has been studied. Catalytic reduction is difficult because of the tendency of sulphur compounds to poison catalysts. However, with a large excess of catalyst or under more forcing conditions, tetrahydrothiophene can be obtained:

\[
\begin{align*}
\text{H}_2/\text{MoS}_2 & \quad \text{atm} \\
\end{align*}
\]
Pyrolysis

Thiophene is thermally very stable and gives hydrogen sulphide, hydrogen and methane as the only gaseous products on pyrolysis at 800-825°. At 825° thiophene affords some benzene.²⁵³

Oxidation

The thiophene sulphur atom shows very few of the reactions expected of a sulphide. The oxidation to the sulphone is difficult to achieve, but a study of the oxidation of substituted thiophenes with perbenzoic or peracetic acid showed that sulphones could be obtained from poly-substituted methyl- and phenyl-thiophenes.²⁵⁴ The presence of electron-withdrawing groups, such as nitro, inhibited oxidation.

\[
\text{Me} \quad \text{S} \quad \text{Me} \quad \xrightarrow{\text{PhCO}_3\text{H}, \text{CHCl}_3/0^\circ} \quad \text{Me} \quad \text{S} \quad \text{O} \quad \text{O} \quad \text{Me}
\]

In the case of thiophene itself, the intermediate sulphoxide and sulphone react further, to give mostly intractable products.²⁵⁵

Hydrogen peroxide oxidises thiophene to a product of formula \((\text{C}_4\text{H}_4\text{S})_2\text{O}_3\) which is believed to arise by Diels-Alder combination of the sulphoxide and sulphone.²⁵⁶

\[
\text{S} \quad \xrightarrow{\text{H}_2\text{O}_2} \quad \text{SO} \quad + \quad \text{S} \quad \xrightarrow{\text{O}_2} \quad \text{SO} \quad \text{S} \quad \text{O}_2
\]

The aromatic character of thiophenes is destroyed by their conversion into such 1,1 dioxides.
Oxidative Degradation

It is known\(^\text{257}\) that the action of nitric acid on thiophene results in the oxidative decomposition of the thiophene molecule with an apparently quantitative conversion of sulphur to sulphuric acid. Angeli and Claminian\(^\text{258}\) found that 3,4-dibromothiophene and tetrabromothiophene gave dibromomaleic acid when treated with cold, concentrated nitric acid. In a similar manner, 3-methyl-2,4,5-tribromothiophene gave bromocitraconic acid, \(\text{HOOCC(Br) = C(CH}_3\text{)COOH}\). The action of ozone on a cold suspension of thiophene in water gave oxalic acid, carbon dioxide and sulphuric acid. With oxygen in the presence of light, formic acid was formed in addition to oxalic acid. Succinic acid is formed by bubbling air through a suspension of thiophene in aqueous thallic hydroxide\(^\text{259}\).

Levitt and Howard\(^\text{260}\) studied the oxidative degradation of thiophene by nitric acid. They found that the products formed by the action of 8M nitric acid on thiophene in cyclohexane were 2-nitrothiophene, 2,5-dinitrothiophene, maleic acid, oxalic acid and sulphuric acid. In the light of the evidence obtained during their investigation Levitt and Howard\(^\text{260}\) concluded that oxidative decomposition of thiophene by nitric acid follows the sequence shown below.

\[
\begin{align*}
\text{S} & \rightarrow \text{S} & \text{NO}_2 \\
\text{NO}_2 & \rightarrow \text{NO}_2 \\
\text{H}_2\text{SO}_4 + \text{HC} & \rightarrow \text{CH}_2 \text{CO}_2 \text{H} \\
\text{CO}_2 \text{H} & \rightarrow 4\text{CO}_2
\end{align*}
\]

The authors were doubtful about the mechanism of conversion of 2,5-dinitrothiophene to maleic acid but suggest that the ring cleavage is preceded by oxidation at the sulphur atom. The formation of a short-lived sulphone or sulphoxide cannot be excluded. This would lead to the
decreasing availability of the sulphur atom's lone electron pairs for resonance stabilization of the aromatic system.

Since thiophene itself is susceptible to oxidation by nitric acid, great care is required in the nitration of thiophene derivatives with sulphuric/nitric acid mixtures. Because of the oxidative nature of the process one would expect thiophene derivatives containing electron releasing substituents e.g. -NH₂ to be particularly susceptible to degradation. Butler⁴⁶ found that during the nitration of thiophene with sulphuric/nitric acids, nitrosation was an unwanted side-reaction. Although the nitroso derivatives can be subsequently oxidised to yield the nitro-derivatives other reactions can also occur. Butler⁴⁶ believes that thiophene, in common with other heterocyclic compounds, is particularly susceptible to nitrosation.
CHAPTER 9

DEGRADATION (OXIDATION) OF
THIOPHENE DERIVATIVES
DEGRADATION/OXIDATION OF SUBSTITUTED THIOPHENES

DISCUSSION

Nitration of 2-Acetamidothiophene-3-carboxylic acid

The simultaneous dinitration and decarboxylation of 2-acetamidothiophene-3-carboxylic acid is accomplished by nitrating the compound in sulphuric acid with a sulphuric acid-nitric acid mixture at < 0°C:

\[
\text{S} \quad \text{CO}_2\text{H} \quad \stackrel{\text{HNO}_3}{\longrightarrow} \quad \text{S} \quad \text{NO}_2
\]

\[
\text{NHAc} \quad \quad \quad \quad \quad \quad \quad \quad \text{NHAc}
\]

H\textsubscript{2}\text{SO}_4

The nitration is found to occur only in moderate yield to give the bis-nitroderivative which results from nitration at C5 followed by nitrodecarboxylation at C3. 2-Acetamidothiophene-3-carboxylic acid can be mononitrated in the 5-position under the appropriate conditions in 88% yield. The second nitrodecarboxylation step proceeds in only 53% yield. Thus, the overall yield for the simultaneous dinitration and decarboxylation of 2-acetamidothiophene-3-carboxylic acid, under industrial conditions, is 47%. By studying the sequence of reactions involved in nitrodecarboxylation it was hoped, in the system of commercial interest, to improve the overall yield. During the industrial isolation of the product, 2-acetamido-3,5-dinitrothiophene, no other products (e.g. of oxidation/degradation) were detectable. The actual isolation procedure involves drowning the nitration mixture into ice-water, which precipitates the final product. A good deal of frothing had previously been observed upon drown-out under industrial conditions.

The industrial preparation of 2-acetamido-3,5-dinitrothiophene was repeated on a laboratory scale and the unsatisfactory yield of product was confirmed.
Degradation via Hydrolysis

Both 2-acetamido-5-nitrothiophene-3-carboxylic acid and the corresponding dinitro derivative were found to be susceptible to hydrolysis in concentrated sulphuric acid. The amines produced in this way were unstable in presence of sulphuric acid alone but were particularly unstable in presence of nitric acid:

\[
\begin{align*}
\text{NO}_2 & \text{S} \text{NHAc} \\
\text{H}_2\text{SO}_4 & \rightarrow \\
\text{NO}_2 & \text{S} \text{NH}_2
\end{align*}
\]

The great instability of both 2-amino-5-nitrothiophene-3-carboxylic acid and 2-amino-3,5-dinitrothiophene accounts for the fact that neither of these amines was isolated as a reaction product during the industrial nitration of 2-acetamidothiophene-3-carboxylic acid.

Degradation in Sulphuric Acid/Nitric Acid

A $^{13}$C spectrum of 2-acetamido-5-nitrothiophene-3-carboxylic acid in 98% sulphuric acid alone revealed an initial hydrolysis reaction to an amine, which was recoverable by drown-out of the reaction mixture. However, the amine was unstable when kept for longer periods in sulphuric acid. A similar effect was observed in the case of 2-amino-3,5-dinitrothiophene. When the amines were dissolved in a sulphuric-nitric acid mixture, $^{13}$C spectra indicated rapid degradation reactions, neither amine being recoverable from the nitration mixture.

The link between hydrolysis and degradation was demonstrated by
studying the variation in the rate of degradation with both sulphuric acid and nitric acid concentration. The rates of degradation were obtained by measuring the rate of decrease in U.V. absorbance at a fixed wavelength. The results for 2-acetamido-3,5-dinitrothiophene are shown in table 1.

<table>
<thead>
<tr>
<th>% H₂SO₄</th>
<th>k₁obs (hydrolysis)</th>
<th>[HNO₃]</th>
<th>k₁obs (degradation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>98.6</td>
<td>3.1 x 10⁻⁴ sec⁻¹</td>
<td>0.88 x 10⁻² M</td>
<td>3.8 x 10⁻⁴ sec⁻¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.75 x 10⁻² M</td>
<td>3.1 x 10⁻⁴ sec⁻¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.50 x 10⁻² M</td>
<td>4.0 x 10⁻⁴ sec⁻¹</td>
</tr>
<tr>
<td>89.1</td>
<td>1.1 x 10⁻⁵ sec⁻¹</td>
<td>0.88 x 10⁻² M</td>
<td>2.0 x 10⁻⁵ sec⁻¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.75 x 10⁻² M</td>
<td>1.2 x 10⁻⁵ sec⁻¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.50 x 10⁻² M</td>
<td>1.2 x 10⁻⁵ sec⁻¹</td>
</tr>
<tr>
<td>82.7</td>
<td>6.3 x 10⁻⁶ sec⁻¹</td>
<td>0.88 x 10⁻² M</td>
<td>6.4 x 10⁻⁶ sec⁻¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.75 x 10⁻² M</td>
<td>6.5 x 10⁻⁶ sec⁻¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.50 x 10⁻² M</td>
<td>6.1 x 10⁻⁶ sec⁻¹</td>
</tr>
</tbody>
</table>

TABLE 1: Rates of hydrolysis and degradation of 2-acetamido-3,5-dinitrothiophene in sulphuric acid and in sulphuric-nitric acid mixtures.

It can be seen from table 1 that the rate of degradation of 2-acetamido-3,5-dinitrothiophene is effectively independent of nitric acid concentration, the k₁obs [degradation] being the experimentally determined first order rate constant for the degradation of the thiophene derivative. The rate of degradation in sulphuric-nitric acid mixtures is approximately equal to the rate of hydrolysis in the equivalent sulphuric acid solution.

2-Amino-3,5-dinitrothiophene was found to be extremely unstable in sulphuric-nitric acid mixtures. For example, in 98% sulphuric acid, the
experimentally determined first-order rate constant was $2.3 \times 10^{-1} \text{ sec}^{-1}$, at a nitric acid concentration of $1.75 \times 10^{-2} \text{ M}$, and the rate of oxidation of this amine showed a first-order dependence upon nitric acid concentration. The second-order rate constant for this amine oxidation is thus $13 \text{ l mol}^{-1} \text{ sec}^{-1}$. This information, together with that presented in table 1, indicates that the degradation of 2-acetamido-3,5-dinitrothiophene in sulphuric-nitric acid mixtures proceeds via the corresponding amine:-

![Chemical structure diagram]

A similar effect was observed in the case of 2-acetamido-5-nitrothiophene-3-carboxylic acid, the starting material for nitrodecarboxylation. The rate of degradation of this compound (as the methyl ester) was dependent upon its rate of hydrolysis. However, the significance of this observation with regard to the industrial nitration of 2-acetamido-5-nitrothiophene-3-carboxylic acid is questionable. The product of hydrolysis, 2-amino-5-nitrothiophene-3-carboxylic acid is extremely unstable in presence of nitric acid but is also presumably highly activated towards nitrodecarboxylation. Thus, under industrial nitration conditions, degradation of both 2-amino-5-nitrothiophene-3-carboxylic acid and particularly 2-amino-3,5-dinitrothiophene are undesirable side-reactions.

**2-Acylamino-3,5-Dinitrothiophenes**

A series of 2-acylamino-3,5-dinitrothiophenes were prepared by
acylation and nitration of 2-amino-5-nitrothiophene-3-carboxylic acid. The rates of hydrolysis (in sulphuric acid alone) and oxidation (in sulphuric-nitric acid mixtures) are again interrelated (see tables 14 and 16 in Experimental Section). This is illustrated in table 2 which shows the yield of 2-acylamino-3,5-dinitrothiophene obtained by nitrodecarboxylation of the corresponding 2-acylamino-5-nitrothiophene-3-carboxylic acid.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (Product)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-H</td>
<td>73%</td>
</tr>
<tr>
<td>-CH₃</td>
<td>56%</td>
</tr>
<tr>
<td>-CH₂Cl</td>
<td>81%</td>
</tr>
<tr>
<td>-CH₂CH₃</td>
<td>50%</td>
</tr>
<tr>
<td>-C(CH₃)₃</td>
<td>42%</td>
</tr>
</tbody>
</table>

**TABLE 2: Yields of product obtained by nitrodecarboxylation of 2-acylamino-5-nitrothiophene-3-carboxylic acids.**

The improved yield of product obtained in the case of the formamido and chloroacetamido derivatives is a direct consequence of their reluctance to hydrolyse by the A-1 mechanism in concentrated sulphuric acid. Each of the other amides (both starting material and product) is susceptible to hydrolysis in concentrated sulphuric acid to an unstable amine, resulting in a decrease in yield of dinitro product. The rates of degradation of all amides (other than formamido- and chloroacetamidothiophenes) were dependent upon sulphuric acid concentration in a similar manner to their hydrolysis rates, but virtually independent of
nitric acid concentration. This again supports a degradation route via the amine. However, whilst no hydrolysis of formamido- and chloroacetamido-derivatives was detectable in 98% sulphuric acid, degradation did occur in sulphuric-nitric acid mixtures, albeit at a slower rate than for the hydrolysable amides. This suggests that degradation of the intact amide must also be considered. Thus the yield of dinitro product obtained by nitrodecarboxylation of the 2-formamido- and 2-chloroacetamido-activated thiophene carboxylic acids is considerably better than that obtained in the case of the other thiophene amides, but is not entirely satisfactory owing to the instability of the amides themselves in sulphuric-nitric acid mixtures.

The rates of degradation of intact amides were obtained by determining the rate of decrease in U.V. absorbance at a suitable fixed wavelength. Good, linear pseudo first-order kinetic plots were obtained during several half-lives when the nitric acid concentration was at least ten times that of the substrate. In the case of the free amines, both 2-amino-5-nitrothiophene-3-carboxylic acid and 2-amino-3,5-dinitrothiophene are extremely unstable in presence of nitric acid and only approximate rates of degradation were obtainable (see table 17 in Experimental Section).

Substituent Effects

The oxidative nature of the degradation process in sulphuric-nitric acid mixtures is indicated by the fact that electron-withdrawing groups tend to stabilise a thiophene. This is illustrated in table 3 which shows the rates of degradation of a variety of thiophenes under identical reaction conditions.
<table>
<thead>
<tr>
<th>Thiophene Derivative</th>
<th>$k_2$ (degradation)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Thiophene Derivative 1" /></td>
<td>$2.5 \times 10^{-4}$</td>
</tr>
<tr>
<td><img src="image2" alt="Thiophene Derivative 2" /></td>
<td>13.1</td>
</tr>
<tr>
<td><img src="image3" alt="Thiophene Derivative 3" /></td>
<td>$3.8 \times 10^{-6}$</td>
</tr>
<tr>
<td><img src="image4" alt="Thiophene Derivative 4" /></td>
<td>$5.8 \times 10^{-5}$</td>
</tr>
</tbody>
</table>

**TABLE 3:** Second-order rate constants for degradation of thiophene derivatives in sulphuric-nitric acid mixtures (98% $\text{H}_2\text{SO}_4$) at 25°C.

The results in table 3 are in contrast to the exceptional stability of 5-nitrothiophene-3-carboxylic acid. Campagne et al. report a 90% recovery of this compound from a sulphuric-nitric acid mixture at 70°C:

```
\[
\text{NO}_2 \quad \text{S} \quad \text{CO}_2\text{H} \\
\text{NO}_2 \quad \text{S} \quad \text{NHCHO} \\
\text{NO}_2 \quad \text{S} \quad \text{NHCOCH}_2\text{Cl} \\
\text{NO}_2 \quad \text{S} \quad \text{CO}_2\text{H} \\
\]
```

Further proof of the oxidative nature of the degradation process was afforded by considering the stability of other thiophene derivatives to nitrating media. For example, 2-formamido-4,5-dimethylthiophene-3-
carboxylic acid was considerably less stable to oxidation than 2-formamido-5-nitrothiophene-3-carboxylic acid.

A series of 2-substituted thiophene-5-carboxylic acids were prepared and during a study of the effect of such substituents upon the rate of nitrodecarboxylation it was observed qualitatively that the greater the activation the less stable was the end product. Thus 2-methyl-3,5-dinitrothiophene was more stable than the corresponding 2-methoxy derivative etc. Indeed, in the latter case, some difficulty was experienced in measuring the rate of formation of dinitro product, because of its instability in sulphuric-nitric acid mixtures. Conversely, 3-nitrothiophene-5-carboxylic acid was relatively stable to oxidation.

Further attempts to obtain information regarding the nature of the oxidation process involved the preparation of methyl 2-N-methylacetamido-3-nitrothiophene-5-carboxylate. A qualitative investigation of the stability of this compound in sulphuric-nitric acid mixtures revealed that the N-methyl group had very little influence upon the oxidation rate.

Isolation of Oxidation Products

In the reaction of industrial interest all attempts to isolate products other than those of conventional nitration were unsuccessful.

When 2-acetamido-3,5-dinitrothiophene was treated with sulphuric acid alone hydrolysis to the unstable amine occurred. This amine was isolable by drown-out of the reaction solution into ice-water. However, upon prolonged treatment of 2-amino-3,5-dinitrothiophene with concentrated sulphuric acid, the amine was completely degraded and no solid was precipitated upon drown-out into water. All attempts to isolate any product from the drown-out solution were unsuccessful.

When 2-acetamido-3,5-dinitrothiophene was treated with a sulphuric-
nitric acid mixture, $^{13}$C spectra of the reaction solution revealed a gradual decrease in intensity of the four aromatic carbon peaks and a shift of the acetyl carbon peaks to the positions corresponding to protonated acetic acid (at 194.0 and 21.1 ppm from T.M.S.). No peaks corresponding to 2-amino-3,5-dinitrothiophene were detected. These observations agree with the kinetic results discussed above in suggesting degradation via the amine, which is extremely unstable and barely detectable in the presence of nitric acid. The complex changes in $^{13}$C spectra did not result in formation of any peaks comparable in intensity with the original aromatic carbon peaks (other than those at 194.0 and 21.1 ppm). Only a complex series of low-intensity peaks remained, suggesting several products, each present in low concentration. Again, all attempts to isolate any products from the dark and rather viscous reaction mixtures were unsuccessful.

When 2-chloroacetamido-3,5-dinitrothiophene was dissolved in a sulphuric-nitric acid mixture, $^{13}$C spectroscopy revealed behaviour similar to that of the 2-acetamido derivative. Although the degradation process was appreciably slower, due to the increased resistance to hydrolysis, a gradual decrease in intensity of the original peaks did occur, resulting eventually in a complex spectrum involving a large number (20-25) of low-intensity peaks. However, the free acyl peaks were again apparent, corresponding to protonated chloroacetic acid.

A mass spectrometric analysis of the gases produced during the reaction of 2-acetamido-3,5-dinitrothiophene with sulphuric-nitric acid mixtures revealed the presence of carbon dioxide and sulphur dioxide and various nitrogen oxides, including nitric oxide and nitrogen dioxide. Carbon dioxide was further liberated upon drawn-out of this reaction solution into ice-water. Sulphur dioxide was also present upon treatment of 2-acetamido-3,5-dinitrothiophene with nitric acid alone, suggesting oxidation of the
ring sulphur atom. Attempts to quantify the gas analysis were unsuccessful owing to the viscous and tarry nature of the reaction mixtures.

Summary

Very little information exists in the literature regarding the oxidation of thiophene derivatives by nitric acid or sulphuric-nitric acid mixtures. Levitt and Howard investigated the products of oxidative degradation of thiophene itself by nitric acid. They observed a quantitative conversion of the sulphur atom to sulphuric acid, and the presence of maleic acid and oxalic acid upon treatment of thiophene with 8M nitric acid. No such reaction products (or related compounds) were present in any appreciable concentration upon treatment of the amido-thiophenes, of industrial interest, with nitric acid and sulphuric-nitric acid mixtures. However, carbon dioxide was detected as a degradation product.

A primary cause of low yields during the nitration of 2-acetamido-5-nitrothiophene-3-carboxylic acid is the hydrolysis of both this compound and of the dinitro product to amines which are rapidly oxidized in sulphuric-nitric acid mixtures. Various attempts to suppress this oxidation reaction and thereby increase the yield were made. Decreasing the concentration of sulphuric acid (< 90%) led to a decrease in the rate of hydrolysis, but also led to a decrease in the rate of nitrode-carboxylation. When the acetamido group was replaced by another amido group less susceptible to hydrolysis, such as formamido or chloroacetamido, the yield was higher. Thus nitration of 2-formamidothiophene-3-carboxylic acid under industrial nitration conditions gave a 70% yield of 2-formamido-3,5-dinitrothiophene. Under identical reaction conditions the corresponding 2-acetamido derivative gave only a 46% yield of dinitro product. Industrially it has been observed that the overall nitration process requires a half-molar excess of nitric acid for production
of a satisfactory product in optimum yield.

It might thus be concluded that the nitrodecarboxylation reaction is very useful synthetically, since it eliminates the necessity for a separate protodecarboxylation reaction. However, because this reaction is slower than the corresponding nitrodeprotonation, the contact time of the activated thiophene compounds with nitric acid present in the reaction solution results in unsatisfactory yields owing to competing oxidation reactions. Attempts to suppress the degradation reaction by addition of other species such as urea (to prevent oxidative nitrosation) or acetic anhydride (to suppress hydrolysis) did not result in any improvement in yield. Further analysis of the oxidation processes and the products (or intermediates) involved would be desirable as a possible means of improving the yield of desired product.
PART 5.

EXPERIMENTAL
(A) SYNTHESIS

Melting points are quoted in °C and are uncorrected. Infra-red spectra were recorded on a Unicam SP200G spectrometer. Ultraviolet spectra were obtained on a Unicam SP800 spectrophotometer and proton magnetic resonance spectra on a Perkin-Elmer R10 instrument operating at 60 MHz. $^{13}$C spectra were recorded on a JEOL FX60 in the F.T. mode at 15 MHz with 30° pulse and 1 sec repetition, deuterium-lock and external T.M.S. as standard. For thiophene compounds (~400 mg) in sulphuric acid (98%, 2ml) a minimum of 1000 pulses (~20 mins) were required for a satisfactory $^{13}$C spectrum. In all cases, the $^{13}$C spectra were in accordance with the structures assigned to new thiophene compounds.

Unless otherwise stated laboratory grade reagents were used in the preparations. Extracts were always dried over anhydrous magnesium sulphate irrespective of whether or not this is specifically stated in the text. Thin-layer chromatography was performed using silica plates developed with iodine vapour. The solvent system was made up of ethyl acetate-methylene chloride mixtures and diethyl ether-petroleum spirit mixtures. Diethyl ether was dried over sodium wire, and methylene chloride over calcium chloride.

Kinetic Determinations

(a) Apparatus

The reactions were monitored spectrophotometrically using a Unicam SP800 spectrophotometer fitted with a scale expander, constant wavelength scanner, programme controller and automatic cell changer. The reactions were carried out in spectroscopic grade fused silica cells with a 10 mm path length. The cell block was thermostatted by water circulated from
an external bath held at $25.0 \pm 0.1{}^\circ C$. The temperature of the reaction mixture was $25.4 \pm 0.1{}^\circ C$ as the spectrometer was itself thermostatted at a temperature substantially higher than ambient in order to maintain a constant wavelength. The rate data refer to a temperature of $25.4 \pm 0.1{}^\circ C$.

(b) Reagents

Sulphuric acid solutions were prepared by addition of AnalaR sulphuric acid (98% w/w) to an appropriate volume of water. They were standardised against sodium hydroxide (prepared from B.D.H. concentrated volumetric solutions) using phenolphthalein as indicator. Alternatively sulphuric acid concentrations were determined by the freezing-point method. (See Chapter

Sulphuric acid/nitric acid solutions were prepared by weight. Substrate solutions were generally in the concentration range $10^{-3} - 10^{-4}$ M.

(c) Techniques

Kinetic runs were performed at a known temperature with the Unicam SP800 spectrophotometer.

1) Hydrolysis

Solutions of the substrate in sulphuric acid (of known concentration, thermostatted at $25^\circ$) were made up, appropriately diluted ($\sim 10^{-4}$ M) and transferred to a spectroscopic cell. Changes in U.V. spectrum were then recorded as a function of time.

II) Nitration

Known volumes of solutions of the aromatic ($\sim 10^{-4}$ M) and nitric acid (of known concentration) dissolved separately in the same sulphuric acid solution (of known concentration), and maintained at the same temperature, were mixed. The mixture was shaken and rapidly transferred to a
spectroscopic cell. Changes in U.V. spectrum were then recorded as a function of time.

(d) **Evaluation of Rate Data**

The rate data fitted a second-order rate equation in all cases for the nitration reactions. In each instance the concentration of each reactant was varied independently of the other to ensure that there were no gross deviations in the second order rate constants.

The integrated form of the rate equation for the second-order process:-

\[
\text{A} + \text{B} \rightarrow \text{Products}
\]

is
\[
(a - b)k_2t = \ln\left(\frac{b(a-x)}{a(b-x)}\right)
\]  
(1)

where \(a\) and \(b\) are the initial concentrations of \(A\) and \(B\) respectively, and \(x\) is the amount of reaction that has occurred in time \(t\); \(k_2\) is the second-order rate constant.

When \(b \gg a\) and hence \(b \gg x\) equation (1) simplifies to:

\[
-bk_2t = \ln\left(\frac{a-x}{a}\right)
\]  
(2)

The rate data obtained from the SP800 were in the form of absorbance values, as a function of time. Beer's law states that:

\[
\text{Absorbance} = \varepsilon \cdot c \cdot l
\]

where \(c\) is the concentration of the absorbing species, \(l\) is the path-length and \(\varepsilon\) is a constant characteristic of the substrate and the wavelength, - the molar extinction coefficient. Thus it is possible to evaluate the rate data directly from the absorbance values without need to convert absorbance into absolute concentration.

Equation (2) becomes:
-bkt = ln \(A_\infty - X\) + constant \hspace{1cm} (3)

where \(A_\infty\) is the absorbance at \(t = \infty\) and \(X\) is the absorbance at time \(t\). 

\(k_1\), the pseudo first-order rate constant is thus obtained from a plot of \(\ln (A - X)\) against time \((k_1 = k_b)\).

In practice equation (3) was used when \(b > 10a\) which was true for all the substrates. The experimental conditions for nitration, for example, were such that the concentration of nitric acid was in considerable excess over the concentration of substrate, and so pseudo first-order kinetics were observed.

The rate data from the SP800 are expressed in terms of the arbitrary absorbance units, \(A\) and \(X\). The data were obtained as a continuous plot of \(X\) versus \(t\). A suitable number of points were read off the curve and then evaluated as described above. Good linear plots were obtained up to 80% reaction.

As the rate constant was obtained from the slope of the graph it was not necessary to know the origin of the time axis.

Thus, in summary, the reactions were followed by measuring the ultraviolet absorption at a fixed wavelength as a function of time. Most of the reactions were performed under pseudo first-order conditions by using at least a ten-fold excess of nitric acid (and sulphuric acid) over aromatic compound.
(1) 2-ACETAMIDOThIOPHENE-3-CARBOXYLIC ACID

(A) Synthesis

Scheme:

\[
\begin{array}{c}
\text{S} \quad \text{S} \\
\text{OH} \quad \text{OH}
\end{array}
\begin{array}{c}
\leftrightarrow \\
\text{2HSCH}_2\text{CHO} + \text{CNCH}_2\text{CO}_2\text{H}
\end{array}
\]

\[
\begin{array}{c}
\downarrow \text{OH}^-/\text{H}_2\text{O}
\end{array}
\]

\[
\begin{array}{c}
\text{COO}^-
\end{array}
\]

\[
\begin{array}{c}
\text{NH}_2
\end{array}
\]

\[
\begin{array}{c}
\text{pH} 9 \downarrow \text{Ac}_2\text{O}
\end{array}
\]

\[
\begin{array}{c}
\text{CO}_2\text{H}
\end{array}
\]

\[
\begin{array}{c}
\text{NHCOC}_3\text{H}_3
\end{array}
\]

(a) 2,5-Dihydroxy-1,4-Dithiane

A solution of chloroacetaldehyde (7.8 g) in water (20 ml) was added dropwise, with stirring, to a solution of sodium hydrosulphide (5.6 g) in water (20 ml) at 0-5°C. The mixture was stirred for 2 hrs and the precipitated product filtered off (6.8 g, 89.5%), m.p. 128°C, (lit. 1, 2 127-128°C).

(b) 2-Acetamidothiophene-3-carboxylic acid

Cyanoacetic acid (8.5 g, 0.1 mole) was added to a mixture of sodium
hydroxide (6.0 g) in water (25 ml), followed by the mercaptoacetaldehyde dimer (7.6 g, 0.05 mole). The resulting mixture was heated at 90° for 10 min, cooled to 20°, and acetic anhydride (20.4 g) added during 20 min. The pH of the mixture was maintained between 7 and 9 by the addition of an aqueous solution of sodium hydroxide. The mixture was acidified with an aqueous solution of hydrochloric acid, and the precipitated solid filtered off, washed with water and dried (16.5 g, 89.2%) m.p. 217° (from butanol).

Found: C, 45.6%; H, 3.7%; N, 7.6%.
Calculated for: C_{7}H_{7}NO_{3}S; C, 45.4%; H, 3.6%; N, 7.6%.
REATIONS

2-Acetamidothiophene-3-Carboxylic Acid in Concentrated Sulphuric Acid

\( ^{13}C \) Spectra

An initial \( ^{13}C \) spectrum (\( \sim 20 \) mins) of 2-acetamidothiophene-3-carboxylic acid (0.4 g) in sulphuric acid (98\%, 2 ml) revealed a complex series of peaks, culminating (after 3 hrs) in a series of seven peaks, which retained their intensity for a few days. The final acetyl peaks were at 21.1 and 194.0 ppm\(^{261}\). At least one intermediate was present during the series of changes in spectrum.

Anhydro Derivative

2-Acetamidothiophene-3-carboxylic acid (10 g) was refluxed with acetic anhydride (20 ml) for 2 hr. The solution was cooled, tested for completion of reaction (t.l.c.) and evaporated to dryness. The residual solid was boiled with petrol (100/120\(^{0}\), 100 ml), carbon screened, and the solution filtered and cooled. Pale yellow crystals were obtained (4.6 g, 51.1\%) m.p. 117\(^{0}\) (from petrol, 60/80\(^{0}\)).

Found: C, 50.1\%; H, 2.9\%; N, 8.0\%.

Calculated for: \( C_7H_5NO_2S \), C, 50.4\%; H, 3.0\%; N, 8.4\%.

\( ^1H \) N.M.R. peaks (CCl\(_4\)) at 2.85\( \tau \) and 3.05\( \tau \) (2 doublets) and 7.7\( \tau \) (singlet) were in accordance with the product of the reaction below (ratio of peaks 1 : 1 : 3):

\[
\text{\begin{align*}
\begin{array}{c}
\text{S} \\
\text{H} \\
\text{N} \\
\text{C} = \text{O} \\
\text{H} \\
\text{C} = \text{O} \\
\text{CH}_3
\end{array}
\end{align*}
\] \xrightarrow{-\text{H}_2\text{O}}

\[
\text{\begin{align*}
\begin{array}{c}
\text{S} \\
\text{H} \\
\text{N} \\
\text{C} = \text{O} \\
\text{C} \\
\text{CH}_3
\end{array}
\end{align*}
\] \]

An infra-red spectrum of the product showed the absence of the N-H
absorption.

$^{13}\text{C Spectra}$

A $^{13}\text{C}$ spectrum of the anhydro derivative revealed a complex series of peaks originally and after 3 hrs a series of seven peaks were present which retained their intensity over a few days. This spectrum was identical with that of 2-acetamidothiophene-3-carboxylic acid in sulphuric acid after several hours i.e. free acetyl. Most of the complex series of peaks in the earlier spectrum could also be identified in the shorter-term spectrum of 2-acetamidothiophene-3-carboxylic acid. A similar effect was observed in 92% and 96% sulphuric acid.

Isolation of Products

A solution of 2-acetamidothiophene-3-carboxylic acid (10 g) in sulphuric acid (30 ml, 98%) was stirred at room temperature and 2 ml portions of the solution drowned into ice-water at 30 min intervals. After 30 min only starting material was recoverable (32%) but thereafter no reaction products were detectable. The anhydro derivative could not be isolated at any stage.

The drown-out solution (containing reaction mixture after 1 hr) was extracted with ethyl acetate but no organic product was obtained. Isolation of the anhydro complex was also attempted by drowning out into a bicarbonate solution, thus eliminating the possibility of dilute acid hydrolysis of the anhydride. However, no organic product other than starting material, was obtained.

Sulphonic Acid Intermediates

The possibility that 2-acetamidothiophene-3-carboxylic acid is sulphonated in concentrated sulphuric acid was investigated. Hurd's
procedure for isolation of 2-acetamidothiophene-5-sulphonic acid was adopted.

2-Acetamidothiophene-3-carboxylic acid (2 g) was dissolved in sulphuric acid (98%, 2 ml) and stirred at room temperature for 1 hr. The solution was drowned into ice-water, 0.15 g of starting material filtered off, and the remainder neutralized with barium carbonate. The barium sulphate, thus precipitated, was filtered off and the remaining solution evaporated to dryness. The small amount of black, tarry solid remaining contained some inorganic salt and no organic product was identifiable.

Extraction at the drown-out stage was attempted with several extraction solvents, followed by evaporation to dryness. Again, no sulphonic acid or other organic product was obtained.

Re-Acetylation

Since the acetamido group is susceptible to hydrolysis in sulphuric acid an attempt was made to re-acetylate any amine present in sulphuric acid, before isolation.

A solution of 2-acetamidothiophene-3-carboxylic acid (2 g) in sulphuric acid (98%, 8 ml) was stirred for 1 hr at room temperature and drowned into a cold acetic anhydride/dilute sulphuric acid mixture. This solution was filtered and stirred at room temperature overnight. The solution was then concentrated by evaporating off excess acetic anhydride, acetic acid and water. The remainder was neutralized with barium carbonate, filtered, and evaporated to dryness. Again no organic products were identifiable. Variations upon this general attempt at isolation of intermediates proved equally unsuccessful.
'H N.M.R.

'H N.M.R. spectra of 2-acetamidothiophene-3-carboxylic acid in sulphuric acid (D₂SO₄) were not conclusive but did suggest that a nuclear proton peak was decreasing in intensity over 2-3 hrs. There was also a small shift in the methyl protons peak over a similar period. Spectra were unclear because of large sulphuric acid peaks, poor solubility and the viscous nature of the solutions.

¹³C Spectrum of Acetic Acid in Sulphuric Acid

A ¹³C spectrum of acetic acid in sulphuric acid (98%) revealed two peaks at 194.0 and 21.1 ppm (from T.M.S.). These peaks are believed to be due to protonated acetic acid²⁺, CH₃CO₂H⁺.
(2) 2-ACETAMIDO-5-NITROTHIOPHENE-3-CARBOXYLIC ACID

(A) Synthesis

Scheme

2-Acetamidothiophene-3-carboxylic acid (5.6 g, 0.03 mol) was dissolved in sulphuric acid (98%, 20 ml) and the solution cooled to -15°C. A solution of nitric acid (d 1.42, 1.9 g, 0.03 mol) in sulphuric acid (98%, 5 ml) was added, dropwise, with stirring -10°C. The mixture was stirred for 10 min at -10°C, poured into an ice-water mixture and the precipitated solid filtered off, washed with water, and dried (6.2 g, 89.9%). m.p. 239°C (from aq. methanol).

Found: C, 36.5%; H, 2.5%; N, 12.1%.

Calculated for: C7H6N2O5S; C, 36.5%; H, 2.6%; N, 12.2%.

13C Spectrum in Sulphuric Acid

A 13C spectrum of 2-acetamido-5-nitrothiophene-3-carboxylic acid in sulphuric acid (98%) revealed a series of changes occurring over ~3 hrs. Initial peaks at 180.3, 167.8, 148.9, 147.0, 131.0, 119.5 and 22.2 ppm (from T.M.S.) were rapidly replaced by peaks at 194.0, 166.1, 156.0, 148.8, 142.3, 125.4 and 21.1 which, themselves, were unstable (see hydrolysis discussion for schematic representation of 13C spectra).

After 3 hrs only a complex series of low intensity peaks remained together with two peaks, which had retained their intensity, at 21.1 and 194.0 ppm. These are the characteristic peaks corresponding to protonated acetic acid261 suggesting that the reaction in sulphuric acid is a
hydrolysis reaction producing an unstable amine.

$^{13}$C Spectrum in Sulphuric/Nitric Acid

To a solution of 2-acetamido-5-nitrothiophene-3-carboxylic acid in sulphuric acid was added an equimolar solution of nitric acid (d, 1.42). A $^{13}$C spectrum of this mixture revealed a changed spectrum from peaks at 180.3, 167.8, 148.9, 147.0, 131.0, 119.5 and 22.2 ppm to peaks at 181.6, 144.5, 143.2, 134.4, 125.7 and 22.6 ppm. Carbon dioxide was also liberated.

The $^{13}$C spectral changes corresponded to a nitrodecarboxylation reaction (see later).
(B) KINETICS

(a) HYDROLYSIS

For reaction:

\[
\text{Plots of } \log(A_\infty - A_t) \text{ against time were linear over first 60% of reaction where } A_\infty = \text{the absorbance at } t = \infty \\
\text{i.e. the maximum absorbance}
\]

\[
A_t = \text{absorbance at time } t.
\]

(Thiophene Derivative) = 2.21 \times 10^{-4} M

Wavelength = 430 nm

<table>
<thead>
<tr>
<th>% H₂SO₄</th>
<th>Mean % H₂SO₄</th>
<th>k₁ obs (sec⁻¹)</th>
<th>Mean k₁ obs (sec⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>98.0</td>
<td>98.0</td>
<td>7.8 \times 10⁻⁴</td>
<td>8.1 \times 10⁻⁴</td>
</tr>
<tr>
<td>98.0</td>
<td></td>
<td>8.4 \times 10⁻⁴</td>
<td></td>
</tr>
<tr>
<td>90.3</td>
<td>90.2</td>
<td>1.4 \times 10⁻⁴</td>
<td>1.2 \times 10⁻⁴</td>
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<td></td>
<td>1.0 \times 10⁻⁴</td>
<td></td>
</tr>
<tr>
<td>82.7</td>
<td>82.7</td>
<td>0.32 \times 10⁻⁴</td>
<td>0.35 \times 10⁻⁴</td>
</tr>
<tr>
<td>82.7</td>
<td></td>
<td>0.37 \times 10⁻⁴</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 1: Rates of hydrolysis of 2-acetamido-5-nitrothiophene-3-carboxylic acid in sulphuric acid solutions.

Product Analysis

2-Acetamido-5-nitrothiophene-3-carboxylic acid (2 g) was dissolved in sulphuric acid (98%, 8 ml). A \(^{13}\)C spectrum of this solution indicated the formation of free acetyl peaks (at 194.0 and 21.1 ppm from T.M.S.)
as standard). After 1 hr the solution was drowned into ice-water. The precipitated solid was filtered, washed with water and dried. (0.52 g, 31.9%). m.p. 202° (from methanol).

Found: C, 32.1%; H, 2.2%; N, 14.7%.

Calculated for: C₅H₄N₂O₄S - C, 31.9%; H, 2.1%; N, 14.9%.

The product was identical with that obtained by dilute acid hydrolysis of 2-acetamido-5-nitrothiophene-3-carboxylic acid, and is confirmed as 2-amino-5-nitrothiophene-3-carboxylic acid.
For reaction:-

\[
\begin{array}{c}
\text{NO}_2 \text{S} \quad \text{NHCOCH}_3 \\
\text{HNO}_3 \\
\text{H}_2\text{SO}_4 \\
\text{NO}_2 \text{S} \quad \text{NHCOCH}_3
\end{array}
\]

Plots of \( \log(A_\infty - A_t) \) against time gave good linear pseudo first-order kinetic plots during several half-lives when the nitric acid concentration was at least ten times that of the substrate.

In order to calculate the second-order rate constants, values of the observed first-order rate constants are divided by the nitric acid concentration. Detailed rate data for the above reaction are shown in table 2.

For all nitration runs:-

(Thiophene Derivative) \( = 3.1 \times 10^{-4} \text{ M} \)

\[
\text{Wavelength} = 315 \text{ nm}
\]

<table>
<thead>
<tr>
<th>Mean %</th>
<th>Molarity H(_2)SO(_4)</th>
<th>Molarity HNO(_3)</th>
<th>( k_1 ) obs (sec(^{-1}))</th>
<th>( k_2 ) obs (1 mol(^{-1})sec(^{-1}))</th>
<th>Mean</th>
</tr>
</thead>
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<td>80.9</td>
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<td>1.75x10(^{-2})</td>
<td>4.7x10(^{-6})</td>
<td>5.3x10(^{-4})</td>
<td>5.5x10(^{-4})</td>
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<td></td>
<td>3.50x10(^{-2})</td>
<td>20.0x10(^{-6})</td>
<td>5.7x10(^{-6})</td>
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<td>82.4</td>
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<td>1.75x10(^{-2})</td>
<td>2.3x10(^{-5})</td>
<td>2.6x10(^{-3})</td>
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<td>3.50x10(^{-2})</td>
<td>4.3x10(^{-5})</td>
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<td></td>
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</tr>
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<td>1.75x10(^{-2})</td>
<td>9.4x10(^{-5})</td>
<td>2.7x10(^{-3})</td>
<td></td>
</tr>
<tr>
<td></td>
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<td>2.3x10(^{-4})</td>
<td>2.6x10(^{-4})</td>
<td></td>
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</tr>
<tr>
<td>86.1</td>
<td>0.88x10(^{-2})</td>
<td>1.75x10(^{-2})</td>
<td>6.3x10(^{-4})</td>
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<tr>
<td>89.9</td>
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<td>1.75x10(^{-2})</td>
<td>1.2x10(^{-3})</td>
<td>1.36x10(^{-1})</td>
<td>1.3x10(^{-1})</td>
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<tr>
<td></td>
<td>3.50x10(^{-2})</td>
<td>2.3x10(^{-3})</td>
<td>1.31x10(^{-1})</td>
<td></td>
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</tr>
</tbody>
</table>

**TABLE 2**: Rate of nitration of 2-acetamido-5-nitrothiophene-3-carboxylic acid in nitric acid/sulphuric acid solutions.

**Product Analysis**

2-Acetamido-5-nitrothiophene-3-carboxylic acid (2.3 g, 0.01 mol) was
dissolved in sulphuric acid (98%, 10 ml) and the solution cooled to -5⁰. A solution of nitric acid [d 1.42, 0.95 g] in sulphuric acid (98%, 5 ml) i.e. 1.5 mole of nitric acid per mole of substrate, was added dropwise, with stirring, < 0⁰. The mixture was stirred for 30 min after completion of the addition and tested for completion of the nitration by t.l.c. A further small quantity of nitric acid (0.02 g) was required for completion. The reaction mixture was poured slowly into ice-water and a good deal of frothing was observed. After stirring for 2 hr < 5⁰ the mixture was filtered and washed free of acid with cold water. The product, 2-acetamido-3,5-dinitrothiophene, was dried at 70⁰ (1.3 g, 58.3%), m.p. 178⁰ (from butanol).

Found: C, 31.2%; H, 2.0%; N, 18.2%.

Calculated for: C₆H₅N₃O₅S: C, 31.2%; H, 2.2%; N, 18.2%.
(c) OXIDATION - DEGRADATION

Since 2-acetamido-5-nitrothiophene-3-carboxylic acid readily nitro-decarboxylates in sulphuric-nitric acid mixtures the oxidation of this derivative was studied by means of its methyl ester (which is stable to nitrodecarboxylation).

Methyl 2-acetamido-5-nitrothiophene-3-carboxylate

Methyl cyanoacetate (9.9 g, 0.1 mol) was added to a mixture of sodium hydroxide (6.0 g) in water (25 ml), followed by mercaptoacetaldehyde dimer (7.6 g, 0.05 mol). The resulting mixture was heated at 80° for 30 mins, cooled to 25° and acetic anhydride (20.4 g) added dropwise with stirring. The pH of the mixture was maintained between 7 and 9 by the addition of an aqueous solution of sodium hydroxide. The mixture was acidified with an aqueous solution of hydrochloric acid and the precipitated solid filtered off, washed with water and dried. (14.2 g, 71.3%). m.p. 163° (from aq. methanol).

Found: C, 48.3%; H, 4.5%; N, 6.7%.

Calculated for: C₈H₈N₂O₅S: C, 48.2%; H, 4.5%; N, 7.0%.

The methyl-2-acetamidothiophene-3-carboxylate (2.0 g, 0.01 mol) produced above was nitrated in sulphuric acid (98%, 10 ml) at 0° with a solution of nitric acid (d 1.42, 0.6 g, 0.01 mol) in sulphuric acid (98%, 3 ml). The mixture was poured into ice-water and the precipitated methyl 2-acetamido-5-nitrothiophene-3-carboxylate filtered off, washed with water and dried. (2.2 g, 91.7%) m.p. 184° (from aq. methanol).

Found: C, 39.1%; H, 3.0%; N, 11.2%.

C₈H₈N₂O₅S requires: C, 39.3%; H, 3.3%; N, 11.5%.

Oxidation by Nitric/Sulphuric Acid

A $^{13}$C spectrum of methyl-2-acetamido-5-nitrothiophene-3-carboxylate
in sulphuric acid (98%) revealed a similar series of changes to those for the carboxylic acid i.e. hydrolysis to an unstable amine.

A $^{13}$C spectrum of methyl-2-acetamido-5-nitrothiophene-3-carboxylate in sulphuric/nitric acid revealed that no nitrodecarboxylation occurred. However, a rapid decrease in intensity of the original peaks did occur producing a complex series of low intensity peaks, the change being complete after $\sim 3$ hrs. This was an oxidation/degradation reaction since no products were recoverable.

A $^{13}$C spectrum of methyl-2-amino-5-nitrothiophene-3-carboxylate in sulphuric acid showed a slowly changing spectrum. When nitric acid was added an instantaneous decrease in intensity of all peaks was observed giving a large number of low intensity peaks. The amine is thus extremely unstable in presence of nitric acid and no products were recoverable.

Rates of hydrolysis and approximate rates of degradation were obtained by U.V. spectroscopy, the degradation rates being determined by measuring the rate of decrease in U.V. absorbance at a fixed wavelength. Good pseudo, first-order kinetic plots were obtained for the hydrolysis reactions and approximate linear plots were obtained for the degradation reactions.

For all runs:

\[
\text{(Methyl-2-acetamido-5-nitrothiophene-3-carboxylate)} = 2.8 \times 10^{-4} \text{M}
\]

Wavelength = 430 nm (hydrolysis)

" = 315 nm (degradation)
| Mean % H₂SO₄ | HYDROLYSIS | | DEGRADATION | | | | Molarity | k₁ obs | sec⁻¹ | | | | HNO₃ | k₁ obs | sec⁻¹ |
|-------------|------------|---|-------------|---|---|---|---|---|---|
| 98.6        | 8.8x10⁻⁴   |   | 0.88x10⁻²   | 8.8x10⁻⁴ |
|             |            |   | 1.75x10⁻²   | 9.1x10⁻⁴ |
|             |            |   | 3.50x10⁻²   | 9.1x10⁻⁴ |
| 89.1        | 1.4x10⁻⁴   |   | 0.88x10⁻²   | 1.4x10⁻⁴ |
|             |            |   | 1.75x10⁻²   | 1.6x10⁻⁴ |
|             |            |   | 3.50x10⁻²   | 2.1x10⁻⁴ |
| 82.7        | 0.56x10⁻⁴  |   | 0.88x10⁻²   | 0.54x10⁻⁴ |
|             |            |   | 1.75x10⁻²   | 0.58x10⁻⁴ |
|             |            |   | 3.50x10⁻²   | 0.59x10⁻⁴ |

TABLE 3: Rate of hydrolysis and degradation of methyl-2-acetamido-5-nitrothiophene-3-carboxylate in sulphuric acid and sulphuric/nitric acid respectively.

**Product Analysis**

(a) **Hydrolysis**

Methyl-2-acetamido-5-nitrothiophene-3-carboxylate (2 g) was dissolved in sulphuric acid (98%, 8 ml) and the solution stirred at room temperature for 1 hr. The solution was drowned into ice-water and the precipitated solid filtered, washed with water and dried. (0.35 g, 21.8%) m.p. 131° (from butanol).

Found: C, 35.4%; H, 2.8%; N, 13.6%.

C₆H₆N₂O₄S requires: C, 35.6%; H, 3.0%; N, 13.9%.

Infra-red spectra (-NH₂ absorption) confirmed the product as methyl-2-amino-5-nitrothiophene-3-carboxylate.
(b) Degradation

To a solution of methyl-2-acetamido-5-nitrothiophene-3-carboxylate (2 g) in sulphuric acid (98%, 8 ml) was added dropwise, with stirring, a solution of nitric acid (d 1.42, 1.0 g) in sulphuric acid (98%, 5 ml). The mixture was stirred at room temperature for 1 hr, and then drowned into ice-water. A small amount (< 0.1 g) of starting material was precipitated but no other products were extractable. Neutralization of the drown-out solution and subsequent extraction again failed to produce any degradation products other than unidentifiable tarry, black solids.

A $^{13}$C spectrum of the starting material in sulphuric/nitric acid revealed a complex series of changes resulting in a spectrum containing a large number of low-intensity peaks together with two much higher intensity peaks at 21.1 and 194.0 ppm (after ~1 hr). The solution was dark and viscous and pressure developed in the N.M.R. tube.

A $^{13}$C spectrum of methyl-2-amino-5-nitrothiophene-3-carboxylate in sulphuric/nitric acid was identical to the final spectrum of the corresponding amide (with absence of peaks at 21.1 and 194.0 ppm). No amine peaks were detectable at any stage.
(3) 2-ACETAMIDO-3,5-DINITROTHIOPHENE

(A) Synthesis

2-Acetamidothiophene-3-carboxylic acid (5.6 g, 0.03 mol) was dissolved in sulphuric acid (98%, 20 ml) and the solution cooled to 0\(^\circ\). The mixture was then stirred for 30 mins to ensure complete solution. A solution of nitric acid (d 1.42, 4.75 g, 0.075 mol) in sulphuric acid (98%, 10 ml) was added, dropwise, with stirring < 0\(^\circ\). The mixture was stirred for 30 mins after completing the addition and was then tested for completion of the nitration (by t.l.c.). The reaction solution was poured slowly, with stirring into ice-water and a good deal of frothing was observed. After stirring for 2 hrs the precipitated solid was filtered off, washed with water, and dried. (3.2 g, 46.2%), m.p. 179\(^\circ\) (from butanol) (lit. 180\(^\circ\)).

Found: C, 31.2%; H, 2.0%; N, 18.2%.

Calculated for: C\(_6\)H\(_5\)N\(_3\)O\(_5\)S: C, 31.2%; H, 2.2%; N, 18.2%.

The final product consisted of yellow needles which were confirmed as 2-acetamido-3,5-dinitrothiophene by infra-red spectroscopy. Mixed m.p. 179\(^\circ\).

\(^{13}\)C Spectrum in Sulphuric Acid

A \(^{13}\)C spectrum of 2-acetamido-3,5-dinitrothiophene (400 mg) in sulphuric acid (98%, 2 ml) revealed a series of changes occurring over 3-4 hrs. Initial peaks at 181.6, 144.5, 143.2, 134.4, 125.7 and 22.6 ppm (from T.M.S.) were rapidly replaced by peaks at 194.0, 156.2, 139.1, 134.6,
129.2 and 21.1 which themselves, were unstable over longer periods. After 12 hrs, only a complex series of low intensity peaks remained together with the higher intensity, characteristic peaks at 21.1 and 194.0 ppm.

\[ ^{13}\text{C Spectrum in Sulphuric/Nitric Acid}\]

To a solution of 2-acetamido-3,5-dinitrothiophene in sulphuric acid was added an equimolar solution of nitric acid (d 1.42). A gradual decrease in intensity of the original peaks was observed. After 3-4 hrs only a complex spectrum containing a large number of low intensity peaks was observed together with two peaks of higher intensity at 194.0 and 21.1 ppm (from T.M.S.) (see discussion of \(^{13}\text{C}\) behaviour earlier).

\[ ^{13}\text{C Spectrum in Oleum Solutions}\]

A \(^{13}\text{C}\) spectrum of 2-acetamido-3,5-dinitrothiophene in various oleum solution (containing up to 25% \(\text{SO}_3\)) revealed complex changes resulting in a large number of low intensity peaks. The two peaks of higher intensity at 194.0 and 21.1 ppm were again present. No products were recoverable and there was no resemblance between the final spectrum in oleum and that in sulphuric-nitric acid.
(B) KINETICS
(a) HYDROLYSIS

For reaction:

![Chemical structure](image)

Detailed rate data were obtained as for 2-acetamido-5-nitrothiophene-3-carboxylic acid.

(Substrate) = 2.05 x 10^{-4} M

Wavelength = 430 nm

% H₂SO₄ | Mean k₁ obs (sec⁻¹) | Mean k₁ obs (sec⁻¹)
---|---|---
99.5 | 99.6 | 4.8 x 10⁻⁴ | 4.4 x 10⁻⁴
99.7 | 99.6 | 4.2 x 10⁻⁴ | 4.4 x 10⁻⁴
99.6 | 99.6 | 4.2 x 10⁻⁴ | 4.4 x 10⁻⁴
98.2 | 98.6 | 2.9 x 10⁻⁴ | 3.1 x 10⁻⁴
98.5 | 98.6 | 3.0 x 10⁻⁴ | 3.1 x 10⁻⁴
99.1 | 99.1 | 3.4 x 10⁻⁴ | 3.4 x 10⁻⁴
93.4 | 93.4 | 6.1 x 10⁻⁵ | 5.9 x 10⁻⁵
93.7 | 93.7 | 5.8 x 10⁻⁵ | 5.9 x 10⁻⁵
93.4 | 93.4 | 5.8 x 10⁻⁵ | 5.9 x 10⁻⁵
89.3 | 89.3 | 1.2 x 10⁻⁵ | 1.1 x 10⁻⁵
88.9 | 89.1 | 0.9 x 10⁻⁵ | 1.1 x 10⁻⁵
89.1 | 89.1 | 1.2 x 10⁻⁵ | 1.1 x 10⁻⁵
86.4 | 86.4 | 8.0 x 10⁻⁶ | 8.3 x 10⁻⁶
86.4 | 86.7 | 8.5 x 10⁻⁶ | 8.3 x 10⁻⁶
87.3 | 87.3 | 8.4 x 10⁻⁶ | 8.3 x 10⁻⁶
82.6 | 82.6 | 6.3 x 10⁻⁶ | 6.3 x 10⁻⁶
82.8 | 82.7 | 6.4 x 10⁻⁶ | 6.3 x 10⁻⁶
82.7 | 82.7 | 6.2 x 10⁻⁶ | 6.3 x 10⁻⁶
75.4 | 75.4 | 8.7 x 10⁻⁶ | 8.5 x 10⁻⁶
75.4 | 75.3 | 8.4 x 10⁻⁶ | 8.5 x 10⁻⁶
75.1 | 75.1 | 8.4 x 10⁻⁶ | 8.5 x 10⁻⁶
70.0 | 70.0 | 1.0 x 10⁻⁵ | 1.1 x 10⁻⁵
69.3 | 69.4 | 0.9 x 10⁻⁵ | 1.1 x 10⁻⁵
68.9 | 68.9 | 1.4 x 10⁻⁵ | 1.1 x 10⁻⁵

TABLE 4: Rates of hydrolysis of 2-acetamido-3,5-dinitrothiophene in sulphuric acid solutions.
Product Analysis

2-Acetamido-3,5-dinitrothiophene (2 g) was dissolved in sulphuric acid (98%, 8 ml), and stirred at room temperature for 3 hrs. The reaction solution was drowned into ice-water and the precipitated solid filtered, washed with water and dried (0.86 g, 52.4%), m.p. 176° (from aq. methanol).

Found: C, 25.7%; H, 1.5%; N, 22.1%.

C₄H₃N₃O₄S requires: C, 25.4%; H, 1.6%; N, 22.2%.

The product was identical (¹³C and I.R. spectra) with authentic 2-amino-3,5-dinitrothiophene obtained by dilute acid hydrolysis of the amide. Mixed m.p. 175°.
Oxidation-Degradation

$^{13}$C and U.V. spectra of 2-acetamido-3,5-dinitrothiophene in sulphuric-nitric acid mixtures revealed that the compound was unstable and not recoverable after ~ 3-4 hrs.

Rates of oxidation/degradation were obtained by U.V. spectroscopy by measuring the rate of decrease in absorbance at a certain, fixed wavelength. Approximately linear pseudo first-order plots were obtained.

(Substrate) $= 3.1 \times 10^{-4} M$

Wavelength $= 315 \text{ nm}$

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<th>Mean % H$_2$SO$_4$</th>
<th>Molarity HNO$_3$</th>
<th>$k_{1 \text{ obs}} (\text{sec}^{-1})$</th>
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<td>82.7</td>
<td></td>
<td>$3.50 \times 10^{-2}$</td>
<td>$6.1 \times 10^{-6}$</td>
</tr>
</tbody>
</table>

TABLE 5: Rate of degradation of 2-acetamido-3,5-dinitrothiophene in sulphuric-nitric acid mixtures.

Product Analysis

To a solution of 2-acetamido-3,5-dinitrothiophene (2 g) in sulphuric acid (98%, 8 ml) was added dropwise, with stirring, a solution of nitric acid (d 1.42, 1.0 g) in sulphuric acid (98%, 5 ml). The mixture was stirred at room temperature for 2 hrs. and then drowned into ice-water. The only product obtainable was the starting material (17%). Neutralization of the drown-out solution and subsequent extraction again failed to
produce any degradation products other than unidentifiable tars. $^{13}$C spectra of the reaction products revealed only a large number of peaks present in very low concentration.

**Mass Spectrometry**

A mass spectrometric analysis of the gases produced during the reaction of 2-acetamido-3,5-dinitrothiophene with sulphuric-nitric acid revealed the presence of carbon dioxide and sulphur dioxide, as well as various nitrogen oxides. Carbon dioxide was liberated upon drown-out of this reaction solution into ice-water. Sulphur dioxide was also present upon treatment of 2-acetamido-3,5-dinitrothiophene with nitric acid alone, suggesting oxidation of the ring sulphur atom.

Attempts to quantify the gas analysis were unsuccessful due to the nature of the reaction mixtures etc (tarry and highly viscous).
2-Formamidothiophene-3-carboxylic acid

Cyanoacetic acid (8.5 g, 0.1 mol) was added to a mixture of sodium hydroxide (6.0 g) in water (25 ml) followed by mercaptoacetaldehyde dimer (7.6 g, 0.05 mol). The mixture was stirred at 20° for 24 hrs and then slowly added to a mixture of formic acid (30.6 g) and acetic anhydride (30.6 g), which had previously been stirred together for 1 hr at 20°, and then cooled to 0°. The mixture was stirred for 1 hr, acidified with an aqueous solution of hydrochloric acid to pH 3 and the precipitated solid filtered off, washed with water and dried (14.6 g, 85.4%), m.p. 241° (from butanol).
Found: C, 42.3%; H, 2.9%; N, 8.5%.

C₆H₅NO₃S requires: C, 42.1%; H, 2.9%; N, 8.2%.

(B) REACTIONS

¹³C Spectrum in Sulphuric Acid

A ¹³C spectrum of 2-formamidothiophene-3-carboxylic acid (0.4 g) in sulphuric acid (98%, 2 ml) revealed a stable series of six peaks. There was no evidence of hydrolysis or anhydro-ring formation. The original peaks retained their intensity over a period of days and the starting material was recoverable in good yield after 3 days (83%).

(¹³C peaks at 168.5, 166.7, 148.0, 136.2, 133.0 and 120.4 ppm (from T.M.S.).)
(5) 2-FORMAMIDO-5-NITROTHIOPHENE-3-CARBOXYLIC ACID

(A) SYNTHESIS

2-Formamidothiophene-3-carboxylic acid (5.1 g, 0.03 mol) was dissolved in sulphuric acid (98%, 20 ml) and the solution cooled to \(-15^\circ\). A solution of nitric acid (d 1.42, 1.9 g, 0.03 mol) in sulphuric acid (98%, 5 ml) was added, dropwise, with stirring < \(-10^\circ\). The mixture was stirred for 10 min at \(-10^\circ\), poured into an ice-water mixture and the precipitated solid filtered off, washed with water, and dried (6.1 g, 93.8%) m.p. 244\(^\circ\) (from aq. methanol).

Found: C, 33.1%; H, 1.9%; N, 12.9%.

Calculated for: C\(_6\)H\(_4\)N\(_2\)O\(_5\)S: C, 33.3%; H, 1.9%; N, 13.0%.

\(^{13}\)C Spectrum in Sulphuric Acid

A \(^{13}\)C spectrum of 2-formamido-5-nitrothiophene-3-carboxylic acid in sulphuric acid (98%) revealed a series of six peaks which retained their intensity over a period of days. The starting material was recoverable upon draw-out after 4 days (81%).

\(^{13}\)C Spectrum in Sulphuric/Nitric Acid

To a solution of 2-formamido-5-nitrothiophene-3-carboxylic acid in sulphuric acid (98%) was added an equimolar solution of nitric acid (d 1.42). A \(^{13}\)C spectrum of this mixture revealed a changed spectrum from peaks at 167.8, 167.1, 148.8, 146.6, 131.3 and 119.1 ppm (from T.M.S.) to peaks at 167.1, 145.2, 143.1, 133.2 and 125.5 ppm. Carbon dioxide was liberated, the \(^{13}\)C spectral changes corresponding to a nitrodecarboxylation reaction.
(B) KINETICS

(a) HYDROLYSIS

No hydrolysis of 2-formamido-5-nitrothiophene-3-carboxylic acid was detectable in concentrated sulphuric acid either by $^{13}$C or U.V. spectroscopy. The amide was recoverable from 82.7%, 90.2% and 98.0% sulphuric acid after several hours at room temperature.

(b) NITRATION

\[
\begin{align*}
\begin{array}{c}
\text{NO}_2 \\
\text{S} \\
\text{NHCHO}
\end{array}
\begin{array}{c}
\text{CO}_2\text{H}
\end{array}
\xrightarrow{\text{HNO}_3} \\
\begin{array}{c}
\text{NO}_2 \\
\text{S} \\
\text{NHCHO}
\end{array}
\begin{array}{c}
\text{NO}_2
\end{array}
\begin{array}{c}
\text{H}_2\text{SO}_4
\end{array}
\end{align*}
\]

Kinetic details are as for the corresponding acetamido derivative — again good linear pseudo first-order kinetic plots were obtained.

\(\text{[Thiophene Derivative]} = 4.3 \times 10^{-4}\text{ M}\)

Wavelength = 310 nm
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**TABLE 6: Rate of nitration of 2-formamido-5-nitrothiophene-3-carboxylic acid in nitric acid/sulphuric acid solutions.**

**Product Analysis**

2-Formamido-5-nitrothiophene-3-carboxylic acid (2.2 g, 0.01 mol) was dissolved in sulphuric acid (98%, 10 ml) and the solution cooled to -5⁰. A solution of nitric acid (d 1.42, 0.95 g) in sulphuric acid (98%, 5 ml) was added, dropwise, with stirring < 0⁰. The mixture was stirred for 30 min after completion of the addition and then drowned into ice-water. After stirring for 2 hr at 0-5⁰ the mixture was filtered and washed free of acid with cold water. The product, 2-formamido-3,5-dinitrothiophene, was dried at 50⁰ (1.6 g, 72.7%) m.p. 185⁰ (from aq. methanol).

Found: C, 27.6%; H, 1.1%; N, 19.4%.

Calculated for: C₅H₃N₃O₅S: C, 27.7%; H, 1.4%; N, 19.4%. 

(A) SYNTHESIS

Scheme:–

2-Formamidothiophene-3-carboxylic acid (0.03 mol) was dissolved in sulphuric acid (98%, 20 ml) and the solution cooled to 0°C. The mixture was stirred for 30 min to ensure complete solution. A solution of nitric acid (d 1.42, 0.075 mol) in sulphuric acid (98%, 10 ml) was added, dropwise, with stirring < 0°C. The mixture was stirred for 30 mins after completing the addition and was then poured slowly, with stirring into ice-water. After stirring for 2 hrs the precipitated solid was filtered off, washed with water, and dried (4.5 g, 70.3%) m.p. 186°C (from aq. methanol).

Found: C, 27.9%; H, 1.6%; N, 19.5%.
Calculated for: C₅H₅N₃O₅S: C, 27.7%; H, 1.4%; N, 19.4%.

The final product consisted of yellow needles which were confirmed as 2-formamido-3,5-dinitrothiophene by infra-red spectroscopy.

13C Spectrum in Sulphuric Acid

A 13C spectrum of 2-formamido-3,5-dinitrothiophene (0.4 g) in sulphuric acid (98%, 2 ml) revealed a series of five peaks which retained their intensity over a period of days. The starting material was recoverable upon drown-out after 4 days (86%).

13C Spectrum in Sulphuric/Nitric Acid

To a solution of 2-formamido-3,5-dinitrothiophene in sulphuric acid was added an equimolar solution of nitric acid (d 1.42). A rather slow
decrease in intensity of the original peaks was observed but the starting material was recoverable in good yield after 4 hrs (81%). However after 24 hrs only a complex series of low intensity peaks were present in the $^{13}$C spectrum and the only recoverable product was a few milligrams of starting material.

$^{13}$C Spectrum in Oleum Solutions

A $^{13}$C spectrum of 2-formamido-3,5-dinitrothiophene in various oleum solutions revealed complex changes which resulted in a large number of low intensity peaks. No products were recoverable after 24 hrs.
(B) **KINETICS**

(a) **HYDROLYSIS**

No hydrolysis of 2-formamido-3,5-dinitrothiophene was detectable in concentrated sulphuric acid either by $^{13}$C or U.V. spectroscopy. The amide was recoverable from 82.7%, 90.2% and 98.0% sulphuric acid after several hours at room temperature.

(b) **OXIDATION-DEGRADATION**

$^{13}$C and U.V. spectra of 2-formamido-3,5-dinitrothiophene in sulphuric-nitric acid mixtures revealed that the compound was unstable for longer periods.

Rates of oxidation/degradation were obtained by U.V. spectroscopy. Approximately linear pseudo first-order plots were obtained.

(Substrate) = 5.3 x 10$^{-4}$ M

Wavelength = 320 nm

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<th>$k_2$ obs (1 mol$^{-1}$ sec$^{-1}$)</th>
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<td>1.75x10$^{-2}$</td>
<td>15.3x10$^{-7}$</td>
<td>0.87x10$^{-4}$</td>
</tr>
<tr>
<td></td>
<td>3.50x10$^{-2}$</td>
<td>32.1x10$^{-7}$</td>
<td>0.82x10$^{-4}$</td>
</tr>
<tr>
<td>82.7</td>
<td>0.88x10$^{-2}$</td>
<td>3.8x10$^{-7}$</td>
<td>4.3x10$^{-5}$</td>
</tr>
<tr>
<td></td>
<td>1.75x10$^{-2}$</td>
<td>7.7x10$^{-7}$</td>
<td>4.4x10$^{-5}$</td>
</tr>
<tr>
<td></td>
<td>3.50x10$^{-2}$</td>
<td>15.6x10$^{-7}$</td>
<td>4.5x10$^{-5}$</td>
</tr>
</tbody>
</table>

**TABLE 7**: Rate of degradation of 2-formamido-3,5-dinitrothiophene in sulphuric-nitric acid mixtures.

**Product Analysis**

To a solution of 2-formamido-3,5-dinitrothiophene (2 g) in sulphuric
acid (98%, 8 ml) was added, dropwise, with stirring, a solution of nitric acid (d 1.42, 1.0 g) in sulphuric acid (98%, 5 ml). The mixture was stirred at room temperature for 36 hrs and then drowned into ice-water. No products were precipitated and extraction of both this drown-out solution and the neutralized drown-out solution failed to produce any degradation products other than unidentifiable tars. $^{13}$C spectra of the final reaction solution revealed only a complex series of peaks of very low intensity. This reaction solution was black and viscous after 36 hrs.
(7) 2-AMINO-5-NITROTHIOPHENE-3-CARBOXYLIC ACID

(A) SYNTHESIS

Scheme:

\[
\begin{align*}
\text{NO}_2 & \quad \text{S} & \quad \text{NHCOCH}_3 \\
\text{CO}_2 & \quad \text{H} \\
\text{H}_2\text{SO}_4
\end{align*}
\]

2-Acetamido-5-nitrothiophene-3-carboxylic acid (4.6 g, 0.02 mol) was added to a mixture of dilute sulphuric acid (2 M, 90 ml) and cellosolve (10 ml). The mixture was gently refluxed for 6 hrs and after ensuring that hydrolysis was complete (t.l.c.) the solution of product was filtered whilst still hot and the filtrate cooled in a freezing mixture. The crystalline product was filtered off, washed with cold water and dried (3.1 g, 81.6%) m.p. 192° (from aq. methanol).

Found: C, 32.1%; H, 2.1%; N, 15.0%.
Calculated for: C₅H₄N₂O₄S: C, 31.9%; H, 2.1%; N, 14.9%.

\[\text{\textsuperscript{13}C Spectrum in Sulphuric Acid}\]

A \textsuperscript{13}C spectrum of 2-amino-5-nitrothiophene-3-carboxylic acid (400 mg) in sulphuric acid (98%, 2 ml) revealed a series of peaks at 166.1, 156.0, 148.8, 142.3 and 125.4 ppm (from T.M.S.). However, after 3 hrs only a complex series of low intensity peaks remained. No products were isolable from this reaction solution suggesting that the free amine is unstable in concentrated sulphuric acid. The final \textsuperscript{13}C spectrum was identical to that obtained when the corresponding acetamido compound was stirred in sulphuric acid for 4 hrs (ignoring the acetyl peaks).

\[\text{\textsuperscript{13}C Spectrum in Sulphuric/Nitric Acid}\]

To a solution of 2-amino-5-nitrothiophene-3-carboxylic acid in sulphuric acid was added an equimolar amount of nitric acid (d 1.42). A
$^{13}$C spectrum of this mixture revealed only a large number of low intensity peaks, with no evidence of any starting material or nitrated product. No products were isolable from this reaction solution suggesting that 2-amino-5-nitrothiophene-3-carboxylic acid is extremely unstable in presence of sulphuric-nitric acid mixtures.
ACYLATION OF 2-AMINO-5-NITROTHIOPHENE-3-CARBOXYLIC ACID

SYNTHESIS

General Scheme:

\[
\begin{align*}
\text{RCOCI} & \quad \text{or} \quad (\text{RCO})_2\text{O} \\
\text{NO}_2 & \quad \text{S} \quad \text{NH}_2
\end{align*}
\]

The method used was a variation upon the procedure for acetylation of amino acids\(^{2}\).\(^{2}\)

\[(a)\]

2-Amino-5-nitrothiophene-3-carboxylic acid (5 g) was refluxed with ethyl acetate (100 ml) and monochloroacetyl chloride (5 ml) for 2 hrs. The mixture was filtered, cooled and the excess ethyl acetate and chloroacetyl chloride evaporated. The residue consisted of a dark brown solid and repeated recrystallization from aqueous methanol gave a yellow crystalline product (4.8 g, 78.1%). m.p. 234º (from aqueous methanol).

Found: C, 32.0%; H, 2.0%; N, 10.4%.

C\(_7\)H\(_5\)N\(_2\)O\(_4\)Cl\(_5\)S requires: C, 31.8%; H, 2.0%; N, 10.6%.

\[^{13}\text{C} \text{ Spectrum in Sulphuric/Nitric Acid}\]

A \(^{13}\text{C}\) spectrum of the amide in sulphuric acid alone revealed a non-changing spectrum i.e. behaviour similar to that of the formamido derivative. However, in presence of nitric acid, a change in spectrum occurred due to a nitrodecarboxylation reaction. Carbon dioxide was liberated.
2-Amino-5-nitrothiophene-3-carboxylic acid (5 g) was refluxed with propionyl chloride (6 ml) in ethyl acetate (60 ml) for 4 hrs. The solution was cooled, filtered and the excess propionyl chloride and ethyl acetate evaporated. A dark brown solid remained which on recrystallization from aqueous methanol gave a yellow crystalline compound (2.4 g, 42.3%). m.p. 205° (from aq. methanol).

Found: C, 39.4%; H, 3.4%; N, 11.4%.

C₈H₈N₂O₅S requires: C, 39.3%; H, 3.3%; N, 11.5%.

1³C Spectrum in Sulphuric/Nitric Acid

A ¹³C spectrum of the amide in sulphuric acid alone revealed a series of changes occurring over 1-2 hrs. The original eight carbon peaks were replaced by eight other peaks, which were themselves rather unstable, i.e. very similar behaviour to the corresponding acetamido derivative. In presence of nitric acid a change in the original ¹³C spectrum occurred due to a nitrodecarboxylation reaction. Again the final product was unstable in sulphuric-nitric acid.

Isobutyryl chloride (5 ml) was refluxed with 2-amino-5-nitrothiophene-3-carboxylic acid (3 g) in ethyl acetate (40 ml) for 8 hrs. The solution was filtered and the solvent and volatile chlorides evaporated leaving a dark solid which was recrystallized from aqueous methanol (1.3 g, 42.2%). m.p. 201° (from eq. methanol).
Found: C, 41.9%; H, 3.7%; N, 10.9%.

C$_9$H$_{10}$N$_2$O$_5$S requires: C, 41.9%; H, 3.9%; N, 10.9%.

$^{13}$C Spectrum in Sulphuric/Nitric Acid

The $^{13}$C spectral behaviour of this amide in both sulphuric acid and sulphuric-nitric acid mixtures was identical to that of the propionyl and acetyl derivatives i.e. hydrolysis to an unstable amine in sulphuric acid alone and nitrodecarboxylation to a further unstable compound in nitric-sulphuric acid mixtures.

(d) 

Pivaloyl chloride (trimethyl acetyl chloride) (5 ml) was refluxed with 2-amino-5-nitrothiophene-3-carboxylic acid (3 g) in ethyl acetate (40 ml) for 8 hrs. After filtering, the solvent and volatile chlorides were evaporated leaving a brown solid and a black oil. The solid was separated and recrystallized from aqueous methanol. (1.6 g, 45.9%). m.p. 206$^\circ$ (from aq. methanol).

Found: C, 44.4%; H, 4.2%; N, 10.1%.

C$_{10}$H$_{12}$N$_2$O$_5$S requires: C, 44.1%; H, 4.4%; N, 10.3%.

$^{13}$C Spectrum in Sulphuric/Nitric Acid

The $^{13}$C spectral behaviour of this amide in both sulphuric acid and sulphuric-nitric acid mixtures was again very similar to the acetyl and propionyl derivatives, i.e. hydrolysis to an unstable amine in sulphuric acid alone and nitrodecarboxylation in sulphuric-nitric acid mixtures.
(a) HYDROLYSIS

Rate data were obtained in an identical manner to that described earlier for 2-acetamido-5-nitrothiophene-3-carboxylic acid. Good linear pseudo first-order kinetic plots were obtained for all amides although the amine, formed as product, was rather unstable in the more concentrated acid.

\[(\text{Thiophene Amide}) = 2.30 \times 10^{-4} \text{ M}\]

Wavelength \(= 430 \text{ nm}\)

For reaction:

\[
\begin{align*}
\text{2-acylamino-5-nitrothiophene-3-carboxylic acid} & \rightarrow \text{amino acid}
\end{align*}
\]

<table>
<thead>
<tr>
<th>% H(_2)SO(_4)</th>
<th>(R)</th>
<th>CH(_2)Cl</th>
<th>CH(_2)CH(_3)</th>
<th>CH(CH(_3))(_2)</th>
<th>C(CH(_3))(_3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>98.0</td>
<td>&lt; 10(^{-8})</td>
<td>9.3\times10^{-4}</td>
<td>9.8\times10^{-4}</td>
<td>7.7\times10^{-3}</td>
<td></td>
</tr>
<tr>
<td>90.2</td>
<td>&lt; 10(^{-8})</td>
<td>2.4\times10^{-4}</td>
<td>3.1\times10^{-4}</td>
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<td></td>
</tr>
<tr>
<td>82.7</td>
<td>&lt; 10(^{-8})</td>
<td>1.0\times10^{-4}</td>
<td>1.3\times10^{-4}</td>
<td>0.7\times10^{-3}</td>
<td></td>
</tr>
<tr>
<td>75.3</td>
<td>&lt; 10(^{-8})</td>
<td>1.1\times10^{-4}</td>
<td>1.6\times10^{-4}</td>
<td>1.4\times10^{-3}</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 9:** Rates of hydrolysis of 2-acylamino-5-nitrothiophene-3-carboxylic acid solutions.

**Product Analysis**

The 2-acylamino-5-nitrothiophene-3-carboxylic acid (2 g) was dissolved in sulphuric acid (98%, 8 ml). After stirring for 1 hr at room temperature...
the solution was drowned into ice-water. The precipitated solid was filtered, washed with water and dried. Apart from the chloroacetamido derivative, the product in all cases was identified as 2-amino-5-nitrothiophene-3-carboxylic acid, m.p. 202°C (from methanol). This is the product obtained from hydrolysis of the acetamido derivative in concentrated sulphuric acid. In the case of the chloroacetamido derivative the only detectable product was the starting material, recoverable in good yield. The product analysis results are summarized in table 10.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>-NHCOCH₂Cl</td>
<td>-NHCOCH₂Cl</td>
<td>97%</td>
</tr>
<tr>
<td>-NHCOCH₂CH₃</td>
<td>-NH₂</td>
<td>41%</td>
</tr>
<tr>
<td>-NHCOCH(CH₃)₂</td>
<td>-NH₂</td>
<td>38%</td>
</tr>
<tr>
<td>-NHCO(CH₃)₃</td>
<td>-NH₂</td>
<td>59%</td>
</tr>
</tbody>
</table>

TABLE 10: Product Analysis for the reaction of 2-acylamino-5-nitrothiophene-3-carboxylic acids with concentrated sulphuric acid.

(b) NITRATION

Rate data for the nitration of the acylamino thiophene derivatives were obtained in an identical manner to that described earlier for the corresponding acetamido derivative.

Fairly good linear, pseudo first-order kinetic plots were obtained but the unstable product (in all cases apart from the chloroacetamido thiophene derivative) was again a problem.
For reaction:

\[
\begin{array}{c}
\text{Thiophene Amide} \quad \text{(HNONO}_3 \text{)} \\
\begin{array}{c}
\text{Mean } k_2 \text{ (obs)} \left(1 \text{ mol}^{-1} \text{ sec}^{-1}\right) \\
\text{Product Analysis}
\end{array}
\end{array}
\]

<table>
<thead>
<tr>
<th>% H\textsubscript{2}SO\textsubscript{4}</th>
<th>R</th>
<th>CH\textsubscript{2}Cl</th>
<th>CH\textsubscript{2}CH\textsubscript{3}</th>
<th>CH(CH\textsubscript{3})\textsubscript{2}</th>
<th>C(CH\textsubscript{3})\textsubscript{3}</th>
</tr>
</thead>
<tbody>
<tr>
<td>80.2</td>
<td></td>
<td>8.5x10\textsuperscript{-1}</td>
<td>1.1x10\textsuperscript{-1}</td>
<td>6.4x10\textsuperscript{-1}</td>
<td>2.3x10\textsuperscript{-1}</td>
</tr>
<tr>
<td>86.1</td>
<td></td>
<td>2.1x10\textsuperscript{-1}</td>
<td>2.9x10\textsuperscript{-2}</td>
<td>1.7x10\textsuperscript{-1}</td>
<td>4.5x10\textsuperscript{-2}</td>
</tr>
<tr>
<td>83.5</td>
<td></td>
<td>4.7x10\textsuperscript{-2}</td>
<td>7.7x10\textsuperscript{-3}</td>
<td>4.0x10\textsuperscript{-2}</td>
<td>1.3x10\textsuperscript{-2}</td>
</tr>
<tr>
<td>80.9</td>
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<td>5.3x10\textsuperscript{-4}</td>
<td>1.9x10\textsuperscript{-3}</td>
<td>1.1x10\textsuperscript{-3}</td>
</tr>
</tbody>
</table>

**TABLE 11**: Rates of nitration of 2-acylamino-5-nitrothiophene-3-carboxylic acids in nitric/sulphuric acid solutions.

The 2-acylamino-5-nitrothiophene-3-carboxylic acid (0.01 mol) was dissolved in sulphuric acid (98%, 10 ml) and the solution cooled to -5\degree C. A solution of nitric acid (d 1.42, 0.95 g) in sulphuric acid (98%, 5 ml) i.e. 1.5 mole of nitric acid per mole of substrate, was added dropwise, with stirring < 0\degree C. The mixture was stirred for 30 min at 0\degree C and then drowned into ice-water. After stirring for 2 hr < 5\degree C the mixture was filtered and washed free of acid with cold water. The product, 2-acylamino-3,5-dinitrothiophene, was dried at 50\degree C. Product analysis details are summarized in tables 12 and 13.
For reaction:

![Chemical structure](image)

<table>
<thead>
<tr>
<th>R</th>
<th>Melting Point (Product)</th>
<th>Yield (Product)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-CH₂Cl</td>
<td>172 ° (from butanol)</td>
<td>81.3%</td>
</tr>
<tr>
<td>-CH₂CH₃</td>
<td>146 ° ( &quot; &quot; )</td>
<td>49.6%</td>
</tr>
<tr>
<td>-CH(CH₃)₂</td>
<td>139 ° ( &quot; &quot; )</td>
<td>51.4%</td>
</tr>
<tr>
<td>-C(CH₃)₃</td>
<td>143 ° ( &quot; &quot; )</td>
<td>42.1%</td>
</tr>
</tbody>
</table>

**TABLE 12:** Product Analysis for nitration of 2-acylamino-5-nitrothiophene-3-carboxylic acids.

For reaction:

![Chemical structure](image)

<table>
<thead>
<tr>
<th>R</th>
<th>C, H, N Analysis (Product)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-CH₂Cl</td>
<td>C, 27.1%; H, 1.2%; N, 15.8%. C₆H₄N₃O₅ClS requires: C, 27.1%; H, 1.2%; N, 15.8%.</td>
</tr>
<tr>
<td>-CH₂CH₃</td>
<td>C, 34.1%; H, 3.1%; N, 17.2%. C₇H₇N₃O₅S requires: C, 34.3%; H, 2.9%; N, 17.1%.</td>
</tr>
<tr>
<td>-CH(CH₃)₂</td>
<td>C, 37.3%; H, 3.5%; N, 16.3%. C₈H₉N₃O₅S requires: C, 37.1%; H, 3.5%; N, 16.2%.</td>
</tr>
<tr>
<td>-C(CH₃)₃</td>
<td>C, 39.8%; H, 3.9%; N, 15.4%. C₉H₁₁N₃O₅S requires: C, 39.6%; H, 4.0%; N, 15.4%.</td>
</tr>
</tbody>
</table>

**TABLE 13:** Product Analysis for nitration of 2-acylamino-5-nitrothiophene-3-carboxylic acid.
(9) 2-ACYLAMINO-3,5-DINITROTHIOPHENES

(A) SYNTHESIS

General Scheme:

\[
\begin{array}{c}
\text{NO}_2 \quad \text{S} \quad \text{NHCOR} \\
\text{CO}_2\text{H} \\
\end{array}
\xrightarrow{\text{HNO}_3} 
\begin{array}{c}
\text{NO}_2 \quad \text{S} \quad \text{NHCOR} \\
\end{array}
\]

The method of synthesis is that described for the 'product analysis' in the nitration of 2-acylamino-5-nitrothiophene-3-carboxylic acids. The experimental details and analyses of the dinitro products are summarized in tables 12 and 13.

\[^{13}\text{C} \text{Spectra in Sulphuric Acid (98%)}\]

2-Chloroacetamido-3,5-dinitrothiophene showed very similar \[^{13}\text{C}\] spectral behaviour to the corresponding formamido derivative i.e. six peaks which retained their intensity over a period of days. The amide was recoverable in good yield after 4 days (91%). All other amides studied (R = CH\(_2\)CH\(_3\), CH(\(\text{CH}_3\))\(_2\) and C(\(\text{CH}_3\))\(_3\)) showed very similar behaviour to the corresponding 2-acetamido derivative i.e. hydrolysis to 2-amino-3,5-dinitrothiophene in 2-3 hrs, the amine itself being unstable for longer periods in sulphuric acid.

\[^{13}\text{C} \text{Spectra in Sulphuric/Nitric Acid}\]

Again the 2-chloroacetamido derivative behaved in a similar manner to the formamido compound i.e. a slow decrease in intensity of the original peaks, the starting material being recoverable in good yield after 4 hrs (86.5%). However, after 48 hrs, only a complex series of low intensity peaks remained in the \[^{13}\text{C}\] spectrum. The other amides behaved in a similar manner to the acetamido compound i.e. a faster decrease in intensity of the original peaks. After 3-4 hrs only a complex series of
low intensity peaks remained together with some peaks of higher intensity corresponding to free acyl.
(B) KINETICS

(a) HYDROLYSIS

For reaction:

\[
\begin{array}{c}
\text{NO}_2 \text{S} \text{NHCOR} \\
\text{NO}_2 \text{S} \end{array} \xrightarrow{\text{H}_2\text{SO}_4} \begin{array}{c}
\text{NO}_2 \text{S} \\
\text{NH}_2
\end{array}
\]

Detailed rate data were obtained in a similar manner to the acetamido and formamido derivatives.

(Thiophene Amide) = \(2.50 \times 10^{-4}\) M

Wavelength = 430 nm

<table>
<thead>
<tr>
<th>Mean (% \text{H}_2\text{SO}_4)</th>
<th>(R = )</th>
<th>CH(_2)Cl</th>
<th>CH(_2)CH(_3)</th>
<th>CH(CH(_3)(_2))</th>
<th>C(CH(_3)(_3))</th>
</tr>
</thead>
<tbody>
<tr>
<td>98.0</td>
<td>&lt; 10(^{-8})</td>
<td>3.6 \times 10^{-4}</td>
<td>4.9 \times 10^{-4}</td>
<td>3.7 \times 10^{-3}</td>
<td></td>
</tr>
<tr>
<td>90.2</td>
<td>&lt; 10(^{-8})</td>
<td>5.1 \times 10^{-5}</td>
<td>5.8 \times 10^{-5}</td>
<td>7.2 \times 10^{-4}</td>
<td></td>
</tr>
<tr>
<td>82.7</td>
<td>&lt; 10(^{-8})</td>
<td>2.8 \times 10^{-5}</td>
<td>3.0 \times 10^{-5}</td>
<td>2.5 \times 10^{-4}</td>
<td></td>
</tr>
<tr>
<td>75.3</td>
<td>&lt; 10(^{-8})</td>
<td>3.1 \times 10^{-5}</td>
<td>3.8 \times 10^{-5}</td>
<td>4.3 \times 10^{-4}</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 14: Rates of hydrolysis of 2-acylamino-3,5-dinitrothiophenes in sulphuric acid solutions.

Product Analysis

The 2-acylamino-3,5-dinitrothiophene derivative (2 g) was dissolved in sulphuric acid (98%, 10 ml). The solution was stirred at room temperature for 3 hrs and then drowned into ice-water. The precipitated solid was filtered, washed with water and dried. In all cases, apart from the chloroacetamido derivative, the product was identified as 2-amino-3,5-dinitrothiophene m.p. 176\(^{\circ}\) (from aq. methanol). In the case of the
chloroacetamido derivative only the starting material was recoverable from the reaction solution. The product analysis results are summarized in table 15.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>-NHCOCH₂Cl</td>
<td>-NHCOCH₂Cl</td>
<td>96%</td>
</tr>
<tr>
<td>-NHCOCH₂CH₃</td>
<td>-NH₂</td>
<td>43%</td>
</tr>
<tr>
<td>-NHCOCH(CH₃)₂</td>
<td>-NH₂</td>
<td>37%</td>
</tr>
<tr>
<td>-NHOCOC(CH₃)₃</td>
<td>-NH₂</td>
<td>58%</td>
</tr>
</tbody>
</table>

TABLE 15: Product Analysis for the reaction of 2-acylamino-3,5-dinitrothiophenes with concentrated sulphuric acid.
(b) **OXIDATION-DEGRADATION**

Detailed rate data for the oxidation/degradation of the acylamino thiophenes in sulphuric/nitric acid were obtained in a similar manner to that employed for 2-acetamido-3,5-dinitrothiophene degradation, studied earlier. Approximately linear, pseudo first-order kinetic plots were obtained.

For reaction:

\[
\begin{align*}
\text{NO}_2 & \quad \text{HNO}_3 \\
\text{S} & \quad \text{H}_2\text{SO}_4 \\
\text{NHCOR} & \quad \text{Products}
\end{align*}
\]

(Thiophene Amide) = 3.1 x 10^{-4} M

Wavelength = 315 nm

<table>
<thead>
<tr>
<th>Mean % H₂SO₄</th>
<th>Molarity</th>
<th>Molarity HNO₃</th>
<th>R</th>
</tr>
</thead>
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<tr>
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<td>CH₂Cl</td>
</tr>
<tr>
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<td>4.1 x 10^{-7}</td>
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<td></td>
<td>3.5 x 10^{-4}</td>
<td>3.7 x 10^{-4}</td>
<td>CH(CH₃)₂</td>
</tr>
<tr>
<td></td>
<td>4.9 x 10^{-4}</td>
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<td>C(CH₃)₃</td>
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<td>98.6</td>
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<td>CH₂Cl</td>
</tr>
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<td>2.0 x 10^{-7}</td>
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<td>CH(CH₃)₂</td>
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<td></td>
<td>5.6 x 10^{-5}</td>
<td>5.6 x 10^{-5}</td>
<td>C(CH₃)₃</td>
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<td>1.75 x 10^{-2}</td>
<td>CH₂Cl</td>
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<td>CH(CH₃)₂</td>
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<tr>
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<td>2.9 x 10^{-5}</td>
<td>3.3 x 10^{-5}</td>
<td>C(CH₃)₃</td>
</tr>
<tr>
<td>98.6</td>
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<td>1.75 x 10^{-2}</td>
<td>CH₂Cl</td>
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<tr>
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<tr>
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<td>2.9 x 10^{-5}</td>
<td>CH(CH₃)₂</td>
</tr>
<tr>
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<td>2.9 x 10^{-5}</td>
<td>3.3 x 10^{-5}</td>
<td>C(CH₃)₃</td>
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**TABLE 16**: Rates of degradation of 2-acylamino-3,5-dinitrothiophenes in sulphuric-nitric acid mixtures.

**Product Analysis**

To a solution of 2-acylamino-3,5-dinitrothiophene (2 g) in sulphuric acid (98%, 10 ml) was added dropwise, with stirring, a solution of nitric acid (d 1.42, 1.0 g) in sulphuric acid (98%, 5 ml). The mixture was stirred at room temperature for 3 hrs (36 hrs for chloroacetamido derivative) and then drowned into ice-water. Despite several extractions
of both this and the neutralized solution the only recoverable material was a few milligrams of starting material.

$^{13}$C Spectra of the reaction products revealed only a complex series of low intensity peaks and some peaks of higher intensity, corresponding to the free acyl moiety. Oxidation via the amine is suspected in all cases, since many of the final complex, low intensity spectra were similar for different amides. In the case of the chloroacetamido derivative the free acyl peaks were again present (after 36 hrs). However these could arise via direct oxidation of the amide.
2-Amino-3,5-dinitrothiophene

(A) SYNTHESIS

Scheme:

2-Acetamido-3,5-dinitrothiophene (4.6 g, 0.02 mol) was added to a mixture of sulphuric acid (2 M, 100 ml) and cellosolve (10 ml). The mixture was refluxed for 5 hrs and the solution of product filtered whilst still hot. After cooling the filtrate in a freezing mixture the crystalline product was filtered off, washed with cold water and dried (3.4 g, 89.9%). m.p. 176° (from aq. methanol).

Found: C, 25.4%; H, 1.3%; N, 22.4%.
Calculated for: C₄H₃N₃O₄S: C, 25.4%; H, 1.6%; N, 22.2%.

Hydrolysis of the formamido derivative required only a 1 hr reflux time in sulphuric acid (2 M) whereas hydrolysis of the chloroacetamido derivative was complete in 30 mins (at room temperature). The product in each case was 2-amino-3,5-dinitrothiophene.

13C Spectrum in Sulphuric Acid

A 13C spectrum of 2-amino-3,5-dinitrothiophene (400 mg) in sulphuric acid (98%, 2 ml) revealed a series of peaks at 156.2, 139.1, 134.6 and 129.2 ppm (from T.M.S.). After 5 hrs, only a complex series of low intensity peaks remained. No products were isolable from this reaction solution suggesting that the free amine is rather unstable in concentrated sulphuric acid. The final, complex 13C spectrum was identical to the 13C spectrum of the corresponding acetamido derivative in sulphuric acid (after 6-8 hrs), excluding the free acetyl peaks.
To a solution of 2-amino-3,5-dinitrothiophene in sulphuric acid was added an equimolar amount of nitric acid (d 1.42). A $^{13}$C spectrum of this solution revealed a complex series of low intensity peaks. No products were isolable from this reaction solution (after only 5 min reaction time) suggesting that 2-amino-3,5-dinitrothiophene is extremely unstable in presence of sulphuric-nitric acid mixtures. The spectrum obtained was identical to the $^{13}$C spectrum of the corresponding acetamido derivative in sulphuric-nitric acid (after 4 hrs), again excluding the free acetyl peaks.
(B) KINETICS

(a) OXIDATION-DEGRADATION

Rates of oxidation/degradation were obtained by U.V. spectroscopy, but are only approximate because 2-amino-3,5-dinitrothiophene is extremely unstable in presence of nitric acid.

(Substrate) = 2.9 x 10^{-4} M

Wavelength = 435 nm

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<th>Molarity</th>
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<th>k_2 obs (1 mol^{-1} sec^{-1})</th>
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<td>5.71</td>
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TABLE 17: Rate of degradation of 2-amino-3,5-dinitrothiophene in sulphuric-nitric acid mixtures.

Product Analysis

No products of degradation of 2-amino-3,5-dinitrothiophene were isolable (see corresponding acetamido derivative).
(11) 2-ACETAMIDO-5-NITROTHIOPHENE

(A) SYNTHESIS

Scheme:

\[
\begin{align*}
\text{CO}_2\text{H} & \quad \rightarrow \quad \text{NHCOCH}_3 \\
\text{S} & \quad \text{NHCOCH}_3 \\
\text{NO}_2 & \quad \text{NHCOCH}_3 \\
\text{S} & \quad \text{NHCOCH}_3
\end{align*}
\]

(a) 2-Acetamidothiophene

A mixture of 2-acetamidothiophene-3-carboxylic acid (5.6 g, 0.03 mol) and N,N-dimethylaniline (25 ml) was heated and stirred for 1 hr at 195°. The mixture was cooled to 25°, diluted with water (100 ml) and the N,N-dimethylaniline removed by steam distillation. The hot aqueous residue was filtered, the filtrate cooled to 15° and the product which crystallized out was filtered, washed with cold water, and dried. (3.3 g, 78.6%). m.p. 161° (from water) (lit. 162°).

Found: C, 50.8%; H, 4.6%; N, 10.0%.
Calculated for: C\text{6}H\text{7}NOS: C, 51.1%; H, 5.0%; N, 9.9%.

(b) 2-Acetamido-5-Nitrothiophene

2-Acetamidothiophene (7.05 g, 0.05 mol) was dissolved in sulphuric acid (98%, 100 ml) and the temperature reduced until the mixture started to freeze at -12°. A mixture of nitric acid (3.2 g, 0.05 mole) in
sulphuric acid (25 ml) was added dropwise with vigorous stirring and cooling, allowing the temperature to fall to \(-15^\circ\). After completion of the addition the mixture was stirred for a further 15 min at \(-15^\circ\) and then drowned into ice-water. The precipitated solid was filtered off, washed with water and dried (7.9 g, 84.9%).

The product was fairly pure but further purification was obtained by eluting with acetone from an alumina column, and recrystallization from water/methanol. m.p. 226\(^\circ\) (from aq. methanol).

Found: C, 38.7%; H, 3.3%; N, 14.9%.

\(C_6H_6N_2O_3S\) requires: C, 38.7%; H, 3.2%; N, 15.1%.

Nitration of 2-acetamidothiophene with an equimolar quantity of nitric acid, under the same reaction conditions as those employed for nitration of 2-acetamidothiophene-3-carboxylic acid, gave a mixture of the 3- and 5- nitro isomers (t.l.c.), the latter predominating.

\[\text{\(^{13}\)C Spectrum in Sulphuric Acid}\]

A \(\text{\(^{13}\)C}\) spectrum of a solution of 2-acetamido-5-nitrothiophene (400 mg) in sulphuric acid (98%, 2 ml) revealed a shift in acetyl peaks to the 'free acetyl' positions at 21.1 and 194.0 ppm (from T.M.S.). Despite a rapid decrease in intensity of the nuclear amide peaks only a small increase in intensity of the amine peaks was observed. Eventually, after 7-8 hrs only the shifted acetyl peaks and a series of low intensity peaks were present. Apparently, 2-acetamido-5-nitrothiophene undergoes rapid hydrolysis to an unstable amine in concentrated sulphuric acid. The amine is not isolable from the acid solution.

\[\text{\(^{13}\)C Spectrum in Sulphuric/Nitric Acid}\]

To a solution of 2-acetamido-5-nitrothiophene in sulphuric acid was added an equimolar solution of nitric acid (d 1.42). An identical
$^{13}$C spectrum to that of 2-acetamido-3,5-dinitrothiophene was subsequently obtained suggesting a nitration of the original compound.
(B) KINETICS

(a) NITRATION

For reaction:

\[
\begin{array}{c}
\text{NO}_2 \text{S} \text{NHCOCH}_3 \\
\xrightarrow{\text{HNO}_3 \text{H}_2\text{SO}_4}
\end{array} \rightarrow
\begin{array}{c}
\text{NO}_2 \text{S} \text{NHCOCH}_3
\end{array}
\]

Rate data were obtained in an identical manner to that described for nitration of 2-acetamido-5-nitrothiophene-3-carboxylic acid. Good linear, pseudo first-order kinetic plots were obtained but some difficulty was experienced due to the instability of both starting material and product in presence of sulphuric-nitric acid mixtures. For all nitration runs:

\[
\text{(Thiophene Derivative)} = 3.4 \times 10^{-4} \text{ M}
\]

Wavelength = 310 nm

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<th>Mean % H\textsubscript{2}SO\textsubscript{4}</th>
<th>Molarity HNO\textsubscript{3}</th>
<th>k\textsubscript{1 obs} (sec\textsuperscript{-1})</th>
<th>k\textsubscript{2 obs} (1 mol\textsuperscript{-1} sec\textsuperscript{-1})</th>
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</tbody>
</table>

TABLE 18: Rates of nitration of 2-acetamido-5-nitrothiophene in nitric acid-sulphuric acid solutions.
Product Analysis

2-Acetamido-5-nitrothiophene (1.9 g, 0.01 mol) was dissolved in sulphuric acid (98%, 10 ml) and the solution cooled to -5°. A solution of nitric acid (d 1.42, 0.6 g) in sulphuric acid (98%, 5 ml) was added dropwise, with stirring, < 0°. The mixture was stirred for 20 minutes at -5° and then drowned into ice-water. The precipitated solid was filtered off, washed with water, and dried (1.9 g, 82.6%), m.p. 179° (from butanol).

Found: C, 31.2%; H, 1.9%; N, 18.4%.

C₆H₅N₃O₅S requires: C, 31.2%; H, 2.2%; N, 18.2%.

The product was identical with a sample of 2-acetamido-3,5-dinitrothiophene prepared by nitration of 2-acetamidothiophene-3-carboxylic acid.
(12) METHYL-3-AMINOTHIOPHENE-2-CARBOXYLATE

(A) SYNTHESIS

(1) \[ \text{CH}_2\text{CH-CN} + \text{Cl}_2 \rightarrow \text{CH}_2\text{CH-CN} + \text{Cl} \text{Cl} \]

(2) \[ \text{CH}_2\text{CH-CN} + \text{NaOMe} \rightarrow \text{NH}_2 \text{CO}_2\text{Me} \]

\[ \text{HS} \rightarrow \text{CH}_2\text{CO}_2\text{Me} \]

2,3-Dichloropropionitrile

Dry chlorine was introduced into a mixture of acrylonitrile (5.3 g, 0.1 mol) and pyridine (1.4 g), with cooling, until the increase in weight amounted to addition of an equimolar amount of chlorine (7.1 g). The products were shaken with water and the organic layer was dried over anhydrous calcium chloride. After evaporating, the product was distilled under reduced pressure, collecting the fraction boiling at 56-61°/13 mm (8.0 g, 66.0%). N.M.R. (CCl₄) \text{\tau} 4.4 (triplet) and \text{\tau} 5.5 (doublet) in ratio 1 : 2.

Methyl-3-aminothiophene-2-carboxylate

A suspension of sodium methoxide (2.9 g, 0.05 mol) in dry ether (25 ml) was mixed, with cooling and stirring, with methyl 2-mercaptoacetate (3.2 g, 0.03 mol) in ether (3 ml). 2,3-Dichloropropionitrile (2.5 g, 0.02 mol) in dry ether (10 ml) was added dropwise, with stirring, over 90 min. After further stirring for 30 min water was added and the mixture acidified with acetic acid. The organic layer was separated and the aqueous layer extracted with ether. The combined extracts were fractionally distilled.
The fraction b.p. 96-101°/0.1 mm was a light yellow oil which solidified on standing (2.1 g, 66.9%) m.p. 64° (from petrol) (lit. 65°).

Found: C, 45.7%; H, 4.5%; N, 8.9%.

C₆H₇NO₂S requires: C, 45.8%; H, 4.5%; N, 8.9%.

**Acetylation**

Methyl-3-aminothiophene-2-carboxylate (2 g) was heated with acetic anhydride (10 ml) at 70° for 30 min. After cooling, the solution was poured into water (50 ml) and the precipitated solid filtered, washed with water and dried (2.3 g, 91.1%). m.p. 98° (from aq. ethanol).

Found: C, 48.3%; H, 4.6%; N, 7.2%.

C₈H₇NO₃S requires: C, 48.2%; H, 4.5%; N, 7.0%.

I.R. and ¹³C spectra were consistent with the methyl ester of 3-acetamidothiophene-2-carboxylic acid.

**Formylation**

Methyl-3-aminothiophene-2-carboxylate (2 g) was added to equal volumes of acetic anhydride and formic acid (10 ml) and the mixture stirred at room temperature for 30 min. The solution was then poured into water (50 ml) and the precipitated solid filtered, washed with water and dried (2.2 g, 93.6%) m.p. 87° (from aq. ethanol).

Found: C, 45.4%; H, 3.5%; N, 7.6%.

C₇H₇NO₃S requires: C, 45.4%; H, 3.8%; N, 7.6%.

I.R. and ¹³C spectra were consistent with the methyl ester of 3-formamidothiophene-2-carboxylic acid.

**¹³C Spectra in Sulphuric Acid**

A ¹³C spectrum of methyl-3-acetamidothiophene-2-carboxylate (400 mg)
in sulphuric acid (98%, 2 ml) revealed a series of eight peaks which retained their intensity for over 24 hrs. There was no evidence for cyclisation to an anhydride and only a very slow hydrolysis reaction occurred, producing the free acetyl peaks. The starting material was recoverable in good yield after 36 hrs (86%). The corresponding formamido derivative showed no tendency to hydrolyse and was stable for a period of days in sulphuric acid.

Nitration

Methyl-3-acetamidothiophene-2-carboxylate (2 g) was dissolved in sulphuric acid (98%, 5 ml) and the solution cooled to 0°C. A solution of nitric acid (0.8 g) in sulphuric acid (98%, 10 ml) was added dropwise, with stirring, < 0°C. The reaction mixture was stirred at 0°C for 5 min and then drowned into ice-water. The precipitated solid was filtered off, washed with water, and dried. (2.1 g, 85.6%). m.p. 121°C (from ethanol).

Found: C, 39.5%; H, 3.3%; N, 11.6%.

C₈H₈N₂O₅S requires: C, 39.3%; H, 3.3%; N, 11.5%.

I.R. and ¹³C spectroscopy confirmed the product as a mono-nitrated thiophene, and t.l.c. indicated the presence of only one main product:

Proof of Structure

Methyl-3-amino-4(or 5)-nitrothiophene-2-carboxylate

Methyl-3-acetamido-nitrothiophene-2-carboxylate (4.8 g, 0.02 mol) was added to a mixture of dilute sulphuric acid (2 M, 90 ml) and cellosolve (10 ml). The mixture was gently refluxed for 8 hrs and the solution of product filtered whilst still hot. The filtrate was cooled in a freezing
mixture and the crystalline product was filtered off, washed with water and
dried (3.0 g, 75.0%). m.p. 97° (from aq. methanol).

Found: C, 35.2%; H, 3.0%; N, 13.6%.
C₆H₇N₂O₄S requires: C, 35.6%; H, 3.0%; N, 13.9%.

Methyl-4(or 5)-nitrothiophene-2-carboxylate

Methyl-3-amino-4(or 5)-nitrothiophene-2-carboxylate (24.4 g, 0.1 mol) was dissolved in dioxan (90 ml) and concentrated hydrochloric acid (75 ml). A saturated solution of sodium nitrite (0.2 mol) was added stepwise, with stirring at -5° and the diazonium salt solution stirred for 20 min at -5°. The reaction mixture was then added to a solution of copper acetate (0.4 g) in ethanol (200 ml) and the mixture warmed to 70°. After stirring for 30 min at 70° the solution was cooled, diluted and ether extracted. Evaporation of the ether extracts left an oil, which was dissolved in methanol. A solution of sodium hydroxide (3.0 g) in water (20 ml) was added dropwise with stirring, maintaining the pH < 10-11. The reaction solution was refluxed for 30 min, cooled and re-acidified with dilute hydrochloric acid. This precipitated an off white solid which was filtered off, washed with water, and dried (7.4 g, 42.8%). m.p. 151° (from water).

Found: C, 34.5%; H, 1.4%; N, 8.1%.
C₅H₃N₄O₄S requires: C, 34.7%; H, 1.7%; N, 8.1%.

The product was identical (I.R., ¹³C and m.p.) to 4-nitrothiophene-2-carboxylic acid, prepared by nitration of thiophene-2-carboxylic acid (see later). This demonstrates the fact that the original nitro group was in the 4-position and that the product of nitration of methyl-3-acetamido-thiophene-2-carboxylate is the 4-nitro isomer:-
Methyl-3-acetamido-4-nitrothiophene-2-carboxylate (2 g) was added to a 50% aqueous methanol solution (20 ml). Sodium hydroxide (2 M, 10 ml) was added dropwise, maintaining the pH at 9-10. The mixture was refluxed for 30 min, during which time the substrate dissolved. The solution was filtered and the filtrate acidified to pH 2 with dilute hydrochloric acid. The precipitated solid was filtered off, washed with water and dried (0.71 g, 35.2%) m.p. 144° (from aq. methanol).

Found: C, 36.5%; H, 2.3%; N, 12.1%.

C₆H₅N₂O₅S requires: C, 36.5%; H, 2.6%; N, 12.2%.

¹³C and I.R. spectroscopy confirmed the product as the carboxylic acid - there was no evidence for basic hydrolysis of the amide group. The thiophene nucleus was found to be unstable in presence of excess sodium hydroxide.

¹³C Spectrum in Sulphuric Acid

A ¹³C spectrum of 3-acetamido-4-nitrothiophene-2-carboxylic acid (400 mg) in sulphuric acid (98%, 2 ml) revealed a series of seven peaks which retained their intensity over a period of days. There was no evidence of hydrolysis and the starting material was recoverable in good yield after 24 hrs (93%).

¹³C Spectrum in Sulphuric/Nitric Acid

To a solution of 3-acetamido-4-nitrothiophene-2-carboxylic acid in sulphuric acid was added an equimolar solution of nitric acid (d 1.42).
A rather slow decrease in intensity of the original peaks was observed but the starting material was recoverable in good yield after 2 hrs (94%). There was no evidence of hydrolysis or nitrodecarboxylation.

**Nitrodecarboxylation**

3-Acetamido-4-nitrothiophene-2-carboxylic acid was treated with a sulphuric acid-nitric acid mixture in an identical manner to that used preparatively for nitrodecarboxylation of 2-acetamido-5-nitrothiophene-3-carboxylic acid. However, there was no evidence for carbon dioxide evolution either during the addition of mixed acid or on drown-out. The starting material was recovered in 96% yield. Nitrodecarboxylation was eventually detected in 90% sulphuric acid at 25°C. T.L.C. showed absence of starting material after 4 hrs treatment with excess nitric acid. Drown-out of the reaction mixture into ice-water gave 3-acetamido-2,4-dinitrothiophene (32%). m.p. 131°C (from water).

Found: C, 31.4%; H, 1.9%; N, 18.3%

C₆H₅N₃O₅S requires: C, 31.2%; H, 2.2%; N, 18.2%.

**¹³C Spectrum in Sulphuric Acid**

A ¹³C spectrum of 3-acetamido-2,4-dinitrothiophene (400 mg) in sulphuric acid (98%, 2 ml) revealed a hydrolysis reaction occurring at a similar rate to that for 2-acetamido-3,5-dinitrothiophene. After 12 hrs only a complex series of low intensity peaks remained together with the higher intensity, characteristic peaks at 21.1 and 194.0 ppm (from T.M.S.).

The hydrolysis of the dinitroamide in sulphuric acid would account for the poor yield of product obtained in the nitrodecarboxylation of 3-acetamido-4-nitrothiophene-2-carboxylic acid.
(13) METHYL-2-AMINO-4,5-DIMETHYLTHIOPHENE-3-CARBOXYLATE

(A) SYNTHESIS

Scheme:

\[
\begin{align*}
\text{CH}_3 \quad \text{CO}_2\text{CH}_3 \quad \text{Et}_3\text{N} \quad \text{MeOH} \\
\text{CO} \quad \text{CH}_2 \quad \text{S} \quad \rightarrow \\
\text{NH}_2 \quad \text{CO}_2\text{CH}_3
\end{align*}
\]

Methyl ethyl ketone (7.2 g, 0.1 mol) was mixed with methyl cyanoacetate (9.9 g, 0.1 mol) and powdered sulphur (3.2 g, 0.1 mol). Methanol (25 cm³) was added and the mixture stirred with triethylamine (10 ml), with cooling. After initial stirring and cooling the mixture was gently refluxed for 4hrs, during which time the sulphur dissolved. The reaction solution was allowed to stand at room temperature overnight and the crystalline product was filtered off, washed with water and dried. (7.4 g, 38.6%). m.p. 120° (from methanol).

Found: C, 51.7%; H, 6.0%; N, 7.5%.

Calculated for: C₇H₁₁N₂O₂S: C, 51.9%; H, 5.9%; N, 7.5%.

I.R. and ¹³C spectroscopy confirmed the structure of the product as methyl-2-amino-4,5-dimethylthiophene-3-carboxylate.

Acetylation

Methyl-2-amino-4,5-dimethylthiophene-3-carboxylate (1 g) was dissolved in cold acetic anhydride (5 ml) at 5°. The mixture was stirred for an hour and then drowned into ice-water. An oil separated, which upon stirring for a few hours solidified. The brown solid was filtered off, washed with water, and dried (1.1 g, 93.0%). m.p. 71° (from aq. methanol).
Found: C, 52.9%; H, 5.7%; N, 6.2%.

**C_{10}H_{13}NO_3S** requires: C, 52.9%; H, 5.7%; N, 6.2%.

I.R. and $^{13}$C spectroscopy confirmed the product as methyl-2-acetamido-4,5-dimethylthiophene-3-carboxylate.

**Formylation**

A mixture of formic acid (2 ml) and acetic anhydride (2 ml) was stirred and allowed to warm to 40° for 10 min. The solution was then cooled to 0 - 5° and methyl-2-amino-4,5-dimethylthiophene-3-carboxylate (1 g) added portionwise with stirring. The mixture was stirred for 30 min, during which time a precipitate developed. This was filtered, washed with water and dried (1.1 g, 92.3%). m.p. 68° (from aq. methanol).

Found: C, 50.5%; H, 5.2%; N, 6.7%.

**C_{9}H_{11}NO_3S** requires: C, 50.7%; H, 5.2%; N, 6.6%.

I.R. and $^{13}$C spectroscopy confirmed the product as methyl-2-formamido-4,5-dimethylthiophene-3-carboxylate.

**Hydrolysis of Ester**

Methyl-2-acetamido-4,5-dimethylthiophene-3-carboxylate (2 g) was added to a 50% aqueous methanol solution (20 ml). A sodium hydroxide solution (2 M, 12 ml) was added and the mixture refluxed for 30 min, during which time the amide dissolved. The solution was then cooled and filtered. The filtrate was acidified with dilute hydrochloric acid to pH 2 and the precipitated solid filtered off, washed with water, and dried (1.2 g, 62.2%) m.p. 207° (from aq. methanol).

I.R. and $^{13}$C spectroscopy confirmed the product as 2-acetamido-4,5-dimethylthiophene-3-carboxylic acid. No evidence was found for any basic hydrolysis of the acetamido group.
Found: C, 51.0%; H, 5.4%; N, 6.4%.

\[ \text{C}_6\text{H}_{11}\text{NO}_3\text{S} \text{ requires: C, 50.7%; H, 5.2%; N, 6.6%.} \]

When an analogous method was employed for hydrolysis of the corresponding formamido ester, basic hydrolysis of the amido group was found to compete with the ester hydrolysis, the product of the reaction being 2-amino-4,5-dimethylthiophene-3-carboxylic acid (38%):

\[
\begin{array}{c}
\text{Me} & \text{CO}_2\text{Me} \\
\text{Me} & \text{S} & \text{NHCHO} \\
\end{array} \xrightarrow{\text{NaOH aq. MeOH}} \begin{array}{c}
\text{Me} & \text{CO}_2\text{H} \\
\text{Me} & \text{S} & \text{NH}_2 \\
\end{array}
\]

This thiophene derivative was then re-formylated with formic acid/acetic anhydride to yield 2-formamido-4,5-dimethylthiophene-3-carboxylic acid (83%). m.p. 243° (from aq. methanol).

Found: C, 48.0%; H, 4.4%; N, 6.9%.

\[ \text{C}_8\text{H}_9\text{NO}_3\text{S} \text{ requires: C, 48.2%; H, 4.5%; N, 7.0%.} \]

13C Spectrum in Sulphuric Acid

A 13C spectrum of 2-acetamido-4,5-dimethylthiophene-3-carboxylic acid (500 mg) in sulphuric acid (98%, 2 ml) revealed a series of nine peaks which retained their intensity over a period of days. There was no evidence of any hydrolysis and the starting material was recoverable after 24 hrs (84%). Similarly the analogous formamido derivative (and both esters) were stable to hydrolysis and were recoverable in good yield from sulphuric acid solutions.

Nitrodecarboxylation

2-Acetamido-4,5-dimethylthiophene-3-carboxylic acid (2.1 g, 0.01 mol) was dissolved in sulphuric acid (98%, 10 ml) and the solution cooled to 0°. A solution of nitric acid (0.9 g) in sulphuric acid (98%, 10 ml) was
added dropwise, with stirring $< 0^\circ$. The reaction mixture was stirred at $0^\circ$ for 10 min and then drowned into ice-water. The precipitated solid was filtered off, washed with water, and dried. (1.1 g, 52.4%) m.p. 186$^\circ$ (from aq. methanol).

Found: C, 45.2%; H, 4.5%; N, 12.9%.

C$_8$H$_{10}$N$_2$O$_3$S requires: C, 44.9%; H, 4.7%; N, 13.1%.

I.R. and $^{13}$C spectroscopy confirmed the product as being 2-acetamido-3-nitro-4,5-dimethylthiophene:

\[
\begin{align*}
\text{CH}_3 & \quad \text{CO}_2\text{H} & \quad \text{HNO}_3 \\
\text{CH}_3 & \quad \text{S} & \quad \text{NHCOCH}_3 \\
\text{CH}_3 & \quad \text{S} & \quad \text{NHCOCH}_3
\end{align*}
\]

$^{13}$C Spectrum in Sulphuric Acid

A $^{13}$C spectrum of 2-acetamido-3-nitro-4,5-dimethylthiophene (400 mg) in sulphuric acid (98%, 2 ml) revealed a hydrolysis reaction, complete in $\sim 3$-4 hrs. After 12 hrs only a complex series of low intensity peaks remained together with the 'free acetyl' peaks at 194.0 and 21.1 ppm. The hydrolysis to an unstable amine in this way would account for the poor yield of product in the nitrodecarboxylation of 2-acetamido-4,5-dimethylthiophene-3-carboxylic acid.
(A) SYNTHESIS (attempted)

Proposed scheme:

The method is a variation upon Gewald's procedure for preparation of 2-hydroxy-4-phenylthiophene-3-carboxylic acid.

2-Hydroxy-3-Cyano-4,5-Dimethylthiophene

Sodium (2 g) was added to dry ethanol (50 ml) and the mixture warmed to reflux for 30 mins. After cooling, a solution of methyl-2-amino-4,5-dimethylthiophene-3-carboxylate (9.2 g, 0.05 mol) in dry ethanol (75 ml) was added dropwise, with stirring. The mixture was stirred and refluxed for 4 hrs. Ethanol (75 ml) was distilled off and the mixture cooled and poured into ice-water (150 ml). Acidification with hydrochloric acid precipitated a solid, which was filtered off, washed with water and dried.
Spectroscopic analysis revealed this to be unreacted starting material, together with some ethyl ester (trans-esterification) (86%). There was no evidence for formation of a cyano or hydroxy-compound. The experiment was repeated with dry methanol but, again, only unreacted starting material was obtained. Further modifications of the above procedure also failed to produce any of the desired product.
(15) 2-HALOGENO (or 2-HYDROXY)-4,5-DIMETHYLTHIOPHENE-3-CARBOXYLIC ACID

(A) SYNTHESIS (Attempted)

Proposed scheme:

\[
\begin{align*}
\text{Me} & \quad \text{CO}_2\text{Me} \\
\text{Me} & \quad \text{S} \quad \text{NH}_2 \\
\text{Me} & \quad \text{S} \quad \text{Cl}
\end{align*}
\]

- \text{HONO} \quad \text{HCl}

\[
\begin{align*}
\text{Me} & \quad \text{CO}_2\text{Me} \\
\text{Me} & \quad \text{S} \quad \text{N}_2\text{Cl}^-
\end{align*}
\]

- \text{CuCl/HC1}

\[
\begin{align*}
\text{Me} & \quad \text{CO}_2\text{Me} \\
\text{Me} & \quad \text{S} \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{CO}_2\text{H} \\
\text{Me} & \quad \text{S} \quad \text{Cl}
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{CO}_2\text{H} \\
\text{Me} & \quad \text{S} \quad \text{OH}
\end{align*}
\]

2-Chloro-4,5-dimethylthiophene-3-carboxylic acid (attempt)

Methyl-2-amino-4,5-dimethylthiophene-3-carboxylate (2 g) was dissolved in dioxan (10 ml) and concentrated hydrochloric acid (10 ml). The solution was cooled to -5°C and a solution of sodium nitrite (2 M, 10 ml) added dropwise, with stirring, ensuring that the temperature did not rise above 0°C. When excess nitrous acid was detected the solution was added portionwise to a cold solution of copper I chloride (5 g) in concentrated hydrochloric acid (10 ml). The mixture became extremely viscous (addition product) but on warming to room temperature and stirring vigorously nitrogen was evolved. Some solid separated at this point but was mainly
inorganic salt. Several extractions with carbon tetrachloride and subsequent evaporation of the solvent left only a tarry black residue. This was mixed with aqueous methanol (10 ml) and refluxed with sodium hydroxide (0.3 g) for 30 min. Re-acidification to pH 2 did not produce any precipitate. When an analogous experiment was performed, replacing the original amino ester with the corresponding amino acid no chloro derivative was isolable, the only products being black, tarry solids which were not identifiable.

2-Hydroxy-4,5-dimethylthiophene-3-carboxylic acid (attempt)

Methyl-2-amino-4,5-dimethylthiophene-3-carboxylate (2 g) was dissolved in dioxan (10 ml) and concentrated hydrochloric acid (10 ml). The solution was cooled to -50 and a solution of sodium nitrite (2 M, 10 ml) added dropwise, with stirring, ensuring that the temperature did not rise above 00. When excess nitrous acid was detected the solution was allowed to stand at room temperature for a few minutes before being drowned into warm water (200 ml). The solution was heated on a water bath at 500 for 20 mins until no more nitrogen was evolved. Some black, tarry solid separated on cooling but was not identifiable. Extraction with various solvents and subsequent evaporation failed to produce any of the desired hydroxy thiophene derivative. The experiment was repeated with the acid rather than the original ester but, again, no formation of a hydroxy compound was evident.

Deamination of Methyl-2-amino-4,5-dimethylthiophene-3-carboxylate

Methyl-2-amino-4,5-dimethylthiophene-3-carboxylate (18.5 g, 0.1 mol) was dissolved in dioxan (90 ml) and concentrated hydrochloric acid (75 ml). A saturated solution of sodium nitrite (0.2 mol) was added stepwise with stirring at -50 and the diazonium salt solution kept for 20 mins at -50. This mixture was then added to a solution of copper acetate (0.4 g) in
ethanol (200 ml) and the resulting solution warmed to 70°, for 30 mins. Ethanol (100 ml) was distilled off and the remaining solution diluted and extracted with ether. Evaporation of the ether extracts left an oil which was dissolved in methanol and sodium hydroxide solution and refluxed for 30 min. Upon cooling and re-acidifying the 4,5-dimethylthiophene-3-carboxylic acid was precipitated as a white solid (6.4 g, 41.3%). m.p. 149° (from aq. methanol).

Found: C, 53.9%; H, 5.0%; N, 0.1%.
C₇H₈O₂S requires: C, 53.8%; H, 5.1%.

I.R. spectroscopy confirmed the absence of the amino group.

Substitution

Attempts were made to substitute in the 2-position of 4,5-dimethylthiophene-3-carboxylic acid but conventional electrophilic substitution reactions e.g. halogenation, alkylation were unsuccessful. The starting material was recoverable in rather poor yield in most cases but none of the desired substitution products were isolable.
Cyclohexanone (52 ml, 0.5 mol) was dissolved in ethanol (125 ml) together with ethyl cyanoacetate (68 ml) and sulphur (16 g, 0.5 mol). Diethylamine (38 ml) was added to the mixture, which was then heated and stirred (at 60°) for 1 hr. During this time the sulphur dissolved and the solution became red. The mixture was then cooled to 0° and the crystals which precipitated were filtered, washed with dilute hydrochloric acid and air dried (79.5 g, 71.3%). m.p. 117° (from aq. ethanol).

Found: C, 58.9%; H, 6.6%; N, 6.2%.

C_{11}H_{15}NO_2S requires: C, 58.7%; H, 6.7%; N, 6.2%.

All attempts to replace the amino group by a variety of other substituents (by diazotisation or deamination and subsequent substitution) were unsuccessful. Procedures similar to those for the diazotisation of the corresponding 4,5-dimethyl derivative were adopted but, again, none of the desired substitution products were isolable.
SYNTHESIS

Scheme:

(1) \[2\text{CH}_3\text{COCH}_2\text{Cl} + \text{NaSH} \rightarrow \text{CH} \]

\[
\begin{array}{c}
\text{Me} \\
\text{Me} \\
\text{OH} \\
\text{Me} \\
\text{OH} \\
\end{array}
\]

(2) \[+ \text{CNCH}_2\text{CO}_2\text{Et} \rightarrow \text{Et}_3\text{N} \rightarrow \text{Me} \\
\text{Me}
\]

Sodium hydrogen sulhide (5 M, 100 ml) was stirred with ethanol (100 ml) at 0-5°, and chloroacetone (40 ml) was added dropwise, with stirring, maintaining the temperature below 5°. After a few minutes the dimer of mercaptoacetone precipitated. Ethyl cyanoacetate (56.5 g, 0.5 mol) was added, followed by triethylamine (30 ml), and the resulting mixture was stirred at reflux for 15 mins. The solution was cooled to 60° and the precipitated sodium chloride filtered off. The filtrate was diluted with an equal volume of water and the precipitated solid was filtered off, washed repeatedly with water, and dried (56.8 g, 61.4%) m.p. 82° (from methanol).

Found: C, 51.6%; H, 5.9%; N, 7.4%.

Calculated for: C_{8}H_{11}NO_{2}S: C, 51.9%; H, 5.9%; N, 7.5%.

I.R. and \(^{13}\)C spectra were consistent with ethyl-2-amino-4-methylthiophene-3-carboxylate. This thiophene derivative cannot be synthesised by direct sulphur insertion with acetone and ethyl cyanoacetate since acetone undergoes bisthiolisation, giving a disulphide.
Acetylation

Ethyl-2-amino-4-methylthiophene-3-carboxylate (10 g) was suspended in acetic anhydride (25 ml) and warmed to 40°. The substrate dissolved and the temperature rose to 80°. After 10 mins, the solution was cooled and diluted with water (100 ml). The precipitated solid was filtered off, washed with water, and dried (11.1 g, 93.4%). m.p. 83° (from aq. methanol).

Found: C, 53.2%; H, 5.4%; N, 6.2%.
C₁₀H₁₃NO₃S requires: C, 52.9%; H, 5.7%; N, 6.2%.

I.R. and ¹³C spectra were in accordance with ethyl-2-acetamido-4-methylthiophene-3-carboxylate.

Ester Hydrolysis

Ethyl-2-acetamido-4-methylthiophene-3-carboxylate (2 g) was refluxed with sodium hydroxide (0.5 g) in an aqueous methanol solution (20 ml) for 30 min. Upon cooling, the solution was acidified to pH 2 with concentrated hydrochloric acid. The precipitated solid was filtered off, washed with water, and dried (1.2 g, 60.5%). m.p. 219° (from aq. methanol).
Found: C, 48.2%; H, 4.3%; N, 6.9%.

C₈H₉NO₃S requires: C, 48.2%; H, 4.5%; N, 7.0%.

I.R. and ¹³C spectra were in accordance with 2-acetamido-4-methylthiophene-3-carboxylic acid.

**¹³C Spectrum in Sulphuric Acid**

A ¹³C spectrum of 2-acetamido-4-methylthiophene-3-carboxylic acid (400 mg) in sulphuric acid (98%, 2 ml) revealed a complex series of changes analogous to those obtained when 2-acetamidothiophene-3-carboxylic acid was dissolved in sulphuric acid. After 24 hrs, the peaks at 194.0 and 21.1 ppm (from T.M.S.) were again present together with six other well-defined peaks. However, on drown-out, none of the starting material was recoverable and no products could be isolated. This behaviour was again similar to that of 2-acetamidothiophene-3-carboxylic acid.

A ¹³C spectrum of the ethyl ester of this acid showed no initial changes, but rather a slower change producing the free acetyl peaks at 194.0 and 21.1 ppm and no recoverable products.

**Nitration**

2-Acetamido-4-methylthiophene-3-carboxylic acid (2 g) was dissolved in sulphuric acid (98%, 8 ml). The solution was cooled to 0⁰ and a solution of nitric acid (1.5 g) in sulphuric acid (98%, 10 ml) added dropwise, with stirring < 0⁰. The reaction mixture was stirred at 0⁰ for 30 min and then drowned into ice-water. The yellow solid thus precipitated was filtered off, washed with water, and dried (1.1 g, 44.0%). m.p. 183⁰ (from aq. methanol).

Found: C, 34.2%; H, 3.2%; N, 17.1%.

C₇H₇N₃O₅S requires: C, 34.3%; H, 2.9%; N, 17.1%.
I.R. and $^{13}$C spectroscopy confirmed the product as being 2-acetamido-4-methyl-3,5-dinitrothiophene.

$^{13}$C Spectrum in Sulphuric Acid

A $^{13}$C spectrum of 2-acetamido-4-methyl-3,5-dinitrothiophene (400 mg) in sulphuric acid (98%, 2 ml) revealed a hydrolysis reaction, complete in 3-4 hrs. After 12 hrs only a complex series of low intensity peaks remained, together with the free acetyl peaks at 194.0 and 21.1 ppm (from T.M.S.). This hydrolysis to an unstable amine would partly account for the poor yield of product in the nitration of 2-acetamido-4-methylthiophene-3-carboxylic acid.
(18) 2-HYDROXY-4-METHYLTHIOPHENE-3-CARBOXYLIC ACID

(A) SYNTHESIS (attempted)

Proposed Scheme:

\[
\begin{align*}
\text{Me} & \quad \text{CO}_2\text{Et} \\
\text{S} & \quad \text{NH}_2
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{CN} \\
\text{S} & \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{CN} \\
\text{S} & \quad \text{CO}_2\text{H}
\end{align*}
\]

2-Hydroxy-3-cyano-4-methylthiophene

Sodium (3.5 g) was dissolved in dry ethanol (100 ml) and ethyl-2-amino-4-methylthiophene-3-carboxylate (18.5 g, 0.1 mol) was added to this solution. The mixture was refluxed under nitrogen for 4 hr. cooled and ethanol (75 ml) was distilled off. The residue was drowned into water (100 ml) and a little ether (10 ml) was added. The ether layer was separated and discarded. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with ether. Evaporation of the ether extracts left a black, sticky solid which upon recrystallisation became a brown, glassy solid (7.4 g, 57.4%) m.p. 47-49° (lit. 169 48-54°).

Found: C, 51.4%; H, 3.8%; N, 10.3%.

C₆H₅NOS requires: C, 51.8%; H, 3.6%; N, 10.1%.
I.R. and 'H N.M.R. spectra were consistent with 2-hydroxy-3-cyano-4-methylthiophene. ('H N.M.R. (CDCl₃) δ 5.8 (2 H), δ 7.5 (3 H)).

A sharp carbonyl peak in the infra-red spectrum, and ¹³C and 'H N.M.R. spectra indicated that the hydroxy cyano thiophene exists predominantly in the keto form:

\[ \text{Me} \quad \text{S} \quad \text{OH} \quad \text{CN} \quad \text{Me} \quad \text{S} \quad \text{CN} \quad \text{O} \]

**Methylation**

Dimethylsulphate (3.2 g) was added to a stirred solution of 2-hydroxy-3-cyano-4-methylthiophene (3.5 g) and sodium hydroxide (1 g) in water (50 ml) at 0°C. The reaction mixture was warmed under nitrogen and left to stand at room temperature overnight. The solution was then extracted with ether, the ethereal extracts washed twice with 10% sodium hydroxide and water, and the solvent then evaporated. The residue consisted of a dark oily solid which solidified on standing at room temperature. I.R. spectroscopy indicated absence of the carbonyl group (keto form of hydroxy compound) but retention of cyano group (2.3 g, 60.5%) m.p. 45-48°C.

Found: C, 55.2%; H, 4.8%; N, 9.1%.

C₇H₇NOS requires: C, 54.9%; H, 4.6%; N, 9.2%.

**Conversion of -CN to -CO₂H**

All attempts to convert 2-methoxy-3-cyano-4-methylthiophene to the corresponding 3-carboxylic acid with concentrated sulphuric acid were unsuccessful. Conversion of -CN to -CONH₂ was possible, but only in poor yield.

2-Methoxy-3-cyano-4-methylthiophene (1 g) in concentrated hydrochloric
acid (10 ml) was refluxed for 4 hr. under nitrogen. The solution was extracted with ethyl acetate and the solvent evaporated to leave a black solid. Infra-red spectroscopy indicated the reappearance of the hydroxyl group, together with a low intensity carbonyl peak. However, t.l.c. indicated an impure, complex product.

Further variation of the reaction conditions did not improve the conversion of -CN into -CO₂H. Refluxing with perchloric acid led to loss of starting material, whereas refluxing with dilute sulphuric acid led to partial loss of starting material. In neither case could any methoxy acid be isolated as product.
SYNTHESIS (attempted)

Proposed scheme:

\[
\text{OH} \quad - \quad \text{S} \quad - \quad \text{OH} + \quad \begin{array}{c}
\text{CO}_2\text{Et} \\
\text{CH}_2 \\
\text{CO}_2\text{Et}
\end{array} \quad \text{→} \quad \text{EtOH}
\]

This attempted synthesis involved manipulating the synthesis used earlier for preparation of 2-hydroxy-3-cyano-4-methylthiophene.

Mercaptoacetaldehyde dimer (7.6 g, 0.05 mol) was added to a solution of sodium (5 g) in dry ethanol (100 ml). Diethyl malonate (16 g, 0.1 mol) was added dropwise, with stirring, and the solution refluxed for 3 hr. Ethanol (50 ml) was then distilled off and the remaining solution drowned into water (150 ml), and acidified with concentrated hydrochloric acid. A sticky black tar separated with a very strong, unpleasant smell. This did not solidify after standing at room temperature for a week. No identifiable thiophene derivatives could be detected; the black tarry product appeared to be polymeric.

Further attempts to prepare 2-hydroxy-3-cyano thiophene derivatives from simple starting materials were equally unsuccessful. For example, treatment of acetyl acetone and ethyl cyanoacetate with sodium ethoxide and sulphur led to recovery of sulphur but no thiophene products (possibly due to formation of a pyridone derivative). When the same reagents were mixed in presence of triethylamine as base, rather than ethoxide, the
product was that of conventional sulphur insertion, ethyl-2-amino-4-methyl-5-acythiophene-3-carboxylate (18%) m.p. 164° (from ethanol). Hydroxythiophenes are, in general, rather unstable and are known to decompose in air to unstable tars."
(20) 2-METHYL-3-NITROTHIOPHENE-5-CARBOXYLIC ACID

(A) SYNTHESIS

Scheme:

[a] 2-Methyl-5-acetylthiophene

The method employed was that of Hartough and Conley. A mixture of acetic anhydride (10.2 g, 0.1 mol) and 2-methylthiophene (9.8 g, 0.1 mol) was stirred at 60°. Orthophosphoric acid (1 g, 85%) was added dropwise, with stirring at 40-60°. The mixture was then warmed to 100° for 3 hrs, and upon cooling was washed with water and 10% sodium carbonate solution. Distillation gave 2-methyl-5-acetylthiophene (84.5° at 2 mm). (12.9 g, 91.4%).

[b] 2-Methylthiophene-5-carboxylic acid

2-Methyl-5-acetylthiophene (7.0 g, 0.05 mol) was added dropwise, with stirring, to a solution of sodium hypochlorite (0.3 mol) at 60°. The mixture was heated at 80° for 2 hrs, cooled, filtered, and then acidified with concentrated hydrochloric acid. The white precipitate was filtered, washed with water and dried (5.6 g, 78.8%) m.p. 137° from petrol 60/80°. (lit. 269 137-138°).
Found: C, 50.5%; H, 4.3%.

Calculated for: C\textsubscript{6}H\textsubscript{5}O\textsubscript{2}S: C, 50.7%; H, 4.2%.

(c) 2-Methyl-3-nitrothiophene-5-carboxylic acid

Rinkes\textsuperscript{31} obtained the 3-nitro compound in poor yield. A better method is that of Campaigne\textsuperscript{33}.

2-Methylthiophene-5-carboxylic acid (6 g, 0.05 mol) was dissolved in sulphuric acid (98%, 12 ml) at 0\degree. A solution of nitric acid (d 1.42, 0.38 mol) in sulphuric acid (98%, 20 ml) was added dropwise, with stirring ensuring that the temperature did not rise above -10\degree. The reaction mixture was drowned into ice-water and steam distilled. Upon cooling, the residue yielded 2-methyl-3-nitrothiophene-5-carboxylic acid (4.3 g, 53.8%). m.p. 180\degree (from aq. ethanol) (lit.\textsuperscript{33} 179-180.5\degree).

Found: C, 38.5%; H, 2.4%; N, 7.4%.

Calculated for: C\textsubscript{6}H\textsubscript{5}NO\textsubscript{4}S: C, 38.5%; H, 2.7%; N, 7.5%.

I.R. and \textsuperscript{13}C spectra confirmed the product as the 3-nitro isomer.
(B) KINETICS

NITRATION

For reaction:

$$\text{CO}_2\text{H} - \text{NO}_2$$

For reaction:

$$\text{HNO}_3$$

$$\text{H}_2\text{SO}_4$$

$$\text{NO}_2$$

$$\text{CO}_2$$

$$\text{S} - \text{CH}_3$$

$$\text{S} - \text{CH}_3$$

Plots of $\log(A_\infty - A_t)$ against time were linear, giving good pseudo
first-order kinetic plots during several half-lives when the nitric acid
concentration was at least ten times that of the substrate.

$A_\infty$ = the U.V. absorbance at a fixed wavelength at $t = \infty$, i.e. the
maximum absorbance (for nitration)

$A_t$ = absorbance at time $t$.

In order to calculate the second-order rate constants, values of the
observed first-order rate constants are divided by the nitric acid concentration

For all nitration runs:

(Thiophene Derivative) $= 4.1 \times 10^{-4}$ M

Wavelength $= 340$ nm
TABLE 19: Rate of nitration of 2-methyl-3-nitrothiophene-5-carboxylic acid in nitric acid/sulphuric acid solutions.

<table>
<thead>
<tr>
<th>% H₂SO₄</th>
<th>HNO₃ (sec⁻¹)</th>
<th>k₁ obs</th>
<th>k₂ obs</th>
<th>Mean k₂ obs</th>
</tr>
</thead>
<tbody>
<tr>
<td>80.9</td>
<td>0.88x10⁻²</td>
<td>4.2x10⁻⁷</td>
<td>4.8x10⁻⁵</td>
<td>4.8x10⁻⁵</td>
</tr>
<tr>
<td></td>
<td>1.75x10⁻²</td>
<td>8.4x10⁻⁷</td>
<td>4.8x10⁻⁵</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.50x10⁻²</td>
<td>16.7x10⁻⁷</td>
<td>4.8x10⁻⁵</td>
<td></td>
</tr>
<tr>
<td>82.4</td>
<td>0.88x10⁻²</td>
<td>1.7x10⁻⁶</td>
<td>1.9x10⁻⁴</td>
<td>1.9x10⁻⁴</td>
</tr>
<tr>
<td></td>
<td>1.75x10⁻²</td>
<td>3.3x10⁻⁶</td>
<td>1.9x10⁻⁴</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.50x10⁻²</td>
<td>6.8x10⁻⁶</td>
<td>1.9x10⁻⁴</td>
<td></td>
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Product Analysis

2-Methyl-3-nitrothiophene-5-carboxylic acid (1.9 g, 0.01 mol) was dissolved in sulphuric acid (98%, 10 ml) and the solution cooled to 0°.

A solution of nitric acid (d 1.42, 0.95 g) in sulphuric acid (98%, 5 ml) was added dropwise, with stirring, < 5°. The mixture was stirred for 30 min after completion of the addition and tested for completion of the nitration by t.l.c. The reaction mixture was drowned into ice-water and the precipitated solid filtered off, washed with water, and dried (1.6 g, 84.2%). m.p. 99° (from aq. methanol) (lit. 33 98-99°).
Found: C, 32.2%; H, 2.0%; N, 14.7%.

Calculated for: C₅H₄N₂O₄S: C, 31.9%; H, 2.1%; N, 14.8%.

I.R. and ¹³C spectroscopy confirmed the product as 2-methyl-3,5-dinitrothiophene.

Campagne³³ reported nitrodecarboxylation of 2-methyl-3-nitrothiophene-5-carboxylic acid in nitric-sulphuric acid mixtures above -4⁰ but a quantitative recovery of starting material was obtained at -5⁰.
2-METHYL-3-NITROTHIOPHENE

(A) SYNTHESIS

Scheme:

\[ \text{NO}_2 \quad \text{Me} \quad \text{S} \quad \text{CO}_2 \text{H} \quad \text{Cu} \quad \text{quinoline} \quad \text{NO}_2 \quad \text{Me} \quad \text{S} \]

The procedure adopted here was a modification upon that of Snyder\textsuperscript{172}. 2-Methyl-3-nitrothiophene-5-carboxylic acid (5.8 g) was mixed with dry quinoline (22.5 g) and copper (3.8 g). The mixture was heated slowly on an oil-bath and then vacuum distilled at 10 mm Hg. The oil temperature was raised to 150°C. The distillate was drowned into ice-water and acidified with concentrated hydrochloric acid. The remaining organic layer was taken up in ether and the acid water phase extracted with ether. The combined ether extracts were washed with sodium carbonate solution and water. Evaporation of the solvent gave a white solid as residue (2.7 g, 62.8%) m.p. 44°C (from petrol 40/60°C) (lit.\textsuperscript{172} 44-45°C).

Found: C, 41.8%; H, 3.6%; N, 9.8%.

Calculated for: C\textsubscript{5}H\textsubscript{5}NO\textsubscript{2}S: C, 42.0%; H, 3.5%; N, 9.8%.
NITRATION

Plots of \( \log(A_\infty - A_t) \) against time were linear and pseudo first-order kinetics were applicable throughout. For all nitration runs:

\[ \text{(Thiophene Derivative)} = 3.8 \times 10^{-4} \text{ M} \]

Wavelength = 340 nm

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<tr>
<th>Mean % ( \text{H}_2\text{SO}_4 )</th>
<th>Molarity ( \text{HNO}_3 ) (mol/l)</th>
<th>( k_1 \text{obs} ) (sec(^{-1}))</th>
<th>( k_2 \text{obs} ) (1 mol(^{-1}) sec(^{-1}))</th>
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Mean \( k_2 \text{obs} \) (10^-3 mol\(^{-1}\) sec\(^{-1}\))

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<td>1.4x10^-1</td>
</tr>
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<td>83.5</td>
<td>1.4x10^-1</td>
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</tbody>
</table>

TABLE 20: Rate of nitration of 2-methyl-3-nitrothiophene in nitric acid/sulphuric acid solutions.

Product Analysis

2-Methyl-3-nitrothiophene (1.4 g, 0.01 mol) was dissolved in sulphuric
acid (98%, 10 ml), and the solution cooled to 0°. A solution of nitric acid (d 1.42, 0.90 g) in sulphuric acid (98%, 5 ml) was added dropwise, with stirring, < 5°. The mixture was stirred for 10 min and then drowned into ice-water. The precipitated solid was filtered, washed with water, and dried. (1.75 g, 93.1%) m.p. 100° (from aq. methanol).

The product was identical to the 2-methyl-3,5-dinitrothiophene, prepared earlier by nitrodecarboxylation of 2-methyl-3-nitrothiophene-5-carboxylic acid.

Found: C, 32.0%; H, 2.1%; N, 14.9%.

Calculated for: C₅H₄N₂O₄S: C, 31.8%; H, 2.1%; N, 14.9%.
(22) 2-ETHYL-3-NITROTHIOPHENE-5-CARBOXYLIC ACID

(A) SYNTHESIS

Scheme:

```
\[ \begin{array}{c}
\text{S} \\
\text{CH}_2\text{CH}_3 \\
\text{CH}_3\text{CO} \\
\text{S} \\
\text{CH}_2\text{CH}_3 \\
\end{array} \] \\
\text{Ac}_2\text{O} \\
\begin{array}{c}
\text{S} \\
\text{CH}_2\text{CH}_3 \\
\text{CO}_2\text{H} \\
\text{S} \\
\text{CH}_2\text{CH}_3 \\
\end{array} \\
\text{NaOCl} \\
\begin{array}{c}
\text{S} \\
\text{CH}_2\text{CH}_3 \\
\text{NO}_2 \\
\text{S} \\
\text{CH}_2\text{CH}_3 \\
\end{array} \\
\text{HNO}_3 \\
\begin{array}{c}
\text{S} \\
\text{CH}_2\text{CH}_3 \\
\text{CO}_2\text{H} \\
\text{S} \\
\text{CH}_2\text{CH}_3 \\
\end{array} \\
\text{H}_2\text{SO}_4
```

(a) 2-Ethyl-5-acetyltiophene

The procedure adopted was identical to that used earlier for preparation of the corresponding 2-methyl derivative.

A mixture of acetic anhydride (10.2 g, 0.1 mol) and 2-ethylthiophene (11.2 g, 0.1 mol) was stirred at 65°C. Orthophosphoric acid (85%, 1 g) was added dropwise, with stirring, at 55-65°C. The mixture was then warmed to 100°C for 3 hrs, and upon cooling was washed with water and 10% sodium carbonate solution. Distillation gave 2-ethyl-acetyltiophene (94-95°C at 2 mm). (13.1 g, 92.3%).

(b) 2-Ethylthiophene-5-carboxylic acid

2-Ethyl-5-acetyltiophene (7.7 g, 0.05 mol) was added dropwise, with stirring, to a solution of sodium hypochlorite (0.3 mol) at 60°C. The mixture was heated at 80°C for 2 hrs, cooled, filtered and then acidified
with concentrated hydrochloric acid. The white precipitate was filtered, washed with water and dried. (6.5 g, 83.3%). m.p. 141° (from petrol 60/80°).

Found:  C, 53.8%;  H, 5.2%.

C₇H₅O₂S requires:  C, 53.8%;  H, 5.1%.

(c) 2-Ethyl-3-nitrothiophene-5-carboxylic acid

2-Ethylthiophene-5-carboxylic acid (7-8 g, 0.05 mol) was dissolved in sulphuric acid (98%, 15 ml) at 0°. A solution of nitric acid (d 1.42, 0.38 mol) in sulphuric acid (98%, 20 ml) was added dropwise, with stirring, ensuring that the temperature did not rise above -10°. The solution was drowned into ice-water and steam distilled. Upon cooling, the residue yielded 2-ethyl-3-nitrothiophene-5-carboxylic acid (6.9 g, 68.7%) m.p. 186° (from aq. methanol).

Found:  C, 41.6%;  H, 3.2%;  N, 7.3%.

C₇H₇NO₄S requires:  C, 41.8%;  H, 3.5%;  N, 7.0%.

I.R. and ¹³C spectra confirmed the product as the 3-nitro isomer.
(B) KINETICS

NITRATION

For reaction:

\[
\begin{align*}
\text{CO}_2\text{H} & \quad \text{NO}_2 \\
\text{S} & \quad \text{CH}_2\text{CH}_3
\end{align*}
\]

\[
\text{HNO}_3 \rightarrow \quad \text{H}_2\text{SO}_4
\]

Good, linear pseudo first-order kinetic plots were obtained, in a similar manner to the corresponding 2-methyl derivative.

For all nitration runs:

\[(\text{Thiophene Derivative}) = 5.3 \times 10^{-4} \text{ M}\]

Wavelength = 340 nm

<table>
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<tr>
<th>Mean</th>
<th>Molarity</th>
<th>(k_1) obs</th>
<th>(k_2) obs</th>
<th>Mean</th>
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TABLE 21: Rate of nitration of 2-ethyl-3-nitrothiophene-5-carboxylic acid in nitric acid/sulphuric acid solutions.
Product Analysis

2-Ethyl-3-nitrothiophene-5-carboxylic acid (2.0 g, 0.01 mol) was dissolved in sulphuric acid (98%, 10 ml) and the solution cooled to 0°C. A solution of nitric acid (d 1.42, 0.95 g) in sulphuric acid (98%, 5 ml) was added dropwise, with stirring, < 5°C. The mixture was stirred for 30 min and then drowned into ice-water. The precipitated solid was filtered, washed with water, and dried (1.7 g, 85.0%). m.p. 101°C (from aq. methanol).

Found: C, 35.5%; H, 2.8%; N, 14.0%.

C\textsubscript{5}H\textsubscript{5}N\textsubscript{2}0\textsubscript{4}S requires: C, 35.6%; H, 3.0%; N, 13.9%.

I.R. and \textsuperscript{13}C spectroscopy confirmed the product as being 2-ethyl-3,5-dinitrothiophene.
2-Ethyl-3-nitrothiophene-5-carboxylic acid (6.0 g, 0.03 mol) was mixed with dry quinoline (22.5 g) and copper (3.8 g). The mixture was heated slowly on an oil bath and then vacuum distilled at 10 mm Hg. The oil temperature was raised to 150°. The distillate was drowned into ice-water and acidified with concentrated hydrochloric acid. The remaining organic layer was taken up in ether and the acid water phase extracted with ether. The combined ether extracts were washed with sodium carbonate solution and water. Evaporation of the solvent gave a white solid as residue (2.9 g, 61.7%) m.p. 49° (from petrol 40/60°).

Found: C, 45.9%; H, 4.5%; N, 9.1%.

C₆H₇NO₂S requires: C, 45.9%; H, 4.5%; N, 8.9%.
(B) KINETICS

NITRATION

For reaction:

\[
\text{NO}_2 + \text{CH}_3\text{CH}_2\text{S} \xrightarrow{\text{HNO}_3, \text{H}_2\text{SO}_4} \text{NO}_2\text{CH}_3\text{CH}_2\text{S} \quad \text{(Thiophene Derivative)}
\]

Good, linear pseudo first-order kinetic plots were obtained throughout.

For all nitration runs:

\[
(\text{Thiophene Derivative}) = 4.2 \times 10^{-4} \text{ M}
\]

Wavelength = 340 nm

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TABLE 22: Rate of nitration of 2-ethyl-3-nitrothiophene in nitric/sulphuric acid solutions.
Product Analysis

2-Ethyl-3-nitrothiophene (1.6 g, 0.01 mol) was dissolved in sulphuric acid (98%, 10 ml) and the solution cooled to 0\(^{\circ}\). A solution of nitric acid (d 1.42, 0.90 g) in sulphuric acid (98%, 5 ml) was added dropwise, with stirring, < 5\(^{\circ}\). The mixture was stirred for 10 min and then drowned into ice-water. The white precipitate was filtered, washed with water, and dried (1.8 g, 89.1%) m.p. 102\(^{\circ}\) (from aq. methanol).

The product was identical to the 2-ethyl-3,5-dinitrothiophene, prepared earlier by nitrodecarboxylation of 2-ethyl-3-nitrothiophene-5-carboxylic acid.

Found: C, 35.8%; H, 3.1%; N, 13.9%.

\(\text{C}_{6}\text{H}_6\text{N}_2\text{O}_4\text{S}\) requires: C, 35.6%; H, 3.0%; N, 13.9%.
(24) 2-CHLORO-3-NITROTHIOPHENE-5-CARBOXYLIC ACID

(A) SYNTHESIS

Scheme:

\[
\begin{align*}
\text{NaOCl} & \quad \text{HCl} \\
\text{I} & \quad \text{I} \\
\text{NO}_2 & \quad \text{HNO}_3/\text{H}_2\text{SO}_4
\end{align*}
\]

(a) 2-Chlorothiophene-5-carboxylic acid

The procedure was a variation upon that of Bunnett\textsuperscript{32}.

Thiophene-2-carboxylic acid (6 g, 0.046 mol) was added to a solution of sodium hypochlorite (0.084 mol) and excess sodium hydroxide (total volume of 800 ml). Concentrated hydrochloric acid (6 M, 50 ml) was added to this solution dropwise, with stirring, at 50\(^\circ\). The temperature rose slightly, the pH dropped to 1 and a white precipitate appeared. Sodium chloride (210 g) was added with vigorous stirring and the white solid obtained by filtration of the chilled solution was 2-chlorothiophene-5-carboxylic acid (2.6 g, 34.9%) m.p. 149\(^\circ\) (from methanol) (lit.\textsuperscript{32} 149-150\(^\circ\)).

Found: C, 36.9%; H, 1.7%.

Calculated for: \(\text{C}_5\text{H}_3\text{ClO}_2\text{S}\): C, 36.9%; H, 1.8%. 

(b) 2-Chloro-3-nitrothiophene-5-carboxylic acid

2-Chlorothiophene-5-carboxylic acid (1 g) was dissolved in concentrated sulphuric acid (98%, 10 ml). The solution was cooled to -20° and a solution of nitric acid (70%, 1.5 ml) in sulphuric acid (98%, 10 ml) added dropwise, with stirring, < -20°. The reaction mixture was then drowned into ice-water, basified with sodium carbonate, filtered to remove insoluble dinitro product (m.p. 121°, 22%) and the filtrate was acidified with concentrated hydrochloric acid. This precipitated 2-chloro-3-nitrothiophene-5-carboxylic acid (0.85 g, 62.5%) m.p. 158° (from aq. methanol) (lit. 1 156.5-157.5°).

Found: C, 28.8%; H, 1.3%; N, 6.7%.

C₅H₂CINO₄S requires: C, 28.9%; H, 1.0%; N, 6.7%.

I.R. and ¹³C spectroscopy confirmed the product as the 3-nitro isomer.
[B] KINETICS

NITRATION

For reaction:

\[
\text{\begin{array}{c}
\text{CO}_2\text{H} & \text{S} & \text{Cl} \\
\text{NO}_2
\end{array}} \xrightarrow{\text{HNO}_3} \text{\begin{array}{c}
\text{NO}_2 & \text{S} & \text{Cl} \\
\text{CO}_2
\end{array}}
\]

Good linear, pseudo first-order kinetic plots were obtained, in a similar manner to the corresponding 2-alkyl derivatives.

For all nitration runs:

(Thiophene Derivative) = \(6.0 \times 10^{-4}\) M

Wavelength = 350 nm

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<th>Molarity (\text{HNO}_3)</th>
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<th>(k_2) (\text{obs} (1\ \text{mol}^{-1}\ \text{sec}^{-1}))</th>
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TABLE 23: Rate of nitration of 2-chloro-3-nitrothiophene-5-carboxylic acid in nitric acid/sulphuric acid solutions.

Product Analysis

2-Chloro-3-nitrothiophene-5-carboxylic acid (2.1 g, 0.01 mol) was dissolved in sulphuric acid (98%, 10 ml) and the solution cooled to 0°.
A solution of nitric acid (d 1.42, 0.95 g) in sulphuric acid (98%, 5 ml) was added dropwise, with stirring, < 5°. The mixture was stirred for 2 hr and then drowned into ice-water. The precipitated solid was filtered, washed with water and dried (1.8 g, 85.7%). m.p. 121° (from aq. methanol) (lit. 21 121-122°).

Found:  C, 22.7%; H, 0.5%; N, 13.4%.
Calculated for:  C₄HClN₂O₄S:  C, 23.0; H, 0.5%; N, 13.4%.

I.R. and ¹³C spectroscopy confirmed the product as 2-chloro-3,5-dinitrothiophene.
2-Chloro-3-nitrothiophene-5-carboxylic acid (2.1 g, 0.01 mol) was refluxed with mercuric oxide (10 g) and glacial acetic acid (100 ml) for 12 hrs. The reaction solution was diluted with 2 volumes of ice-water to precipitate a colourless mercury derivative. This solid was added to dilute hydrochloric acid (100 ml) and the solution steam distilled. The solid product was taken up in ether, the solvent evaporated and the residue recrystallised from hexane (0.76 g, 47.5%) m.p. 48° (from hexane) (lit. 21 49.5-50.5°).

Found: C, 29.2%; H, 1.4%; N, 8.7%.
Calculated for: C₄H₂ClNO₂S: C, 29.4%; H, 1.2%; N, 8.6%.

I.R. and ¹³C spectroscopy confirmed the product as 2-chloro-3-nitrothiophene.
(B) KINETICS
NITRATION

For reaction:

\[
\begin{array}{c}
\text{NO}_2 \\
\text{Cl} \\
\text{H}_2\text{SO}_4 \\
\text{S} \\
\text{NO}_2 \\
\text{Cl}
\end{array} \xrightarrow{\text{HNO}_3} \begin{array}{c}
\text{NO}_2 \\
\text{Cl} \\
\text{H}_2\text{SO}_4 \\
\text{S} \\
\text{NO}_2 \\
\text{Cl}
\end{array}
\]

Good linear pseudo first-order kinetic plots were obtained throughout.

For all nitration runs:

\[(\text{Thiophene Derivative}) = 2.8 \times 10^{-4} \text{ M}\]

Wavelength = 350 nm

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</tr>
</tbody>
</table>

TABLE 24: Rate of nitration of 2-chloro-3-nitrothiophene in nitric/
sulphuric acid solutions.

Product Analysis

2-Chloro-3-nitrothiophene (1.6 g, 0.01 mol) was dissolved in
sulphuric acid (98%, 10 ml) and the solution cooled to 0°C. A solution of
nitric acid (d 1.42, 0.90 g) in sulphuric acid (98%, 5 ml) was added dropwise, with stirring, < 50°. The mixture was stirred for 30 min and then drowned into ice-water. The white precipitate was filtered, washed with water, and dried (1.9 g, 90.5%) m.p. 122° (from eq. methanol) (lit.21 121-122°).

Found: C, 23.1%; H, 0.8%; N, 13.6%.
Calculated for: C₄HClN₂0₄S: C, 23.0%; H, 0.5%; N, 13.4%.

I.R. and ¹³C spectroscopy confirmed the product as 2-chloro-3,5-dinitrothiophene, identical to the product of nitration of 2-chloro-3-nitrothiophene-5-carboxylic acid.
(26) 2-BROMO-3-NITROTHIOPHENE-5-CARBOXYLIC ACID

(A) SYNTHESIS

Scheme:

\[
\begin{align*}
\text{HAc} & \quad \text{Br}_2 \\
\text{Thiophene-2-carboxylic acid} & \quad \text{Bromine} \\
\text{Br} & \quad \text{HNO}_3/\text{H}_2\text{SO}_4
\end{align*}
\]

(a) 2-Bromothiophene-5-carboxylic acid

The procedure adopted was a variation upon that of Steinkopf. To a solution of thiophene-2-carboxylic acid (5 g, 0.04 mol) in acetic acid (50%, 100 ml) at 0°C was added dropwise, with stirring, a solution of bromine (6.1 g, 0.04 mol) in acetic acid (50%, 50 ml) at 0°C. The mixture was stirred for 1 hr at 0°C, filtered, and the filtrate drowned into ice-water. The white precipitate was filtered, washed with water, and dried (3.8 g, 46%) m.p. 141°C (from water) (lit. 270 141-142°C).

Found: C, 28.8%; H, 1.2%.

Calculated for: C₅H₃BrO₂S: C, 29.0%; H, 1.45%.

(b) 2-Bromo-3-nitrothiophene-5-carboxylic acid

2-Bromothiophene-5-carboxylic acid (1 g) was dissolved in sulphuric acid (98%, 10 ml). The solution was cooled to -20°C and a solution of nitric acid (70%, 1.5 ml) in sulphuric acid (98%, 10 ml) added dropwise, with stirring, < -20°C. The reaction mixture was then drowned into ice-
water, sodium carbonate added to pH 11 and the solution filtered to remove insoluble dinitro product (m.p. 135°, 21%). The filtrate was acidified with concentrated hydrochloric acid and the 2-bromo-3-nitrothiophene-5-carboxylic acid filtered, washed with water, and dried (0.95 g, 79.2%) m.p. 172° (from water).

Found: C, 23.6%; H, 1.1%; N, 5.6%.

C₅H₂BrNO₄S requires: C, 23.8%; H, 0.8%; N, 5.5%.

I.R. and ¹³C spectroscopy confirmed the product as the 3-nitro isomer.
(B) KINETICS

NITRATION

For reaction:

\[
\begin{array}{c}
\text{CO}_2\text{H} \quad \text{Br} \\
\text{S} \\
\text{SO}_2\text{H}
\end{array}
\begin{array}{c}
\text{NO}_2 \\
\text{HNO}_3 \\
\text{H}_2\text{SO}_4
\end{array}
\begin{array}{c}
\text{CO}_2 \\
\text{Br} \\
\text{S}
\end{array}
\]

Good linear, pseudo first-order kinetic plots were obtained, in a similar manner to the corresponding 2-chloro derivative.

For all nitration runs:

(Thiophene Derivative) = 5.4 x 10^-4 M

Wavelength = 350 nm

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TABLE 25: Rate of nitration of 2-bromo-3-nitrothiophene-5-carboxylic acid in nitric acid/sulphuric acid solutions.
Product Analysis

2-Bromo-3-nitrothiophene-5-carboxylic acid (2.5 g, 0.01 mol) was dissolved in sulphuric acid (98%, 10 ml) and the solution cooled to 0°. A solution of nitric acid (d 1.42, 0.95 g) in sulphuric acid (98%, 5 ml) was added dropwise, with stirring, < 5°. The mixture was stirred for 2 hr and then drowned into ice-water. The precipitated solid was filtered, washed with water, and dried (2.2 g, 88.0%) m.p. 136° (from aq. methanol) (lit.21 136-137°).

Found: C, 18.8%; H, 0.8%; N, 11.3%.
Calculated for: C₄H₇BrN₂O₄S: C, 19.0%; H, 0.4%; N, 11.1%.

I.R. and ¹³C spectra were in accordance with 2-bromo-3,5-dinitrothiophene.
2-Bromo-3-nitrothiophene-5-carboxylic acid (2.5 g, 0.01 mol) was refluxed with mercuric oxide (10 g) and glacial acetic acid (100 ml) for 12 hrs. The reaction solution was diluted with 2 volumes of ice-water to precipitate a colourless mercury derivative. This solid was added to dilute hydrochloric acid (100 ml) and the solution steam distilled. The solid product was taken up in ether, the solvent evaporated, and the residue recrystallised from hexane (0.85 g, 40.5%) m.p. 79° (from hexane) (lit. 81-83°).

Found: C, 22.9%; H, 0.9%; N, 6.8%.

C₄H₂BrNO₂S requires: C, 23.1%; H, 1.0%; N, 6.7%.

I.R. and ¹³C spectroscopy confirmed the product as 2-bromo-3-nitrothiophene.
Good linear pseudo first-order kinetic plots were obtained throughout.

For all nitration runs:

\[(\text{Thiophene Derivative}) = 3.0 \times 10^{-4} \text{ M}\]
\[\text{Wavelength} = 350 \text{ nm}\]

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<th>$k_2$ obs (1 mol$^{-1}$sec$^{-1}$)</th>
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**TABLE 26:** Rate of nitration of 2-bromo-3-nitrothiophene in nitric/sulphuric acid solutions.
Product Analysis

2-Bromo-3-nitrothiophene (2.1 g, 0.01 mol) was dissolved in sulphuric acid (98%, 10 ml) and the solution cooled to 0°C. A solution of nitric acid (d 1.42, 0.90 g) in sulphuric acid (98%, 5 ml) was added dropwise, with stirring, < 5°C. The mixture was stirred for 30 min and then drowned into ice-water. The white precipitate was filtered, washed with water, and dried (2.3 g, 90.9%). m.p. 135°C (from aq. methanol) (lit. 21 136-137°C).

Found: C 19.0%; H 0.6%; N 11.0%.

Calculated for: C₄HBrN₂O₄S: C 19.0%; H 0.4%; N 11.1%.

I.R. and ¹³C spectroscopy confirmed the product as 2-bromo-3,5-dinitrothiophene, previously prepared by nitrodecarboxylation of 2-bromo-3-nitrothiophene-5-carboxylic acid.
(28) 2-METHOXY-3-NITROTHIOPHENE-5-CARBOXYLIC ACID

(A) SYNTHESIS

Scheme:

(a) Methyl-2-bromo-3-nitrothiophene-5-carboxylate

2-Bromo-3-nitrothiophene-5-carboxylic acid (10 g) was esterified by refluxing in methanol (25 ml) and concentrated sulphuric acid (1 ml) for 5 hrs. Drown-out into ice-water gave the methyl ester (9.8 g, 93.3%) m.p. 103° (from petrol 40/60).

Found: C, 27.0%; H, 1.7%; N, 5.3%.

C₆H₄BrNO₄S requires: C, 27.1%; H, 1.5%; N, 5.3%.

(b) Methyl-2-methoxy-3-nitrothiophene-5-carboxylate

Methyl-2-bromo-3-nitrothiophene-5-carboxylate (2 g, 0.01 mol) was dissolved in methanol (20 ml) and refluxed gently. Potassium hydroxide (0.48 g, 0.008 mol) in water (1 ml) was added, dropwise, with stirring. The bright red reaction solution was refluxed for 25 mins, cooled and diluted with water (25 ml). Acidification precipitated methyl-2-methoxy-3-nitrothiophene-5-carboxylate (1.3 g, 80.0%). m.p. 130° (from petrol 80/100).

Found: C, 38.7%; H, 2.9%; N, 6.4%.

C₇H₇NO₅S requires: C, 38.7%; H, 3.2%; N, 6.5%.
(c) 2-Methoxy-3-nitrothiophene-5-carboxylic acid

The methyl ester was hydrolysed to the corresponding acid by addition of an equimolar solution of sodium hydroxide to a solution of the ester in methanol at pH 8 - 9. The mixture was gently refluxed for 30 mins, drowned into ice-water and neutralized with hydrochloric acid. An ether extraction and subsequent evaporation of the dry ether extracts gave 2-methoxy-3-nitrothiophene-5-carboxylic acid (38%) m.p. 188° (from eq. methanol).

Found: C, 35.4%; H, 2.4%; N, 6.9%.

C$_8$H$_5$NO$_5$S requires: C, 35.5%; H, 2.5%; N, 6.9%.

When the nucleophilic substitution of methoxide for bromide$^{21}$ was attempted directly with the carboxylic acid the potassium salt of the acid precipitated out from the methanolic solution upon addition of potassium hydroxide. No further reaction of the salt was detectable.
(B) KINETICS

NITRATION

For reaction:

\[ \text{CO}_2\text{H} \quad \text{NO}_2 \quad \overset{\text{HNO}_3}{\longrightarrow} \quad \text{NO}_2 \quad \text{OMe} \]

Good linear pseudo first-order kinetic plots were obtained throughout.

For all nitration runs:

\[ \text{(Thiophene Derivative)} = 4.1 \times 10^{-4} \text{ M} \]

Wavelength = 380 nm

<table>
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<th>Mean Molarity</th>
<th>( k_1 \text{ obs} ) (sec(^{-1}))</th>
<th>( k_2 \text{ obs} ) (1 mol(^{-1}) sec(^{-1}))</th>
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TABLE 27: Rate of nitration of 2-methoxy-3-nitrothiophene-5-carboxylic acid in nitric/sulphuric acid solutions.

Product Analysis

2-Methoxy-3-nitrothiophene-5-carboxylic acid (2.0 g, 0.01 mol) was
dissolved in sulphuric acid (98%, 10 ml) and the solution cooled to 0°. A solution of nitric acid (d 1.42, 0.95 g) in sulphuric acid (98%, 5 ml) was added dropwise, with stirring, < 5°. The mixture was stirred for 20 min and then drowned into ice-water. The precipitated solid was filtered, washed with water, and dried (1.8 g, 90.2%) m.p. 139° (from aq. methanol) (lit. 138-139°).

Found: C, 29.4%; H, 1.8%; N, 13.7%.

Calculated for: C₅H₄N₂O₅S: C, 29.4%; H, 2.0%; N, 13.7%.

I.R. and ¹³C spectra were in accordance with 2-methoxy-3,5-dinitrothiophene.
2-ACETAMIDO-3-NITROTHIOPHENE-5-CARBOXYLIC ACID

(A) SYNTHESIS (attempted)

Scheme:

\[ \text{MeOH/H}^+ \]

\[ \text{Sn/HCl} \]

\[ \text{Ac}_2\text{O} \]

\[ \text{OH}^-/\text{MeOH} \]

5-Nitrothiophene-2-carboxylic acid 274

A mixture of 4- and 5-nitro isomers is obtained irrespective of the nitrating medium 31,272.

A solution of fuming nitric acid (8.4 ml, 0.2 mol) in sulphuric acid (98%, 8.4 ml) was added dropwise, with stirring, to a solution of thiophene-2-carboxylic acid (12.8 g, 0.1 mol) in sulphuric acid (98%,
12 ml) at -10 to -15°. The reaction mixture was then drowned into ice-water and the yellow precipitate filtered and shaken with sodium bicarbonate. The residue, obtained by filtration was 2-nitrothiophene (6%) m.p. 45° (from petrol 40/60) (lit.31 45.5°).

The sodium bicarbonate solution was re-acidified to yield a mixture of 4- and 5-nitro acids. In order to separate the isomers use was made of the low solubility of the barium salt of the 4-nitro acid31. The mixture of acids was boiled with a barium carbonate solution, filtered, and the filtrate allowed to cool overnight. Crystals of barium-4-nitrothiophene-2-carboxylate separated. The remaining solution was re-acidified to yield, primarily, 5-nitrothiophene-2-carboxylic acid. The above procedure for separation of the 4-nitro salt was repeated with a minimal quantity of barium carbonate. The 4-nitrothiophene-2-carboxylic acid (5.8 g, 33.5%) was isolated by acidifying a boiling solution of the salt. The 5-nitro isomer was isolated by acidification of the filtrate containing its soluble barium salt (9.2 g, 53.2%). m.p. of 5-NO₂ derivative 157° (from water) (lit.31 158°).

Found: C, 35.0%; H, 1.9%; N, 8.2%.
Calculated for: C₅H₃NO₄S: C, 34.7%; H, 1.7%; N, 8.1%.
m.p. of 4-NO₂ derivative 152° (from water) (lit.31 154°).

'H N.M.R.

'H N.M.R. spectroscopy distinguishes between the 4- and 5-nitro isomers.
4-Nitrothiophene-2-carboxylic acid

5-Nitrothiophene-2-carboxylic acid
(b) **Methyl-5-nitrothiophene-2-carboxylate**

5-Nitrothiophene-2-carboxylic acid (3 g) was esterified by refluxing in methanol (15 ml) and sulphuric acid (98%, 0.2 ml) for 5 hrs. Drowning into ice-water precipitated methyl-5-nitrothiophene-2-carboxylate (2.6 g, 80.2%). m.p. 74° (from petrol 60/80) (lit.273 74-75°).

(c) **Methyl-5-acetamidothiophene-2-carboxylate**

Methyl-5-nitrothiophene-2-carboxylate (1.87 g, 0.01 mol) was added to stannous chloride (6.8 g, 0.03 mol) in concentrated hydrochloric acid (9.6 ml). The temperature rapidly rose to 85° and the red solution was cooled and stirred vigorously for 4 hr. A sodium hydroxide solution (10%) was added dropwise to pH 10 and the reaction mixture was then extracted with ether. Evaporation of the dry ether extracts gave a brown oil as residue. Upon treatment with acetic anhydride and subsequent drown-out into ice-water methyl-2-acetamidothiophene-5-carboxylate was obtained as a cream solid (1.0 g, 50.2%). m.p. 170° (from water) (lit.273 169°).

Found: C, 48.1%; H, 4.6%; N, 7.0%.
Calculated for: C₆H₅NO₃S: C, 48.2%; H, 4.5%; N, 7.0%.

(d) **Methyl-2-acetamido-3-nitrothiophene-5-carboxylate**

Methyl-2-acetamidothiophene-5-carboxylate (1 g) was dissolved in concentrated sulphuric acid (98%, 5 ml). Fuming nitric acid (2 ml) in concentrated sulphuric acid (98%, 5 ml) was added dropwise, with stirring, < 0°. The reaction mixture was drowned into ice-water and the precipitated nitro ester filtered, washed with water and dried (0.72 g, 58.5%). m.p. 202° (from aq. methanol) (lit.273 200-1°).

Found: C, 39.5%; H, 3.0%; N, 11.6%.
Calculated for: C₆H₆N₂O₅S: C, 39.3%; H, 3.3%; N, 11.5%.
Attempted Ester Hydrolysis

All attempts to hydrolyse methyl 2-acetamido-3-nitrothiophene-5-carboxylate to the corresponding carboxylic acid proved to be unsuccessful. Efforts to hydrolyse the ester in weakly basic conditions by refluxing in aq. methanol and adding an equimolar solution of sodium hydroxide dropwise (pH 9 - 10) resulted in preferential hydrolysis of the amide to amine. This amine was subsequently unstable in presence of excess base. Modification of the ester function by preparation of the ethyl and t-butyl esters did not enable preferential ester hydrolysis to occur.

Attempts to hydrolyse the ester group at the methyl-2-acetamidothiophene-5-carboxylate stage were equally unsuccessful. Despite careful control of pH, no amido acid was recoverable from the basic solution.

Alternative Route

\[
\begin{align*}
\text{NO}_2 & \quad \text{Br} & \quad \text{S} & \quad \text{CO}_2\text{H} \\
\text{NO}_2 & \quad \text{Br} & \quad \text{S} & \quad \text{CO}_2\text{Me} \\
\text{NHAc} & \quad \text{S} & \quad \text{CO}_2\text{Me} \\
\text{NO}_2 & \quad \text{Br} & \quad \text{S} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

2-Bromo-3-nitrothiophene-5-carboxylic acid (10 g) was esterified by refluxing in methanol (25 ml) and sulphuric acid (98%, 1 ml) for 5 hrs. Drown-out into ice-water gave the methyl ester (9.8 g, 93.3%).

Methyl-2-amino-3-nitrothiophene-5-carboxylate

Methyl-2-bromo-3-nitrothiophene-5-carboxylate (2 g) in methanol (20 ml) was treated with concentrated ammonium hydroxide (7 ml) and the mixture
heated at 60° for 3 hrs. Cooling to 0° gave dark needles (1.1 g, 68.1%).
m.p. 214° (from aq. methanol). I.R. spectrum indicated the presence of an
amino group.

Found: C, 35.8%; H, 2.9%; N, 13.6%.
C₆H₄N₂O₄S requires: C, 35.6%; H, 3.0%; N, 13.9%.

Acetylation

Treatment of methyl-2-amino-3-nitrothiophene-5-carboxylate with acetic
anhydride at 80° for 2 hrs gave only recovery of starting material. The
method employed was a variation upon the procedure for acetylating amino acids²⁶²

The amino ester (1 g) was refluxed with acetyl chloride (1.5 ml) in
ethyl acetate (20 ml) for 24 hrs. The solution was cooled and the solvent
and excess acetyl chloride evaporated to yield the acetylated product
(0.68 g, 56.2%). m.p. 201° (from aq. methanol) (lit.²⁷³ 200-1°).

Found: C, 39.1%; H, 3.3%; N, 11.3%.
Calculated for: C₆H₆N₂O₄S: C, 39.3%; H, 3.3%; N, 11.5%.

Attempted Hydrolysis

Further attempts to hydrolyse the ester grouping of methyl-2-
acetamido-3-nitrothiophene-5-carboxylate were equally unsuccessful.
Methyl-2-amino-3-nitrothiophene-5-carboxylate and the corresponding
carboxylic acid were the only isolable products (in only moderate yield).

Acetylation of 2-amino-3-nitrothiophene-5-carboxylic acid required
refluxing with acetyl chloride in ethyl acetate for several hours and was
accompanied by reaction at the carbonyl group resulting in anhydride
formation. Hydrolysis of the anhydride (e.g. in pyridine) could not be
accomplished without accompanying hydrolysis of amide to amine.
Alternative Route

A further attempt to synthesise the acetamido activated carboxylic acid was made by attempted displacement of bromide with acetamide. However, there was no evidence of nucleophilic substitution upon refluxing the bromo acid with acetamide in methanol for 48 hrs. Attempts to prepare the acetamide anion as a nucleophile in situ were also unsuccessful. Upon addition of potassium t-butoxide to a solution of the bromo-acid in butanol and refluxing for 1 hr, the only detectable product was the 2-t-butoxy-3-nitrothiophene-5-carboxylic acid. Further modifications were also unsuccessful.

A literature report on the preparation of 2-acetamidothiophene-5-carboxylic acid by oxidation of 2-acetamido-5-thiophenealdehyde has been shown to be in error\textsuperscript{276,277}. The oxidation was performed with Fehling's solution and the authors mistook acid potassium tartrate for the desired acetamido acid.

An attempt was made to prepare 2-acetamido-3-nitrothiophene-5-carboxylic acid by oxidation of 2-acetamido-3-nitro-5-acetylthiophene\textsuperscript{21} with hypochlorite\textsuperscript{269} but the amide did not appear to be stable under the oxidation conditions.
(30) 3-NITROTHIOPHENE-5-CARBOXYLIC ACID

(A) SYNTHESIS

\[
\begin{array}{c}
\text{S} \\ \text{CO}_2\text{H}
\end{array}
\xrightarrow{\text{HNO}_3, \text{H}_2\text{SO}_4}
\begin{array}{c}
\text{S} \\ \text{NO}_2 \\ \text{CO}_2\text{H}
\end{array}
+ \begin{array}{c}
\text{S} \\ \text{CO}_2\text{H}
\end{array}
\]

3-Nitrothiophene-5-carboxylic acid was obtained as a by-product in the attempted preparation of 2-acetamido-3-nitrothiophene-5-carboxylic acid, and was separated from the 2-nitro isomer by means of its weakly soluble barium salt (see previous preparation).

**Attempted Nitrodecarboxylation**

Treatment of a solution of 3-nitrothiophene-5-carboxylic acid in sulphuric acid with excess nitric acid at room temperature failed to produce any nitrodecarboxylated product. The starting material was recoverable after 48 hrs standing at room temperature (54.8%). Attempted nitrodecarboxylation at higher temperatures led to degradation of the starting material.

The 2-nitrothiophene-5-carboxylic acid derivative was similarly stable to any further nitration reaction.
(31) 2-N-METHYL ACETAMIDO-3-NITROTHIOPHENE-5-CARBOXYLIC ACID

(A) SYNTHESIS (attempted)

Scheme:

\[ \text{CO}_2\text{Me} \begin{array}{c} \text{NO}_2 \\ \text{S} \\ \text{Br} \end{array} \xrightarrow{\text{MeNH}_2} \xrightarrow{\text{OH}^-/\text{MeOH}} \begin{array}{c} \text{CO}_2\text{Me} \\ \text{S} \\ \text{NHMe} \end{array} \xrightarrow{\text{Ac}_2\text{O}} \begin{array}{c} \text{CO}_2\text{H} \\ \text{S} \\ \text{NMe}_{\text{Ac}} \end{array} \]

(a) Methyl-2-N-methylamino-3-nitrothiophene-5-carboxylate

Methyl-2-bromo-3-nitrothiophene-5-carboxylate (2 g) in methanol (20 ml) was treated with a 30% solution of methylamine in methanol (3 g amine). The mixture was heated at 50°C for 20 min and upon cooling to 0°C yellow needles precipitated (1.4 g, 81.2%) m.p. 155°C (from aq. methanol). Infra-red spectra indicated the presence of an amino group and absence of halogen.

Found: C, 38.6%; H, 3.8%; N, 12.9%.

C\text{H}_7\text{NO}_4\text{S} requires: C, 38.9%; H, 3.7%; N, 13.0%.

'\text{H} N.M.R. (\text{CCl}_4): 1.97(s), 6.13(s), 6.62(d) and 1.50(d) in ratio 1:3:3:1

The N-methyl protons appear as a doublet due to the restricted rotation of the N-H bond (o-NO\textsubscript{2} effect).

(b) Methyl 2-N-methylacetamido-3-nitrothiophene-5-carboxylate

The amine (2 g) was acetylated by refluxing with acetyl chloride (3 g) in ethyl acetate (20 ml) for 24 hrs. The excess solvent and acetyl chloride were evaporated to yield the acetamido derivative (62.3%).
m.p. 101° (from aq. methanol).

Found: C, 41.9%; H, 3.9%; N, 10.8%.

C₉H₁₀N₂O₅S requires: C, 41.9%; H, 3.9%; N, 10.9%.

c) 2-N-Methylacetamido-3-nitrothiophene-5-carboxylic acid

Attempts to hydrolyse the amido ester to the amido acid were unsuccessful since, as encountered earlier, the amide is extremely susceptible to basic hydrolysis. The amino ester was isolable from the reaction mixture but no amido acid was obtainable. Further variation of the reaction conditions failed to produce the desired product.

13C Spectrum in Sulphuric/Nitric Acid

A 13C spectrum of methyl-2-N-methylacetamido-3-nitrothiophene-5-carboxylate in a sulphuric-nitric acid mixture revealed that the N-methyl group had very little influence upon the rate of degradation of the amide. After 24 hrs only a complex series of low intensity peaks remained in the 13C spectrum, together with the acetyl peaks (of higher intensity) at 194.0 and 21.1 ppm (from T.M.S.).
(A) SYNTHESE

Scheme:

(a) Methyl-2-methylthio-3-nitrothiophene-5-carboxylate

To a solution of methyl-2-bromo-3-nitrothiophene-5-carboxylate (2 g) and methane thiol (0.75 g) in methanol (25 ml) was added dropwise, with stirring, a solution of potassium hydroxide (0.5 g) in water (1 ml). The solution was stirred for 12 hrs at room temperature and then drowned into ice-water to yield a cream solid (1.65 g, 88.5%) m.p. 78° (from aq. methanol).

Found: C, 36.0%; H, 2.8%; N, 6.0%.

C$_7$H$_7$NO$_4$S$_2$ requires: C, 36.1%; H, 3.0%; N, 6.0%.

(b) 2-Methylthio-3-nitrothiophene-5-carboxylic acid

The ester was readily hydrolysed to the corresponding carboxylic acid by refluxing in methanol and adding an equimolar quantity of sodium hydroxide solution (10%) dropwise. The solution was stirred for 30 mins at 60° and then diluted with an equal volume of water. Acidification with concentrated hydrochloric acid precipitated a colourless solid (66%)
m.p. 132° (from aq. methanol).

Found: C, 32.6%; H, 2.5%; N, 6.3%.

C₆H₅NO₄S₂ requires: C, 32.9%; H, 2.3%; N, 6.4%.

(B) NITRODECARBOXYLATION (attempted)

2-Methylthio-3-nitrothiophene-5-carboxylic acid (2 g, 0.01 mol) was dissolved in concentrated sulphuric acid (12 ml) and a solution of nitric acid (d 1.42, 2 ml) in sulphuric acid (98%, 10 ml) added dropwise < 0°. There was no evidence of carbon dioxide being liberated. After stirring for 20 min at 0° the reaction mixture was drowned into ice-water to precipitate a white solid, a sulphone (1.9 g, 76.0%). m.p. 183° (from aq. methanol).

Found: C, 28.9%; H, 2.0%; N, 5.6%.

C₆H₅NO₄S₂ requires: C, 28.7%; H, 2.0%; N, 5.6%.

The formation of the sulphone was confirmed by infra-red spectroscopy:

\[ \text{CO}_2\text{H} \quad \text{S} \quad \text{SMe} \quad \text{NO}_2 \quad \overset{\text{HNO}_3}{\text{H}_2\text{SO}_4} \quad \text{CO}_2\text{H} \quad \text{S} \quad \text{SO}_2\text{Me} \quad \text{NO}_2 \]

A similar oxidation was observed upon treatment of the methyl ester with nitric-sulphuric acid mixtures. The sulphone 'activated' carboxylic acid showed no tendency to nitrodecarboxylate at room temperature with a ten-fold excess of nitric acid.
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