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**NOTTINGHAM POLYTECHNIC**

# Synthesis of Polysubstituted Fatty Acids

via

# Thiophene Intermediates

being a thesis submitted to the

Council for National Academic Awards

for the Degree of

Doctor of Philosophy

by

Adrian Paul Gledhill, C. Chem., M.R.S.C.

October, 1991

## PREFACE

The work described in this thesis was carried out by the author in the laboratories of the Department of Physical Sciences, Nottingham Polytechnic, between January, 1987 and April, 1990.

Throughout the period of this research programme the author has not been registered for any other award of the CNAA nor with any other degree-awarding body; no material contained in this thesis has been used in any other submission for an academic award.

The author wishes to express his gratitude to Dr. J.M. Barker for his guidance and supervision, and Dr. P.R. Huddleston for helpful discussions. The author also wishes to thank Dr. R. Davy's of Shell Research, Sittingbourne, for his kind assistance, elemental analysis, mass spectra and high resolution nmr spectra. Thanks are due to Mr. M.L. Wood for $^{13}C$ nmr spectra, Mr. J.J. Cummins for providing experimental details for preparing methyl 4-hydroxy-2.2'-bithienyl-5-carboxylate, and to Gay for her patience and help during the typing of this manuscript.

Finally, I am indebted to my Mother and Father for their constant encouragement, and to my Grandparents, Mr. and Mrs. R.V. Hodgkinson for their benevolence.

Adrian Paul Gledhill
Nottingham Polytechnic

## ABSTRACT

**Synthesis of Polysubstituted Fatty Acids via Thiophene Intermediates**

**A. Gledhill.**

This thesis is an investigation into the possibility of preparing polysubstituted fatty acids - seco-acids - via Raney nickel desulphurisation of polysubstituted thiophene intermediates.

A variety of hydroxythiophene carboxylates were prepared. A number of these were O-methylated, saponified and either decarboxylated or converted to acid chlorides. Two examples were O-glycosidated.

Acetoxy - and aryloxy - derivatives of several hydroxythiophene carboxylates were prepared and subjected to Fries rearrangement. The reaction failed in the majority of cases, with cleavage of the ester occurring without subsequent rearrangement. Five esters were successfully Fries rearranged to give thienyl and dithienyl ketones.

A number of polysubstituted thienyl and dithienyl ketones were prepared using Friedel-Crafts acylation.

Raney nickel desulphurisation of thienyl and dithienyl ketones gave seco acids, with only moderate success. The products obtained were found to be impure in the majority of cases. However, one model seco acid was prepared.

A study of the stereoselectivity of the Raney nickel desulphurisation process with respect to hydroxy groups attached directly to a thiophene ring proved inconclusive.

An investigation into the Raney nickel desulphurisation of thiophenes containing optically active side-chains demonstrated that no racemisation of chiral centres occurs.

## ABBREVIATIONS

| | |
|---|---|
| TBS | - t-butyldimethylsilyl |
| 9-BBN | - 9-borabicyclo [3.3.1] nonane |
| CuOTf | - copper (11) trifluoromethane sulphonate |
| Bn | - benzyl |
| Tr | - triphenylmethyl |
| $Bu^t$ | - tertiarybutyl |
| Me | - methyl |
| Et | - ethyl |
| MeOH | - methanol |
| Ph | - phenyl |
| Th | - thienyl |
| Ac | - acetyl |
| EtOAc | - ethyl acetate |
| t-BuOK | - potassium-t-butoxide |
| Ar | - Aryl |

| | |
|---|---|
| NMR | - nuclear magnetic resonance spectroscopy |
| δ | - s-singlet - q-quartet |
| | - d-doublet - m-multiplet |
| | - t-triplet |
| | - J-coupling constant (Hz) |

| | |
|---|---|
| IR | - infra-red spectroscopy |
| | - V - Vmax ($cm^{-1}$) |
| | - b - broad |
| p.s.i. | - pounds per square inch |

## CONTENTS

EXPERIMENTAL SECTION

## INSTRUMENTATION

The following information applies to all experimental sections:

Melting points were determined using open capillary tubes in an electrically heated Gallenkamp melting point apparatus and are uncorrected.

Microanalysis and mass spectroscopy were carried out by the analysis sections of Shell Research Ltd., Sittingbourne.

$^{1}H$ nmr spectra were recorded on a Hitachi Perkin-Elmer R-24B 60 MHz spectrometer with tetramethylsilane as internal standard in the solvents indicated.

Infra-red spectra were recorded on a Perkin-Elmer 157 G Grating Infra-red spectrophotometer.

$^{13}C$ nmr spectra were recorded on a JEOL 5NM-C-60Q 60 MHz spectrometer with tetramethylsilane as internal standard in deuterated chloroform.

Column chromatography was carried out using silica gel, 60-120 mesh.

Aluminium, tin and titanium chlorides were all anhydrous.

# INTRODUCTION

## 1. The Macrolide Antibiotics.

### 1.1. Introduction.

The macrolide antibiotics are of great interest due to their antibacterial activity, especially against gram-positive bacteria (including anaerobes), gram-negative cocci, and mycoplasmas.

The first macrolide antibiotic to be isolated was obtained from a strain of streptomyces, by Brockmann and Henkel in 1950[1]. They named it pikromycin due to its bitter taste. Soon afterwards streptomyces organisms yielded several other antibiotics which appeared to be chemically and antimicrobially related to pikromycin. Chemical characterization of these antibiotics led to the disclosure of the structures of methymycin [2], erythromycin A[3] and B[4] and carbomycin A (magnamycin) [5-8], all showing a common feature - a macrocyclic lactone. Woodward [6] proposed the term "macrolide" to describe this class of compounds.

The macrolide antibiotics are classified according to the size of the macrocyclic ring as either 12-, 14- or 16- membered macrolides. Their overall constitutional structures include a wealth of stereochemical features, involving numerous asymmetric centres and conformational possibilities among lactone rings containing an array

of substituents. The structures (1 (a) and 1 (b)) illustrate this point:-

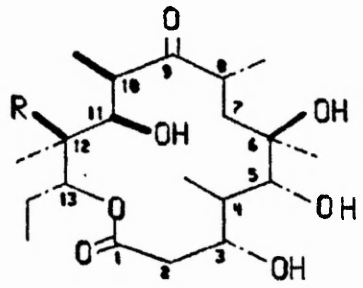



Figure 1(a) R = OH; eythronolide A
(b) R = H; eythronolide B

It should be pointed out that the macrolide antibiotics are glycosides and that the sugar moiety is essential for antibiotic activity. This means the synthesis of a macrolide antibiotic is not complete without glycosidation. For example, the macrolides (1 (a) and 1 (b)) must both have the sugars D-desosamine and L-cladinose in the C-5 and C-3 positions respectively (2 (a) and 2 (b)) in order to be classed as macrolide antibiotics:-

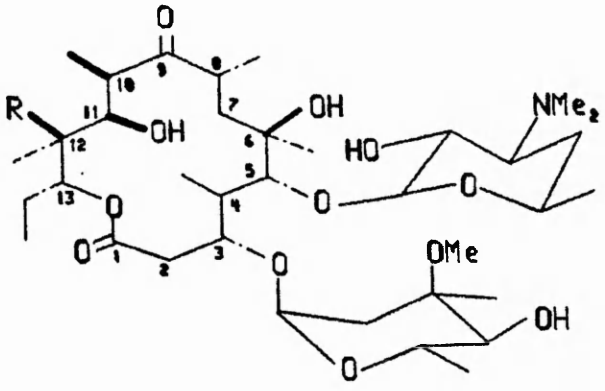


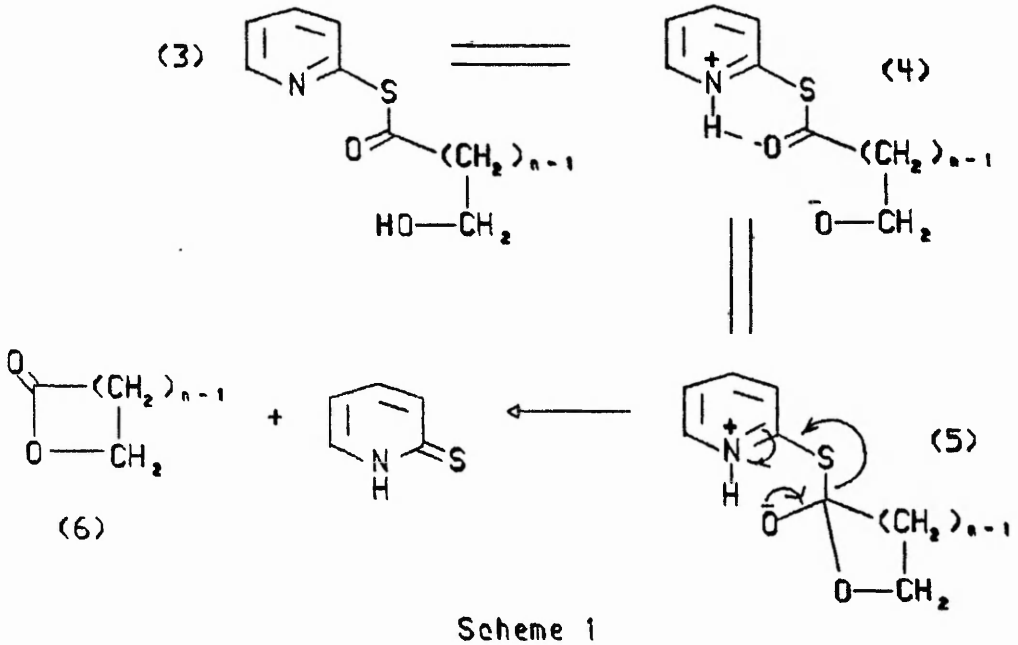

Figure 2(a) R = OH; erythromycin A
(b) R = H; erythromycin B

A total of sixteen sugars have been identified with the macrolide antibiotics: five of these are amino, and eleven are neutral sugars. The majority of macrolide antibiotics contain at least one sugar moiety and glycosidation is still a major synthetic problem. By 1984 [9] only four macrolide antibiotics, methymycin [10], erythromycin A[11], carbomycin B[12], and tylosin [13] had been synthesised, with moderate success.

## 1.2. The Total Synthesis of the Aglycones of the Macrolide Antibiotics.

The macrolide antibiotics, with their multiple asymmetric centres and complex array of functional groups present a challenge that has been the focus of intense synthetic interest. Two fundamental problems have been identified in association with macrolide synthesis. One of these, the construction of a medium or large-size lactone, was solved in the first total synthesis of methymycin in 1975 [10], [14] and later of pyrenophorin [15], vermiculine [16] and nonactin [17], [18]. These lactones were constructed from their corresponding seco acids. This was achieved despite the view which prevailed at the time (based on earlier work by Stoll [19]) which indicated that such intramolecular cyclisations were not favoured. With the establishment of the viability of the "seco acid" approach, a variety of methods for this macrolactonisation are now available [14], [20]. An approach which is now often employed, Corey's "double activation method" [21,22] involves prolonged refluxing of a dilute solution of the thiol ester (3) in a high-boiling, inert solvent to complete lactonisation (4-6), as shown

below in scheme 1, where formation of the doubly-activated intermediate (4) leads to a collapse to the tetrahedral carbonyl adduct (5) from which the lactone (6) is formed by elimination:-



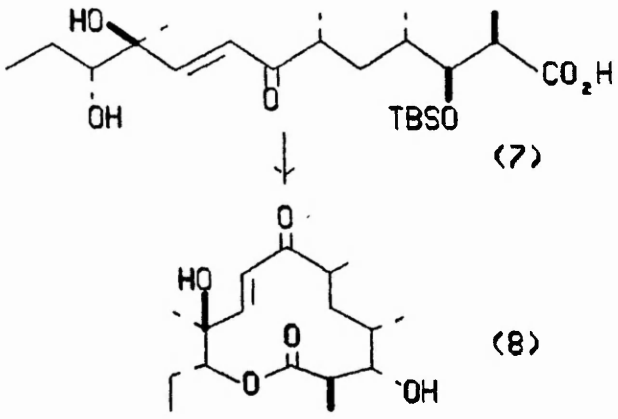
Scheme 1

It has since been discovered by Gerlach [23] that silver perchlorate considerably accelerates this reaction, enabling completion within an hour at room temperature.

The second fundamental problem associated with macrolide synthesis, the introduction of chiral centres into a straight-chain aliphatic acid still has no satisfactory solution. The synthetic methodology needed to overcome this problem has developed primarily along four general pathways which will now be discussed.

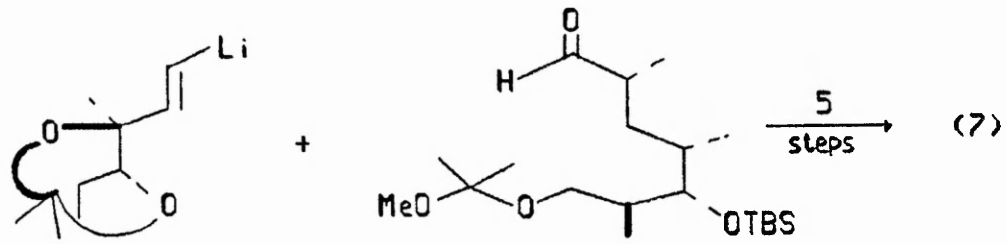
## 1.3. Ring-Cleavage Methods.

Here, the clearly defined cis/trans relationship of substituents on a cyclic system is employed as a means of generating acyclic systems with the required stereochemistry via ring-cleavage. An excellent example of this method of macrolide synthesis is seen in Grieco's[24] synthesis of the seco acid (7), which upon lactonisation gives methylonide (8), as shown in equation 1:-




Equation 1

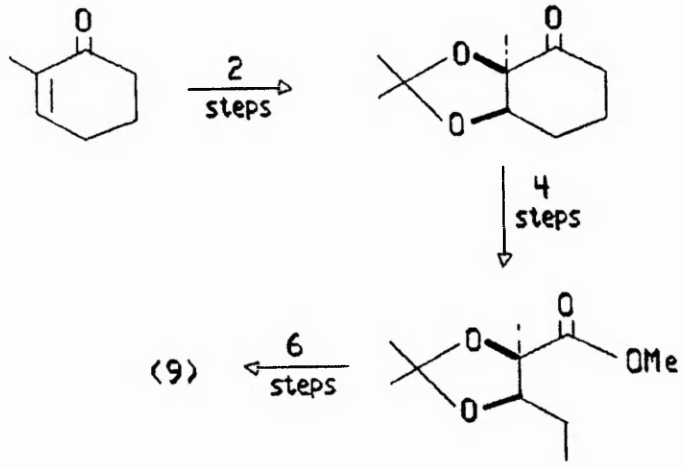
The Grieco seco acid synthesis is based upon the coupling of the racemic, nucleophilic C-1--->C-7 fragment (10), as in equation 2:-




(9) (10)

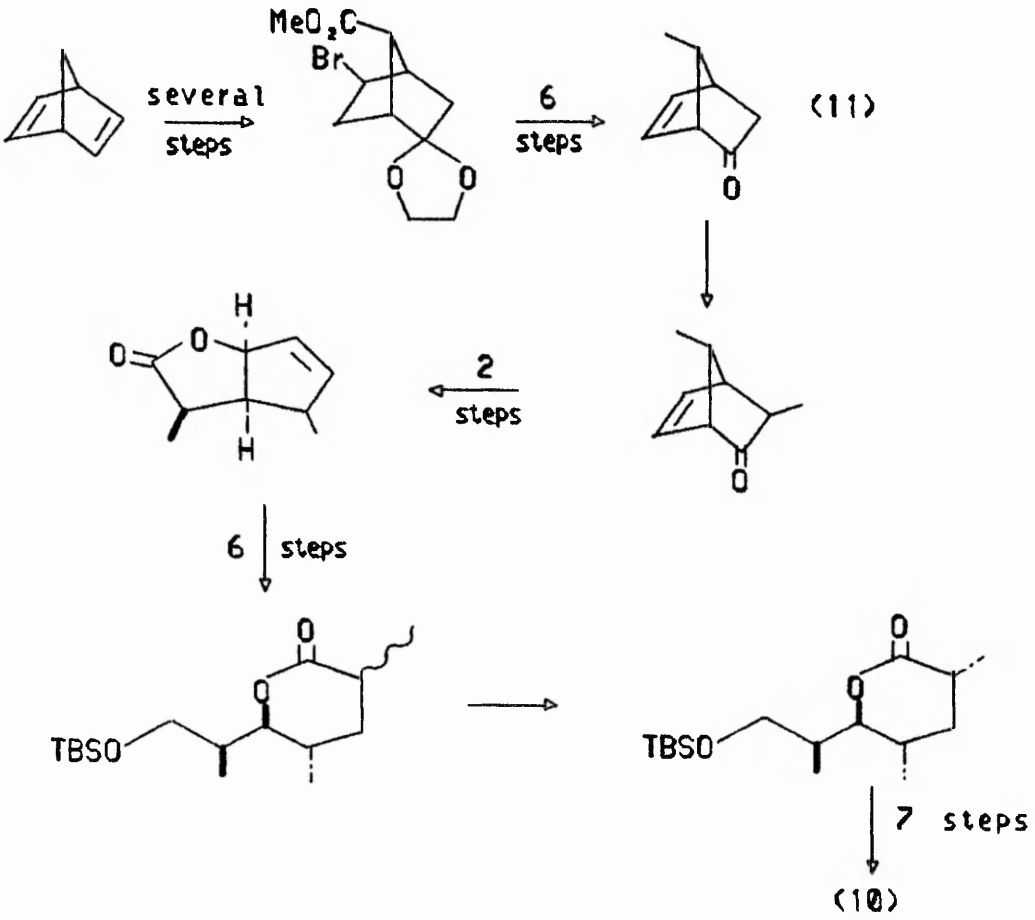
Equation 2

Fragment (9) was prepared from the cyclohexenone in 12 steps via the route shown in scheme 2:-




Scheme 2

Fragment (10) was prepared from (11), obtained from norbornadiene, using the following, multi-stage synthetic route (scheme 3):-

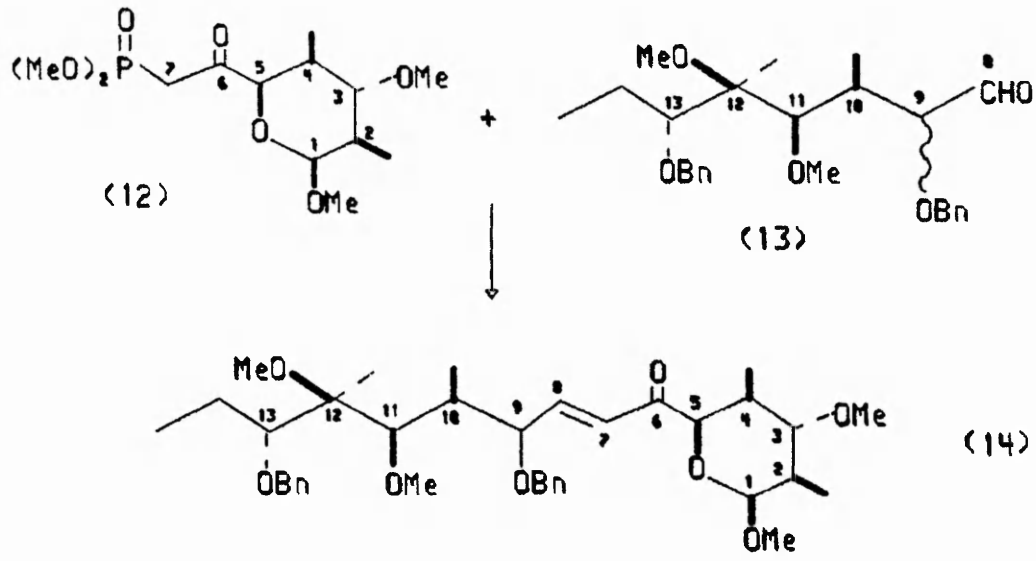



Scheme 3

Coupling of the two fragments (9) and (10), followed by a further four steps, gave a 1:1 mixture of racemic (7) and an unwanted diastereomer. In all the synthesis comprises of a total of 32 major steps starting from norbornadiene and gives an overall yield of 0.07% from (11).

1.4. The Sugar Approach.

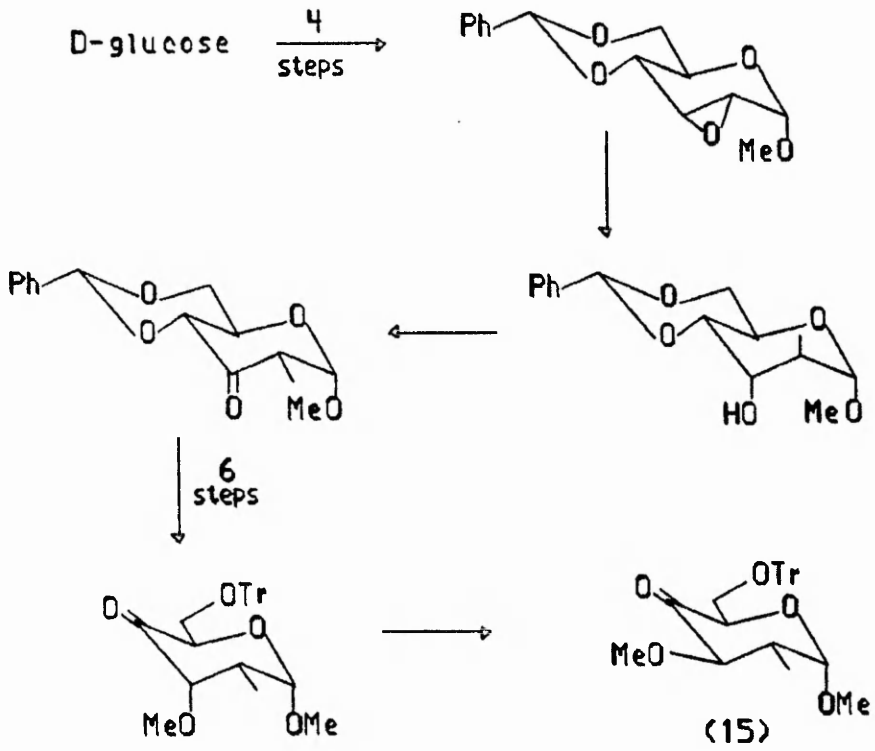
This method of macrolide synthesis utilizes the built-in stereochemistry of monosaccharides such as glucose, transferring it into that of segments of macrolides through appropriate chemical operations. Thus, readily available monosaccharides serve as a "chiral pool" of available starting materials. This method, originally proposed by Miljkovic[25], was used in the elegant synthesis of an erythronolide A seco acid derivative by Hanessian and co-workers[26], reported in 1978. This synthesis is based upon the coupling of the carbohydrate-derived C-1--->C-7 and C-8--->C-13 fragments, (12) and (13) respectively, giving (14) (the stereocentres at C-6 and C-8 are undefined). Equation 3 shows this coupling:-




Equation 3

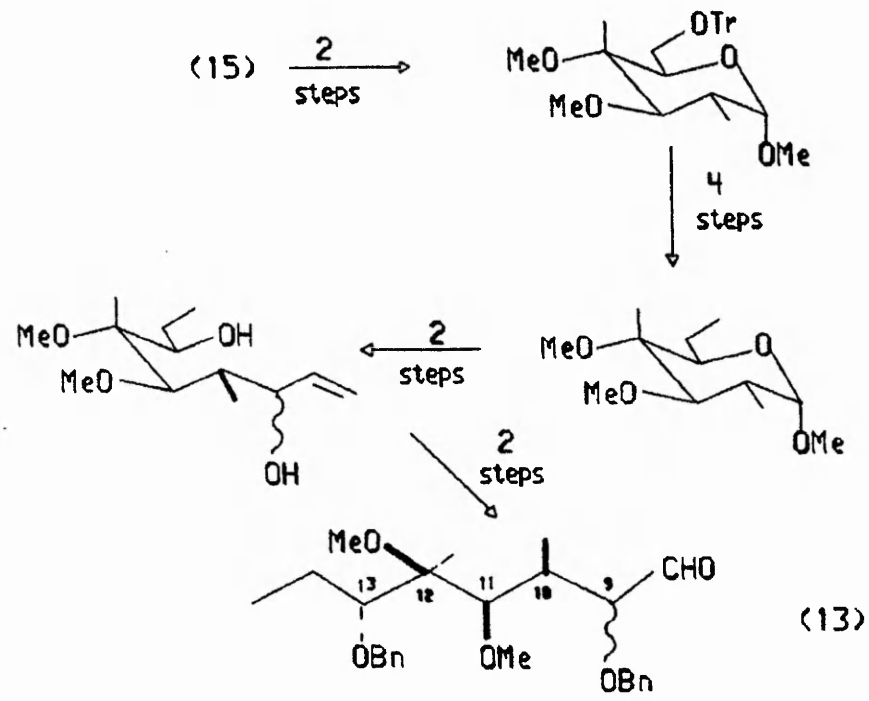
These two enantiomerically-correct fragments were prepared from a common precursor, (15) (which has the correct stereochemistry)

obtained from manipulation of D-glucose using the conformational bias of the pyranose ring system. The stereocontrolled synthesis of (15) was accomplished in five stages from D-glucose, involving a total of fourteen reactions. These syntheses are summarised in scheme 4 :-



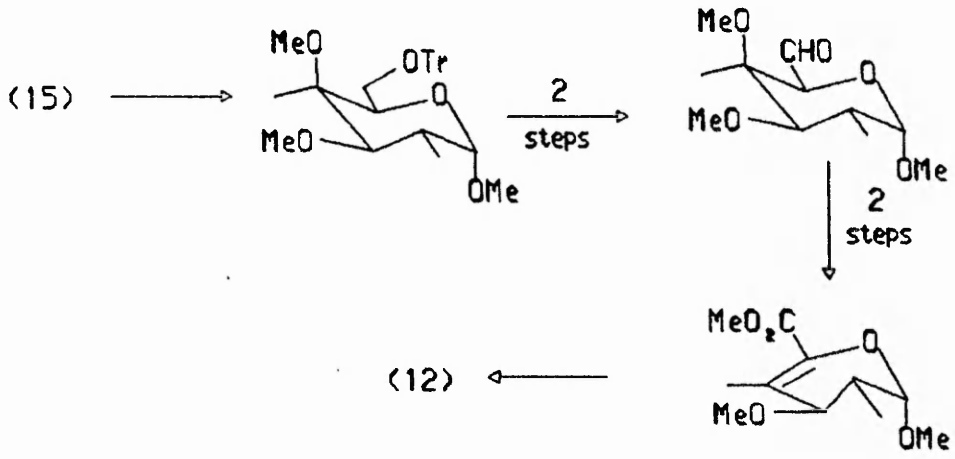

Scheme 4

(15) is then converted in five further stages to the C-9--->C-13 segment (13) as in scheme 5:-



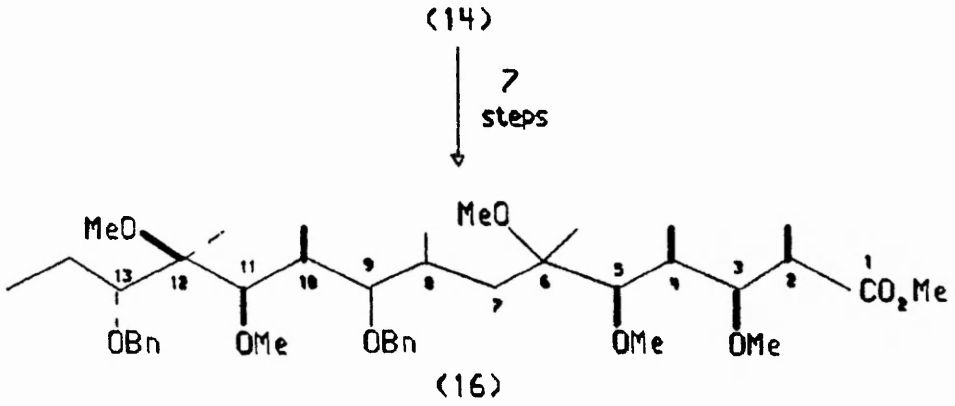

Scheme 5

The other fragment, (12), was synthesised in four stages from (15), using a total of six steps as follows in scheme 6:-




Scheme 6

The two fractions were combined via a Horner-Emmons[27] reaction to give (14). Introduction of the C-6 and C-8 methyl bearing chiral-centres was then carried out without significant stereocontrol, and the mixture of diastereomers produced was converted into the seco acid derivative (16) as in equation 4. The total synthesis of this seco acid using this route consisted of 31-steps from D-glucose and gave an overall yield of 2%.

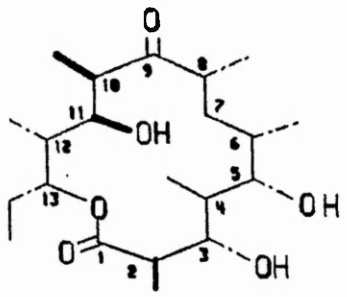



Equation 4

## 1.5. Acyclic Method[28]

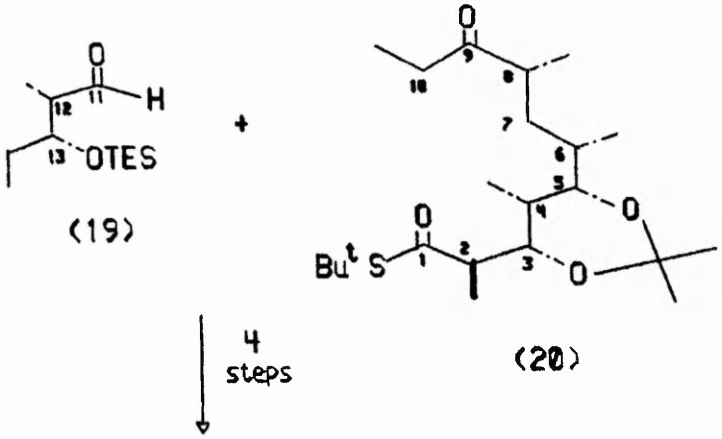
Here, chiral chain segments of a macrolide are stereoselectively constructed from acyclic precursors. The advantage of this approach is that repetition of such a synthetic operation, if executed with high diastereoselection (and enantioselection) at each operation, would simplify the synthetic design for, and minimise the number of steps to, a seco acid. Problems associated with this acyclic stereoselection have been investigated intensely in recent years. Masamune[29] synthesised 6-deoxyerythronolide B (17) using a series

of four syn-type aldol condensations to build up the C-1--->C-13 carbon skeleton with the simultaneous control of eight new chiral centres (i.e. two new chiral centres set up for each aldol step). This synthesis was the first to use only acyclic stereocontrol by the aldol reaction (using chiral enolates), to construct a complete macrolide seco acid.



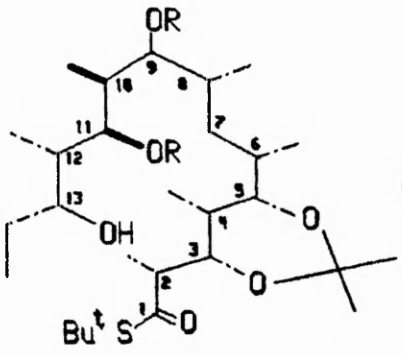
(17) 6-deoxyerythronolide B

The synthesis of the seco-acid derivative (18), the precursor to (17), is based on the aldol coupling of the enantiomerically correct C-1--->C-10 and C-11--->C-13 fragments, (19) and (20), respectively - see equation 5:-



(19)

(20)

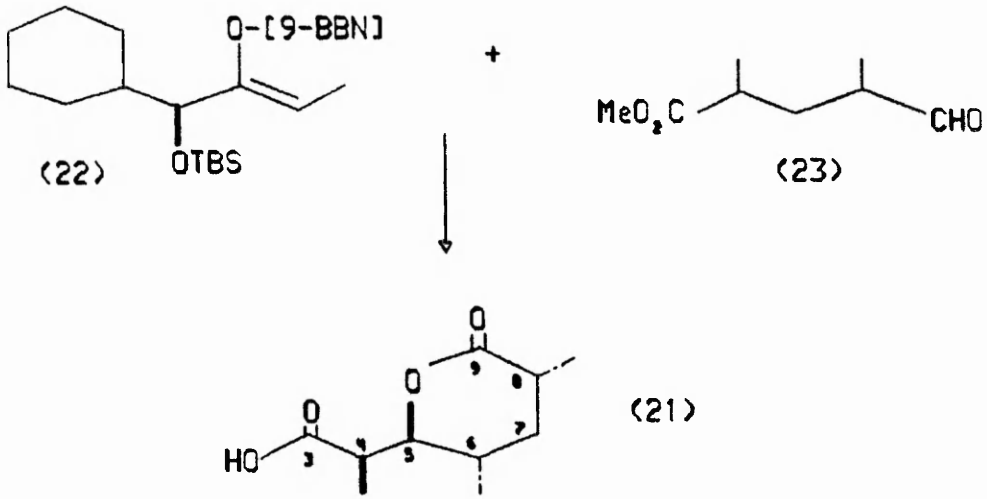



(18)

R = $COCHCl_2$

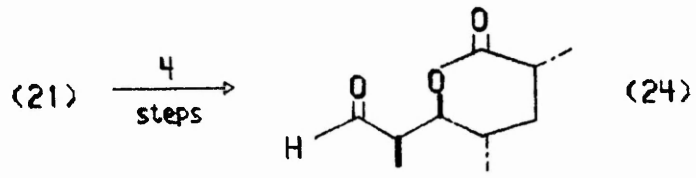
Equation 5

Fragment (20) was synthesised from the appropriate Prelog-Djerassi lactonic acid[30], (21), which was prepared by reaction of the S-boron enolate (22) and optically pure aldehyde (23). This stage is shown in equation 6:-

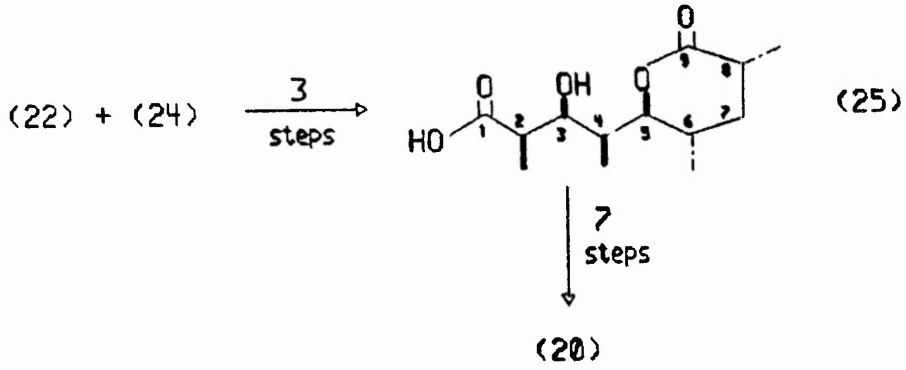



Equation 6

The same boron enolate (22) was then condensed with the aldehyde (24) derived from the lactonic acid (21) - equation 7, to give the acid (25) with the correct stereochemistry at C-2--->C-3, with 93% stereoselectivity. This was then converted, via seven further steps, to fragment (20), as in equation 8:-



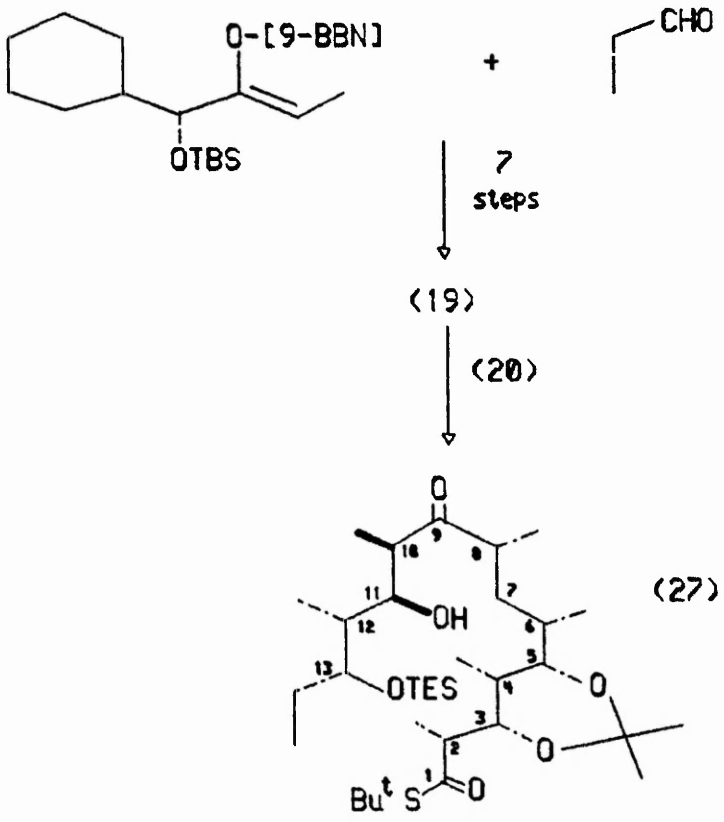

Equation 7




Equation 8

Fragment (19), containing the C-12--->C13 asymmetric carbons, was prepared with 99% stereoselectivity by the enantioselective aldol addition of R-enolate (26) to propanal, followed by a series of six steps. The final, and most remarkable, aldol condensation was the addition of the lithium 2-enolate of ketone (20) to aldehyde (19),

which gave the adduct stereoisomer (27) with control of the C-10--->C-11 chiral centres in 94% stereoselectivity as in scheme 7:-

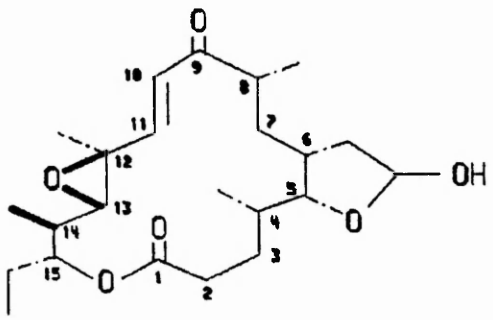



Scheme 7

This was then converted into the seco-acid derivative (18), by reduction of the C-9 ketone, followed by protection and desilylation. Macrolactonisation of (18) by the Masamune activated thioester method [31], using CuOTf, followed by oxidation at C-9, gave 6-deoxyerythronolodide B (17). This synthesis involved a total of 27 steps from starting materials, giving the macrolide in 4.5% overall yield.

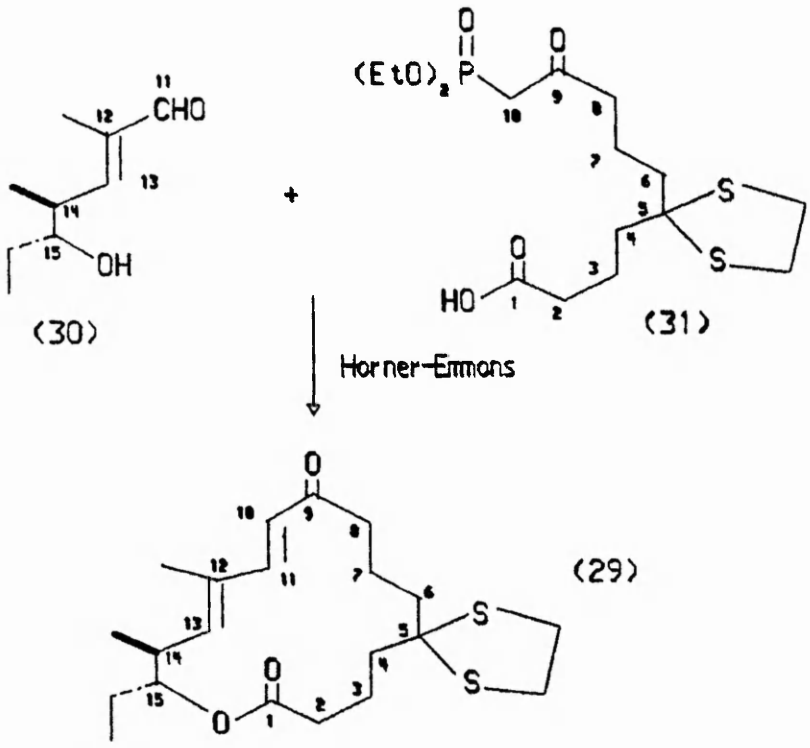
## 1.6. Macrocyclic Approach.

In this approach, new asymmetric centres are stereoselectively introduced into an intact macrolide, or other large ring using the conformational bias of the large ring. An illustration of the potential of this method as a means of macrocyclic stereocontrol in macrolide work is the Still and Novak[32,33] synthesis of racemic 3-deoxyrosaronolide, (28):-



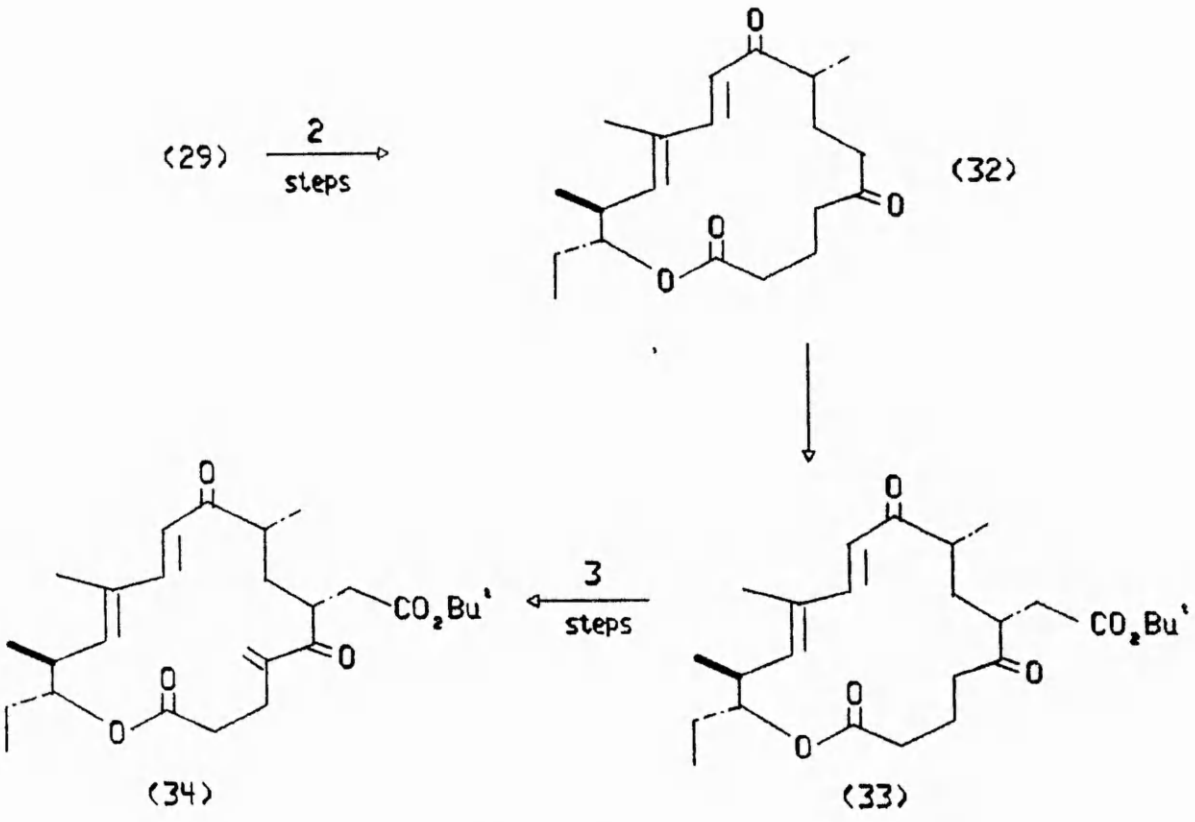

3-deoxyrosaranolide (28)

In this synthesis the simple macrocycle (29) was prepared using the Horner-Emmons procedure[27] from (30) and (31) - scheme 8:-



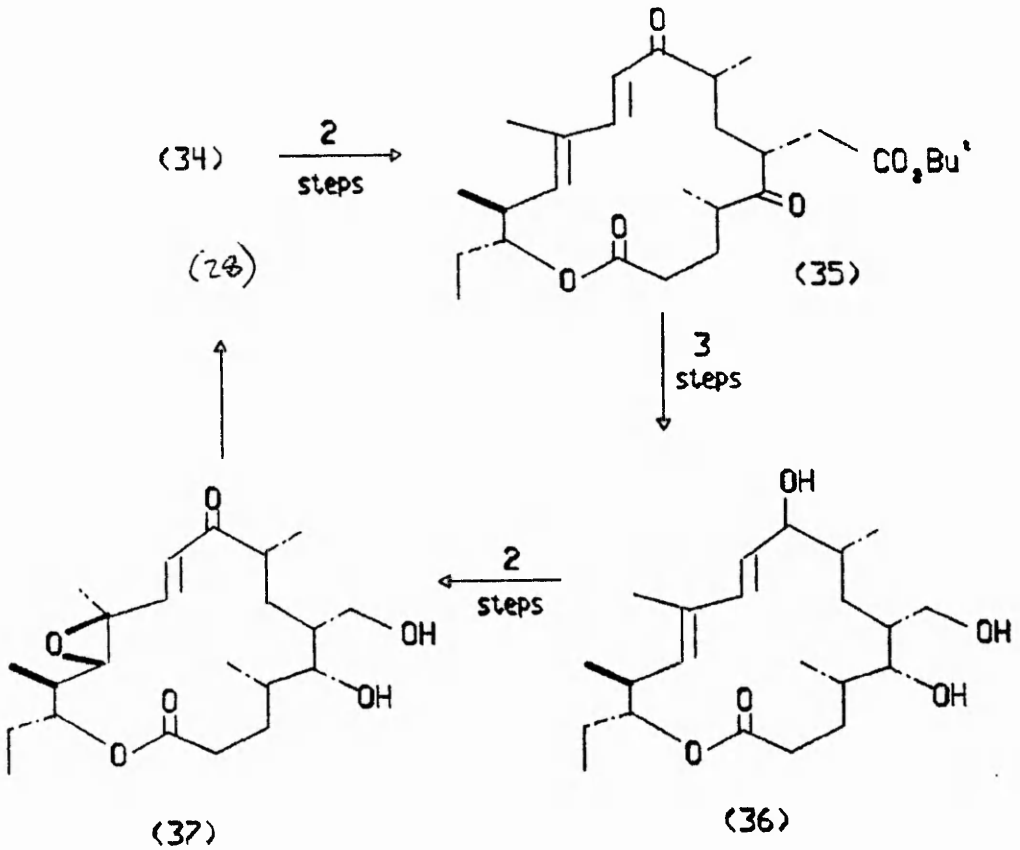

Scheme 8

The synthesis of (28) makes use of the stereocentres at C-14 and C-15, present in the simple macrocycle (29), to control the configurations of the six new chiral centres spanning C-4--->C-13 followed by the deprotonation of (29) giving an enolate at C-8, which, following methylation and deprotection, gave (32) with better than 95% stereoselectivity. Regio- and stereoselective introduction of a C-6 side-chain was carried out by alkylation of the kinetically-generated lithium-enolate of (32) to give (33) with 95% regioselectivity and 85% stereoselectivity. Compound (33) was then converted (via hydroxy methylation of the C-4 lithium enolate followd by elimination), into the methylene ketone (34). These stages are summarised in scheme 9:-




Scheme 9

The 4-methyl derivative (35) was then prepared by conjugate addition of thiophenol followed by Raney nickel desulphurisation, with greater than 95% stereoselectivity. Ester hydrolysis and borohydride reduction of the derived mixed-anhydride then gave the required C-5 alcohol (36) with 83% stereoselectivity. Oxidation at C-9, followed by epoxidation at C-12--->C-13, then gave (37) with 93% selectivity, which on selective oxidation of the primary hydroxyl group gave 3-deoxyrosaranolide (28) in a total of 16 steps giving an overall yield of 0.9%. These reactions are all summarised in scheme 10:-




Scheme 10

## 1.7. Summary of the Methods Employed in Macrolide Synthesis.

It can be seen that, with the exception of the macrocyclic method, an essential part of the synthesis of the aglycones of macrolide antibiotics is the construction of long-chain hydroxy acids i.e. seco acids. However, the effectiveness of these standard seco acid approaches to macrolide synthesis is dependant upon having a seco acid derivative which can adopt a low-energy conformation, resembling the preferred diamond-lattice of the macrolide ring, in order to facilitate efficient lactonisation [11,34]. As shown previously, several general approaches have been developed for the stereocontrolled synthesis of the unique chiral sequences found in the macrolide antibiotics. These have all been applied to the synthesis of individual macrolide structures. Several new purpose designed reagents and reactions for the control of acyclic stereochemistry have been developed for this purpose; the aldol condensation reactions of boron enolates are an excellent example of this. An up to date review in this area has been published by Hoffman[35].

It should be pointed out that all the synthetic procedures utilized in the preparation of these compounds are multi-step, and although the individual steps may be efficient, overall yields are necessarily very low. As it is possible that simpler versions of the macrocyclic aglycones, i.e. those lacking some substituents, may also show biological activity, the work presented in this thesis intends to explore a novel route for the synthesis of simpler seco acids, with some of the stereochemistry secured and which may facilitate the

synthesis of larger quantities of seco acid products. The method explored involves preparation and Raney nickel desulphurisation of polysubtituted thiophene rings. If this were to be successful, the simpler macrocycles so formed might then be further elaborated, as in the case of the macrocyclic approach to macrolide synthesis. The remainder of the introduction will thus provide an examination into the feasibility of this suggested method.

## 2. Reductive Desulphurisation of Thiophene with Raney Nickel.

### 2.1. Background.

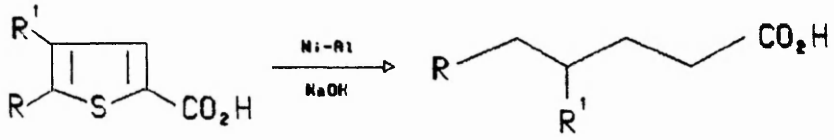
In 1925 a novel method for the preparation of nickel catalyst was patented by Murray Raney[36]. A pulverised silicon alloy was reacted with aqueous sodium hydroxide to produce a pyrophoric, brownish nickel residue with excellent catalytic properties. Further investigation of other nickel alloys and alkali-soluble metals showed that nickel-aluminium alloy could be readily prepared[37] and easily pulverised. The catalyst prepared by this method is known as Raney nickel.

Bougault, Cattelain and Chabrier[38] demonstrated that organosulphur compounds could be desulphurised by Raney nickel and also provided preliminary evidence for the desulphurisation of thiophenes by describing the preparation of thiophene-free benzene and toluene[39]. Soon after this the first important application of the reaction was reported by du Vigneaud and co-workers[40] in their elucidation of the

structure of biotin. The reaction has since found wide application in organic synthesis.

## 2.2. The Raney Nickel Desulphurisation of Thiophene Carboxylic Acids.

Raney nickel desulphurisation of thiophenes was first used by Blicke and Sheets[41,42] in their preparation of aliphatic and aryl aliphatic carboxylic acids. An important development was made by Papa, Schwenk and Ginsberg[43] when they prepared Raney nickel 'in situ' by adding nickel-aluminium alloy to a solution of the carboxylic acid in an excess of aqueous alkali. They used this method to prepare a series of long-chain aliphatic carboxylic acids from the appropriate substituted thiophene carboxylic acids, examples of which are shown in scheme 11:-

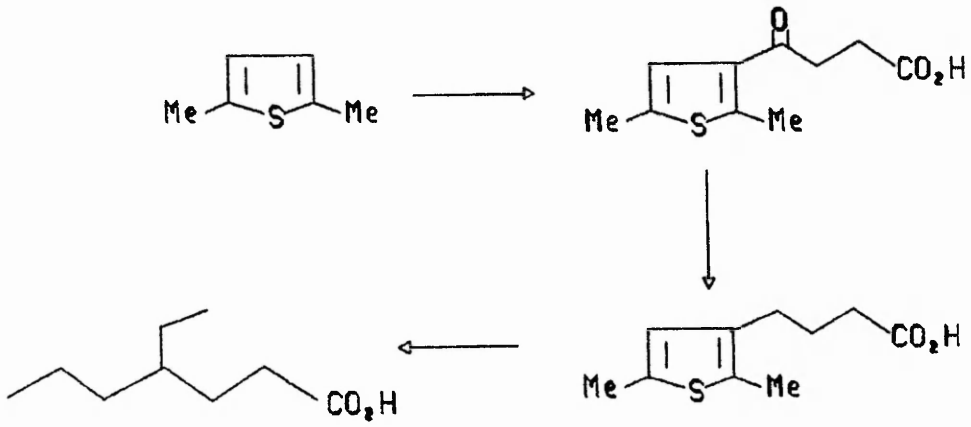



R = R' = H; R = Me, R' = H; R = H, R' = Me

Scheme 11

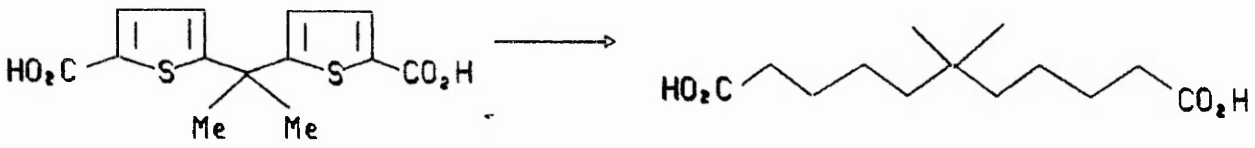
This method was then further developed by Hansen[44] who used it as a means of extending the chain-length of aliphatic carboxylic acids. At approximately the same time, papers by Badger, Buu-Hoi, Gol'dfarb,

Wynberg and their groups were published, in which it was demonstrated that Raney nickel desulphurisation of thiophenes could be applied to a wide variety of compounds. For example, Badger, Rodda and Sasse[45] employed the route illustrated in scheme 12 to make a branched-chain carboxylic acid:-



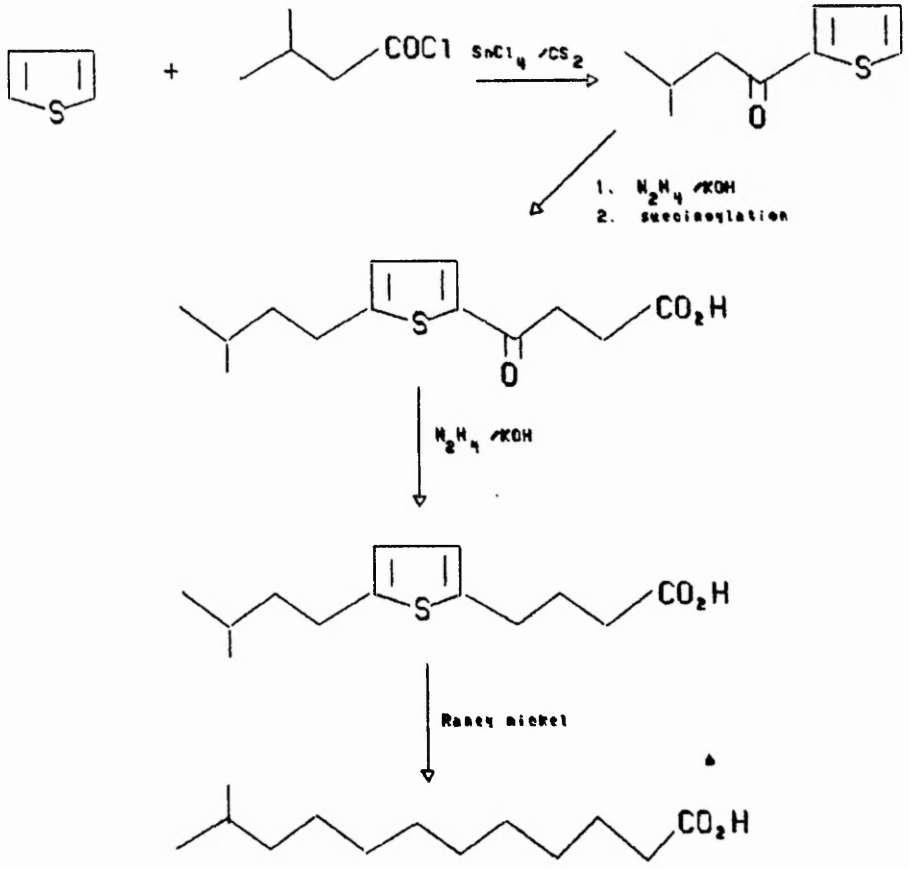

Scheme 12

These workers also synthesised substituted aliphatic dicarboxylic acids via reductive desulphurisation of 2,2' - bis (5-carboxy-2-thienyl) propane [46], with yields of between 51-93%. An example is shown in equation 9:-



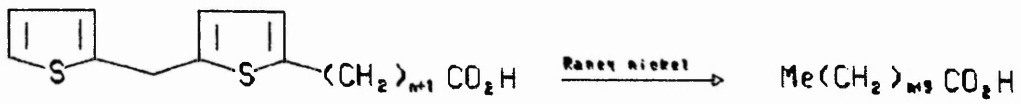

Equation 9

Other groups who have contributed in the synthesis of branched-chain, aliphatic carboxylic acids include Spaeth and Germain[47], Wynberg and Logothetis[48], McGhie et al[49] and Buu-Hoi et al[50-54]. The synthesis by Buu-Hoi et al[50], of 11-methyllauric acid (scheme 13) is another example of the route as a means of preparing branched-chain aliphatic carboxylic acids which may otherwise be difficult to obtain:-

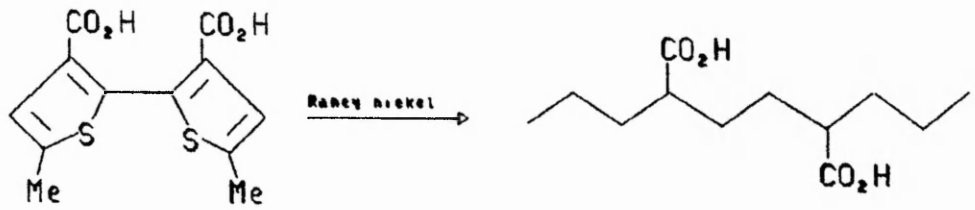



Scheme 13

Since these early papers, a great deal of work has abeen carried out in this field, Gol'dfarb [55-58] and his colleagues, who have published widely in this area, performed a number of desulphurisations of 2,2'-dithienylmethanes and 2,2' and 2,3'-bithienyl carboxylic acids (equations 10 and 11), thereby providing a method of chain extension of 9 and 8 carbon atoms respectively:-




Equation 10



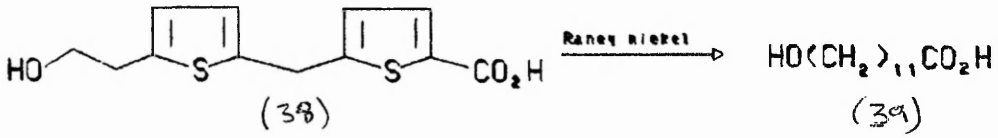

Equation 11

## 2.3. Synthesis of Oxo-, Hydroxy- and Alkoxycarboxylic Acids via Raney Nickel Desulphurisation.

The successful synthesis of aliphatic carboxylic acids with additional oxygen-containing functions from thiophene derivatives is possible, being limited only by the availability of the appropriately

substituted thiophene and the choice of reaction conditions. The following discussion refers to compounds with oxygen-functions present inside chains and to thiophenes containing hydroxy- or alkoxy- groups attached directly to the ring.

Reductive desulphurisation of thiophenic precursors containing an hydroxy or alkoxy group in the side-chain proceeds smoothly, without adversely affecting the substituents. Gol 'dfarb and Kirmalova[55], for example, described the synthesis of 12-hydroxydodecanoic acid, (39), in 94% yield by desulphurisation of the 2,2'-dithienylmethane, (38), as in equation 12:-

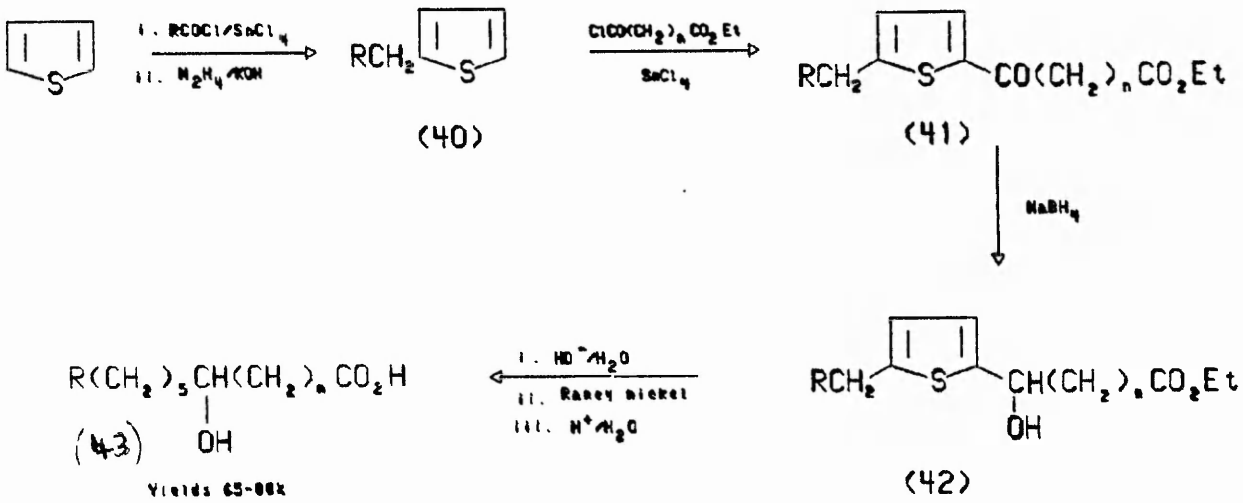


(38) (39)

Equation 12

Miller, Haymaker and Gilman[59] suggested a scheme for the synthesis of long-chain hydroxy carboxylic acids, (scheme 14). This scheme involves the synthesis via Friedel-Crafts acylation (where R=n-alkyl for C-2-->C-17) followed by Wolff-Kishner reduction of n-alkyl thiophenes - figure (40). Further Friedel-Crafts acyclation using the half-ester acid chlorides (where n ranges from 2 to 8) shown, gave the keto-esters (41) which, following borohydride reduction to the hydroxy-esters (42), were then hydrolysed followed by Raney nickel

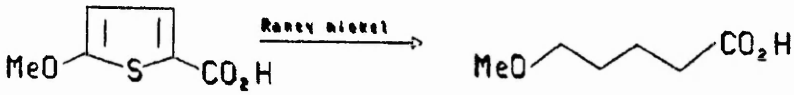
desulphurisation to give the required hydroxy acids (43) in 65-80% yield.




Scheme 14

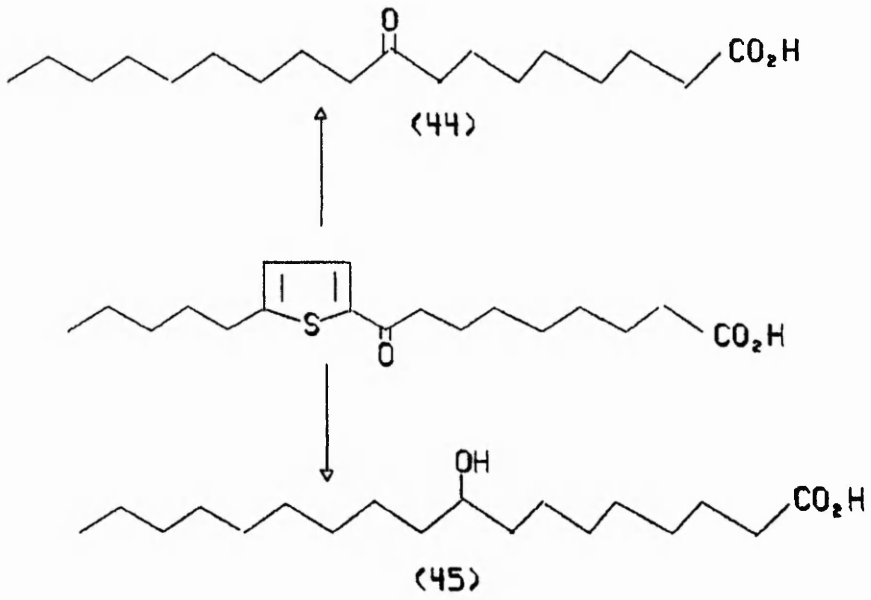
Other groups who have made significant contributions in the area of desulphurisation of thiophenes containing side-chain hydroxy groups include Papa, Schwenk and Ginsberg[43], Badger, Rodda and Sasse[44], Stetter and Rajh[60] and Grey, McGhie and Ross[61].

The preparation of 5-methoxy-and 3-methoxy-valeric acids by Sice[62] and Gronowitz[63], was accomplished by Raney nickel desulphurisation of 5- and 3-methoxythiophene carboxylic acids respectively, as in equation 13:-



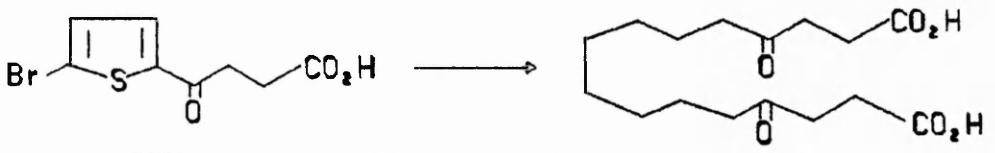

Equation 13

The method of preparation and the quantity of the catalyst used has an influence upon the course of desulphurisation. Grey, McGhie and Ross [61] studied the factors affecting formation of aliphatic hydroxy- and keto acids during hydrogenolysis of various thiophene keto acids. In this, as in an earlier paper [64], they demonstrated that keto acids such as (44) are obtained in yields varying between 20-80% when desulphurisations are performed using either Raney nickel or Raney nickel formed 'in situ' using the Papa-Schwenk method. However, with nickel prepared using the method of Brown [65], hydroxy acids such as (45) are formed. An example of these alternative products is shown in scheme 15:-



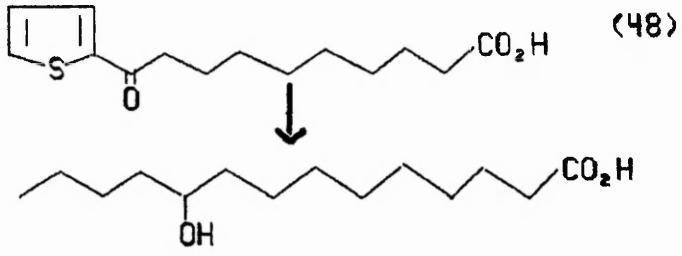

Scheme 15

In their own investigations into the influence of the method of Raney nickel preparation and quantity of catalyst employed, Badger, Rodda and Sasse[46] found that β-(5- bromothenoyl) propionic acid (46) gave only low yields of 4-keto caprylic acid due to the formation of the dimerisation product (47), as in equation 14:-



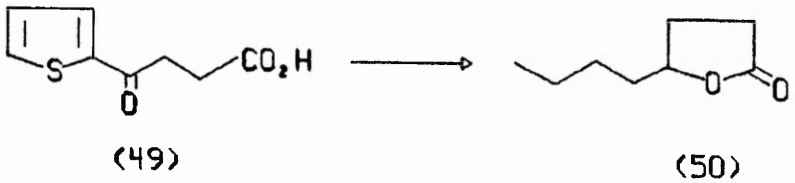
(46) Equation 14 (47)

Papa, Schwenk and Ginsberg obtained 10-hydroxymyristic acid by Raney nickel desulphurisation of 9-(2-thenoyl)-pelargonic acid (48). When the reaction was applied to β-(2-thenoyl)-propionic acid (49) they discovered that upon increasing the amount of Raney nickel the sole product obtained was the lactone (50). These reactions are shown in equations 15 and 16 respectively.



(48)

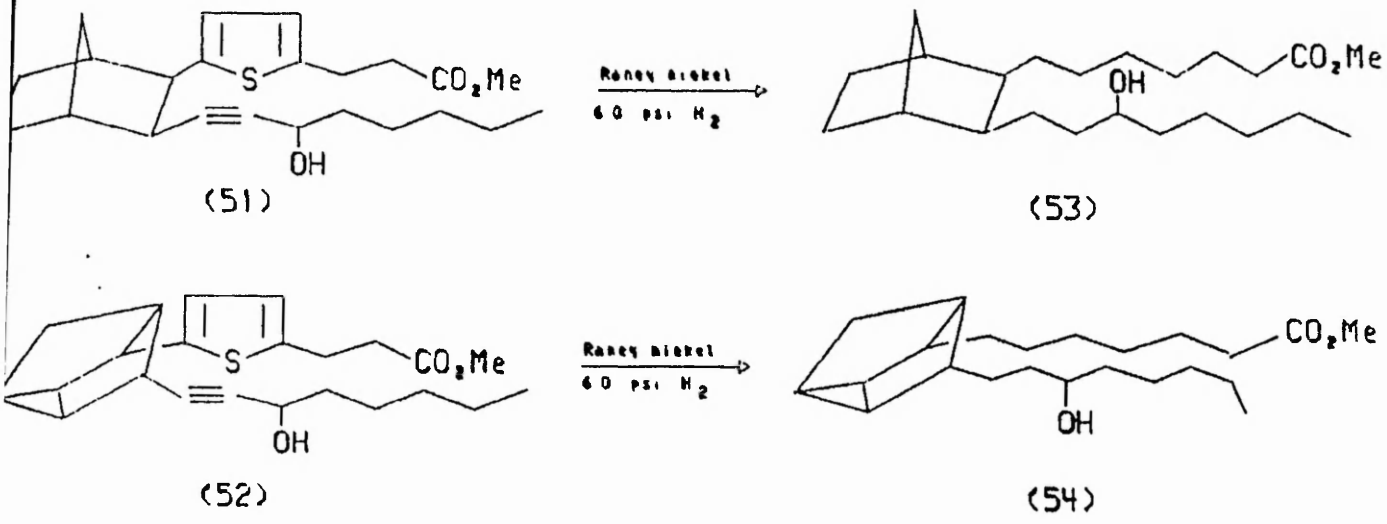
Equation 15



(49) (50)

Equation 16

The synthesis of more complex products in the form of bicyclic (51) and tricyclic (52) prostanoic acids via Raney nickel desulphurisation of the thiophene-containing prostaglandin endoperoxide analogues (53) and (54), was undertaken by Larock, Leach and Bjorge[66]. The desulphurisation, performed under 60 p.s.i. of hydrogen with W7 Raney nickel, proceeded in good yields. This work is summarised in scheme 16:-




Scheme 16

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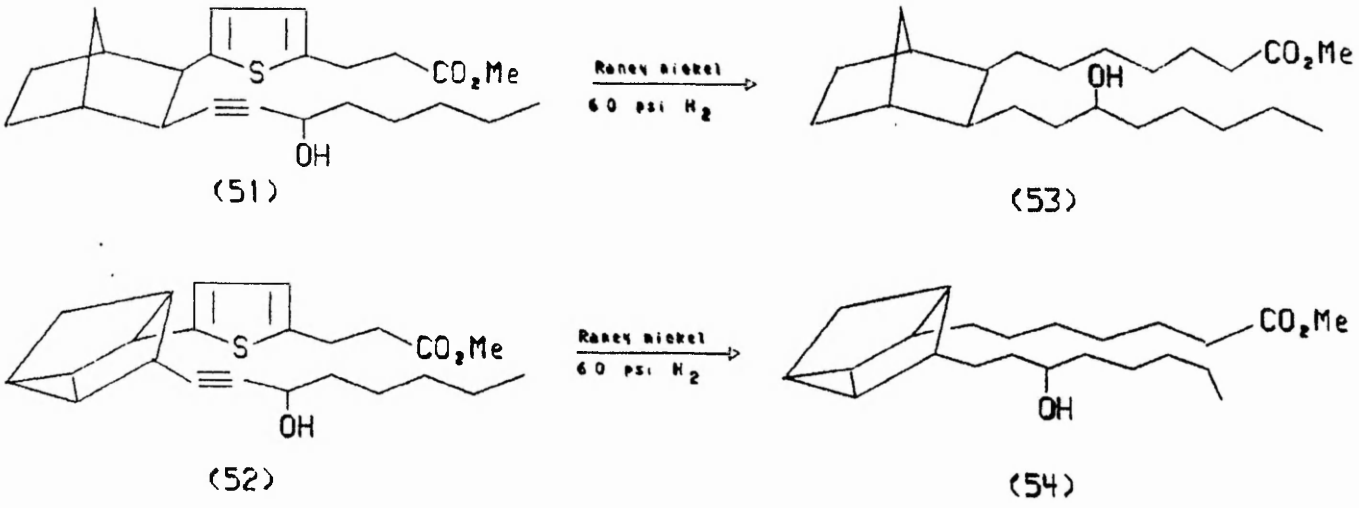



Scheme 16

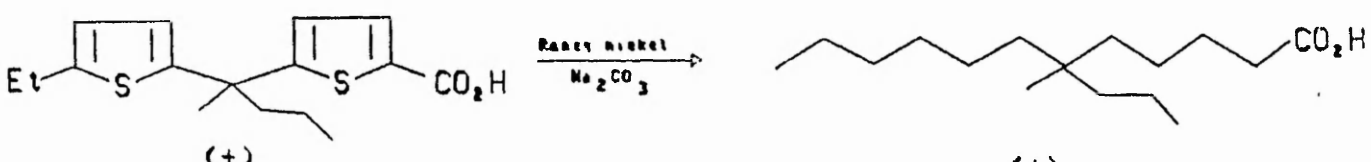
## 2.4 Stereochemical Outcome of the Desulphurisation Process.

That the desulphurisation process does not cause racemisation of chiral centres to occur was demonstrated by Fredga[67] and Petterson[68]. They desulphurised optically active acids such as (55) in order to elucidate the configurations of the desulphurisation products by correlation with the appropriate optically active aliphatic and aromatic acids (equation 17):-


(55)

Equation 17

Wynberg[69] also demonstrated that racemisation does not appear to occur in his synthesis of optically active hydrocarbons containing asymmetric quaternary carbon atoms (equation 18):-




(+) (+)

Equation 18

## 2.4 Stereochemical Outcome of the Desulphurisation Process.

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(55)

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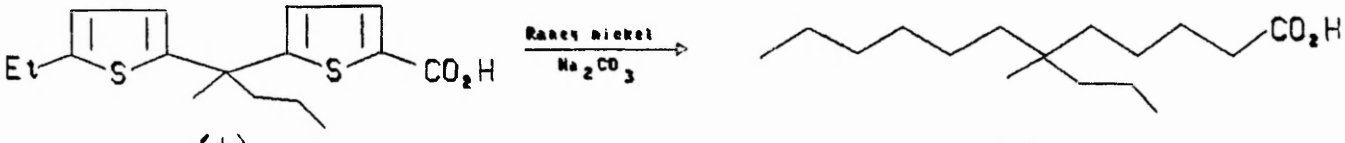
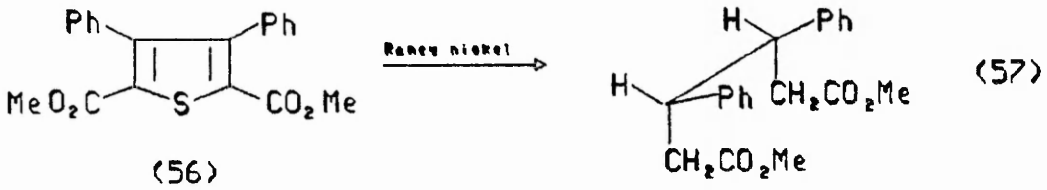



(+) (+)

Equation 18

Dann and Hauck [70] obtained meso-3,4-diphenyladipate (57) from dimethyl-3,4-diphenylthiophene -2,5-dicarboxylic acid (56), indicating that there is, in this case, stereospecificity in the desulphurisation process with respect to substituents attached directly to a thiophene ring, as shown in equation 19:-




(56) (57)

Equation 19

Thus there are precedents in thiophene desulphurisation to suggest that chirality is preserved and that reductions can be carried out which yield only certain stereochemical features.

## 3. Synthesis of Polysubstitued Dithienylketones.

### 3.1. Introduction.

There are two principal methods used in this thesis for preparing substituted dithienylketones, namely the Friedel-Crafts acylation

process and the Fries rearrangement. The general background of these reactions is discussed in this section.

## 3.2. Synthesis using Friedel-Crafts Acylation.

The essential reaction in this process is between an acylating agent (such as an acid chloride) and an aromatic substrate, in the presence of a catalyst, to yield an aromatic ketone, i.e.:-

$$RCOX + ArH \xrightarrow{\text{Catalyst}} ArCOR, Cat., + HX$$

Where X is usually a halogen

Equation 20

## 3.3. Catalysts.

The reaction is very dependant upon the choice of catalyst, the ratio of catalyst:substrate and the choice of solvent. Metallic halides which have been used with acyl halides include aluminium (III) chloride, aluminium (III) bromide, iron (III) chloride and titanium (IV) chloride.

The high catalytic activity of aluminium (III) chloride, i.e. its high Lewis acid strength [71 - 74] can also bring with it certain disadvantages. The catalyst cannot be used, for example, with a number of heterocyclic systems which it decomposes even in the presence of moderating solvents.

The use of aluminium (III) chloride can also give rise to side-reactions such as intra- or inter-molecular migration of alkyl groups [75-77], removal of alkyl groups (especially tertiary) preceding or accompanying acylation [78-84]. Splitting of ortho-alkoxyl groups, both within the acyl halide [85-87] and, more often, on the substrate [88-89], also occurs. These effects, largely due to aluminium (III) chloride, are minimised by use of a solvent such as nitrobenzene in which the catalyst is complexed. Tin (IV) chloride, first employed by Stadnikoff [90], is especially valuable for highly reactive substrates such as oxygen or sulphur heterocycles, which may be unstable in the presence of aluminium (III) chloride. Dermer [91-92] found that the relative activities of halide Lewis acid catalysts for the acylation of toluene are in the following order:-

$$AlCl_3 > SbCl_5 > FeCl_3 > TeCl_2 > SnCl_4 > TiCl_4 > TeCl_4 > BiCl_3 > ZnCl_2$$

In certain cases mineral acids have been employed with marked success. Phosphoric acid has been shown to be a very effective catalyst for use with anhydrides, especially in the thiophene series [93-94] and polyphosphoric acid, first used for cyclisations, has found use in intermolecular acylations. Boron trifluoride and its complexes with ether, methanol and acetic acid are pre-eminent among non-metallic halides capable of catalysing acylations [95].

Boron trifluoride and phosphorus pentachloride have also been used as acylation catalysts [96 - 97]. In almost all cases the optimum amount of catalyst employed is found to be up to, or just over, the calculated stoichiometric amount.

### 3.3. Choice of Solvent.

A variety of solvents have been employed in Friedel-Crafts aromatic ketone synthesis. Nitrobenzene and carbon disulphide are the most commonly used solvents which at the same time govern the types of acylation reactions: essentially homogeneous, and essentially heterogeneous acylations, respectively. Polar solvents such as nitrobenzene dissolve (and solvate) both aluminium (III) chloride and the acyl chloride-aluminium chloride complex, and usually also the aluminium chloride complex of the resulting ketone [98 - 99]. In non-polar solvents such as carbon disulphide, light petroleum or carbon tetrachloride, neither aluminium (III) chloride nor its complex with acyl halides is appreciabl soluble; the reaction is largely heterogeneous throughout its course. Intermediate to these are chlorinated solvents such as dichloroethane or dichloromethane. which do not appreciably dissolve aluminium (III) chloride [99] but are excellent solvents for the final complex. The main influence of the solvent in acylations of benzenoid or heterocyclic systems is on the yield of ketone obtained. There are also less significant differences between solvents with respect to acylation rates [100, 101] and also in orientation of substitution [102 - 105].

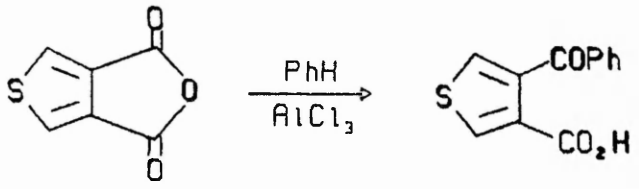
## 3.4. The Friedel-Crafts Acylation of Thiophenes.

Acylation of thiophene leads almost exclusively to monosubstitution. It can be effected by a variety of catalysts. Anhydrous aluminium (III) chloride and to a lesser extent tin (IV) chloride react with thiophene to yield intractable tars. However, this undesirable resinification is largely avoided by adding the catalyst gradually to a mixture of the thiophene and the acylating agent, when the catalyst reacts preferentially with the acylating agent to give the electrophile. In the presence of tin (IV) chloride or titanium (IV) chloride benzene can be used as solvent, since these inorganic chlorides do not initiate reaction between benzene and the acid chloride.

It has been found that acylation of thiophene with acetic anhydride or benzoyl chloride is promoted by catalytic amounts of iodine and hydriodic acid [106] or boron trifluoride complexes [107]. Thiophene, 3-methyl-, and 2,5-dichlorothiophene react with acid anhydrides or acid chlorides, in the presence of orthophosphoric acid, to form acyl derivatives in very good yields [108]. Thiophene can also be acylated with an aliphatic or aromatic acid and phosphorus pentoxide [109].

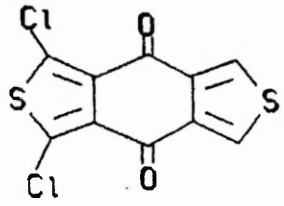
Friedel-Crafts acylation can be succesful with deactivated thiophene rings, although yields are often poor. Ethyl thiophene-2-carboxylate gives the 5-acetyl derivative with acetic anhydride and zinc chloride [110]; esters of thiophene-3-carboxylic acid are also acylated at C-5 [111 - 112]. In a reversal of this approach, a thiophene dicarboxylic

acid anhydride can be used as a monoacylating agent. The reactions of thiophene-3,4-dicarboxylic acid anhydride with benzene-aluminium (III) chloride [113], [114] and with dimethylcadmium [115], (which gave 4-benzoyl- and 4-acetyl thiophene-3-carboxylic acids in 66% and 32% yields respectively), illustrates the possibilities, as in equation 21:-




Equation 21

Thiophenecarboxylic acid chlorides derived from all types of acids behave quite normally as Friedel-Crafts acylating agents. Reactions have been carried out with a very large number of benzene derivatives; biphenyl and fluorene [116], 2- and 3-methoxy benzo (b) thiophenes and a wide range of other heterocyclic systems have been substrates for thenoylation. Aluminium (III) chloride catalysed the bis acylation of 2,5-dichlorothiophene by thiophene-3,4-dicarboxylic acid chloride leading to an excellent yield of the quinone [117], shown in figure (58):-

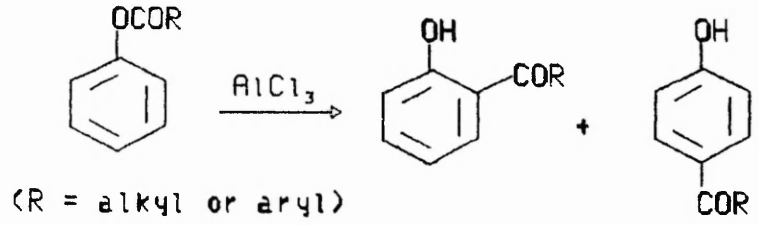



(58)

## 3.4. The Fries Rearrangement.

### Introduction:

The Fries rearrangement is essentially an intramolecular Friedel-Crafts reaction whereby an ester of a phenol rearranges to give a hydroxy-ketone, usually in the presence of aluminium (III) chloride. The reaction was first studied in the benzene series and was first observed in 1908 [115]. A typical rearrangement of the benzene series is shown in equation 22:-



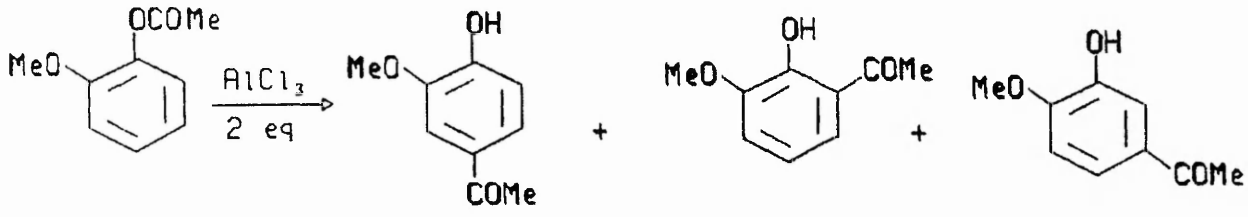

Equation 22

In general, low temperatures (60°C or less), favour rearrangement to the p-isomer whereas higher temperatures (above 160 degrees) favour the o-isomer. The rearrangement is a useful synthetic route to ketones in spite of the fact that it involves two steps -preparation of the ester and then the rearrangement- as compared to the single step Friedel-Crafts synthesis. The yields are usually better and the experimental procedure does not have to be modified greatly to be adapted to a variety of esters.

## 3.5. Choice of Catalyst.

The commonest catalyst employed in the Fries rearrangement is aluminium (III) chloride although other Lewis acids such as tin (IV) chloride, titanium (IV) chloride and zirconium (IV) chloride have also been used. An equimolar ratio of the catalyst: ester substrate is the standard reaction procedure. However, the nature of substituents may affect the quantity of catalyst required. In the rearrangement of guaicol acetate [119], two moles of aluminium (III) chloride are required, and it has been suggested that the extra mole is necessary because a complex is formed with the methoxy group [120].

The guaicol acetate rearrangement [121] is of interest because three products are obtained, the usual two and some arising from meta attack. The latter is rare in Fries rearrangements. Equation 23 shows an example of rearrangemant of this type:-




26.3% 1.0% 5.6%

Equation 23

The Friedel-Crafts reaction of guaicol and acetyl chloride furnishes the same products, making it evident that the formation of the m-product is related to the o-methoxy group and not a peculiarity of the Fries rearrangement. It has also been found that the proportion of p-hydroxyketone produced by phenyl caprylate in the presence of two moles of aluminium chloride is higher (63% para: 30%) ortho) than that in experiments in which only one mole of aluminium chloride is used (45% para: 33% ortho)[122]. It should be noted that the increase in yield of the para product is at the expense of the ortho-product. The influence of catalyst concentration upon product distribution can also be illustrated by results obtained with aluminium (III) chloride and phenyl acetate[123]. At the molar ratio of catalyst to ester shown in parentheses, the ratios of para- to ortho- yields were 2.93(0.5), 2.41(1.0) and 10.1(2.0), the second mole of catalyst causing a large increase in the yield of para- product.

## 3.6. Structure of the Acyl Radical.

The acyl radical may be either aliphatic or aromatic. Rosenmund and Schnurr[124] studied the relative rates at which Fries rearrangement takes place with different esters of thymol. Their results are summarised below, the acyl groups being arranged in order of decreasing rate of reaction:-

$$C_nH_{2n}CO (n=1 \text{ to } 5) > PhCH_2CO > Ph(CH_2)_2CO > PhCH=CHCO > PhCO$$

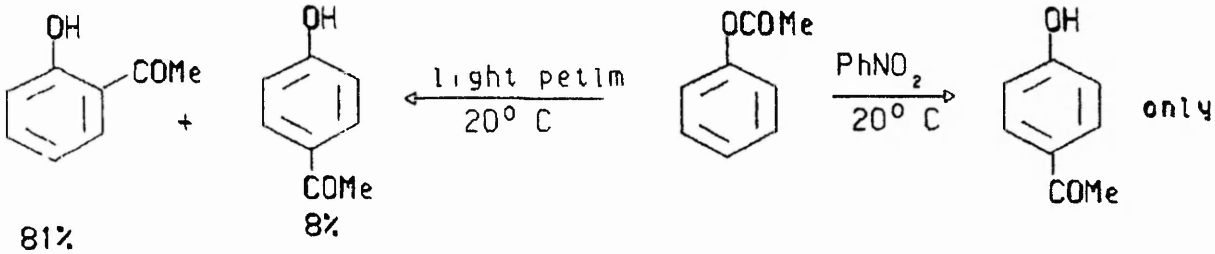
An example of the magnitude of the differences in rate is that after five hours in nitrobenzene at 20 degrees C the rearrangement of thymol acetate was 60% complete, whereas that of thymol benzoate was only 4% complete.

## 3.7. Structure of the Phenoxy Group.

The structure of the phenoxy portion of the ester is the factor of greatest importance in determining whether the Fries rearrangment will take place or not and whether the products will consist principally of the o- or p- hydroxyketone. The presence of a meta-directing group on the aromatic ring usually interferes with the rearrangement. For example, the Fries rearrangement does not occur if the phenolic residue carries a nitro or benzoyl group in either an ortho- or para-position; the presence of an acetyl or carboxyl group in the ortho-position hinders the rearrangement and in the para-position prevents it [125 — 126]. If the phenyl esters contain a single alkyl group in the phenolic ring the position of this substituent has a profound influence on the nature of the product. This is demonstrated by the fact that esters of o-cresol yield predominantly p-hydroxyketones, whilst the m-isomer yields chiefly the o-product, and the p-derivative gives exclusively the latter.

3.8. Choice of Solvent.

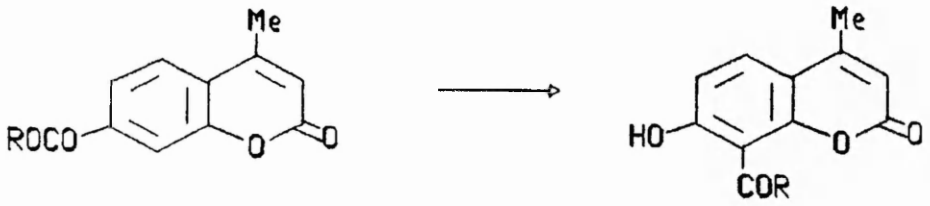
The Fries rearrangement can be carried out in the absence of solvent but the temperature at which the reaction proceeds at a useful rate is lowered by solvents such as nitrobenzene [120, 123]. A large solvent effect on the product distribution can be seen by comparing the rearrangement of phenyl acetate in nitrobenzene [124] and light petroleum [126], as in scheme 17:-




Scheme 17

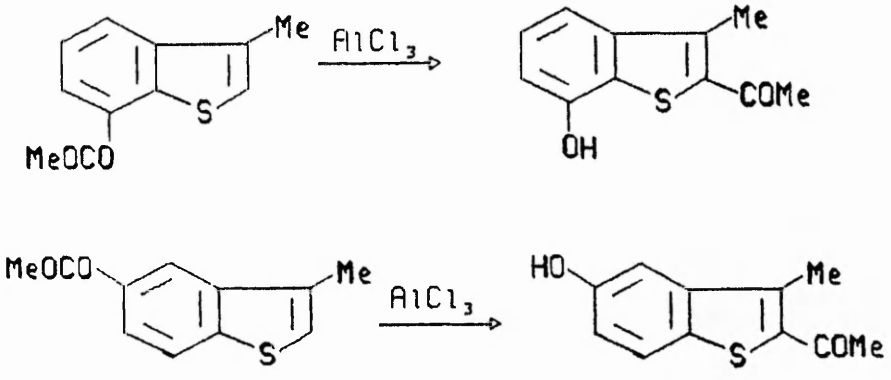
## 3.9. Fries Rearrangement in Heterocyclic Phenols.

The Fries rearrangement has been observed in many heterocyclic systems. For example, the rearrangement proceeds normally in esters of hydroxycoumarins [127 – 130] as in Equation 24.



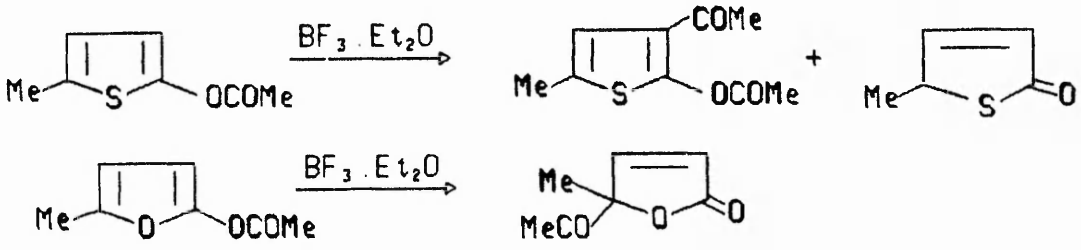

Equation 24

Chapman et al[131] observed the rearrangement in the benzo(b)thiophene series, 7-acetoxy-3-methyl benzo(b)thiophene, on treatment with aluminium (III) chloride in dry benzene, gave 2-acetyl-7-hydroxy-3-methyl benzo(b)thiophene in 78% yield. This result was in accord with an earlier report[132] in which the 5-acetoxy-3-methyl isomer was rearranged to give the 2-acetyl isomer. These reactions are summarised in scheme 18:-




Scheme 18

The rearrangement of 2-acetyloxyfurans and thiophenes with boron trifluoride etherate, studied by Kraus and Roth[133], is shown in scheme 19:-




Scheme 19

Banks[134] investigated the Fries rearrangement of ten 3-alkanoyloxythiophenes, using dichloromethane as solvent and aluminium (III) chloride as catalyst, to give 3-hydroxy-2-alkanoyl thiophenes in good yields. It was found that the structure of both the acyl and 3-thiophenoxy moieties exert an influence on the rearrangment. For example, acetyl esters rearrange at a faster rate than propionyl esters. The presence of an ester or cyano group in the 4-position did not interfere with rearrangement, whereas an acetyl group prevented it; the presence of a second ester group in the thiophene ring also prevents rearrangement, the final product simply being that of deacylation of the hydroxy function.

Since the publication of this work in 1986 no further work in this area has appeared in the literature.

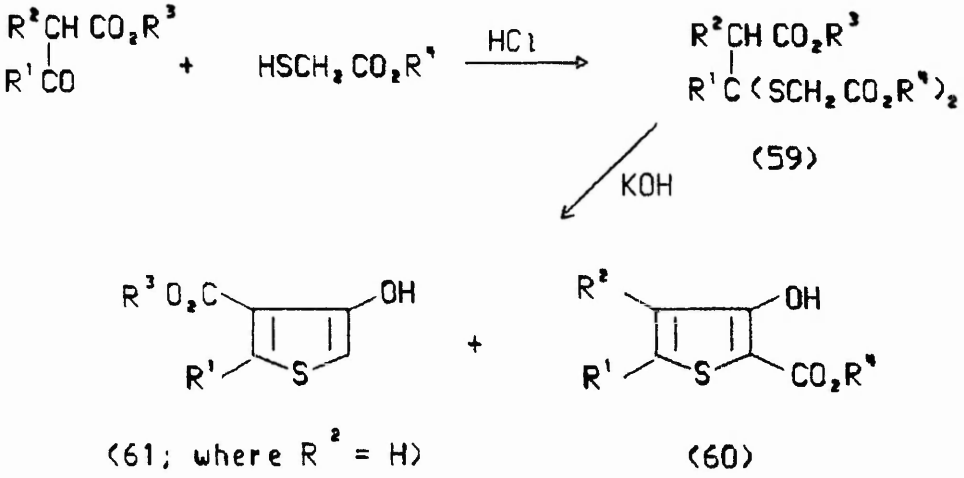
## 4.0. The Synthesis of Hydroxythiophene Carboxylic Acids and their Derivatives.

### 4.1. Introduction.

The synthesis of the various hydroxythiophene carboxylic acids almost always incorporates cyclisation reactions, usually utilising an appropriate thioester. A summary of some of the more general methods employed for the synthesis of hydroxythiophene carboxylic acids used in this thesis is now given, these being amongst the more readily accessible compounds. However, it should be pointed out that other hydroxythiophene carboxylic acids are known.

## 4.2. Synthesis of 3-Hydroxythiophene-2-carboxylic Acids.

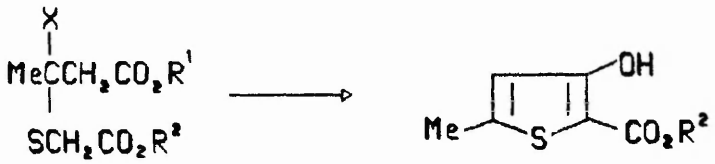
These are readily synthesised via the thioketals (59), formed from β-keto esters and thioglycolates. 3-Hydroxythiophene-2-carboxylates (60) [135-137] are then synthesised by base induced cylisation, in good yield as depicted in scheme 20:-




Scheme 20

When $R^2$=H, 4-hydroxythiophene-3-carboxylate (61) is formed as an alternative product. When $R^1$ is either isopropyl or t-butyl [138] it is formed in approximately 40% yield, but is not a significant product in other cases.

In a related synthesis, Dieckmann cyclisation of the mixed ketals (62a)[139] and (62b)[140], yielded 5-methyl-3-hydroxythiophene-2-carboxylate (63), as shown in equation 25:-

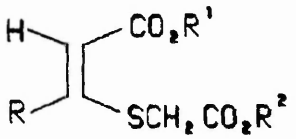



(62); a, X = OH
b, X = SEt

(63)

Equation 25

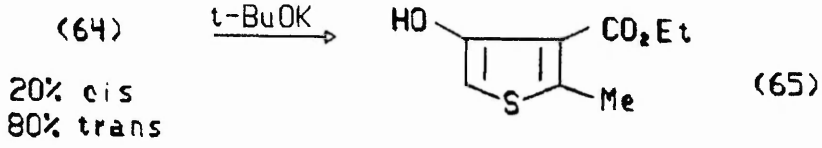
Immediate precyclisation intermediates of the type (64) are implied in the preparation of 3-hydroxythiophene-2-carboxylates from thioglycolates and propiolic esters[141,142]




(64)

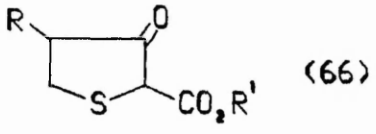
Such intermediates are readily synthesised by the combination of a halogeno acetate and an enethiolate[143-144]. A mixture of the cis (80%) and the trans (20%) forms of (64), [R=H, $R^1$=$R^2$=Et] can be cyclised normally with potassium hydroxide-methanol. However, when the proportions of stereoisomers are reversed, the reaction fails with

this base, although with potassium-t-butoxide cyclisation takes an alternative course to give ethyl 4-hydroxy-2-methylthiophene-3-carboxylate [145] (65), shown in equation 26:-




Equation 26

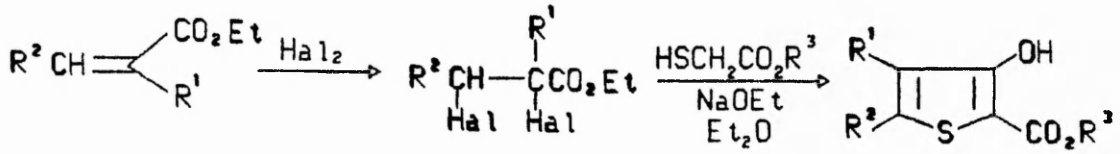
Dehydrogenation of oxotetrahydrothiophenecarboxylates such as (66) and their enol ethers and acetates, all prepared via Dieckmann cyclisations, yields hydroxy thiophene carboxylic acid derivatives.



(66)

Fiesselman and Pfeiffer [139] obtained (60) [$R^1$=Me, $R^2$=H, $R^3$=Et] from bromination of the oxotetrahydrothiophene followed by dehydrobromination. In a more recent method, the cyclic ketone, or one of its enol derivatives, is reacted with sulphuryl chloride in dichloromethane at 0° C, giving excellent results with (66) [R=H, $R^1$=Me] and with the enol acetate and mesylate of the same substance [145].

The Fiesselmann synthesis, in which an α,β-dihalogeno ester [146], or α-chloroacrylate [147] is reacted with an alkyl thioglycolate in the presence of base, as in scheme 21, provides a simple and attractive route to 3-hydroxy thiophene-2-carboxylates (67):-

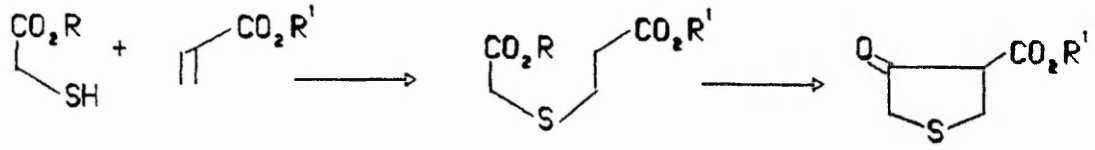



(67)

Scheme 21

4.3. **Synthesis of 4-Hydroxythiophene-3-Carboxylic Acids.**

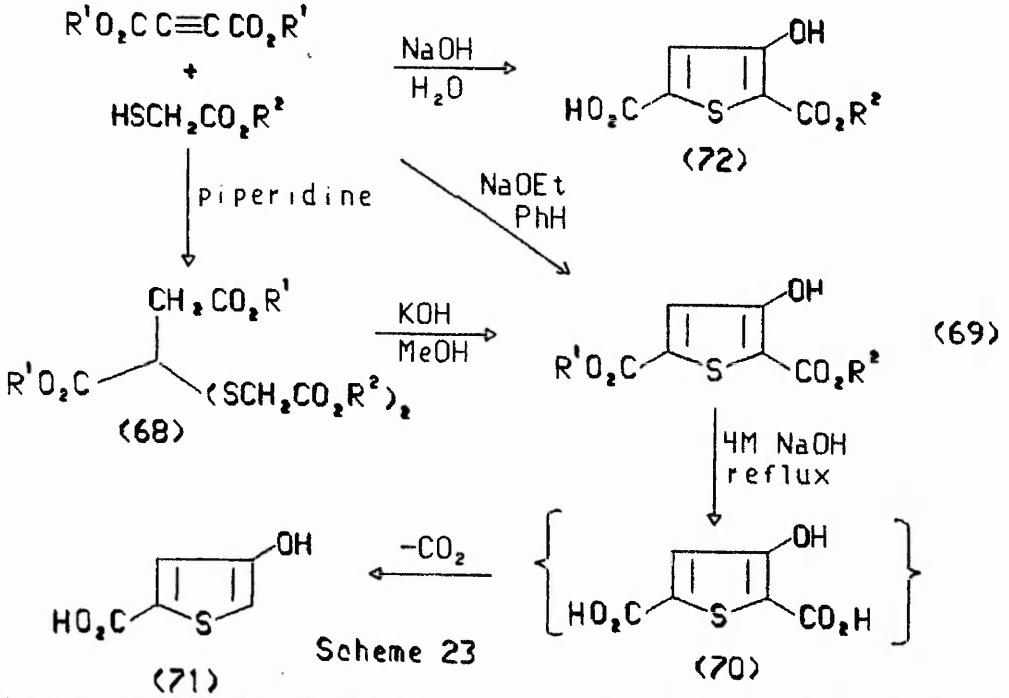
The most commonly used method of preparation of these acids and their derivatives is through the aromatization of 4-oxotetrahydrothiophene-3-carboxylates. The method has proved extremely versatile and enabled the preparation of numerous 4-hydroxy, -methoxy and -acetoxy compounds in this class [148-153]. The use of hydrogen peroxide has also been shown to give good yields from several ethyl 5-aryl-4-oxotetrahydrothiophene carboxylates [154-155]. The starting materials are made via cylisation as shown in scheme 22:-




Scheme 22

## 4.4. Synthesis of 3-Hydroxythiophene-2,5-Dicarboxylic Acids.

Fiesselmann and his co-workers have shown that some interesting variations are possible in the reactions of acetylene dicarboxylates and thioglycolates. In the presence of piperidine the thioketals (68) are obtained.[156] On treatment with potassium hydroxide-methanol these give dialkyl 3-hydroxythiophene-2,5-dicarboxylates (69); vigorous hydrolysis with aqueous sodium hydroxide then gives 4-hydroxythiophene-2-carboxylic acid (71) by way of the diacid (70)[157]. Condensation of the acetylenic ester and glycolate, induced by sodium ethoxide-benzene leads directly to (69)[158] but with aqueous sodium hydroxide the half ester (72) is produced[156-159]. These reactions are summarised in scheme 23:-




Scheme 23

Fiesselmann's synthesis of thiophenes from appropriate 1,2-dihalogeno compounds is also applicable here. Dimethyl 2,3-dibromosuccinate and

methyl thioglycolate form (69), ($R^2$=Me), when treated with potassium hydroxide in methanol [159].

## 4.5. Dihydroxythiophene Carboxylic Acids.

The Hinsberg synthesis of 3,4-dihydroxy thiophene-2,5-dicarboxylates from thiodiacetates and dialkyl oxalates is still the best available. It has been used to prepare the dimethyl [160] and diethyl esters [142] [161 – 163] and a patent [164] gives an account of the results of variations in the solvent, in the thiodiacetate, and in the condensing agents used.

## 4.6. Summary.

It can be seen that it is possible to synthesise a wide variety of hydroxythiophene carboxylic acids, readily and in good yields. It is the aim of this thesis to utilise this in order to prepare a wide range of polysubstituted dithienyl ketones via Friedel-Crafts reactions and Fries rearrangement. These will then form precursors to a large number of seco acids, which may be obtained via the desulphurisation process. This thesis makes an initial investigation into the potential of this route as a means of synthesising various seco acids in good yield from readily available starting materials in a small number of steps.

# RESULTS AND DISCUSSION

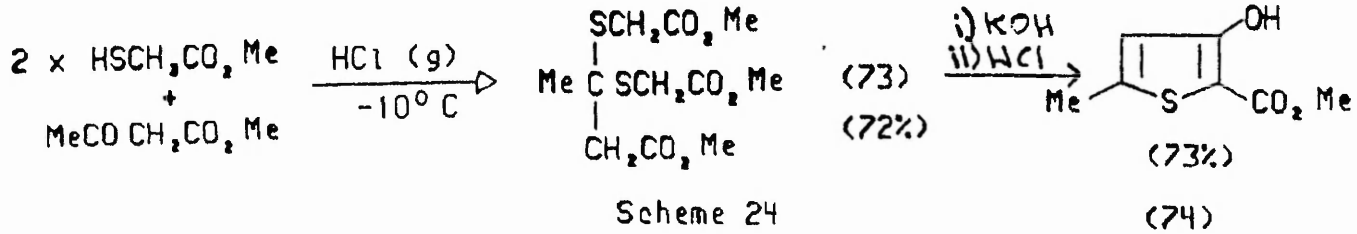
## 5.0. Preparation of Starting Materials.

### Introduction.

Almost all the starting materials employed in the work described in this thesis were obtained using published methods. The general methodology involved Michael-type conjugate addition of the thioglycolate anion to a substrate of the form C=C-X (X being an electron withdrawing group, in this case usually an ester), followed by a Dieckmann condensation [165] (generally brought about by alkoxide). Where this condensation gave the tetrahydrothiophene, oxidation with hydrogen peroxide in methanol [155] was employed.

## 5.1. Synthesis of Hydroxythiophenecarboxylates.

Formation of the thioketal (73) using the acid catalysed addition of 2 molecules of methyl thioglycolate to methyl acetoacetate was followed by base-catalysed cyclisation to give methyl 3-hydroxy-5-methylthiophene-2-carboxylate [135] (74) thus avoiding any oxidation stage:-




Scheme 24

## RESULTS AND DISCUSSION

### 5.0. Preparation of Starting Materials.

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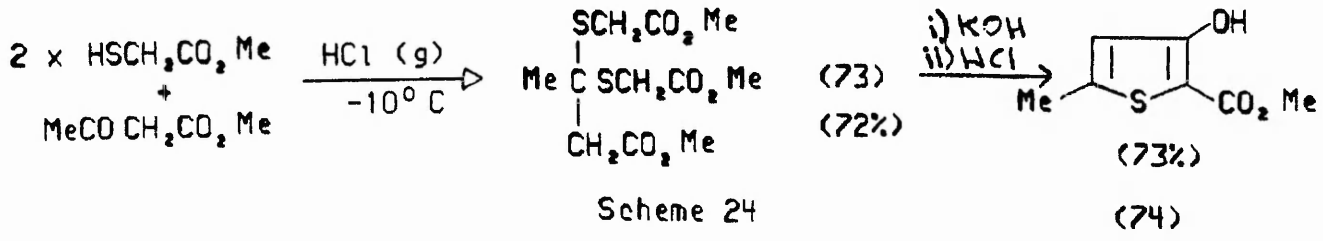
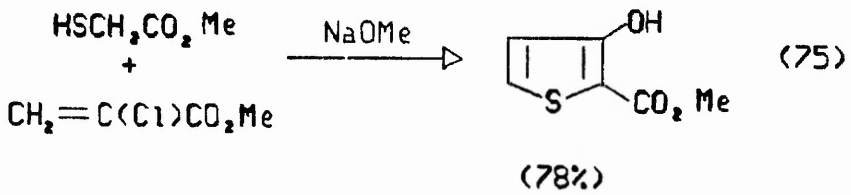



Scheme 24

The need for an oxidation stage is also avoided in the synthesis of methyl 3-hydroxythiophene-2-carboxylate (75), as the cyclisation of the Michael adduct is followed by elimination of hydrogen chloride to yield the thiophene[147].



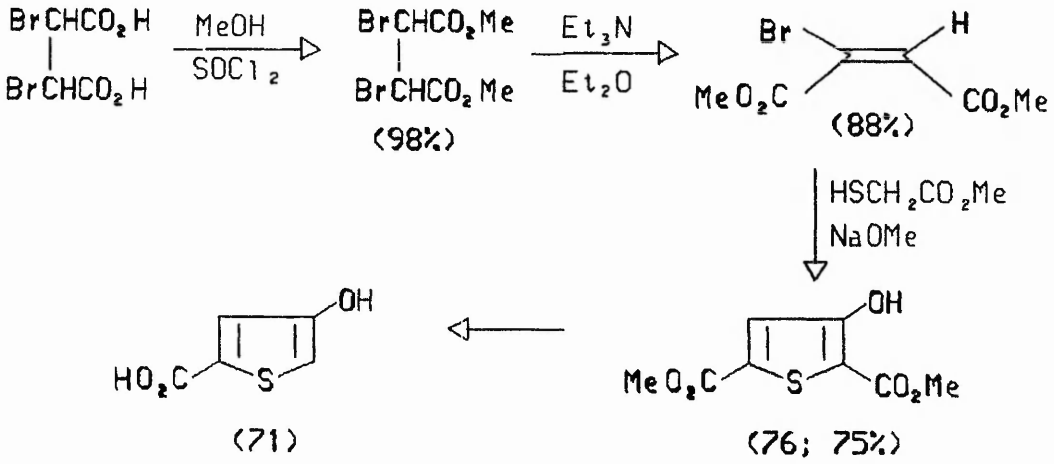

(75)

(78%)

Equation 27

The preparation of dimethyl 3-hydroxythiophene-2,5-dicarboxylate (76) may be brought about by a "one-pot" method in which dimethyl acetylene dicarboxylate is treated with methyl thioglycolate and sodium methoxide[153]. However, for reasons of economy, this compound was prepared using the method developed by Huddleston[166] which involved the esterificaion of the readily available 2,3-dibromosuccinic acid using thionyl chloride in methanol, followed be elimination of hydrogen bromide in the presence of triethylamine in ether to yield

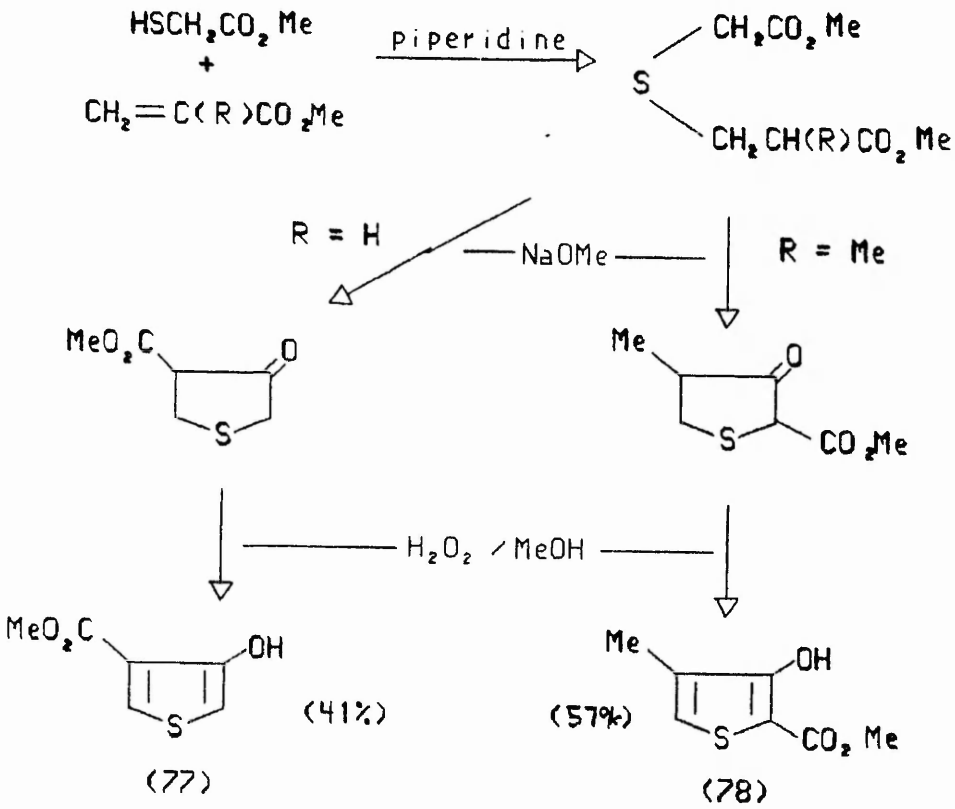
dimethyl bromomaleate. The product (76) was obtained in excellent yield by treatment of the bromomaleate with methyl thioglycolate and sodium methoxide. Hydrolysis with sodium hydroxide followed by decarboxylation then yields the 4-hydroxythiophene-2-carboxylic acid (71), as described by Fiesselmann[141]. These reactions are summarised in scheme 25:-




Scheme 25

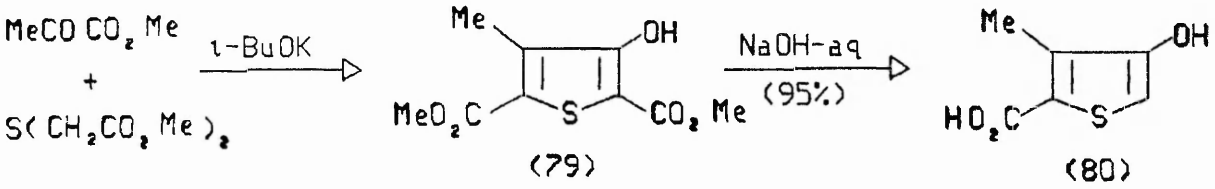
Methyl 3-hydroxythiophene-4-carboxylate (77) and methyl 3-hydroxy-4-methyl-thiophene-2-carboxylate (78) were synthesised from the intermediates prepared by Woodward and Eastman[167] again utilizing

the Michael addition of methyl thioglycolate to a methyl acrylate followed by methoxide ring closure[152]. Aromatisation was accomplished using hydrogen peroxide in methanol[155].



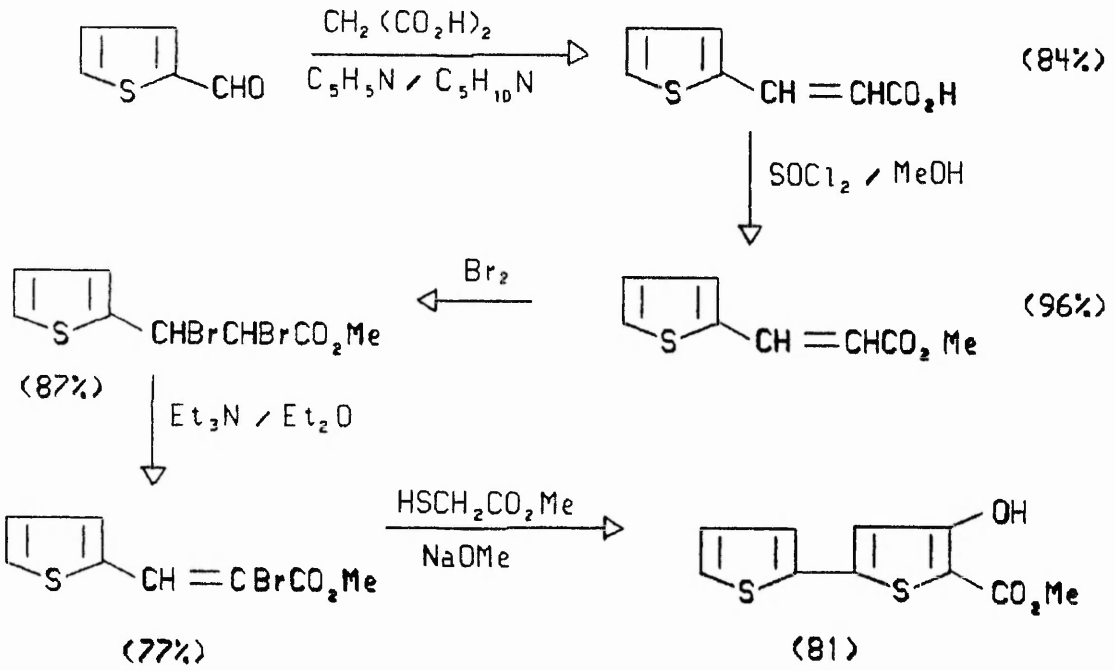

Scheme 26

4-Hydroxy-3-methylthiophene-2-carboxylic acid (80) was prepared using the method of Paranjpe[168]. This involved alkoxide-catalysed condensation of methyl pyruvate with dimethylthiodiacetate to give dimethyl 4-hydroxy-3-methyl thiophene-2,5-dicarboxylate, (79), again via Dieckmann condensation. Saponification by refluxing with 10% aqueous sodium hydroxide then gave (80) :-



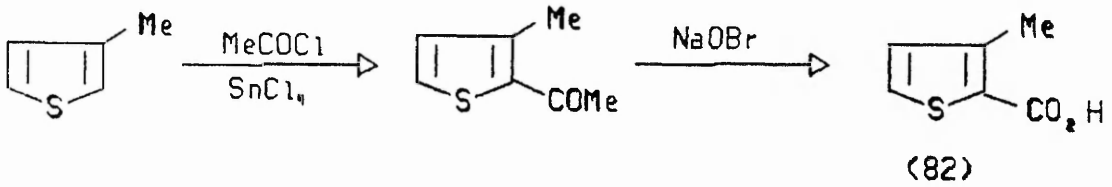

**Scheme 27**

Preparation of methyl 4-hydroxy-2,2'-bithienyl-5-carboxylate (81) was accomplished using a method devised by Cummins[169]. This involved formation of 3-(2-thienyl) acrylic acid using the Perkin reaction of malonic acid with thiophene-2-carboxaldehyde. Formation of the methyl ester using thionyl chloride in methanol was followed by bromination. Elimination of hydrogen bromide followed by a one step Michael addition and Dieckmann condensation then leads to (81) in excellent yield.




**Scheme 28**

3- Methylthiophene-2-carboxylic acid (82) was prepared by Friedel-Crafts acylation of 3-methylthiophene followed by hypobromite oxidation to give the required product in 66% yield:-




(82)

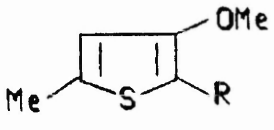
**Scheme 29**

5.2. <u>O-Methylation. Saponification and Decarboxylation of Thiophene Units.</u>

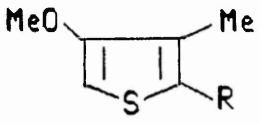
In order to convert the hydroxythiophene carboxylates described previously (5.1.) into acid chlorides, or to use them as a means of obtaining different methoxythiophenes for Friedel-Crafts acylation, it was necessary to O-methylate, saponify and, in the case of compounds used as substitutes for acylation, decarboxylate them. O-methylation was carried out using dimethyl sulphate with potassium carbonate, giving excellent yields in all cases. The usual saponification procedure of heating in 10% aqueous sodium hydroxide also gave excellent yields and decarboxylation was accomplished by heating with

copper bronze under vacuum, the product distilling out. Scheme 30 shows some of the key intermediates that were prepared and the compounds that led to them: -

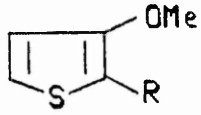
**Key Intermediates: -**



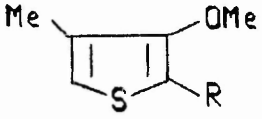

R = $CO_2Me$ (83)
R = $CO_2H$ (84)
R = H (85)




R = $CO_2Me$ (88)
R = $CO_2H$ (89)
R = H (90)




R = $CO_2Me$ (86)
R = $CO_2H$ (87)

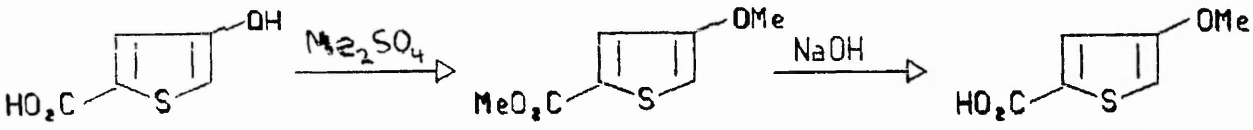



R = $CO_2Me$ (91)
R = $CO_2H$ (92)

**Scheme 30**

Decarboxylation of (84) to (85) was accomplished in 70% yield whilst conversion of (89) into (90) proceeded in 62% yield. Decarboxylation of (92) was not attempted as it would have given the same product as that obtained from (89).

Methyl 4-methoxythiophene-2-carboxylate (93) was prepared in 71% yield by refluxing (71) with two equivalents of dimethyl sulphate. Saponification was then carried out in the usual way to give 4-methoxythiophene-2-carboxylic acid (94):-




(71) (93; 71%) (94; 92%)

**Scheme 31**

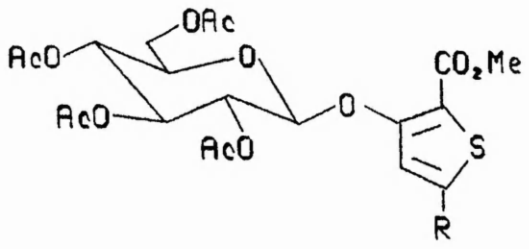
## 6.0. O-Glycodisation of Hydroxythiophene Carboxylates.

### 6.1. Introduction.

It was mentioned in the introduction to this thesis (Section 1.1.) that in order to show antibiotic activity macrolide antibiotics must possess the appropriate sugar moiety (s). To this end it was decided to see if it was possibe to attach sugar residues to hydroxythiophene carboxylates. As the majority of sugar residues found in macrolide antibiotics are rare, and therefore expensive, it was decided to attach a pyranosyl ring to a hydroxythiophene carboxylate. The fact that this proved possible means that it may be possible to attach the appropriate sugars to hydroxythiophene carboxylates and from these prepare seco-acids containing sugar residues. It may even be possible that such seco-acid segments (with appropriate sugar (s)) exhibit biological activity, but it is not within the realms of this thesis to investigate this.

6.2. Preparation of Hydroxythiophene-O-glycosides.

2,3,4,6-Tetra-O-acetyl-oc-D-glucopyranosyl bromide was prepared by treatment of 1,2,3,4,6-penta-O-acetyl-D-glucopyranose with hydrogen bromide in glacial acetic acid as described in Hickinbottom[170]. The bromo compound was then refluxed with methyl 3-hydroxythiophene-2-carboxylate (75) in the presence of potassium carbonate using acetone as solvent to give methyl 3-(tetra-O-acetyl)-β-D-glucopyranoxy)thiophene-2-carboxylate (95) in 38% yield. Similarly, reaction of the bromo compound with methyl 3-hydroxy-5-methyl thiophene-2- carboxylate (74) gave methyl 5-methyl-3-(tetra-O-acetyl-β-D-glucopyranoxy)-2-carboxylate (96) in 43% yield:-




(95); R = H
(96); R = Me

Figure 3

6.3. Discussion.

It should be stressed that no attempt has been made to investigate the stereochemistry of this reaction and the configurations given are

based upon the following rationale; in the presence of bromide ions anomerisation occurs in tetra-O-acetyl-D-glucopyranosyl bromide to give an equilibrium mixture containing at least 93% of the α-anomer [171] (figure 4.). As these compounds have strong electronegative C-1 substituents the anomeric effect is particularly significant and, consequently, there is a marked preference for those anomers which possess conformationally stable rings to which are attached axial bromide. Since the preparation conditions employed allow equilibrium, the more stable anomers are obtained in high yields. Thus bromination of 1,2,3,4,6-penta-O-acetyl-D-glucopyranose gives predominantly 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide.

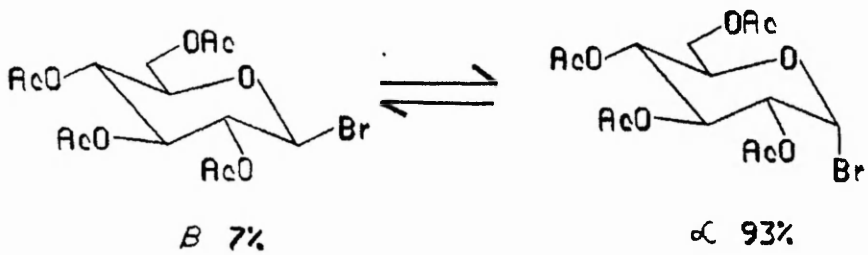



**Figure 4**

Reaction of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide with a phenol proceeds via displacement of halide. Although this is reported [171] to be a unimolecular mechanism, products formed by Walden

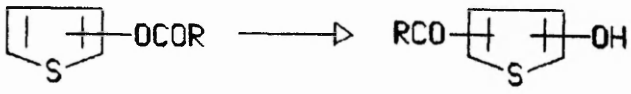
inversion predominate because the halide ions shield the sides of the pyranoid rings from which they depart. In reactions involving 1,2 cis-acylglycosyl halides such as 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide, the halide is displaced with inversion of configuration at C-1. Thus it is suggested by the present author that the likely configurations of the two glycosides synthesised in the present work will be the β-anomers.

## 7.0. Preparation of Polysubstituted Thienyl and Dithienyl Ketones via Fries Rearrangement.

### 7.1. Introduction.

The main aim of the present work was to prepare a series of polysubstituted thienyl and dithienyl ketones containing a variety of hydroxyl functions and methyl groups, which, upon desulphurisation, would yield seco acids similar to those used in the synthesis of the macrolide antibiotics.

The Fries rearrangement of appropriate acylated hydroxy compounds, i.e.:-




**Equation 28**

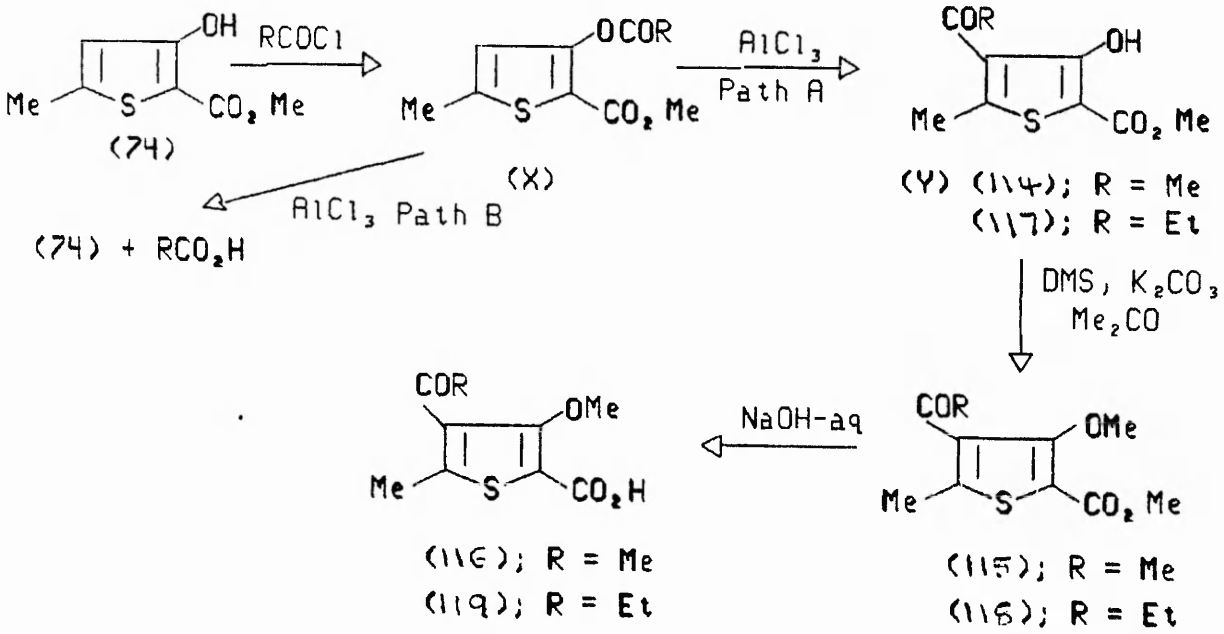
has the advantage of leaving a free hydroxyl group and gives a wide choice of ketonic products which would otherwise be difficult to obtain. The disadvantage of this method is that sometimes deacylation can occur, with no subsequent substitution.

In order to effect Fries rearrangement it was first necessary to prepare a series of esters by acylating the hydroxythiophene carboxylates described in Section 5.1. Acylation was carried out by treatment of the hydroxythiophene with acetic anhydride, or with the appropriate acid chloride in anhydrous pyridine. Where methoxythiophene acid chlorides were employed, they were prepared by refluxing the acid with thionyl chloride, followed by distillation. In some cases the acid chlorides were used without distillation.

The standard reaction conditions used for Fries rearrangement in this study were those employed by Banks[134] for the Fries rearrangement of acetoxythiophenes, i.e. treatment of the ester (1 part by weight) with anhydrous aluminium(III)chloride (3 parts) in dichloromethane at room temperature for 12 hours (see Experimental Section for details). Where Fries rearrangement was unsuccessful and ester cleavage was the result, the component hydroxy thiophene carboxylates and carboxylic acids were recovered and identified by their melting points and proton nmr's.

## 7.2. Esterification and Fries Rearrangement/Attempted Fries Rearrangement of Methyl 3-hydroxy-5-methylthiophene-2-carboxylates(74).

The esters prepared in this series can be divided into three groups; group A comprised of alkanoyl esters; group B, thenoyl esters; and group C, benzoyl esters. The synthesis of these three groups was to enable a thorough study of the Fries reaction of the title esters to be accomplished. The products obtained from successful Fries rearrangement were O-methylated and saponified to provide additional compounds for desulphurisation studies. Scheme 32 summarises the reaction pathways; the results are given in Tables 1a), 1b) and 1c):-




Path B is followed when R = 2-thienyl, phenyl, and variously substituted derivatives of these systems

Scheme 32

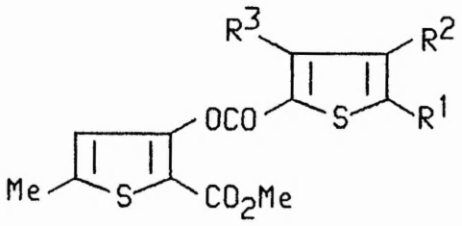
Table 1a

Preparation and Fries rearrangement of alkanoyl esters of methyl 3-hydroxy-5-methylthiophene-2-carboxylate:-

| No | R | %(X) | No. | %(Y) | %(74)+%$RCO_2H$ |
|---|---|---|---|---|---|
| (97) | Me | 82 | (114) | 93 | - |
| (98) | Et | 69 | (117) | 91 | - |
| (99) | cyclohexyl | 78 | - | 0 | 72; not recovered |
| (100) | $CH_2$-2-thienyl | 53 | - | 0 | 76; 58 |
| (101) | $CH_2$-Ph | 91 | - | 0 | 68; 66 |
| (102) | $CH_2$-(4-methoxyphenyl) | 50 | - | 0 | 82, 74 |

Table 1(b)

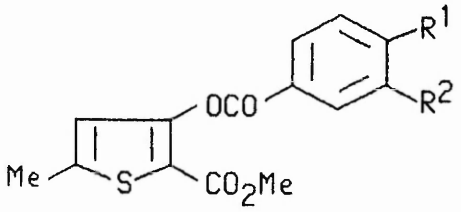
Preparation and attempted Fries rearrangement of 2'-thenoyl esters of methyl 3-hydroxy-5-methylthiophene-2-carboxylate:-



| No | R | %(X) | %(74)%$RCO_2H$ |
|---|---|---|---|
| (103) | $R^1=R^2=R^3=H$ | 85 | 95; 63 |
| (104) | $R^1=R^2=H$; $R^3=OMe$ | 98 | 73; 16 |
| (105) | $R^1=R^2=H$; $R^3=Me$ | 98 | 92; 87 |
| (106) | $R^1=H$; $R^2=OMe$; $R^3=Me$ | 64 | 65; 33 |
| (107) | $R^1=Me$; $R^2=H$; $R^3=OMe$ | 60 | 72, 46 |
| (108) | $R^1=H$; $R^2=OMe$; $R^3=H$ | 54 | 69; 44 |

**Table 1 (c)**

Preparation and attempted Fries rearrangement of benzoyl esters of methyl 3-hydroxy-5-methylthiophene-2-carboxylate:-




| No | R | %(X) | %(74)%$RCO_2H$ |
|---|---|---|---|
| (109) | $R^1=R^2=H$ | 60 | 80; 50 |
| (110) | $R^1=Me$; $R^2=H$ | 63 | 63; 53 |
| (111) | $R^1=NO_2$; $R^2=H$ | 55 | 71; 62 |
| (112) | $R^1=H$; $R^2=OMe$ | 75 | 88; 73 |
| (113) | $R^1=H$; $R^2=NO_2$ | 79 | 65; 66 |

Fries rearrangement of these series of esters was successfully accomplished for only the acetoxy and propionoxy esters (97) and (98). In all the other cases cleavage of the esters occurred without subsequent substitution, the constituent hydroxythiophene carboxylate and carboxylic acid moieties being recovered in the majority of cases.

The two products obtained from the successful Fries rearrangement, methyl 4-acetyl-3-hydroxy-5-methylthiophene-2-carboxylate (114), and methyl 3-hydroxy-5-methyl-4-propionylthiophene-2-carboxylate (117) were O-methylated using dimethyl sulphate and potassium carbonate followed by saponification with 10% sodium hydroxide to provide a variety of compounds for desulpurisation studies.

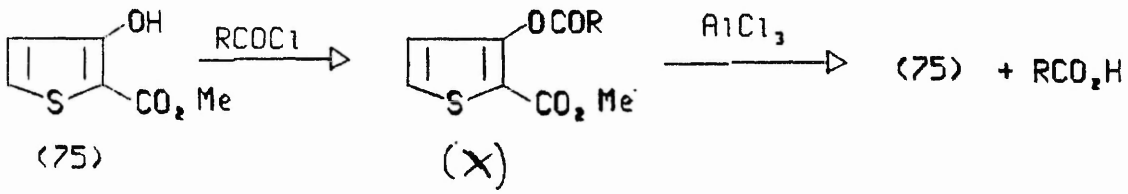
## 7.3. Esterification and Attempted Fries Rearrangement of Methyl 3-hydroxythiophene-2-carboxylate (75).

Four esters were prepared in this series, two alkanoyl esters (acetyl and propionyl) and the thenoyl and benzoyl esters. Fries rearrangement failed in all cases, including the two alkanoyl esters which had been successfully rearranged in the previous series (Section 7.2.). Cleavage of the esters was observed, with recovery of the resulting methyl 3-hydroxythiophene-2-carboxylate and, where appropriate, the aromatic carboxylic acids, in good yields.

Due to lack of success in the Fries rearrangement of this series of esters, no further work was undertaken in preparing esters of methyl 3-hydroxythiophene-2-carboxylate (75). The results obtained are summarised in Table 2;

Table 2.

Preparation and attempted Fries rearrangement of esters of methyl 3-hydroxythiophene-2-carboxylate:-




| No | R | %(X) | %(75)+%$RCO_2H$ |
|---|---|---|---|
| (120) | Me | 80 | 78;- |
| (121) | Et | 72 | 82;- |
| (122) | Ph | 91 | 79;56 |
| (123) | 2'-thienyl | 80 | 67;63 |

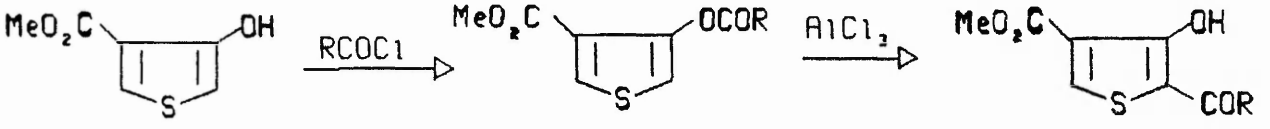
## 7.4. Esterification and Fries Rearrangement/Attempted Fries Rearrangement of Methyl 3-hydroxythiophene-4-carboxylate (77).

A representative range of esters of the title compound were prepared, and Fries rearrangement of these gave similar results to those described in Section 7.2., with successful Fries rearrangement of the acetoxy ester (85) but failure of any of the benzoyl esters and most of the thenoyl esters to rearrange, cleavage again occuring in all

these cases. However, in this series Fries rearrangement of the 2'-thenoyl ester was successfully accomplished to give methyl 3-hydroxy-2-(2'-thienyl)oxythiophene-4-carboxylate (131) in 55% yield, the only aromatic moiety to be successfully Fries rearranged on a hydroxythiophene carboxylate under these conditions. These results are summarised in Table 3;

Table 3.

Preparation and Fries rearrangement/attempted Fries rearrangement of esters of methyl 3-hydroxy thiophene-4-carboxylate:-




(77) (X) (Y)

(or (77) + $RCO_2H$)

| No | R | %(X) | No | %(Y) | %(77)+%$RCO_2H$ |
|---|---|---|---|---|---|
| (124) | Me | 85 | (130) | 100 | - |
| (125) | cyclohexyl | 70 | - | - | 84; not recovered |
| (126) | Ph | 77 | - | - | 91; 95 |
| (127) | 2'-thienyl | 87 | (131) | 55 | - |
| (128) | 3'-methyl-2'thienyl | 90 | - | - | 68; 45 |
| (129) | 3'-methoxy-2'-thienyl | 86 | - | - | 71; 42 |

## 7.3. Esterification and Fries Rearrangement of Methyl 4-hydroxy-2,2'-bithienyl-5-carboxylate (81).

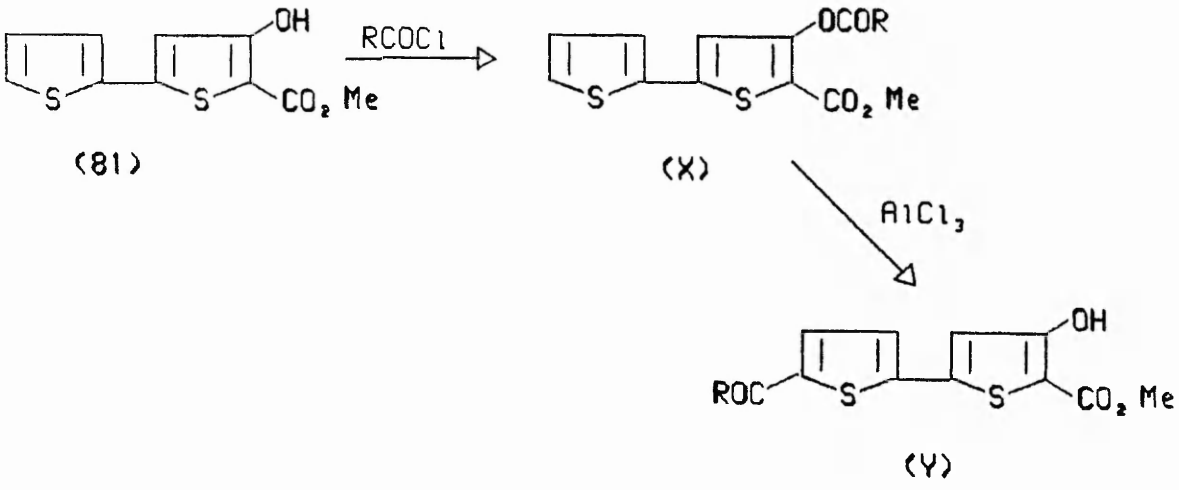
The esters prepared in this series were found to undergo Fries rearrangement readily in all cases. No benzoyl esters were prepared as the aim of this project was to prepare thienyl ketones for desulphurisation to seco acids. It would be interesting, however, to

study the Fries rearrangement upon a range of benzoyl esters of the title compound, but this was not within the scope of the present work.

It should be noted that although the esters prepared in this series all underwent successful Fries rearrangement in good yields, compounds of this type were of limited use for the present work due to their lack of methyl and hydroxy functions. However, this present study did serve the purpose of demonstrating that both the idea and the method employed for the Fries rearrangement of hydroxythiophene carboxylates were sound. The results obtained in the bithienyl series are summarised in Table 4;

Table 4.

Preparation and Fries rearrangement of esters of methyl 4-hydroxy-2,2'-bithienyl-5-carboxylate:-



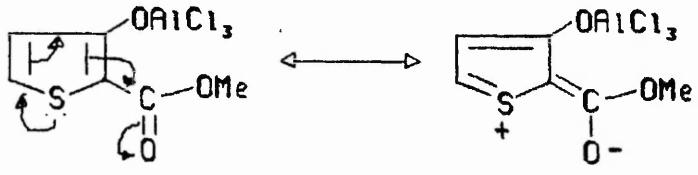
| R | %(X) | No | %(Y) | No |
|---|---|---|---|---|
| Me | 86 | (132) | 75 | (137) |
| 2"-thienyl | 84 | (133) | 92 | (138) |
| 3"-methyl-2"-thienyl | 80 | (134) | 90 | (139) |
| 3"-methoxy-2"-thienyl | 84 | (135) | 62 | (140) |
| 5"-methyl-3"-methoxy-2"-thienyl | 76 | (136) | 70 | (141) |

## 7.4. Discussion of Fries Rearrangements.

The results show clearly that the majority of aroyl esters fail to rearrange (both thenoyl and benzoyl). One reason for this failure may be the effect of the electron-withdrawing carboxylate substituents present in hydroxythiophene substrates. This deactivates the thiophene nucleus towards electrophilic attack, especially when in the 2-position, as it is in most cases in the present work. When this is combined with the reduced reactivity of aromatic acylium ions towards electrophilic substitution (due to the increased stability of the ion caused by delocalisation of the positive charge around the aromatic ring), it may explain, at least in part, the reluctance of aroyl esters of hydroxythiophene carboxylates to undergo Fries rearrangement. Compounds of this type are merely cleaved into the constituent hydroxythiophene carboxylate and the aromatic carboxylic acid.

In the case of methyl 3-acyloxythiophene-2-carboxylates Fries rearrangement failed in all cases, including the acetoxy compound.

The expected product in the rearrangement of the acetate would be methyl 5-acetyl-3-hydroxythiophene-2-carboxylate, but this was not found, presumably due to the deactivation of the 5-position by the carboxylate function in the 2-position as mentioned earlier. This may be explained in part by the stabilisation of the oxygen anion through delocalisation of the negative charge onto the adjacent ester, which can only occur when the ester is in the 2-position. This is demonstrated in the canonical structures shown in Scheme 33:-



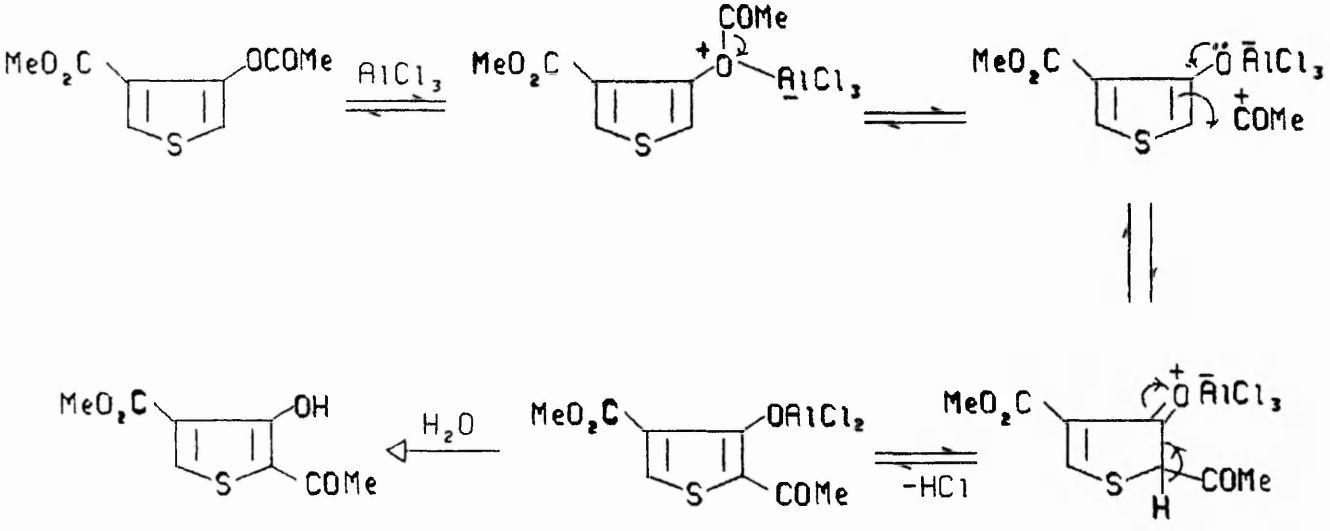

**Scheme 33**

Methyl 3-hydroxy-5-methylthiophene-2-carboxylate (74) is more activated, especially in the free 4-position, due to the activating and o-directing influence of the methyl group in the 5-position. Also, both the hydroxy and carboxylate functions direct to this position (although as the hydroxyl function is probably an oxygen-aluminium chloride complex, it may actually deactivate this position!)

It was found therefore, that methyl 3-hydroxy-5-methylthiophene 2-carboxylate (74) was more reactive towards electrophilic attack than methyl 3-hydroxythiophene-2-carboxylate (75). This was demonstrated by the fact that both the acetoxy- and propionoxy esters underwent rearrangement in excellent yield for the former compound, whereas no rearrangement occured with the latter. However, the less electrophilic aromatic acylium ions (see Section 3.6.) still failed to rearrange, suggesting that the methyl group has only a moderate effect upon activating the compound towards electrophilic substitution.

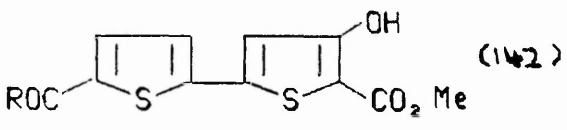
Fries rearrangement of the esters of methyl 3-hydroxythiophene-4-carboxylate (77) was more successful, again supporting the "deactivation postulate" mentioned above. In this case the 2'-thenoyl ester was rearranged in 55% yield, although no further aromatic esters underwent rearrangement. This is interesting as it suggests the 2'-thenoyl acylium ion is actually more electropositive than either the benzoyl radical or the 3'-methoxy-2'-thenoyl acylium ions, both of which would have been expected to rearrange more readily than the 2'-thenoyl acylium ion. No explanation can be given for this observation.

A plausible mechanism for the Fries rearrangement is suggested in Scheme 34. This involves an intermediate pathway, with the adjacent site (for the rearrangement) being activated by the oxygen-aluminium chloride comples:-

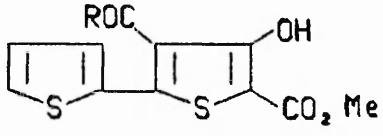



**Scheme 34**

Fries rearrangement of methyl 4-acyloxy-2,2'-bithienyl-5-carboxylates was shown to lead exclusively to methyl 5'-acyl-4-hydroxy-2,2'-bithienyl-5-carboxylates (142) in all cases, with no evidence of formation of any methyl 3-acyl-4-hydroxy-2,2'-bithienyl-5-carboxylates (143).



(142)

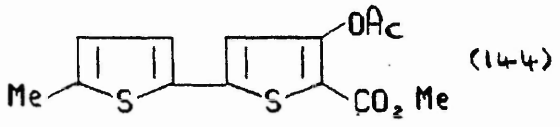


(143)

**Scheme 35**

This demonstrates that although there may be directing influences to the free 3-position, the electron rich free 5'-position is far more reactive towards electrophilic substitution. This position is so much more reactive towards electrophilic substitution that even aromatic acylium ions rearrange readily. It would be interesting to continue this work to see if benzoyl esters would rearrange as readily.

One other explanation for this exclusive rearrangement to the 5'-position may be blocking of the 3-position due to steric hinderance, i.e.:-




(144)

Figure 5

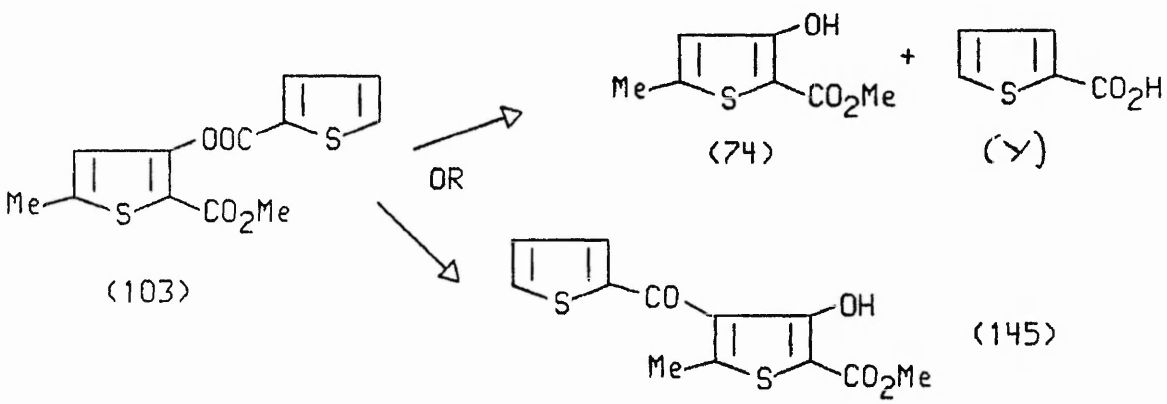
(143) is very crowded, whereas (142) has no other groups near to the free 5'-position to hinder substitution. It would be interesting to prepare methyl 4-acyloxy-5'-methyl-2,2'-bithienyl-5-carboxylate (144) to discover in which position, if any, rearrangement takes place when the 5'-position is blocked. Time did not allow the present author to pursue this enquiry.

## 7.5. Attempted Fries Rearrangement of Methyl 5-methyl-3-(2'-thenoyl) oxythiophene-2-carboxylate (103).

As it became apparent that the normal reaction conditions described above, were not suitable for effecting Fries rearrangement of methyl 3-aryloxythiophene-2-carboxylates, it was decided to undertake a study to see if suitable reaction conditions could be found to enable the reaction to take place in reasonable yields. The title compound was chosen as successful Fries rearrangement had been accomplished for the acetoxy- and propionoxy- esters and because this ester lacks any substituents upon the acyl group which would complicate the investigation (Fries rearrangement often leads to removal and/or rearrangement of other substituent groups). Also, the results recorded in Section 5.5. suggest that the 2'-thenoyl acylium ion may undergo Fries rearrangement more readily than the other aromatic acylium ions, also making this compound a suitable model to study. The results obtained from this study are summarised in Table 5:-

Table 5.

Attempted Fries rearrangement of methyl 5-methyl-3-(2'thenoyl)oxythiophene-2-carboxylate (103) under various reaction conditions:-




| No | Catalyst | Solvent | Rxn time | Rxn T(°C) | %(74) | %(Y) | %(145) |
|---|---|---|---|---|---|---|---|
| a | $AlCl_3$ | $CH_2Cl_2$ | 12 hr | 25 | 95 | 63 | - |
| b | $AlCl_3$ | $CS_2$ | 12 hr | 25 | 86 | 79 | - |
| c | $AlCl_3$ | $Cl(CH_2)_2Cl$ | 12 hr | 25 | 76 | 68 | - |
| d | $AlCl_3$ | $PhNO_2$ | 12 hr | 25 | 81 | 73 | - |
| e | $AlCI_3$ | $CH_3CN$ | 12 hr | 25 | 77 | 69 | - |
| f | $ZnCl_2$/K10 1 mmol/g | $Cl(CH_2)_2Cl$ | 36 hr | 25 | 95% (103) recovered | | |
| g | $AlBr_3$ | $CH_2Cl_2$ | 12 hr | 25 | 98 | 100 | - |
| h | $TlCl_4$ | $CH_2Cl_2$ | 12 hr | 25 | 82 | 79 | - |
| i | $AlCl_3$ | $CH_2Cl_2$ | 12 hr | 40 | 87 | 64 | - |
| j | $AlCl_3$ | $Cl(CH_2)_2Cl$ | 4 hr | 83 | - | - | 64 |
| k | $AlCl_3$ | benzene | 8 hr | 80 | 74 | 22 | - |
| l | $AlCl_3$ | $Ph\text{-}NO_2$ | 5 hr | 210 | Intractable tar | | |
| m | $AlCl_3$ | $CH_3CN$ | 4 hr | 82 | Intractable tar | | |
| n | $TlCl_4$ | none | 0.5 hr | 100 | 60 | 58 | - |
| o | $AlCl_3$ | THF | 12 hr | 67 | 95% (103) recovered | | |

Anhydrous aluminium chloride is the catalyst most commonly employed for Fries rearrangement, and this is reflected in this study. The use of chloroalkanes and carbon disulphide as solvents is also common practice due to their inertness in the reaction, and the usual reaction temperature of 25°C was chosen to reduce undesirable side reactions. In all these cases cleavage of the ester occured.

Nitrobenzene was tried as solvent as it has the advantage that the aluminium chloride complex formed is soluble in this solvent [174]. No improvement was achieved in the results however, with cleavage of the ester again occuring. Similar results were obtained with acetonitrile as solvent. An attempt to effect rearrangement using zinc chloride with K10 montmorillonite clay (in a ratio of 1mmol/g of clay), based upon a method described by Dr. A. Kybett et al[173] for Friedel-Crafts acylation, led to almost total recovery of starting material, and changing the catalyst to aluminium bromide or titanium chloride (used by Martin and Demerseman[174] in their preparation of 2'-hydroxypropiophenones) again led to cleavage of the ester.

At this point it was decided more vigorous conditions were required, at the risk of cracking or auto-destructive alkylation[172]. Aluminium chloride was again used as catalyst in a number of refluxing solvents. Use of dichloromethane and benzene as solvents both led to ester cleavage whilst the use of nitrobenzene and acetonitrile led to the formation of intractable tars; tetrahydrofuran gave almost total recovery of starting material. Heating with titanium chloride at 100°C with no solvent again led to ester cleavage. The only

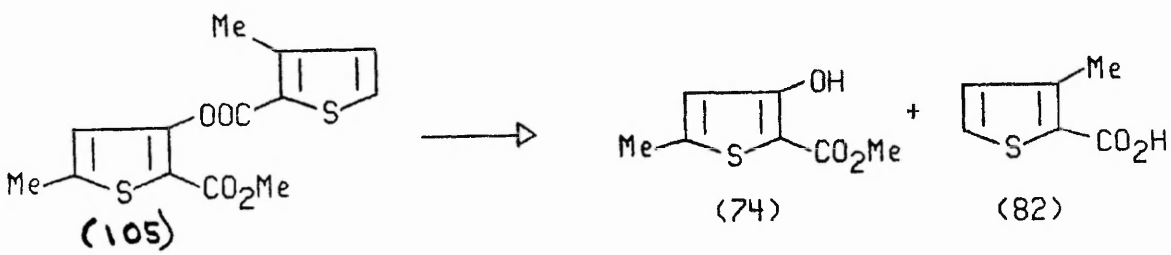
successful system found during this study involved treating the ester with aluminium chloride in 1,2-dichloroethane under reflux, which led to the required ketone, methyl 3-hydroxy-5-methyl-4-(2'-thenoyl)thiophene-2-carboxylate (145) in 64% yield.

## 7.6. Attempted Fries Rearrangement of Methyl 5-methyl-3-(3'-methyl-2'-thenoyl)oxythiophene-2-carboxylate (105).

Following the successful rearrangement of methyl 5-methyl-3-(2'-thenoyl)oxythiophene-2-carboxylate (103) a brief study was undertaken to effect Fries rearrangement of the title compound. The results are given in Table 6; it can be seen that the result in all cases was cleavage of the ester into the constituent hydroxythiophene carboxylate and 3-methylthiophene-2-carboxylic acid (82).

Table 6.

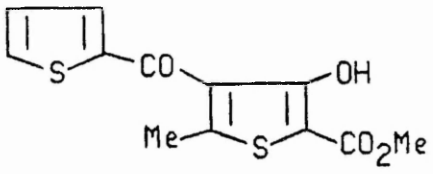
Attempted Fries rearrangement of Methyl 5-methyl-3-(3'-methyl-2'-thenoyl)oxythiophene-2-carboxylate:-



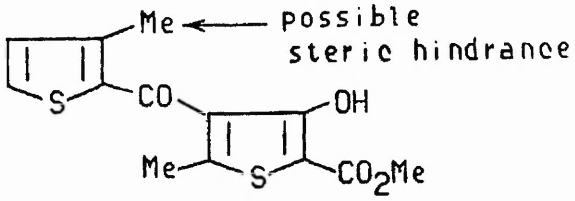
| No | Catalyst | Solvent | Rxn time | Rxn (°C) | %(74) | %(82) |
|---|---|---|---|---|---|---|
| a | $AlCl_3$ | $CH_2Cl_2$ | 18 hr | 25 | 96 | 91 |
| b | $AlCl_3$ | $Cl(CH_2)_2Cl$ | 100 hr | 25 | 76 | 81 |
| c | $AlCl_3$ | $CS_2$ | 18 hr | 25 | 86 | 65 |
| d | $AlCl_3$ | $Cl(CH_2)_2Cl$ | 18 hr | 83 | 89 | 71 |
| e | $AlCl_3$ | $Ph-NO_2$ | 12 hr | 100 | 92 | 76 |

Studies of Fries rearrangements of esters prepared from methyl 3-hydroxy-5-methylthiophene-2-carboxylate (74) were concluded with an attempt to rearrange the benzoyl ester (109) prepared in this series. The conditions employed for the successful rearrangement of methyl 5-methyl-3-(2'-thenoyl)oxythiophene-2-carboxylate (103) were used, but, in this case, the rearrangement was again unsuccessful, cleavage of the ester again occuring.

The results obtained in the study of the attempted Fries rearrangement of methyl 5-methyl-3-(3'-methyl-2'-thenoyl)oxythiophene-2-carboxylate (105) probably demonstrate the decrease in electrophilic nature of the 3'-methyl-2'-thenoyl acylium ion due to the + I effect of the methyl group. It is also possible that steric effects prevent successful rearrangement as the possible rearrangement product; methyl 3-hydroxy-5-methyl-4-(3'-methyl-2'-thenoyl)-thiophene-2-carboxylate (146) is a more crowded molecule then the product obtained in the successful Fries rearrangement of methyl 5-methyl-3-(2'-thenoyl)oxythiophene-2-carboxylate (145).



(145)




(146)

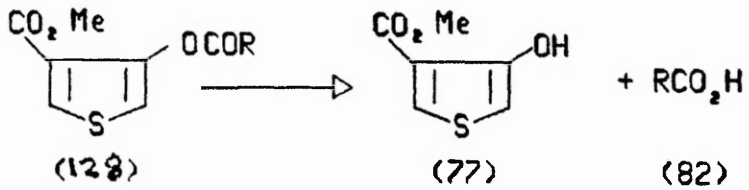
7.7. **Attempted Fries Rearrangement of Methyl 3-(3'-methyl-2'-thenoyl)oxythiophene-4-carboxylate (128).**

The final investigation of Fries rearrangement of esters of hydroxythiophene carboxylates was carried out upon the title compound to see if suitable conditions could be found to effect rearrangement. Methyl 3-(3'-methyl-2'-thenoyl)oxythiophene-4-carboxylate (128) was chosen because both the 3-acetoxy- and 3-(2'thenoyl)oxy-esters ((124) and (127)) undergo rearrangement at room temperature. It was hoped that more vigorous reaction conditions would lead to rearrangement of further esters in this series.

The 3'-methyl-2'-thenoyl ester (128) was again chosen as potential migrant group; the 3'-methoxy-2'-thenoyl (129) could possibly lead to complications due to side reactions at the elevated temperatures employed. The results are summarised in Table 7:-

Table 7.

Attempted Fries rearrangement of methyl 4-(3'-methyl-2'-thenoyl)oxythiopene-2-carboxylate:-




(128) (77) (82)

R = 3-methyl-2-thienyl

| No | Catalyst | Solvent | Rxn time | Rxn T(°C) | %(77) | %(82) |
|---|---|---|---|---|---|---|
| a | $AlCl_3$ | $CH_2Cl_2$ | 12 hr | 25 | 91 | 76 |
| b | $AlCl_3$ | $CH_2Cl_2$ | 12 hr | 40 | 89 | 78 |
| c | $AlCl_3$ | $Cl(CH_2)_2Cl$ | 6 hr | 83 | 90 | 89 |
| d | $AlCl_3$ | $Ph\text{-}NO_2$ | 12 hr | 100 | 87 | 62 |
| e | $TiCl_4$ | None | 2 hr | 100 | 76 | 68 |

Again, under all the conditions employed the result was cleavage of the ester to the constituent methyl hydroxythiophene carboxylate and 3-methyl thiophene-2-carboxylic acid ((77) and (82)). Whilst these results probably reflect the decrease in electrophilic nature of the 3'-methyl-2'-thenoyl acylium ion due to the +I nature of the methyl group it is surprising that no ketone could be obtained, especially as the 2'-thenyol ester undergoes rearrangement readily in this 3,4-disubstituted thiophene to give the expected products. It is possible, again, that steric effects influence the outcome of this reaction.

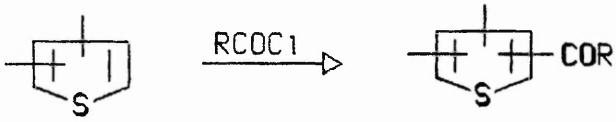
7.8. Conclusions.

The various studies of Fries rearrangements just described have shown that the approach is of only very limited value for the preparation of compounds of the required type. Accordingly, the alternative route employing Friedel-Crafts acylation was explored.

## 8.0. Preparation of Polysubstituted Thienyland Dithienyl Ketones via Friedel-Crafts Acylation.

### 8.1. Introduction.

The alternative approach to producing polysubstituted thienyl and dithienyl ketones was using Friedel-Crafts acylation, i.e.:-




**Equation 29**

Although it is well documented that simple thiophenes readily undergo Friedel-Crafts acylation (see Section 3.4.), the more complex, highly substituted thiophenes it was intended to acylate in this study had

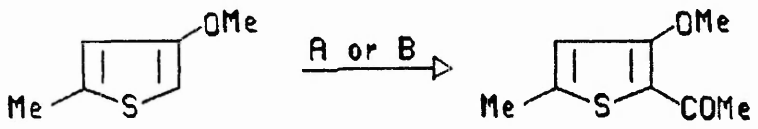
not been previously investigated. It was therefore decided to initiate this work with a brief study of the synthesis of some simple ketones in order to establish suitable reaction conditions.

## 8.2. Preliminary Investigaton.

It has already been mentioned (Section 2.1., Scheme 30) that 2-acetyl-3-methylthiophene was formed in excellent yield using tin(IV) chloride as catalyst and 1,2-dichloroethane as solvent. Application of this method to the preparation of 2-cyclohexanoyl-, 3-methyl-2-cyclohexanoylthiophene and 2-benzoylthiophene gave excellent yields. Di-2-thienyl ketone was prepared using titanium(IV) chloride as catalyst and dichloromethane as solvent, again in excellent yield.

8.3 **Preparation of Polysubstituted thienyl and Dithienyl Ketones.**

It was now decided to attempt the synthesis of some of the more complex polysubstituted thienyl and dithienyl ketones. Acylation of 5-methyl-3-methoxy thiophene (85) using acetic anhydride and orthophosphoric acid gave only low yields (15%) of the required product, 2-acetyl-3-methoxy-5-methyl thiophene (147).



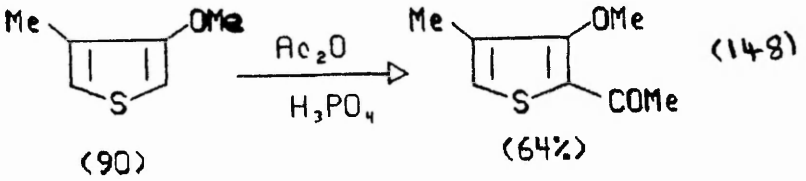

(85) (147)

A; $Ac_2O/H_3PO_4$ (15%); B; $SnCl_4$ / $Cl(CH_2)_2Cl$ (23%)

**Scheme 36**

Repeat of this synthesis using tin(IV)chloride in 1,2-dichloroethane with acetyl chloride as the acylating agent gave only slightly better results. In both cases tarry by-products were recovered in fairly large amounts. It is thought that the activating influences of the 5-methyl- and 3-methoxy- groups upon the 2-position may make this such a reactive species as to cause extensive polymerisation and decomposition of 5-methyl-3-methoxythiophene (85).

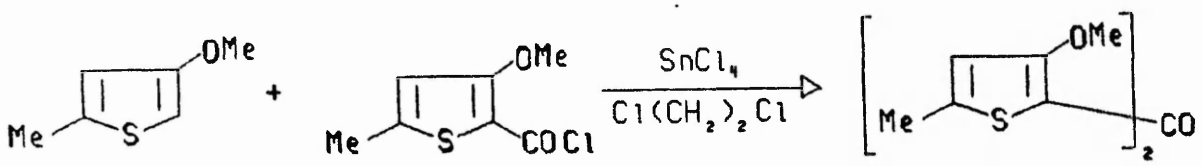
Acylation of 3-methoxy-4-methylthiophene (90) using acetic anhydride and orthophosphoric acid was much more successful, giving 2-acetyl-3-methoxy-4-methyl thiophene (148) in 64% yield:-




(90) (64%) (148)

**Equation 30**

The next target was bis (3-methoxy-5-methyl-2-thienyl)ketone (150). This was formed in good yield (72%) by acylation of 5-methyl-3-methoxythiophene (85) with 5-methyl-3-methoxythiophene-2-carbonyl chloride (149), using tin (IV) chloride as catalyst and 1,2-dichloroethane as solvent:-



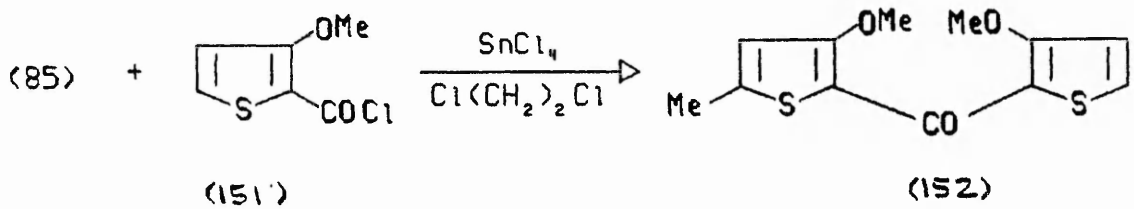

(85) (149) (150)

**Equation 31**

This increased yield compared to that obtained with 5-methyl-3-methoxy-2-acetylthiophene (147), may demonstrate the lower electropositivity of the methyl-3-methoxy-2-thenoyl acylium ion vis a vis the acetyl acylium ion due to delocalisation and hence stabilisation of the positive charge around the thiophene ring in the former.

The same conditions were employed for the synthesis of 2-(3'-methoxy-5'-methyl-2'-thenoyl)-3-methoxy thiophene (152) from 5-methyl-3-methoxy-thiophene (85) and 3-methoxy thiophene-2-carbonyl chloride

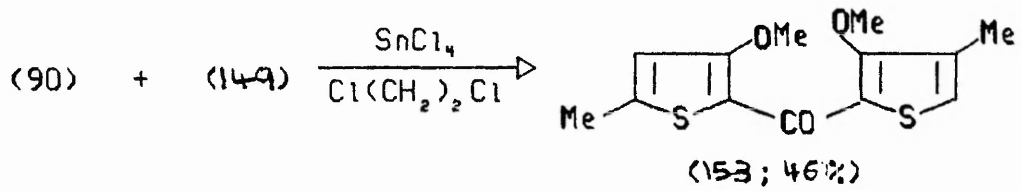
(151). The product was obtained in 65% yield, some resinification occuring during the reaction:-




(151) (152)

**Equation 32**

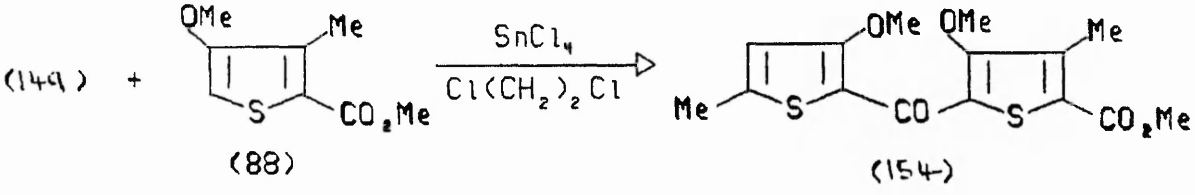
Under the same conditions 2-(3'-methoxy-5'-methyl-2'-thenoyl)-3-methoxy-4-methyl thiophene (153) was prepared (46%) from the appropriate starting materials, (90) and (149):-




(153; 46%)

**Equation 33**

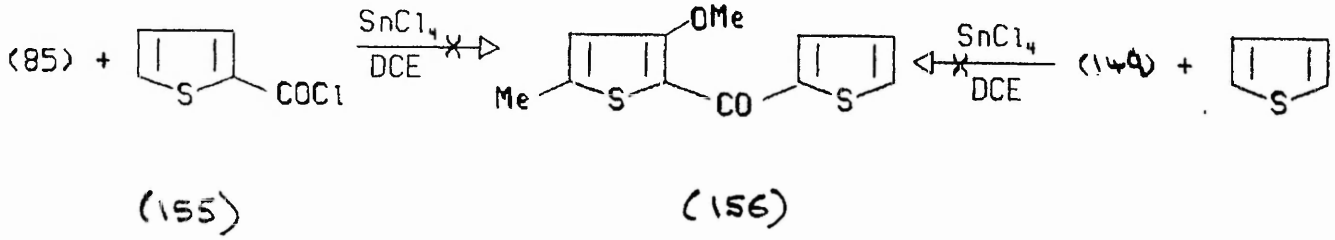
In this case 5-methoxy-3-methyl-thiophene-2-carbonyl chloride (149) was chosen as the acylating agent in the hope of avoiding the resinification which was found to occur during acylation of 5-methyl-3-methoxy thiophene (85), but without success. A further complex bis 2-thienyl ketone, methyl 4-methoxy-3-methyl-2-(3'-methoxy-5'-methyl-2'-thenoyl)thiophene-2-carboxylate (154) was obtained (48%) from the ester (88) and acid chloride (149); once more some resinous by-product was observed:-




**Equation 34**

This last result is interesting as it suggests that deactivation of the free 5-position by the ester group in the 2-position is significantly reduced, possibly due to the activating effect of the methoxy group in the 4-position. In this case it would have been interesting to study the Fries rearrangement of some of the 4-acyloxy-esters of this compound in order to see if more successful results could be obtained. Unfortunately time did not allow a further study along these lines.

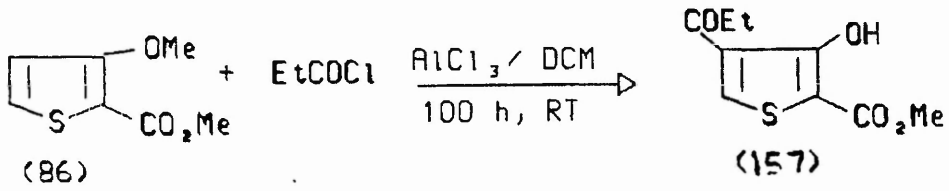
Attempts to synthesise 5-methyl-3-methoxy-2'-thenoyl-thiophene (156) from 5-methyl-3-methoxy thiophene (85) and 2-thenoyl chloride (155) (using tin (IV) chloride in 1,2-dichloroethane) proved unsuccessful, large amounts of polymeric products being formed. The alternative approach using 5-methyl-3-methoxy-thiophene-2-carbonyl chloride (151) and thiophene also resulted in polymerisation.




(155) (156)

Scheme 37

The synthesis of methyl 3-hydroxy-4-propionyl-thiophene-2-carboxylate (157) was achieved by acylation of methyl 3-methoxy-thiophene-2-carboxylate (86) with propionyl chloride, using aluminium chloride as catalyst:-



(86) (157)

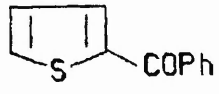
**Equation 35**

This result is interesting when it is considered that 3-acyloxy esters of this hydroxy-thiophene carboxylate completely failed to rearrange under Fries conditions. Similar attempts to effect acylation of methyl 3-methoxy - thiophene-2-carboxylate (86) using 3-methoxy-thiophene-2-carbonyl chloride (151) as the acylating agent failed completely with almost complete recovery of starting materials. Further attempts to achieve this acylation using methyl 5-methyl-3-methoxy - thiophene-2-carboxylate (83) as substrate and propionyl chloride as acylating agent also resulted in complete recovery of starting materials. This is again interesting, since methyl 5-methyl-3-propionoxythiophene-2-carboxylate (98) undergoes Fries

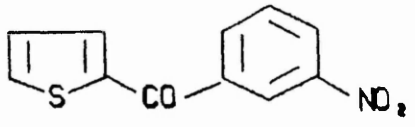
rearrangement readily, whereas methyl 3-propionoxy – thiophene-2-carboxylate (123) fails to rearrange at all.

## 8.4. Direct Acylation with Carboxylic acids and Phosphorous Pentoxide.

Hartough and Kosak[109] reported the acylation of thiophene, in moderate to good yields, by a number of carboxylic acids with phosphorous pentoxide as catalyst in refluxing benzene. Attempts by the present author to repeat this work, with thiophene as substrate and both benzoic and m-nitrobenzoic acids, proved only moderately successful; the yields reported by the earlier authors[109] were not observed. 2-Benzoyl-thiophene (158) was obtained in only 22% (compared to 66%-lit.[109]) and 2-(m-nitrobenzoyl) thiophene (159) in 17% yields, this compound had not been prepared by Hartough:-



(158)



(159)

An attempt to effect acylation of thiophene using 4-methoxy-3-methyl thiophene-2-carboxylic acid (89) by the method just described was completely unsuccessful, with (89) being recovered in 100% yield. In view of these disappointing results this synthetic approach was discontinued.

## 8.5. Summary and Conclusions.

Although Friedel-Crafts acylation gives excellent results when simple thiophenes and mono-substituted thiophenes are used as substrate in the presence of simple acylating agents, the more complex, polysubstituted thiophenes required for the present work gave varied results. In some cases high yields were obtained whilst in others reaction failed to occur. There appeared to be no obvious system to account for this. The Friedel-Crafts acylation method, did, however, provide a number of polysubstituted dithienyl ketones which could not be obtained via the Fries method. In this respect, this investigation was at least partially successful in that it provides a limited alternative to the Fries rearrangement for the preparation of compounds of this nature.

The attempt at preparing dithienyl ketones using the direct acylation method proved initially unsuccessful and was not persisted with.

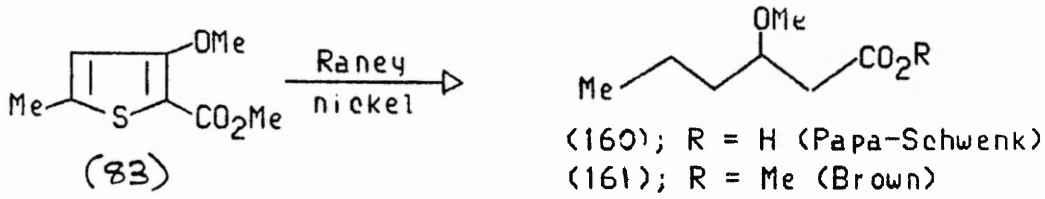
## 9.0. Raney Nickel Desulphurisation of Polysubstituted Thiophenes and Dithienyl Ketones.

### 9.1. Introduction.

Two well known methods of Raney nickel desulphurisation have been employed in this work; that of Papa, Schwenk and Ginsberg[43] (adding Raney alloy to the substrate in aqueous base), commonly called the 'Papa-Schwenk' method of desulphurisation, and the method employed by Brown[65], where freshly prepared Raney nickel is added to an alcoholic solution of the substrate. The former method has the advantage of avoiding the laborious and hazardous preparation of Raney nickel, while the latter has the advantage of milder reaction conditions, reducing the risk of side reactions and decomposition during the desulphurisation process. An added benefit of both processes for the present work is that Raney nickel desulphurisation often leads to reduction of ketone to hydroxy groups[48,175,176].

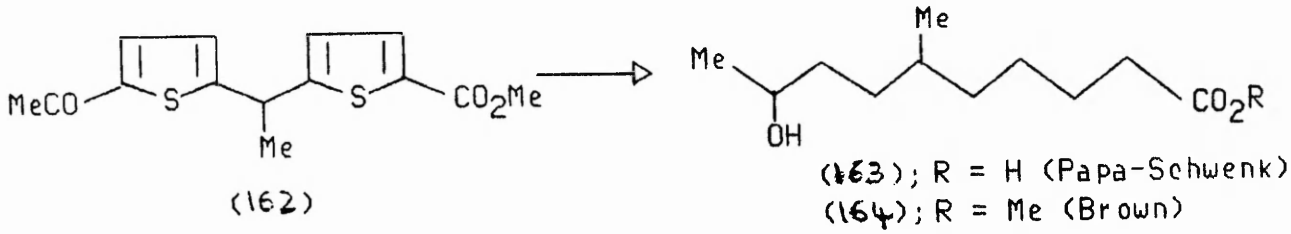
### 9.2. Preliminary Investigation.

An initial investigation was undertaken to discover which process was preferable for the present work, i.e. desulphurisation of the polysubstituted thienyl and dithienyl ketones described earlier in this thesis. Methyl 3-methoxy-5-methylthiophene-2-carboxylate (83) gave only 39% of recovered product, 3-methoxyhexanoic acid (160) using the 'Papa-Schwenk' method, as compared to the corresponding ester (161), which was produced more efficiently (69%) by the alternative process. (Scheme 38).



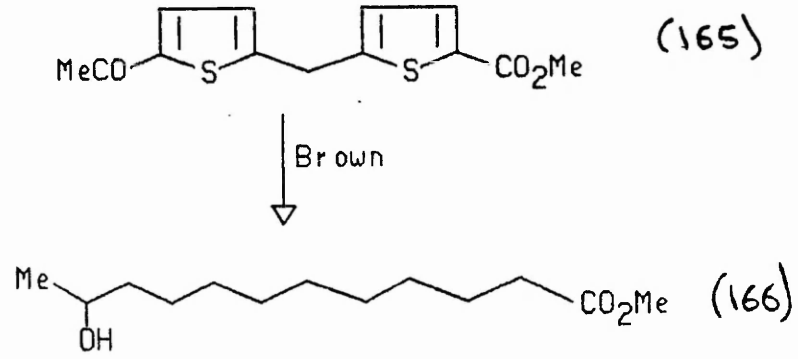

**Scheme 38**

Desulphurisation of 1-(5-acetyl-2-thienyl)-1-(5'-methoxycarbonyl-2'-thienyl)ethane, (162)* again showed no clear advantage to either method, the yields of the acid (163) and the ester (164) being 91% and 87% from the 'Papa-Schwenk' and Brown procedures, respectively:-




**Scheme 39**

An equally good result was obtained from 1-(5-acetyl-2-thienyl)-1-(5'-methoxycarbonyl-2'-thienyl)methane (165) *, using Brown's method, giving methyl 11-hydroxydodecanoate (166). There was insufficient sample available to study desulphurisation of this substrate using the 'Papa-Schwenk' method:-




**Equation 36**

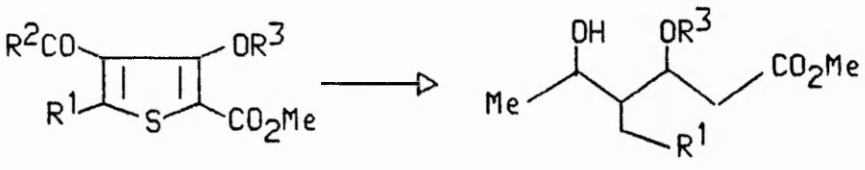
All desulphurisation products prepared in this preliminary investigation were identified by their proton nmr and IR spectra and (where available), by comparison with m.p./b.p.'s recorded in the literature.

* A sample of which was kindly supplied by Dr. G. Khandelwal of Nottingham Polytechnic.

9.3. **Desulphurisation of Polysubstituted Thiophenes.**

The next stage in this study was to examine the desulphurisation of compounds containing a heavily substituted single thiophene ring. The preliminary investigation had shown that no advantage was to be gained using either of the methods of reductive desulphurisation described, with respect to yields and purity of products. It was decided, however, to desulphurise the more complex polysubstituted thiophenes by Brown's method[65]. This was because this method eliminates the use of concentrated base, simplifying the work-up procedure and avoiding complications which this might cause. Methyl 4-ethyl-3,5-dihydroxyhexanoate (167), methyl 4-ethyl-5-hydroxy-3-methoxyhexanoate (168), methyl 4-ethyl-3,5-dihydroxyheptanoate (169) and methyl, 3,5-dihydroxy-4-methylheptanoate (170), were prepared by desulphurisation of the appropriate thiophene precursor, as summarised in Table 8:-

Table 8. **Desulphurisation of Polysubstituted Thiophenes.**

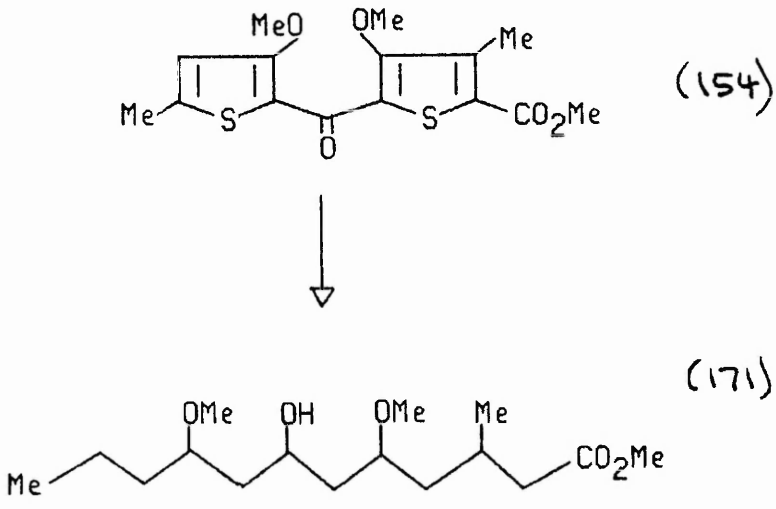


| No | $R^1$ | $R^2$ | $R^3$ | % yield of crude products |
|---|---|---|---|---|
| (167) | $CH_3$ | $CH_3$ | H | 78 |
| (168) | $CH_3$ | $CH_3$ | $CH_3$ | 78 |
| (169) | $CH_3$ | $CH2CH_3$ | H | 67 |
| (170) | H | $CH_2CH_3$ | H | 71 |

All products were identified by their proton nmr and infra-red spectra. No attempt was made to purify the recovered products which contained a number of other substances as well as the desired products. However, TLC indicated that no starting materials were present. It seems likely that the impurities are due to incomplete hydrogenation resulting in the formation of alkenes and ketones, or to full hydrogenation reducing the ketone to an alkane.

9.4. **Reductive Desulphurisation of Polysubsitituted Dithienyl Ketones.**

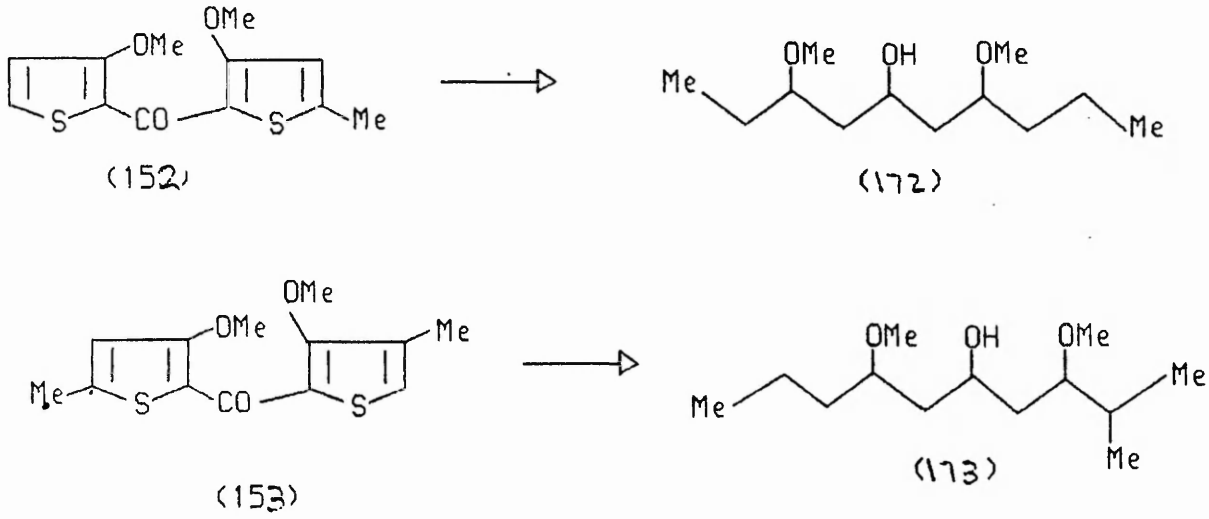
Reductive desulphurisation of the polysubstituted dithienyl ketones prepared from the Friedel-Crafts acylation was now examined; methyl 8-methoxy-6-hydroxy-4-methoxy-3-methylundecanoate (171) was prepared in 67% yield from methyl 4-methoxy-3-methyl-5-(3'-methoxy-5'-methyl-2'-thenoyl)thiophene-2-carboxylate (154) (Equation 37):-




**Equation 37**

This product was a white wax and was identified by its proton and carbon-13 nmr, infra-red and mass spectrometry and microanalytical data. The successful synthesis of this compound was of major

importance to this present work as it demonstrated that it is possible to construct a polyhydroxysubstituted seco acid of C-11 chain length, similar to those found in the macrolide antibiotics, 8-Methoxy-6-hydroxy-4-methoxydecane (172) and 9-methyl-8-methoxy-6-hydroxy-4-methoxydecane (173), were similarly formed from 2-(3'-methoxy-5'-methyl-2'-thenoyl))-3-methoxy thiophene (152) and 2-(3'-methoxy 5'-methyl-2'-thenoyl)-3-methoxy-4-methylthiophene ((153), respectively;




**Scheme 40**

Both products were again identified by their proton nmr and infra-red spectra. Impurities were detected in both products, especially the

latter, which could not be removed. It again seems likely that the impurities are arising from a combination of inefficient and excessive hydrogenation.

9.5. **Summary.**

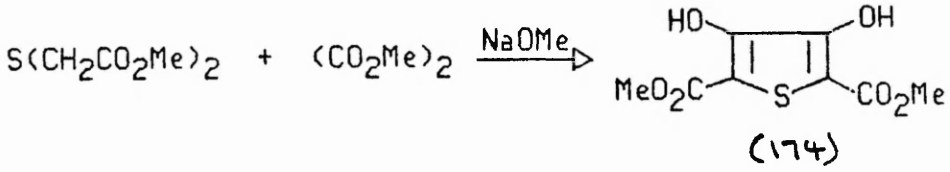
With one exception these desulphurisations gave quite complex mixtures of products, not the single one hoped for. No serious attempt was made to either separate or identify the minor components in these mixtures. However, if this was required it should be possible to determine the number and nature of components present using HPLC techniques. As the intention of the present work was to produce materials in synthetically useful quantities, no further work was carried out in this area. Any future work would have to investigate a means of producing essentially only one product from desulphurisation. This may be possible by using different types of Raney nickel. For example, de-gassed Raney nickel would leave carbonyl groups intact. It might then be possible to selectively reduce these at a later stage. It is apparent however, that further investigation is needed if desulphurisation of polysubstituted dithienyl ketones is to provide a viable alternative route to the synthesis of seco acids.

## 10.0. Investigation to Discover Whether Raney Nickel Desulphurisation is Stereoselective with Respect to Hydroxy Groups Attached Directly to the Thiophene Ring.

### 10.1. Introduction.

It was successfully demonstrated by Dann and Hauck[19] that Raney nickel desulphurisation of dimethyl 3,4-diphenylthiophene-2,5-dicarboxylate leads exclusively to meso dimethyl 3,4-diphenyl adipate (see Section 2.4.). However, this stereoselectivity may be due to steric hindrance caused by the bulk of the phenyl rings. Replacement of the phenyl groups by hydroxyl, as in dimethyl 3,4-dihydroxythiophene-2,5-dicarboxylate (174), might lead to a mixture of stereoisomers. If the desulphurisation were found to be stereoselective, it would add a considerable element of interest to the seco-acid synthesis under study. Accordingly, it was decided to prepare (174) and compare the product(s) obtained from its desulphurisation with prepared reference samples.

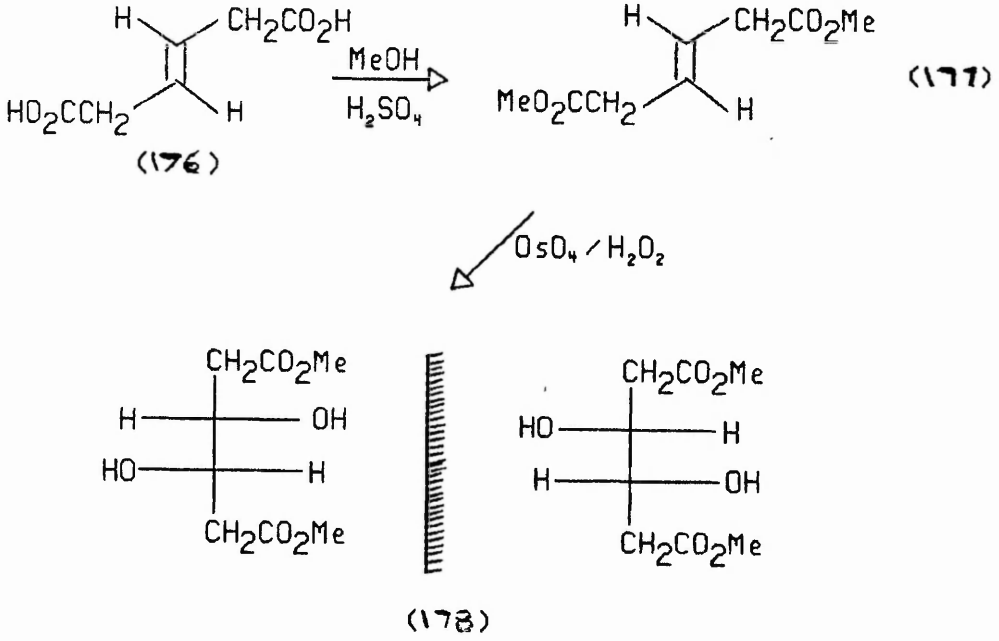
Dimethyl 3,4-dihydroxythiophene-2,5-dicarboxylate (174) was prepared via a Hinsberg[160] reaction, summarised in equation 37:-




(174)

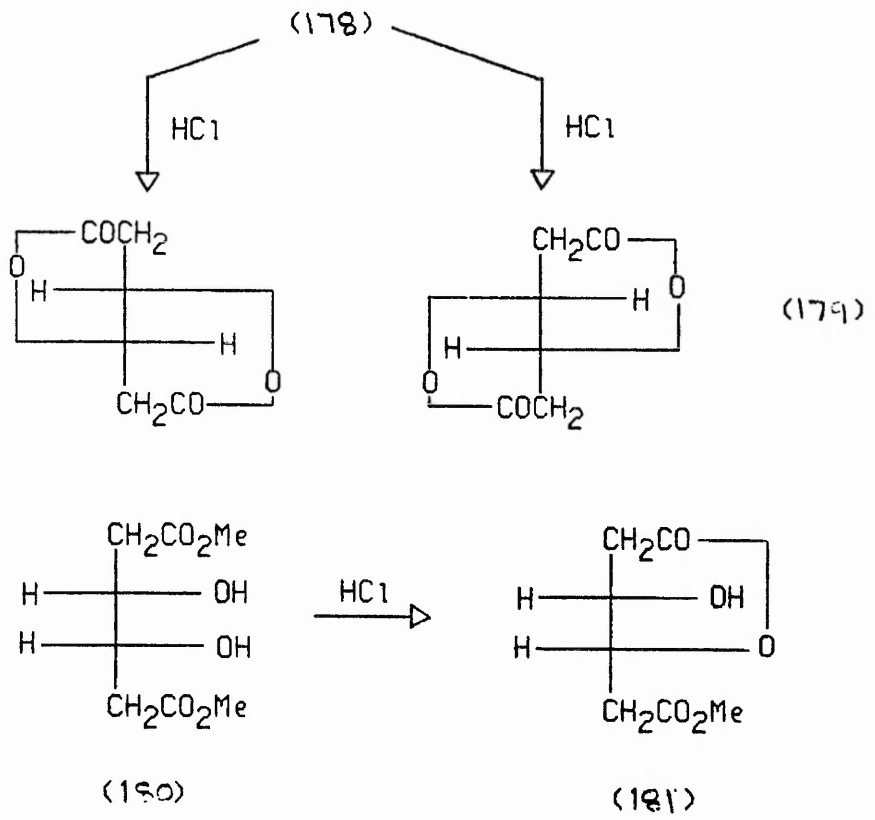
Equation 38

The product (174) was then desulphurised using Raney nickel according to the method of Brown[65] to give dimethyl β,β'-dihydroxyadipate (175) in 46% yield, m.p. 86-88°C. The identity of the product was confirmed by its proton and carbon-13 nmr and infra-red spectra. Synthesis of the required reference compounds, meso and (±) dimethyl β,β'-dihydroxyadipate was now attempted. E-hex-3-ene-1,6-dioic acid (176) was esterified using methanol and concentrated sulphuric acid to give dimethyl 6-hex-3-ene-1,6-dioate (177) in 54% yield. Hydroxylation using osmium tetraoxide/t-butyl hydroperoxide according to the method of Legrand[111] gave (±) dimethyl β,β'-dihydroxyadipate (178), as summarised in scheme 41 below:-




**Scheme 41**

The product was identified by its melting point (77°-78°C), which agreed with that quoted by Legrand[177], and by proton and carbon-13 nmr and infra-red spectra. Lactonisation using hydrochloric acid gave the Y,Y-dilactone of (±)-β,β-dihydroxyadipic acid, (179), again confirmed by comparison of its melting point (129°-130°C) with that of the dilactone obtained by Linstead[178] et al (127°-128°C). This confirmed that the product obtained was the (±) isomer, (178), since the meso isomer, (180), is known to form only the mono-lactone (181)[177,178]:-




**Scheme 42**

The first attempt to prepare the meso compound (180), followed the method of Legrand[177], using osmium tetraoxide with three times the amount of hydrogen peroxide used in the preparation of the (±) isomer (178), and at the elevated temperature of 25°C. However, the melting point indicated that the product was again the racemate, (178). The process was repeated several times, the same result being obtained on each occasion. Attempted synthesis of meso dimethyl β,β'-dihydroxyadipate (180) from E-hex-3-ene-1,6-dioic acid, (176), by treatment with hydrogen peroxide/formic acid at 45°C[179] led to complete recovery of starting material, whilst a further approach to anti-hydroxylation using tungstic oxide/hydrogen peroxide at 70°[180] gave the Y,Y-dilactone (179). A method in the literature due to Linstead[178] similar to that just described also gave this result. At this stage synthesis of meso dimethyl-β,β'-dihydroxy adipate (180) was abandoned due to insufficient time.

Comparison of pure (±) dimethyl β,β'-dihydroxy adipate (178) with dimethyl β,β'-dihydroxyadipate obtained by Raney nickel desulphurisation of (175) suggests that the desulphurisation product consists of a mixture of the (±) and meso isomers. The melting point (86°-88°C) of the desulphurised product falls between that of the pure racemate (78°C) and the meso from (98°C)[177]. While this is in itself inconclusive, spectroscopic evidence also adds weight to the formation of both (±) and meso forms upon desulphurisation of (174). In Table 9 are summarised the peaks identified by high resolution proton nmr (kindly carried out by Dr. R. Davies, of Shell Research, Sittingbourne), in $CDCl_3$ solution using a Bruker 300 MHz nmr

spectrometer) of a sample of dimethyl β,β'-dihydroxy adipate obtained via Raney nickel desulphurisation (175) along with those of (±) dimethyl β,β'-dihydroxyadipate prepared using osmium tetraoxide/t-butyl hydroperoxide (178). Whilst the desulphurisation product is not pure, the presence of peaks such as the multiplet at δ2.47-2.70, the triplet at δ3.73-3.75 and the multiple peaks at δ4.10-4.18 all correspond to peaks and chemical shifts assigned to pure (178) appears to indicate the presence of (±) dimethyl β,β'-dihydroxy-adipate (178) in the desulphurisation product.

Again, however, no definite conclusions can be drawn as to the stereochemical outcome of the desulphurisation process as, although the splitting pattern may be due to the presence of the meso compound (180), it could also be caused by incomplete hydrogenation (as mentioned in Section 9.3.) or other impurities. Thus, this experiment remained inconclusive, although the present author suggests that desulphurisation of dimethyl 3,4-dihydroxy thiophene-2,5-dicarboxylate (174) results in a mixture of (±) and meso-dimethyl β,β'-dihydroxyadipate (178) and (180).

Table 9 **Comparison of High Resolution Proton nmr Spectra of (±) Dimethyl β,β'-dihydroxyadipate Prepared via Raney Nickel Desulphurisation (175) and Osmium tetraoxide/t-butylhydroperoxide Hydroxylation (178).**

| Raney Nickel Desulphurisation Product (175) | | | Osmium tetraoxide/t-butyl hydroperoxide product (178) | | |
|---|---|---|---|---|---|
| Chemical Shift | Peak Type | Interpretation | Chemical Shift | Peak Type | Interpretation |
| 2.47-2.70 | m | $-CH_2-$ | 2.35-2.43 | m | $-CH_2-$ |
| 3.66-3.75 | m | impurity | No peak | -- | --- |
| 3.73-3.75 | t (J=10Hz) | -OH | 3.71-3.74 | + (J=10Hz) | -OH |
| 4.10-4.16 | m | -CH- | 4.15 | d | -CH- |
| 4.12-4.18 | d | $CO_2Me$ | 4.15 | s | $CO_2Me$ |

The inability to prepare meso dimethyl β,β'-dihydroxyadipate (180) means this investigation has not been completed and any future work in this area would have to involve the formation of this compound. This could be accomplished by preparing: dimethyl Z-hex-3-ene-1,6-dioate and attempting cis hydroxylation of this compound again using osmium tetraoxide/t-butyl hydroperoxide. This would then provide the required meso dimethyl β,β'-dihydroxyadipate (180) as a reference compound for comparison with the desulphurisation product (175). It is suggested that any future work in this area begins along these lines.

## 11.0. Reductive Desulphurisation of Optically Active Thiophene Derivatives.

### 11.1. Introduction

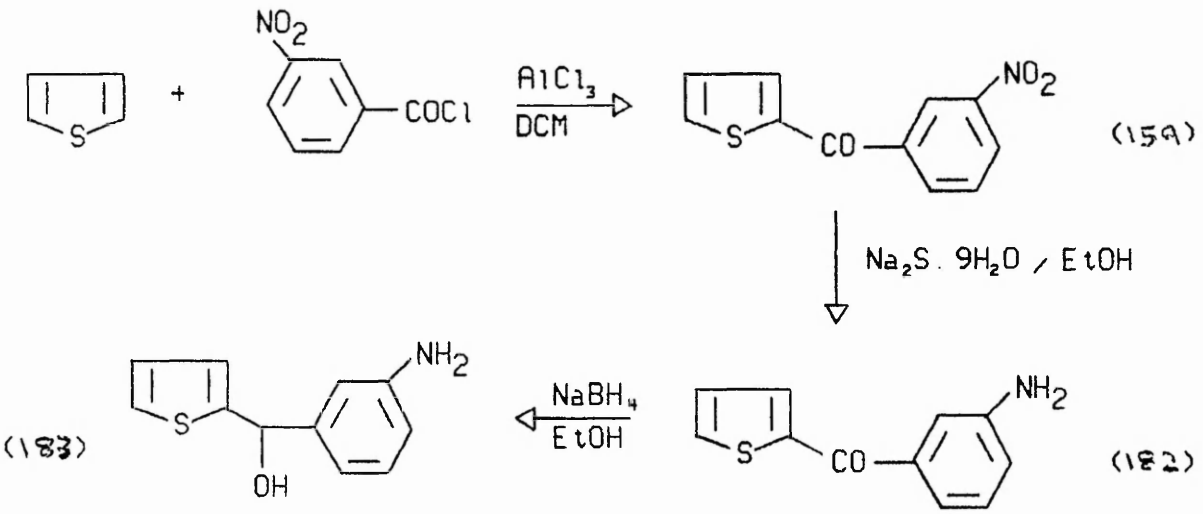
It was intended to complete the present work with an investigation into the desulphurisation of an optically active model thiophene, in order to determine whether chirality is preserved during desulphurisation. This would add a useful dimension to the synthetic approach because, as mentioned previously (Section 1.2.), macrolide antibiotics contain a multitude of asymmetric centres. If no racemisation occurs during the desulphurisation process it should be possible to produce stereochemically pure carbinols (either by resolution with optically active agents or by use of stereospecific reducing agents) which, when desulphurised, would yield seco acids with fixed stereochemistry in at least one centre. The precedents were good, Fredga[67] and Peterson.[68], in their work with optically active thiophene aliphatic and aromatic acids having found that desulphurisation with Raney nickel does not cause racemisation of chiral centres (see Section 2.4.).

### 11.2. Preparation and Desulphurisation of α-Hydroxy-2-(3-aminobenzyl)-thiophene

In the present work α-hydroxy-2-(3-aminobenzyl)thiophene, (183), was chosen as the model compound for the desulphurisation study. It has several advantageous points, possessing a simple, monosubstituted

thiophene ring for facile desulphurisation, a hydroxy group at the chiral centre (as in many seco acids) and an amino function as a "handle" for optical resolution of the compound.

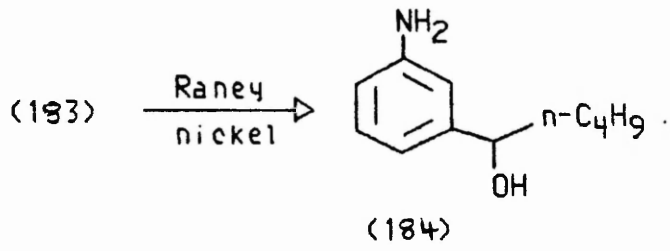
The model compound was readily synthesised using the route summarised in Scheme 43:-




**Scheme 43**

Friedel-Crafts acylation of thiophene in dichloromethane, using aluminium(III)chloride as catalyst and 3-nitrobenzoyl chloride as acylating agent, gave 2-(3-nitrobenzoyl) thiophene (159), (96%). Reduction with sodium sulphide in ethanol led to 2-(3-aminobenzoyl)thiophene (182), (67%)). The required carbinol (183)

was then obtained (76%) following sodium borohydride reduction. Upon Raney nickel desulphurisation of α-hydroxy-2-(3-aminobenzyl)thiophene (183) the required α-hydroxy-n-pentyl)aniline (184), was obtained, i.e.:-

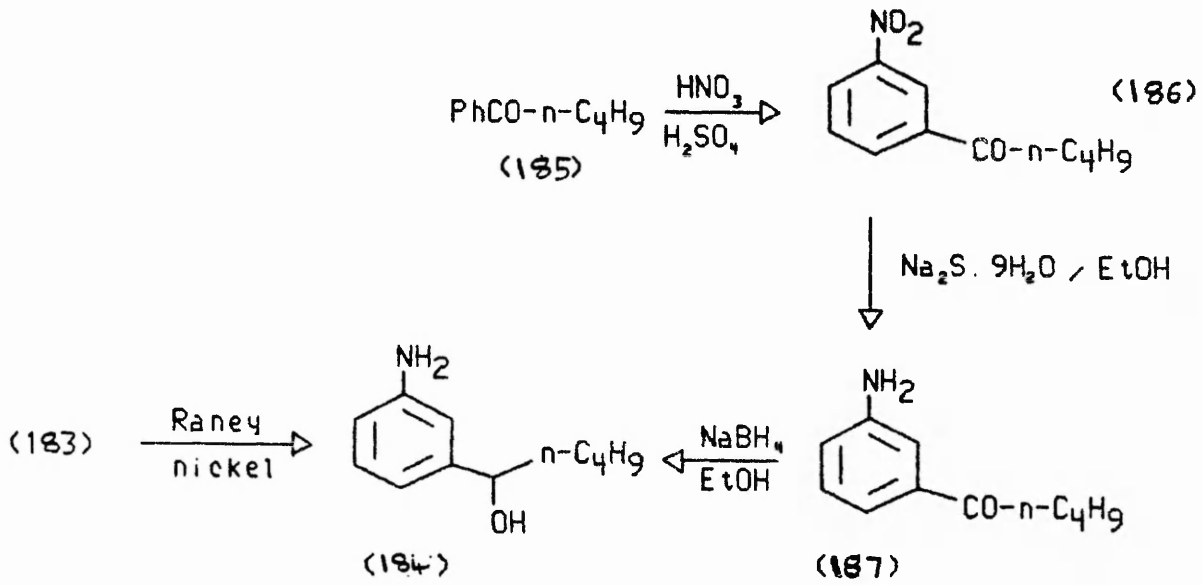



**Equation 34**

Thus it was necessary to prepare a reference sample of (184) which could be resolved and compared with the sample of (184) obtained via desulphurisation of optically pure (183).

Valerophenone (185) was nitrated using a 50:50 mixture of nitric and sulphuric acids at -20°C to give 3-nitrovalerophenone (186), (65%).

Reduction with sodium sulphide gave 3-aminovalerophenone (187), (45%). The required reference compound (184) was then obtained in 90% yield following sodium borohydride reduction of (187). These reactions are summarised in Scheme 44:-




**Scheme 44**

With the model and reference compounds in hand, the next step was to resolve them into the separate (+) and (-) enantiomers. To this end the (+) tartrates of both compounds were prepared by heating equimolar quantities of the amine with (+) tartaric acid in ethanol. The racemic tartrate of α-hydroxy-2-(3-aminobenzyl)thiophene, (183),

formed a solid with m.p. 52-54°C in 92% yield. However, problems were encountered in the preparation of the (+) tartrate of (184), which was syrupy and could not be crystallised.

## 11.3. Stereochemical Studies.

The (+) tartrate salt of (183) was repeatedly recrystallised from acetone to a constant melting point of 62°C. The free base was then obtained and found to have a melting point of 94°C (the melting point of the racemate was measured as 89°C). High resolution proton nmr* using chiral shift reagent showed there to be an enantiomeric excess in the ratio of 1:2.6 (from observation of the carbonyl proton), i.e. there was an excess of 72%. Polarimetry for ethanol solutions showed a rotation of -36.0° for the (+) tartrate of α-Hydroxy-2-(3-aminobenzyl)thiophene, and -1.4° for the free base (183). Raney nickel desulphurisation of carbinol (183) gave the expected product, (-)3-(α-hydroxy-n-pentyl)aniline in good yield; the product was shown by proton nmr to have an enantiomeric excess of 1:2.2 (68%). It had an optical rotation of -8.3°. Thus the present work supports the findings of Fredga[67] and Petterson,[68] showing that Raney nickel desulphurisation of thiophenes does not lead to racemisation of chiral centres of side-chains.

* Courtesy of B. Taylor of Shell Research, Sittingbourne.

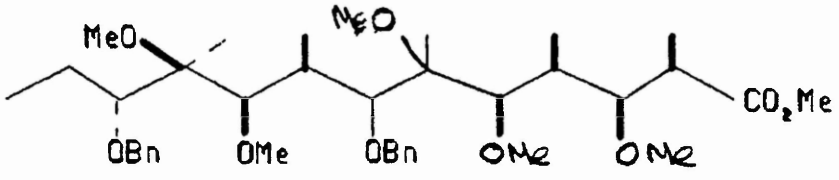
It should be pointed out that the original intention had been to prepare (+) and (-)-α-hydroxy-2-(3-aminobenzyl)thiophene (183) desulphurise the separate enantiomers and compare the resulting products with (+) and (-) 3-(α-hydroxy-n-pentyl)aniline (184). This would have shown without doubt that racemisation had not occurred. However, in view of the findings just discussed and the difficulties encountered in preparing the tartrate of the reference compound (184) it was decided not to pursue this line of enquiry further.

## 12.0 Overall Summary and Conclusions.

The stated aim of this thesis was to investigate the potential of Raney nickel desulphurisation of polysubstituted dithienyl ketones as a means of preparing seco acids similar to those forming the macrolide antibiotics. The successful synthesis and desulphurisation of methyl 4-methoxy-3-methyl-5-(3'-methoxy-5'-methyl-2'-thenoyl)thiophene-2-carboxylate, (154), to give methyl 8-methoxy-6-hydroxy-4-methoxy-3-methyl undecanoate (171) demonstrates the feasibility of this method. However, the failure of substituted thienyl esters to Fries rearrange limits the number of long-chain seco acids that can be formed using this method. Whilst Friedel-Crafts acylation proved moderately successful, this method lacks the versatility to provide a range of polysubstituted dithienyl ketones for desulphurisation to the appropriate seco-acids. It appears, therefore, that the possibility of providing a wide range of seco acids via the suggested process is unlikely.

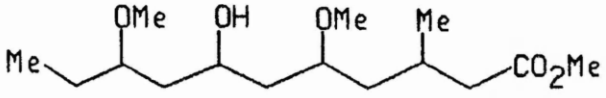
Raney nickel desulphurisation did not proceed as well as expected, leading, in most cases, to impure products. However, it may be possible to overcome this problem by varying the conditions of desulphurisation, and this would not prove a critical factor to this method.

The disadvantage of this method is the apparent lack of any stereochemical control of the products. For example, the seco acid derivative (16), (Section 1.4.):-




(16)

prepared in 31 steps and 2% yield is almost completely stereochemically pure, whereas the seco acid segment (171):-

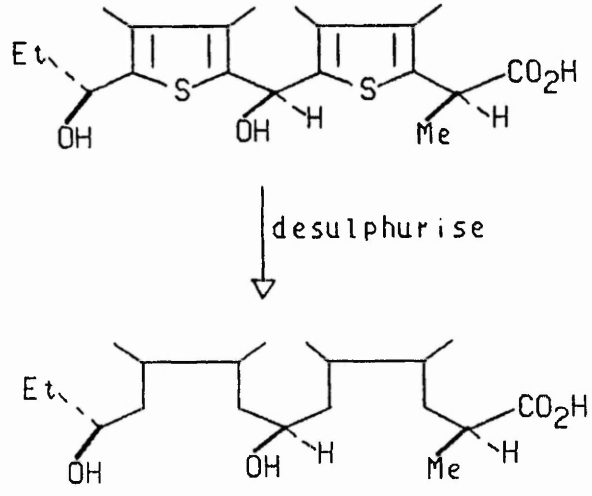



(171)

is obtained in 10 steps with an overall yield of 7.7% and no stereochemical purity.

Although investigations into the stereoselectivity of desulphurisation were inconclusive, it appears that this reaction proceeded without stereoselectivity. A further investigation into establishing and/or controlling the stereochemical outcome of this reaction would go some way towards overcoming this problem. Finally, the present work supports the previous findings of Fredga[67] and Petterson[68] that racemisation of optically pure side-chains does not occur in Raney nickel desulphurisation. Therefore it may be possible to prepare compounds of the type (185) and desulphurise these to seco acid (187)

with some stereochemistry intact (Equation 40). This may well be worth attempting in the future:-




**Equation 40**

It is suggested that any future work in this area concentrates on the points mentioned in this summary.

## 13.0 EXPERIMENTAL SECTION

### 13.1 GENERAL METHODS

#### 1. O-Methylation.

To a solution of the hydroxy compound in acetone was added a slight excess of potassium carbonate, then the mixture was stirred for 10 min. An equivalent excess of dimethyl sulphate was introduced, the mixture was stirred and boiled under reflux until tlc indicated that the starting material had been consumed (2-5 hours). The cooled mixture was filtered, the solids were washed with acetone, and combined filtrate and washings were evaporated to dryness. The crude residue was crystalised from an appropriate solvent.

#### 2. Saponification of Esters.

The compound was heated with an excess of 10% aqueous sodium hydroxide until the mixture became homogeneous, then for a further 10 min. Acidification (conc. hydrochloric acid) gave the product, which was filtered off, washed with water, and crystalised.

Decarboxylation of Acids.

The acid was intimately mixed with an equal volume of copper bronze and the whole was heated under vacuum as in vacuum distillation. The product distilled out and (if necessary), it was redistilled.

4. Acid Chlorides.

The acid was boiled under reflux with an excess of thionyl chloride for 1 h; the excess of reagent was removed in vacuo and the acid chlorides either used without further purification or, in some cases, were purified by distillation.

5. Preparation of Acetoxy Esters of Hydroxythiophenes.

The appropriate hydroxythiophene was boiled under reflux in an excess of acetic anhydride for 2 hours. After cooling, the solution was poured into water and the product was extracted into ether, the ethereal solution was washed with water, saturated sodium hydrogen carbonate and again with water, dried over magnesium sulphate and the solvent was removed on the rotary evaporator. Distillation of the residue furnished the pure acetoxy compound.

6. Preparation of Acyloxythiophenes.

The following procedure, illustrated for the preparation of methyl 5-methyl-3-(2'-thenoyl)oxythiophene-2-carboxylate, is typical. A solution of methyl 3-hydroxy-5-methyl-thiophene-2-carboxylate (3.5g, 0.02M) in dry pyridine (20ml) was stirred at 0°C while 2-chlorocarbonyl thiophene (3g, 0.02M) was added dropwise. When the addition was complete the mixture was stirred at room temperature for 1 hour then heated on the steam bath for a further 30 min. Upon cooling the reaction mixture was poured into ice/water and the product was extracted into dichloromethane (3x20ml), the combined extracts were washed with water (1x25ml), saturated sodium hydrogen carbonate (2x25ml) and water (1x25ml), dried over magnesium sulphate and the solvent was removed on the rotary evaporator. The residue was crystalised from ethanol to give the methyl 5-methyl-3-(2'-thenoyl)oxythiophene-2-carboxylate in 85% yield.

7. Fries Rearrangement of Esters Prepared from Methyl Hydroxythiophene carboxylates.

A stirred solution of the ester in dichloromethane was treated with 5 equivalents of anhydrous aluminium chloride at ambient temperature and left to stir for 24 hours. After addition of the mixture to ice-cold 2M hydrochloric acid the organic layer was separated and combined with a further dichloromethane extract of the aqueous phase. The extracts were washed successively with water, saturated sodium hydrogen carbonate solution, water, dried

($MgSO_4$) and evaporated to yield the product(s). Where cleavage of the ester occurred to give the constituent hydroxy-thiophene carboxylate and carboxylic acid, the acid was recovered, in most cases, by acidification of the sodium hydrogen carbonate layer and extraction into dichloromethane followed by the usual work-up.

8. Papa-Schwenk [43] Method of 'in situ' Desulphurisation.

The thiophene compound (1g) to be desulphurised was dissolved in 10% sodium hydroxide solution (50ml) ethanol (10ml). The solution was heated to 90°C on the steam-bath, and nickel-aluminium alloy (10g) was added in portions, the temperature being kept between 80°-90°C throughout. The reaction was heated at this temperature for 2 hours, then allowed to cool to 40°C and acidified carefully with concentrated hydrochloric acid. The mixture was then allowed to cool and extracted with ether, the product being obtained by removal of the solvent.

9. Preparation of Raney-Nickel (Brown's Method).

The freshly prepared catalyst employed throughout the present work was prepared after the method of Brown.[65] Nickel-aluminium alloy (100g) was suspended in water (270ml) and the suspension was stirred while a solution of sodium hydroxide (300g) in water (600ml) was added slowly. When ca 40ml had been added a vigorous reaction ensued, and ice/water (ca 700ml) was added to prevent frothing over. After 15 min., when the reaction had abated, the remainder of the sodium hydroxide solution was added and the

suspension was stirred for a further 15 min. The beaker was transferred to a steam-bath and heated for 2 h with frequent hand-stirring. When cool, the clear liquid was decanted, and the residue was washed by repeated decantation with 1L portions of distilled water until the washings were neutral to litmus. The catalyst was then washed with 96% ethanol (3x150ml) and absolute ethanol (3x150ml) and stored in a refrigerator in a screw-capped jar filled to the brim with absolute ethanol.

## 13.2 Preparation of Starting Materials.

### Methyl 3-Hydroxy-5-methylthiophene-2-carboxylate.

#### (a) ß.ß-Bis-[Carbomethylmercapto]butyric acid methyl ester (73).

Methyl acetoacetate (140g, 1.2M) was mixed thoroughly with methyl thioglycolate (255g, 2.2M) under anhydrous conditions. The mixture was cooled to $0^{o}C$ and a stream of hydrogen chloride was passed through for a period of 1 h. The reaction mixture was then stirred at room temperature for 120 h, then poured into 500g of crushed ice, the oily product being obtained by separation. The remaining aqueous layer was extracted with dichloromethane and the organic fraction was combined with the oil, washed with water (2x100ml), dried ($MgSO_4$) and the solvent was removed on the rotary evaporator to yield 267g (72%) of colourless oil, identified by its nmr spectrum. $^{1}H$ nmr $\delta(CDCl_3)$ 3,70 (9H, s, $CO_2Me$,, 3.43 (4H, s, $-CH_2-$), 2.80(2H,s,$-CH_2-$), 1.74 (3H, s, Me).

(b) Methyl 3-Hydroxy-5-methylthiophene-2-carboxylate (74).

To 2M potassium hydroxide (1l) in methanol was added thioketal (73) (155g, 0.5M). The mixture was stirred for 3 h at room temperature after, which time 1 litre of ice/water was added; stirring was then continued for a further hour. Acidification with concentration hydrochlorc acid caused precipitation of the product which was obtained by filtration. The crude yield was 63g (73%). The product was recrystallised from ethanol to give white needles, m.p. 53°C (lit. [135], 53°C), $^1$H nmr $\delta(CDCl_3)$ 6.43 (1H s, 4-H, 3.83 (3H, s, OMe), 2.40 (3H, s, Ar Me) and 9.45 (br, 3-OH). Vmax (Nujol) 3300 (br,OH) and 1685 (C=0) $cm^{-1}$. $^{13}$C nmr $\delta(CDCl_3)$ 101.4 (C-2), 164.6 (C-3), 117.8 (C-4), 147.1 (C-5), 166.5 (C=0), 51.6 ($CO_2Me$) and 16.5 (Me).

Methyl 3-Hydroxythiophene-2-carboxylate (75)

A stirred solution of methyl thioglycolate (110g, 1.04M) in 2M sodium methoxide (1l) was cooled in a water bath. To this was added methyl-a-chloroacrylate (125g, 1.04M) drop-wise, over 20 min at such a rate that the temperature remained below 35°C at all times. When the addition was complete, the reaction was stirred at room temperature for 1 h, then the solvent was removed on the rotary evaporator. The residue was acidified with 4M hydrochloric acid and the product was obtained by steam distillation. The solvent was removed and

the residue was distilled to give the hydroxy ester as an oil which rapidly solidified to give 131g (80%) a white solid (131g, 80%), m.p. 43°C lit. [181] 43°C), $^1$H nmr $\delta$($CDCl_3$) 8.65 (1H, s, OH elim. $D_2O$), 7.85 (1H, d, 4Hz, 3-H), 6.35 (1H, d 4Hz, 4-H) and 3.90, s, $CO_2Me$), Vmax (Nujol) 3,500-2,600 (br, CH), 1690 (C=O), and 1660 (C=O) $cm^{-1}$,

4-Hydroxythiophene-2-carboxylic acid.

(a) Meso Dimethyl 2,3-dibromosuccinate.

2,3-Dibromosuccinic acid (138g, 0.5M) was dissolved in methanol (500ml). To this was added thionyl chloride (100ml) over a period of 30 min. The reaction mixture was then stirred at room temperature for 12 h after which time the thionyl chloride and methanol were removed by distillation. The product was obtained as an off white solid in 98% yield. It had m.p. 49°C (lit. [147] 48-50°C) $^1$H nmr $\delta$($CDCl_3$) 2.23 (2H, s, CH) and 3.92 (6H, s, $CO_2Me$).

(b) Dimethylbromomaleate.

Meso Dimethyl 2,3-dibromosuccinate (140g) was dissolved in ether (500ml). To the stirred solution was added triethylamine (70ml) in one portion, causing immediate precipitation to occur. The mixture was stirred for 2 h at room temperature then filtered at the pump. The filtrate was washed with water, dried ($Na_2SO_4$) and the solvent was removed by rotary evaporation to leave a yellow oil (90.6g, 88%) which was used in the following stage without further stage treatment.

(c) Dimethyl 3-Hydroxythiophene-2,5-dicarboxylate (76).

To a stirred solution of 1M sodium methoxide (500ml) was added methyl thioglycolate (65g, 0.6M). To this was added dimethylbromomaleate (136g, 0.6M) dropwise; the temperature was maintained at below 35°C. After the addition was completed the reaction was left to stir at room temperature for 12 h then poured into ice-water (1l). Upon acidification with conc. hydrochloric acid a precipitate formed which was collected by filtering at the pump to give the required product (98.2g, 75%) as a white powder, m.p. 108-111°C, (lit.[159] 111°C).

(d) 4-Hydroxythiophene-2-carboxylic acid (71).

Dimethyl 3-hydroxythiophene-2,5-dicarboxylate (98g 0.45M) was heated under reflux for 1 h with 2M sodium hydroxide. After acidification of the cooled and filtered solution the title compound (43.1g, 65%) was obtained as a white powder, m.p. 202-203°C (lit. [141] 197-199°C). $^1$H nmr $\delta$($CDCl_3$) 6.65 (1H, s, Ar), 7.35 (1H, s, Ar) and 10.30 (1H, br, $CO_2H$, $D_2O$ex). Vmax (Nujol) 3,700 (br, $CO_2H$), 3,300-2,500 (br, OH) and 1710 (C=O) $cm^{-1}$.

Methyl 3-Hydroxythiophene-4-carboxylate.

(a) 1,2'-Dicarbomethoxymethylethylsulphide.

To a stirred mixture of methyl thioglycolate (212g, 2H) and piperidine (2ml) was added methyl acrylate (180g), dropwise, over 45 min. During this time a further 2ml of piperidine were added and the reaction temperature was maintained at 40°C by external cooling. When addition was complete the reaction mixture was heated to 50°C for 5 min, cooled, poured into water (500ml) and separated (the aqueous layer being extracted with dichloromethane and the latter being combined with the organic layer). The dichloromethane solution was then dried ($Na_2SO_4$) and the solvent was removed on the rotary evaporator to give a clear oil (286g, 75%) b.p. 115oC C/0.9mm Hg (lit. [152] 111-112°C/2mm Hg) $^1$H nmr $\delta$($CDCl_3$) 3.70 (3H, s,

Me), 3.65 (3H, s, Me) 3.15 (2H, s, $-CH_2-$) and 2.40-3.00 (4H, m, $-CH_2CH_2-$).

(b) Methyl 3-Oxotetrahydrothiophene-4-carboxylate.

To a refluxing methanolic solution of 6M sodium methoxide (500ml) was added thioether (a) (192g, 1.0M). The mixture was refluxed for 30 min, cooled, poured into 300g ice/water and stirred for 30 min. The solution was acidified with concentrated hydrochloric acid, extracted with dichloromethane, the extracts were washed with water (2x200ml), saturated sodium hydrogen carbonate (4x100ml) and water (2x100ml), then dried ($MgSO_4$) and the solvent was removed on the rotary evaporator. The resulting oil was purified by vacuum distillation to give a white crystalline solid (64.5g, 40%) b.p. 94°C/1.7mm Hg (lit. [152] 109°C/4mm Hg), m.p. 41°C (lit. [152] 38°C, $^1H$ nmr $\delta(CDCl_3)$ 3.72 (7H, s, $-CH_2-S-$, $-CH_2-S-$, $CO_2Me$), Vmax (Nujol) 3,500-3,000 (br, OH), 1,740 (C=O) and 1,670 (C=O), $cm^{-1}$.

(c) Methyl 3-Hydroxythiophene-4-carboxylate (77).

Methyl 3-oxotetrahydrothiophene-4-carboxylate (20g, 0.12M) was dissolved in methanol (200ml) and the solution was heated to reflux. To the refluxing solution was added 35% hydrogen peroxide (40ml). The mixture was allowed to cool then poured into water (250ml). The product was obtained by steam distillation, followed by rotary evaporation (to remove

methanol). Recrystallisation from methanol yielded 8.2g (41%) of a white crystalline solid (8.2g, 41%) m.p. 48°C (lit. [182] 49°C. $^1$H nmr $\delta(CDCl_3)$ 8.75 (1H, s, OH, $D_2O$ ex), 7.90 (1H, d, J, 4.5Hz, 2-H), 6.4 (1H, d, J, 4.5Hz, 5-H) and 3.90 (3H, s, $CO_2Me$), IR, Vmax (Nujol) 3,000 (br, OH) and 1,700 (C=O) $cm^{-1}$.

Methyl-3-hydroxy-4-methylthiophene-2-carboxylate.

(a) 1,2'-Dicarbomethoxymethyl-(2'-methyl)-2-isopropyl sulphide.

To a mixture of methyl thioglycolate (21g, 0.2M) and piperidine (1ml) heated under reflux was added methyl methacrylate (18g, 0.2M), dropwise over 45 min. The mixture was then boiled under reflux for a further 6 h, allowed to cool, and poured into water (50ml). The aqueous mixture was extracted with dichloromethane, the extracts were washed with 1M hydrochloric acid (1x25ml), water (2x25ml), dried ($Na_2SO_4$) and the solvent was removed on the rotary evaporator to give a clear oil. Distillation of the oil gave the pure product (31g, 80%) b.p. 96°C/0.1mmHg, which gave only a single peak upon GC analysis (Alizeon column, oven T 250°C, F.I.D.). $^1$H nmr $\delta(CDCl_3)$ 3.70 (3H s, $CO_2Me$), 3.65 (3H s , $CO_2Me$) 3.25 (2H, s, $-CH_2-$), 2.83 (1H, qd, -CH-), 2.83 (2H, d, $-CH_2$) and 1.23 (3H, s, Me); Vmax (liquid film) 2,920 ($CH_3$ stretch) and 1,650 (C=O); $^{13}$C nmr $\delta(CDCl_3)$ 175.12 ($CO_2$) 170.64 ($CO_2$), 52.27 (-CH-), 51.75 ($-CH_2-$), 39.93 ($CH_3$), 36.10 ($CH_3$), 34.02 ($CH_2$) and 16.82 ($CH_3$).

(b) Methyl 3-Hydroxy-4-methylthiophene-2-carboxylate (78).

Thioether (a) (35g, 0.175M) was added dropwise to refluxing 5M-methanolic sodium methoxide (100ml). The mixture was refluxed for a further hour then allowed to cool and poured into ice/water (100ml). The mixture was treated with concentrated hydrochloric acid until it became acid to litmus. The product was extracted into dichloromethane, the extracts were washed with water (2x50ml), then dried ($Na_2SO_4$). Removal of the solvent on the rotary evaporator yielded an orange oil which, after distillation, (b.p. 97°C/0.1mm Hg) gave a mixture (22g, 72%) of the title compound and an isomeric product. The mixture was dissolved in methanol (400ml) without further purification, the solution was brought to reflux, and 100 volume hydrogen peroxide (50ml) was added dropwise over 1.5 h. The solution was allowed to reflux for a further 2 h until there was no trace of starting material by TLC (50% MeOH: 50% of 1% AcOH) after which heating was ceased. The cool solution was poured into cold water (200ml), the methanol was removed on the rotary evaporator, and the aqueous solution was extracted, with dichloromethane. The organic layer was dried ($Na_2SO_4$) and the solvent was removed to give 12.6g (57%) of an orange/brown oil (12.6g, 57%) which was purified by distillation to give the title compound (8.9g, 40% from crude methyl 4-methyl-3-oxo-tetrahydrothiophene-2-carboxylate) as a clear oil, b.p. 80°C/0.2mmHg (lit. [136] 60°C/0.05mmHg). $^1H$ nmr $\delta(CDCl_3)$ 2.10 (3H, s, 4-Me), 3.86 (3H, s, $CO_2Me$), 6.98

(1H, s, 5-H) and 9.56 (1H, s, -OH, $D_2O$ex). Vmax (film) 3.300 (br, OH) and 1.695 (C=O) $cm^{-1}$.

4-Hydroxy-3-methylthiophene-2-carboxylic Acid.

(a) Dimethyl 4-Hydroxy-3-methylthiophene-2.5-dicarboxylate (79).

To 1M potassium t-butoxide (200ml) was added a mixture of methyl pyruvate (11.4g, 0.11M) and dimethyl thiodiacetate (27g, 0.15M) and the mixture was stirred for 45 min. The reaction mixture was acidified with cold conc. hydrochloric acid and the t-butanol was removed under reduced pressure. The residue was extracted with ether, the extracts were washed with sodium carbonate solution followed by brine, then dried ($MgSO_4$). After removal of the ether on the rotary evaporator the residue was crystalised from aq.methanol to give the title compound (6.1g, 26.5%). It had m.p. 85-86% (from methanol). (lit. [168] 87°C).

(b) 4-Hydroxy-3-methylthiophene-2-carboxylic Acid (80).

Diester (79) was saponified by refluxing with 10% sodium hydroxide solution for 6 h. Acidification gave the title compound in 95% yield, m.p. 184°C (lit. [168] 184°C). $^1H$ nmr $\delta$($CDCl_3$) 2.15 (3H, s, 3-Me), 7.85 (1H, s, 5-H), 8.7 (1H, s, OH, $D_2O$ex) and 11.50 (1H, br, $CO_2H$, $D_2O$ex). Vmax (Nujol) 3.500-2.900 (br, $CO_2H$ and OH) and 1,660 (C=O) $cm^{-1}$.

Methyl 4-Hydroxy-2,2'-bithienyl-5-carboxylate.

(a) 3-(2-Thienyl)acrylic acid.

Thiophene-2-carboxaldehyde (11.2g, 0.1M) and malonic acid (10.4g, 0.1M) were slurried with pyridine (50ml). The mixture was heated to 50°C, piperidine (2ml) was added, the temperature was raised to 100°C for 1 h, then the solution was boiled under reflux for 3 h. After 18 h at ambient temperature the mixture was poured into 150ml of ice/water (150ml), acidified with concentrated hydrochloric acid (25ml) and filtered. The crude precipitate was dissolved in 4M sodium hydroxide, the solution was filtered and the filtrate was diluted with water (100ml). Following acidification with concentrated hydrochloric acid the mixture was extracted with dichloromethane and the organic phase was dried ($MgSO_4$). Removal of the solvent gave the crude product (12.9g, 84%) which was purified by recrystallisation from ethanol to give white plates m.p. 147°C (lit. 145-148°C [183]). $\delta$($CDCl_3$) 6.15 1H, d, J=16Hz, CH) 6.88-7.38 (3H, m, Ar H's), 7.70 (1H, d, J=16Hz, CH) and 9.98 (1H, br, OH, $D_2O$ex).

(b) Methyl 3-(2-thienyl)acrylate.

3-(2-Thienyl)acrylic acid (11.2g, 0.075M) was dissolved in methanol (25ml). To this was added thionyl chloride (5ml) and the mixture allowed to come to reflux. The reaction mixture was allowed to stand for 20 h, when the bulk of the

methanol was removed by distillation. The brown oil remaining was diluted with dichloromethane, washed with water (2x25ml) $Na_2CO_3$ (2x25ml) and again with water (2x25ml), dried ($MgSO_4$) and the solvent was removed to give the product in 96% yield. It had m.p. 48-49°C (from 60-80°C petroleum) (lit. [184] 40-42°C). $^1H$ nmr $\delta(CDCl_3)$ 3.73 (3H, s, $CO_2Me$), 6.15 (1H, d, J=16Hz, CH), 6.95-7.42 (3H, m, Ar H's) and 7.83 (1H, d, J=16z, CH).

(c) Methyl 3-(2-Thienyl)-1,2-dibromopropionate.

Methyl 3-(2-thienyl) acrylate (8.4g, 0.05M) was dissolved in $CH_2Cl_2$ (50ml). To the stirred solution was added bromine (4g, 0.05M), dropwise, over 10 min. The mixture was stirred for 4 h then poured into water (50ml), separated, the organic layer was washed with sodium metabisulphite solution, water and brine, dried ($MgSO_4$) and the solvent was removed to give the title compound as a yellow powder in 87% yield. It had m.p. 87-88°C (from 40-60°C petroleum), lit. [169] 88°C). $^1H$ nmr $\delta(CDCl_3)$ 3.90 (3H, s, $CO_2Me$), 4.74-4.92 (1H, d, J=10Hz, CHBr), 5.62-581 (1H, d, J=10Hz, CHBr) and 6.92-7.50 (3H, m, Ar H's). Vmax (KBr) 3,100 ($CO_2Me$), 1,750 (CH-Br) and 1,710 (C=0) $cm^{-1}$.

(d) Methyl E,Z-2-Bromo-3-(2-thienyl)acrylate.

Methyl 3-(2-thienyl)-1,2-dibromopropionate (8.2g, 25mM) was dissolved in diethyl ether (100ml). To this was added

triethylamine (7ml). The mixture was refluxed for 6 h, filtered to remove triethylamine hydrobromide; A further portion of triethylamine (7ml) was added, and refluxing was continued for 4 h. When cool the organic layer was separated, washed with water (2x25ml) and dried ($MgSO_4$). Removal of the solvent gave the title compound as a pale yellow oil (5.8g, 94%). The $^1H$ nmr spectrum indicated that the required product had been formed. $\delta(CDCl_3)$, 3,78-3.82 (3H, 2xs, E and Z $CO_2Me$), 6.90-7.10 (1H, m, E and Z ArH), 7.20- and 7.50 (2H, Me and Z Ar $H^1$s) and 7.40-7.60 (1H, s, E and Z CH). Vmax (film) 3,100 ($CO_2Me$), 1705 CH-Br) and 1,600 (C=0)$cm^{-1}$.

(e) Methyl 4-Hydroxy-2,2'-bithienyl-5-carboxylate (81).

To a stirred solution of freshly prepared 2M sodium methoxide (50ml) was added methylthioglycolate (5.5g, 0.05M) followed by methyl E,Z-2-bromo-3-(2-thienyl)acrylate (13.3g, 0.05M). The mixture was stirred for 12 h at room temperature then poured into water (100ml). Following acidification with concentrated hydrochloric acid (25ml) the product was extracted into dichloromethane (50ml), the extract was washed with water (2x25ml), dried ($MgSO_4$) and the solvent was removed to give an off-white power powder (9.8g, 82%) which was recrystallised from ethanol as white needles. It had m.p. 71°C (lit. [169] 71°C). $^1H$ nmr $\delta(CDCl_3)$ 9.60 (1H, s, br, -H, $D_2O$ ex), 7.30 (2H, m, Ar$H^1$s), 7.10 (1H, d, Ar H), 6.72 (1H, s, Ar 4-H), and 3.88 (3H, s, $CO_2Me$). Vmax (Nujol),

3,500-3,300 (br, OH) and 1,690 (C=0) $cm^1$, $^{13}C$ $\delta(CDCl_3)$ 102.0 (C-8), 119.2 (C-6), 125.4 (C-3), 126.6 (C-1),, 128.1 (C-2), 136.0 (C-4), 141.0 (C-5) and 169.1 (C-7).

3-Methylthiophene-2-carboxylic Acid.

(a) 2-Acetyl-3-methylthiophene.

3-Methylthiophene (15g, 0.15M) was dissolved in 1,2-dichloroethane (50ml) then added to a solution of acetyl chloride (16g, 0.12M) and of tin (IV) chloride (30g, 0.11M) in 1,2-dichloroethane (50ml) at $0^oC$. The mixture was stirred for 1 h then poured into ice/HCl, the organic layer was separated and washed with water (2x25ml), dried ($MgSO_4$) and the solvent was removed to leave the title ketone (17.5g, 85%) b.p. $111^oC$/6mmHg (lit. [186] $98-99^oC$/14mmHg). $^1H$ nmr $\delta(CDCl_3)$ 2.10 (3H, s, $CH_3$), 2.17 (3H, s, $CH_3$), 6.60 (1H, d, Ar H, J=8Hz, and 7.20 (1H, d, Ar H, J=8Hz). Vmax (film 2,950 ($-CH_3$ and 1,660 (C=)) $cm^{-1}$.

3-Methylthiophene-2-carboxylic Acid (82).

The title compound was obtained by hypobromite oxidation of 2-acetyl-3-methyl-thiophene in 66% yield. It had m.p. $147-148^oC$ (lit. [183] $147-148^oC$). $^1H$ nmr $\delta(CDCl_3$+DMSO-ds) 2.56 (3H, s, Me), 6.90 (1H, d, J=6Hz, 4-H), 7.45 (1H, d, J=6H 5-H) and 12.10 (1H, s, OH, $D_2O$ ex). $^{13}C\delta(CDCl_3)$ ppm 16.1 ($CH_3$), 126.3 (C-2), 131.7 (C-4), 132.0 (C-5), 147.8 (C-3) and 168.6 ($CO_2H$).

## 13.3 O-Methylation, Saponification and Decarboxylation of Thiophene Units.

### Methyl 3-methoxy-5-methylthiophene-2-carboxylate (83).

The title compound was obtained in 90% yield by methylation of methyl 3-hydroxy-5-methylthiophene-2-carboxylate (74) using general method 1, m.p. 69°C (lit. [187], 69°C). $^1$H nmr $\delta$($CDCl_3$) 2.36 (3H, s, ArMe), 3.71 (3H, s, ArOMe), 3.85 (3H, s, $CO_2Me$), 6.48 (1H, s, 4-H). Vmax (Nujol) 1721 (C=O) $cm^{-1}$. $^{13}$C $\delta$ nmr $CDCl_3$ 16.6 (ArMe), 52.4 ($CO_2Me$), 59.0 (-OMe), 106.7 (C-2), 115.1 (C-4), 148.8 (C-5), 161.7 (C-3) and 162.1 (C=O).

### 3-Methoxy-3-methylthiophene-2-carboxylic Acid (84).

The acid was obtained (80%) by saponification of the foregoing ester, as given in general method 2. It had m.p. 168-171°C, (lit. [188] 175-177°C). $^1$H nmr $\delta$($CDCl_3$)+($CD_3$)$_2$SO) 6.70 (1H, s, 4-H, 3.88 (3H, s, ArOMe), 2.42 (3H, s, ArMe) and 10.55 (br, OH), Vmax (Nujol) 3500-2000 (br, OH) and 1660 (C=O) $cm^{-1}$, $^{13}$nmr $\delta$($CDCl_3$), ppm 105.2 (C-2), 163.2 (C-3), 114.2 (C-4), 147.9 (C-5), 16.7 ($CH_3$), 59.3 ($OCH_3$) 160.6 ($CO_2H$), M/e 173 (100%, M+H) and 155 (95%, M-OH).

3-Methoxy-5-methylthiophene (85).

The title compound was prepared (70%) by decarboxylation of the foregoing acid using general method 3. The ether had b.p. 120°C/30mm Hg (lit.[187] 60°C/12mm Hg). $^{1}$H nmr $\delta$($CDCl_3$) 6.35 (1H, d, J=2Hz, 4-H), 5.90 (1H, d, J 2Hz, 2-H), 3.60 (3H s, Ar OMe), and 2.30 (3H, d, ArMe), Vmax (film 1575 $cm^{-1}$, $^{13}$C nmr $\delta$($CDCl_3$) 93.9 (C-2), 157.8 (C-3), 117.8 (C-4), 138.9 (C-5), 56.9 (-OMe) and 15.8 (Me).

Methyl 3-methoxythiophene-2-carboxylate (86).

The title compound was obtained in 66% yield by methylation of methyl 3-hydroxythiophene-2-carboxylate (75) using general method 1. It had m.p. 61-62°C (lit.[63] 62°C) $\delta$($CDCl_3$) 3.85 (3H, s, Ar OMe), 3.90 (3H, s, $CO_2Me$), 6.65 (1H, s, J=6Hz, ArH) and 7.35 (1H, d, J=6Hz, ArH). Vmax (Nujol) 1,710 ($CO_2Me$) $cm^{-1}$.

3-Methoxythiophene-2-carboxylic Acid (87).

The title compound was prepared in 92% yield by saponification of methyl 3-methoxythiophene-2-carboxylate (86) using general method 2. It had m.p. 184°C (lit.[63] 178.5-179.5). $^{1}$H nmr $\delta$($CDCl_3$+DMSO-$D_6$)3.97 (3H, s, OMe), 6.90 (1H, d, 6Hz, 4-H), 7.48 (1H, d, J=6Hz, 5-H) and 8.70 (1H, br, s, -OH, D2Oex). Vmax (Nujol) 3,300 (br, $CO_2H$) and 1,660 (br, C=O) $cm^{-1}$.

Methyl 4-Methoxy-3-methylthiophene-2-carboxylate (88).

Methylation of methyl 4-hydroxy-3-methylthiophene-2-carboxylate by general method 1 gave the title compound (95%), m.p. 65-66$^0$C. (Found; C, 51.6; H, 5.0. $C_8H_{10}O_3S$ requires, 51.6; H, 5.4%). $^1$H nmr $\delta$($CDCl_3$) 7.05 (1H, s, 5-H), 3.95 (3H, s, $CO_2$ Me), 3.80 (3H, s, ArOMe, and 2.10 (3H, s, Ar Me), Vmax (Nujol) 1710cm-$^1$. M/e 187 (100%, M+H) and 155 (M-OMe), $^{13}$C $\delta$($CDCl_3$) 115.7 (C-2) 161.3), 133.2 (C-4), 125.8 (C-5), 161.71 (C=0), 61.8 (-OMe), 51.6 ($CO_2$Me) and 12.8 (ArMe).

4-Methoxy-3-methylthiophene-2-carboxylic Acid (89).

Saponification of the foregoing ester by general method 2 gave the title acid (95%), m.p. 187-189$^0$C. (Found: C 49.2; H, 4.9. $C_7H_8O_3S$ requires C, 48.4; H,4.65%). $^1$H nmr $\delta$($CDCl_3$+$(CD_3)_2SO$) 6.40 (1H, s, 5-H), 3.80 (3-H, s, Ar OMe), 2.35 (3H, s, Ar Me) and 9.45 (s, OH), Vmax (Nujol) 3300-2200 (br, CH) and 1665 (C=0) cm-$^1$. M/e 173 (100%, M-H) and 155 (M=CH) $^{13}$C nmr $\delta$($CDCl_3$) 11.9 (Me), 51.7 ($CO_2$ Me), 57.1 (OMe), 101.4 (C-5, 126.9 (C-2), 135.7 (C-3), 156.9 (C-4) and 164.4 (C=0).

3-Methoxy-4-methylthiophene (90).

The title compound was obtained (66%) by decarboxylation of 4-methoxy-3-methyl thiophene (89) using general method 3. It had b.p. 80$^0$/15mm Hg. $^1$H nmr $\delta$($CDCl_3$) 2.08 (3H, s, ArOMe), 3,78 (3H,

s, ArOMe), 6.15 (1H, d, J=5 Hz, 2-H, and 6.80 (1H, d, J=5Hz, 5-H). m/e 129 (100%, M+H). $^{13}C$ nmr $\delta(CDCl_3)$ 12.5 (Me), 57.2 (OMe), 95.8 (C-5), 120.0 (C-2), 128.9 (C-3) and 157.1 (C-4).

Methyl 3-Methoxy-4-methylthiophene-2-carboxylate (91).

Methylation of methyl 3-hydroxy-4-methylthiophene-2-carboxylate (78) by the general procedure 1 gave the title methoxy compound (85%), b.p. $110^0C$/13mm Hg. $^1Hmr$ $\delta(CDCl_3)$ 7.05 (1H, s, 5-H),3.95 (3H, s, $CO_2Me$, 3.80 (3H, s, ArOMe) and 2.10 (3H, s, ArMe), Vmax (film) 1720 (C=0) $cm^{-1}$, M/e 187 (100%, M+H) and 155 (40%), M-OMe), $^{13}C$ nmr $d(CDCl_3)$ 115.7 (C-2), 161.3 (C-3), 133.2 (C-4), 125.8 (C-5), 161.7 (C=0), 61.8 (OMe), 51.6 ($CO_2Me$) and 12.8 (Me).

3-Methoxy-4-methylthiophene-2-carboxylic Acid (92).

Saponification of the above ester (91) gave the title acid (91%), m.p. 121-122°C. (lit. [188] 119-121°C.) $^1H$ nmr $\delta$ ($CDCl_3$) 7.15 (1H, s, 5-H, 3.95 (3H, s, OMe), 2.15 (3H, s, ArMe) and 11.55 (11.55 (1H, s, $CO_2H$) Vmax (nujol) 3,400-2,000 (br, OH) and 1,660 (br, C=0) $cm^{-1}$, $^{13}C$ nmr d ($CDCl_3$116.1 (C-2), 161.5 (C-3), 132.2 (C-4), 127.8 (C-5), 62.0 (OMe), and 13.0 (Me), no signal was observed for $CO_2H$.

Methyl 4 Methoxythiophene-2-carboxylate (93).

Hydroxythiophene-2-carboxylic acid (71) (14.4g, 0.1M) was treated according to general method 1 with the exception that in this case two equivalents of dimethyl sulphate were used. This gave the title compound in 71% yield. It had m.p. 38°C (lit. [189] 38-39°C). $^{1}H$ nmr $\delta(CDCl_3)$ 7.35 1H, d, ArH, J=4Hz), 6.45 (1H, d, ArH, J=4Hz), 3.90 (3H, s, -OMe) and 3.80 (3H, s, -OMe). Vmax (Nujol) 1710 C=0) $cm^{1}$.

4-Methoxythiophene-2-carboxylic Acid (94).

Saponification of methyl 4-methoxythiophene-2-carboxylate (93), using general method 2 gave the title compound in 92% yield. It had m.p. 168-170°C (lit. 189, 170-171$_o$C. $^{1}H$ nmr $\delta(CDCl_3$ 7.35 (1H, s, ArH), 6.55 (1H, s, ArH), 3.80 (3H, s, OMe). Vmax (Nujol) 3,500) 3,500 (br, $CO_2H$) and 1,660 $cm^{-1}$. $^{13}C$ $\delta(CDCl_3)$ 57.3 (OMe), 104,5 (C-5), 123.7 (C-3), 133.2 (C-2), 157.8 (C-4) and 163 (163.3 ($CO_2H$).

## 14.0 Glycosidation of Methyl Hydroxythiophene-carboxylates.

### 2:3:4:6-Tetraacetyl-a-D-glucosyl Bromide.

A solution of 33% hydrogen bromide in glacial acetic acid (100ml) was cooled to 0°C in an ice bath. To this was added a-D-glucose penta-acetate (15g,0.038m) with stirring. Stirring was continued for a further 2 h at room temperature then the reaction mixture was diluted with chloroform (60ml) and poured into ice/water (200ml). The organic layer was separated and the aqueous layer was extracted with a further portion of chloroform (30ml). The chloroform solutions were combined and washed with water then shaken with anhydrous calcium chloride until clear. The solvent was then removed on the rotary evaporator and the residue treated with light petroleum, bp 40-60°C which caused precipitation of long white needles, (13.4g (86%)), being obtained at the pump, having m.p. 86-87°C (lit. [170] 88°C).

### Methyl 3-(Tetra-O-acetyl-B-D-glucopyranoxy) thiophene-2-carboxylate (95).

Methyl-3-hydroxythiophene-2-carboxylate (75) (2g,0.01m), 2:3:4:6-tetra-O-acetyl-a-D-glucopyranosyl bromide (5.1g, 0.0125m) and potassium carbonate (3g, 0.02m) were refluxed in acetone (50ml) for 2 h, the solution was allowed to cool, and filtered. The liquor was added to water (1x20ml), extracted with ether (2x50ml), washed with carbonate solution (1x20ml), water (1x20ml), dried ($Na_2SO_4$) and the solvent was removed on the rotary evaporator. The product

was crystallised from methanol to give a white powder (1.95g, 38%), m.p. 164-165°C (Found: C, 49.1; H, 5.1. $C_{20}H_{24}O_{12}S$ requires C, 49.2; H, 4.9%), $^1H$ nmr $\delta(CDCl_3)$ 7.45 (1H,d, 6Hz 5-H),7.05 (1H, d, 6Hz, 4-H, 5.30 (1H, d, 3Hz, glucose 1-H) 4.25 (1H, m, unassigned glucose H), 3.85 (3H, s, OMe), 3.50 (1H, m, unassigned glucose H), 2.12 (12H s, $COCH_3$) and 2.10 (4H, complex, glucose $CH_2$+2 unassigned glucose protons), M/e 331 (30%; m-tetra-O-acetyl-a-D-glucopyranose) and 159 (M+H; methyl 3-hydroxythiophene-2-carboxylate), Vmax (Nujol), 1710 (C=0) and 1265 (C=0) $cm^1$.

Methyl 5-Methyl-3-(tetra-O-acetyl-B-D-glucopyrananoxy)-thiophene-2-carboxylate (96).

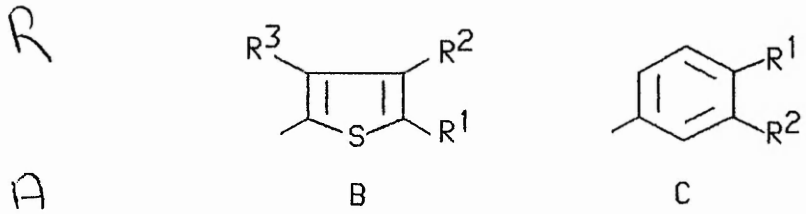
Methyl 3-hydroxy-5-methylthiophene-2-carboxylate (74), (2g, 0.01m), 2:3:4:6-tetra-O-acetyl-a-D-glucopyranosyl bromide (5g, 0.012m) and potassium carbonate (13g, 0.02m) were refluxed in acetone (50ml) for 1 h then the solution was allowed to cool and filtered at the pump. The filtrate was treated as in the previous glycosidation (above) to give an off-white powder (2.5g, 43%) 149-150°C; (Found: C, 49.1; H,5.3, $C_{21}H_{26}O_{12}S$ requires C, 50.2; H, 5.3%) $^1H$ nmr $\delta(CDCl_3)$ 6.70 (1H, s, Ar, 4-H), 5.30 (1H,d, glucose anomeric proton), 4.25 (1H, d, unassigned glucose ring proton), 3.82 (3H, s, $CO_2Me$), 2.68 (1H, m, unassigned glucose ring proton), 2.50 (3H, s, ArMe), 2.15 (6H, s, 2xOAc), 2.10 and 2.05 (8H, complex, 2xOAc and -$CH_2O$-) and 1.60 1H, m, glucose ring proton unassigned), M/e 503 (5%; M+H), 331 (20%; M+H tetra-O-acetyl-&-D-glucopyranose). 173 (25%; M+H methyl 3 hydroxy-5-methyl-thiophene-2-carboxylate). Vmax (Nujol) 1715 (C=0) and 1265 (C-O) cm-$^1$.

## 15.0 Esterification and Fries Rearrangement of Hydroxythiophene Carboxylates.

### Esterification of Methyl 3-hydroxy-5-methylthiophene-2-carboxylate (74).

These esters were prepared using the synthetic procedures described in general method 5 for the acetoxy esters and general method 6 for all other esters. The yields and the physical properties are collected in the following tables. Table 10 gives yields, melting/boiling points and microanalytical data; Table 11 shows the $^{1}H$ nmr signals of the esters (for $CDCl_3$ solutions); Table 12 contains infra-red and mass-spectroscopic data (the latter were obtained under C.I. conditions with $CH_4$). Finally the $^{13}C$ nmr data (for $CDCl_3$ solutions) are shown in Tables 13 (ring carbon values) and 14 (substituent values).

Structures of Prepared Esters.




A B C

| No | A | B | C |
|---|---|---|---|
| 97; | R=Me | 103; $R^1=R^2=R^3=H$ | 109; $R^1=R^2=H$ |
| 98; | R=Et | 104; $R^1=R^2=H; R^3=OMe$ | 110; $R^1=Me; R^2=H$ |
| 99; | R=cyclohexyl | 105 $R^1=R^2=H; R^3=Me$ | 111; $R^1=NO_2; R^2=H$ |
| 100; | $R=CH_2$-2-thienyl | 106; $R^1=H; R^2=OMe; R^3=Me$ | 112; $R^1=H; R^2=OMe$ |
| 101; | $R=CH_2Ph$ | 107; $R^1=Me; R^2=H; R^3=OMe$ | 113; $R^1=H; R^2=NO_2$ |
| 102; | R=p-MeOphenacetyl | 108; $R^1=H; R^2=OMe; R^3=H$ | |

4.2. Table 10.

Yields, m.p./b.p. and microanalytical data:

| | No | % Yield | M.p./b.p./°C | Cryst. Solv. | Formula | Microanalysis |
|---|---|---|---|---|---|---|
| A. | (97) | 82 | 180/0.5 | ----- | $C_9H_{10}O_4S$ | C,50.4;H,4.7 |
| | | | | | Requires | C,50.5;H,4.7 |
| | (98) | 69 | 175/30 | ----- | $C10H_{12}O_4S$ | C,52.2;H,5.1 |
| | | | | | Requires | C,52.6;H,5.3 |
| | (99) | 79 | 91 | EtOH | $C_{14}H_{18}O_4S$ | C,59.8;H,6.4 |
| | | | | | Requires | C,59.8;H,6.5 |
| | (100) | 53 | 60-61 | EtOH | $C_{13}H_{12}O_4S_2$ | C,51.4;H,4.1 |
| | | | | | Requires | C,52.7;H,4.0 |
| | (101) | 91 | 68 | EtOh | $C_{13}H_{14}O_4S$ | C,62.0;H,4.5 |
| | | | | | Requires | C,62.1;H,4.1 |
| | (102) | 50 | 98 | EtOH | $C_{16}H_{16}O_6S$ | C,58.1;H,5.1 |
| | | | | | Requires | C,60.0;H,5.0 |
| B. | (103) | 85 | 126-127 | EtOH | $C_{12}H_{20}O_4S_2$ | C,51.4;H,3.5 |
| | | | | | Requires | C,51.1;H,3.5 |
| | (104) | 98 | 156-157 | EtOH | $C_{13}H_{12}O_6S_2$ | C,49.5;H,3.9 |
| | | | | | Requires | C,50.0;H,3.8 |
| | (105) | 98 | 123-124 | EtOH | $C_{13}H_{12}O_4S$ | C,52.2;H,4.1 |
| | | | | | Requires | C,52.7;H,4.0 |
| | (106) | 64 | 106-107 | EtOH | $C_{14}H_{14}O_6S_2$ | C,51.0;H,4.2 |
| | | | | | Requires | C,51.5;H,4.3 |
| | (107) | 60 | 147-148 | EtOH | $C_{14}H_{14}O_6S_2$ | C,51.4;H,4.4 |
| | | | | | Requires | C,51.5;H,4.3 |
| | (108) | 54 | 109-111 | EtOH | $C_{13}H_{12}O_6S_2$ | C,50.1;H,3.9 |
| | | | | | Requires | C,50.8;H,3.8 |
| C. | (109) | 60 | 124-126 | EtOH | $C_{12}H_{12}O_4S$ | C,60.9;H,4.3 |
| | | | | | Requires | C,60.9;H,4.3 |
| | (110) | 63 | 97-98 | EtOH | $C_{13}H_{14}O_4S$ | C,62.0;H,4.8 |
| | | | | | Requires | C,62.1;H,4.8 |
| | (111) | 55 | 136-137 | EtOH | $C_{14}H_{11}NO_6S$ | C,52.3;H,3.4 N,4.7 |
| | | | | | Requires | C,52.2;H,3.4 N,4.7 |
| | (112) | 75 | 82-83 | EtOH | $C_{15}H_{14}O_6S$ | C,57.0;H,4.3 |
| | | | | | Requires | C,58.8;H,4.6 |
| | (113) | 79 | 140 | EtOH | $C_{14}H_{11}SO_6N$ | C,51.4;H,3.6 N,3.7 |
| | | | | | Requires | C,52.3;H,3.4 N,4.3 |

Table 11.

δ-Values for $^1H$ nmr.

| No. | 4-H | 2'H | 3'H | 4'H | 5'H | 6'H | 5-Me | $CO_2Me$ | Others |
|---|---|---|---|---|---|---|---|---|---|
| A,(97) | 6,52 | --- | --- | --- | --- | --- | 2,42 | 3,75 | OCOMe, 2,25 |
| (98) | 6,60 | --- | --- | --- | --- | --- | 2,42 | 3,86 | $CH_2$, 2,65[m], q<br>$CH_3$, 1,25[m], t |
| (99) | 6,63 | --- | --- | --- | --- | --- | 2,44 | 3,77 | $C_6H_{10}$, 1-3b |
| (100) | 6,70 | --- | 7,5 to 6,9 (m) | | | --- | 2,47 | 3,80 | $CH_2$, 4,20, s |
| (101) | 6,56 | 7,25 | 7,25 | 7,25 | 7,25 | 7,25 | 2,40 | 3,70 | $CH_2$, 3,89, s |
| (102) | 6,65 | 7,40[c] | 6,95[d] | --- | 6,95[d] | 7,40[c] | 2,49 | 3,82[m] | 4'OMe, 3,79[m]<br>$CH^2$, 3,88, s |
| B,(103) | 6,68 | --- | 7,55[b] | 7,05[b] | 7,95[b] | --- | 2,46 | 3,65 | ---------- |
| (104) | 6,45 | --- | --- | 6,65[d] | 7,35[d] | --- | 2,12 | 3,66 | 3'-OMe, 3,52 |
| (105) | 6,70 | --- | --- | 6,92[f] | 7,40[f] | --- | 2,42 | 3,68 | 3'-OMe, 2,52 |
| (106) | 6,79 | --- | --- | --- | 6,55 | --- | 2,48[m] | 3,76[g] | 3'-OMe, 2,45[m]<br>3'-OMe, 3,85[g] |
| (107) | 6,74 | --- | --- | 6,6[i] | --- | --- | 2,45 | 3,74 | 5'-Me, 2,45<br>3'-OMe, 3,92 |
| (108) | 6,45 | --- | 6,85 | --- | 7,62 | --- | 2,45 | 3,70 | 4'-OMe, 3,82 |
| C,(109) | 6,93 | 8,40[b] | 7,65[b] | 7,65[b] | 7,65[b] | 8,40[b] | 2,50 | 3,80 | ---------- |
| (110) | 6,87 | 8,11 | --- | 7,52[h] | 7,52[h] | 8,11[h] | 2,50 | 3,78 | 3'Me, 2,44 |
| (111) | 6,82 | 9,00[h] | --- | 8,50[b] | 7,70[i] | 9,02[b] | 2,51 | 3,75 | ---------- |
| (112) | 6,85 | 8,23[j] | 7,05[j] | --- | 7,05[j] | 8,23[j] | 2,50 | 3,78 | -OMe, 3,90 |
| (113) | 6,80 | 8,38 | 8,38 | --- | 8,38 | 8,38 | 2,50 | 3,75 | ---------- |

[m] J=8Hz; [b] multiplet; [c] doublet; J=9Hz; [d] doublet; J=6Hz [mm]; [gg]; may be interchanged; [f] doublet; J=5Hz; [h] Broad singlet; [i] triplet; J=9 Hz.

Table 12.

| No. | Med. | C=O cm$^{-1}$ $CO_2Me$ | C=O cm$^{-1}$ OCOR | M+H (%) | 100% m/e | Other |
|---|---|---|---|---|---|---|
| A, (97) | a | 1718 | 1782 | 215(85) | 175(M-$C_2H_3$) | |
| (98) | b | 1718 | 1782 | 229(82) | 173(M+H-COR) | |
| (99) | c | 1718 | 1780 | 283(72) | 173(M+HC-OR) | 251(25%, M-OMe |
| (100) | b | 1712 | 1789 | 297(15) | 173(M+H-COR) | |
| (101) | c | 1714 | 1780 | 291(23) | 173(M+H-COR) | |
| (102) | c | 1714 | 1780 | 321(52) | 121($C_7H_5OMe$) | |
| B, (103) | c | 1710 | 1740 | 283(75) | 143$ArCO_2$Meth) | 251(23%, M-OMe |
| (104) | c | 1715 | 1725 | 313(25) | 141(ArCO) | |
| (105) | c | 1709 | 1728 | 297(22) | 125(ArCO) | |
| (106) | c | 1700 | 1730 | 327(25) | 155(ArCO) | |
| (107) | c | 1718 | 1730 | 327(22) | 155(ArCO) | |
| (108) | c | 1716 | 1730 | 313(42) | 141(ArCO) | |
| C, (109) | c | 1708 | 1748 | 277(55) | 245(M-OMe) | |
| (110) | c | 1715 | 1744 | 291(36) | 119(ArCO) | |
| (111) | c | 1690 | 1755 | 322(63) | 150(ArCO) | 290(71%, M-OMe) |
| (112) | c | 1720 | 1758 | 307(15) | 135(ArCO) | |
| (113) | c | 1740 | 1744 | 322(100) | --------- | 151(65%ArCO) |

a, liquid film; b, KBr disc; c, nujol mull.

Tables 13 and 14.

$C^{13}$ Data for Ring Carbon Atoms.

| | No | C-2 | C-3 | C-4 | C-5 | C-1' | C-2' | C-3' | C-4' | C-5' | C-6' |
|---|---|---|---|---|---|---|---|---|---|---|---|
| A, | (97) | 116,2 | 150,6 | 122,0 | 144,9 | --- | --- | --- | --- | --- | --- |
| | (98) | 116,2 | 150,8 | 122,1 | 144,9 | --- | --- | --- | --- | --- | --- |
| | (99) | 116,1 | 150,6 | 122,1 | 144,8 | 43,0 | 28,8 | 25,4 | 25,4 | 28,4 | |
| | (100) | 116,4 | 150,0 | 121,8 | 145,0 | --- | 134,0 | 125,2 | 126,9 | 127,3 | --- |
| | (101) | | Not obtained | | | | | | | | |
| | (102) | 116,4 | 150,4 | 121,9 | 145,0 | 125,2 | 130,6 | 114,1 | 158,9 | 114,1 | 130,6 |
| B, | (103) | 116,2 | 149,9 | 122,1 | 144,9 | --- | 132,5 | 135,1 | 128,0 | 133,8 | --- |
| | (104) | 116,3 | 150,1 | 122,4 | 144,6 | --- | 108,2 | 158,4 | 116,3 | 132,2 | --- |
| | (105) | 116,8 | 149,2 | 122,3 | 144,9 | --- | 125,4 | 148,3 | 131,6 | 131,8 | --- |
| | (106) | 116,7 | 149,8 | 122,3 | 144,5 | --- | 124,2 | 138,7 | 157,0 | 103,6 | --- |
| | (107) | 116,2 | 150,2 | 122,4 | 144,4 | --- | 105,4 | 158,1 | 115,2 | 147,6 | --- |
| | (108) | | Not obtained | | | | | | | | |
| C, | (109) | 116,0 | 150,6 | 122,1 | 144,9 | 129,3 | 130,4 | 128,6 | 133,6 | 128,6 | 130,4 |
| | (110) | 116,2 | 150,5 | 122,1 | 145,0 | 129,0 | 130,8 | 138,4 | 134,4 | 128,5 | 127,5 |
| | (111) | 116,6 | 149,7 | 121,6 | 145,4 | 131,0 | 129,9 | 117,8 | 125,3 | 128,0 | 135,9 |
| | (112) | 116,4 | 150,8 | 122,3 | 144,9 | 121,7 | 132,6 | 114,0 | 163,7 | 114,0 | 132,6 |
| | (113) | 116,1 | 151,0 | 121,5 | 145,4 | 129,8 | 131,5 | 123,7 | 134,9 | 123,7 | 131,5 |

13C Data for Substituent Carbon Atoms.

| | No | 2-CO | OCO | $CO_2Me$ | 5-Me | Other |
|---|---|---|---|---|---|---|
| A. | (97) | 160.9 | 168.2 | 51.6 | 16.2 | OCOMe, 20.6 |
| | (98) | 160.9 | 171.7 | 51.6 | 16.2 | $CH_2$, 27.2; $CH_3$, 8.8 |
| | (99) | 160.9 | 173.2 | 51.7 | 16.2 | |
| | (100) | 160.8 | 168.0 | 51.7 | 16.2 | CHz, 35.0 |
| | (101) | Not obtained | | | | |
| | (102) | 160.9 | 169.3 | 51.7 | 16.2 | CH2, 40.1; 4'-OMe, 55.3 |
| B. | (103) | 161.0 | 159.3 | 51.7 | 16.3 | |
| | (104) | 161.0 | 164.0 | 51.7 | 16.3 | 3'-OMe, 59.2 |
| | (105) | 161.0 | 159.9 | 51.7 | 16.2 | 3'-Me, 16.0 |
| | (106) | 160.9 | 159.8 | 51.7 | 16.3 | 3'-Me, 16.6; 4'-OMe, 57.4 |
| | (107) | 161.0 | 163.7 | 51.6 | 16.2 | 5'-Me, 16.6; 3'-OMe, 59.0 |
| | (108) | Not obtained | | | | |
| C. | (109) | 161.0 | 164.1 | 51.7 | 16.3 | |
| | (110) | 161.0 | 164.2 | 51.7 | 16.4 | 3'-Me, 21.3 |
| | (111) | 160.7 | 162.0 | 51.9 | 16.4 | |
| | (112) | 161.1 | 164.2 | 51.7 | 16.4 | 4'-OMe, 55.5 |
| | (113) | 160.7 | 162.3 | 51.9 | 16.4 | |

Fries Rearrangement Products of Methyl 3-Acyloxy-5-methyl-thiophene-2-carboxylates.

Methyl 4-Acetyl-3-hydroxy-5-methylthiophene-2-carboxylate (114).

The title compound was prepared from (97) using the general method 7, in 93% yield. It had m.p. 111-112°C. (Found: C, 49.9; H, 43. $C_9H_{10}SO_4$ requires C, 50.2; H, 4.7%). $^1H$ nmr δ($CDCl_3$) 3.92 (3H, s, $CO_2Me$), 2.70 and 2.60 (6H, s, Me and 4-$COCH_3$) and 10.45 (1H, s, OH, $D_2O$ ex). Vmax (nujol) 3260 (OH), 1680-1650 (br, C=O) $cm^{-1}$. M/e 215

(90% M+H) and 183 (100% M-OMe). $^{13}C$ nmr ($CDCl_3$) ppm 18.05 (5-Me) 31.10 ($CH_3$ C=0), 51.94 ($CO_2Me$), 100.32 (C-2), 127.13 (C-4), 155.25 (C-3), 163.63 ($CO_2$) 166.09 (C-5) and 184.27 ($CH_2CO$).

Methyl 5-Methyl-3-hydroxy-4-propionylthiophene-2-carboxylate (117).

The title ketone was prepared from (98), using the above procedure, in 91% yield, m.p. 80-81°C. (Found: C, 51.8; H, 5.3. $C_{10}H_{12}SO_4$ requires C,52.6; H,5.3%). $^1H$ nmr $\delta$($CDCl_3$) 3.86 (3H, s, $CO_2Me$), 2.95 (2H, q, 7Hz, -$\underline{CH_2}$-$CH_3$) and 10.48 (1H, s, OH $D_2O$ ex). Vmax (Nujol) 3,600-2,500 (OH), 1670 (br) (C=0). M/e 229 (25% M+H) and 197 (1005, M-OMe). $^{13}C$ nmr $\delta$(CDC13) 8.8 ($\underline{CH_3}CH_2$), 10.05 (5-Me), 36.2 ($\underline{CH_2}$), 51.9 ($CO_2Me$, 100.2 (C-2), 127.0 (C-4, 154.9 (C-3) 163.5 ($\underline{CO_2}Me$), 166.2 (C-5), 197.5 (Et $\underline{C}$=0).

Methyl 5-Methyl-3-methoxy-4-acetylthiophene-2-carboxylate (115).

Methylation of (114) using general method 1 gave the title compound in quantitative yield. It had m.p. 66-67°C (from aqueous ethanol). (Found: C, 52.6; H, 5.1. $C_{10}H_{12}O_4S$ requires C,52.6; H,5.3%). $^1H$ nmr $\delta$($CDCl_3$) 4.05 (3H, s, 3-OMe), 3.86 (3H, s, $CO_2Me$), 2.60 and 2.52 (6H, both s, 5-Me and MeCO). Vmax (Nujol) 1,721 (ester C=0) and 1,685 (MeC=0) $cm^{-1}$. M/e 229 (100%, M+H) and 197 (90%, M-OMe). $^{13}C$ $\delta$($CDCl_3$) 17.3 (5-Me), 30.6 (OMe), 51.9 ($CO_2\underline{Me}$), 63.0 ($CH_3CO$), 112.3 (C-2), 132.0 (C-4), 151.9 (C-5) 161.4 (C-3) and 192.2 (Me$\underline{C}$O).

4-Acetyl-3-methoxy-5-methylthiophene-2-carboxylic acid (116).

The title compound was prepared from (115) using general method 2 in 93% yield. It had m.p. 163-164°C (from ethanol). (Found: C, 50.2; H, 4.7%; $C_9H_{10}O_4S$ requires C, 50.5; H, 4.7%). $^1H$ nmr $\delta(CDCl_3)$ 3.97 (3H, s, -OMe), 2.55 (3H, s, Me), 2.45 (3H, s, $COCH_3$) and 5.40 (1H, br, OH, $D_2O$ ex). Vmax (KBr) 3,500-2,000 (OH), 1.720 (C-O) [OH] and 1645 ($CH_3$ C=O), m/e 215 (85%, M+H) and 197 (100%, M-OH). $^{13}C$ $\delta(CDCl_3)$, 17.1 (5-Me), 30.6 (3-ONe), 62.8 ($CH_3CO$) 113.8 (C-2) 131.9 (C-4), 150.9 (C-5), 160.6 ($\underline{C}O_2H$), 162.0 (C-3) and 194.9 ($CH_3\underline{C}O$).

Methyl 3-methoxy-5-methyl-4-propionylthiophene-2-carboxylate (118).

The title compound was prepared from (119) using general method 1 in 66% yield. It had m.p. 54-55°C (from ethanol). (Found: C, 54.0; H, 5.6%. $C_{11}H_{14}O_4S$ requires C, 54.5 H, 5.8%). $^1H$ nmr $\delta(CDCl_3)$ 3.86 (3H, s, $CO_2Me$), 2.90 (2H, qd, J=7Hz, $\underline{CH_2}CH_3$) and 4.0 (3H, s, 3-OMe). Vmax (Nujol) 1720 and 1685 $cm^{-1}$. M/e 243 (100%, M+H) and 211 (65% M-OMe). $^{13}C$ $\delta(CDCl_3)$ 7.90 ($\underline{C}H_3$-$CH_1$), 17.1 (5-Me), 35.9 (-OMe), 51.9 ($CO_2\underline{Me}$), 151.0 (C-5), 161.1 (C-3) and 198.8 (Et$\underline{C}O$).

3-Methoxy-5-methyl-4-propionylthiophene-2-carboxylic Acid (119).

The title compound was prepared from (118) using general method 2 in 91% yield. It had m.p. 152-153°C (from ethanol). (Found: C, 52.5; H, 4.9. $CH_{10}H_{12}O_4S$ requires C, 52.6; H, 5.26%). $^1H$ nmr

$\delta$($CDCl_3$) 1.15 (3H, t, CH2-$\underline{CH_3}$), 2.55 (3H, s, 5-Me), 2.90 (2H, q, $\underline{CH_3}$), 4.00 (3H, s, -OMe) and 10.50 (1H, br, OH, $D_2O$ ex). Vmax (Nujol), 3.500-2,200 (OH), 1,685 (C=O [OH], and 1,660 (Et C=O). M/e 229 (M+H; 100%), 211 (65%); M-$H_2O$). $^{13}C$ $\delta$($CDCl_3$) 8.0 ($CH_2\underline{CH_3}$) 17.3 (5-Me), 36.04 (-OMe), 63.4 ($CH_3CH_2CO$), 112.3 (C-2), 132.5 (C-4), 152.5 (C-5), 162.0 ($\underline{CO_2}H$), 164.9 (C-3) and 198.7 ($\underline{C}OEt$).

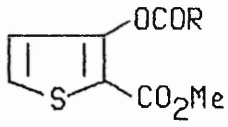
Fries Rearrangement of Esters (99) - (113).

Fries rearrangement of the remaining esters in this series using general method 7 resulted in cleavage to the component methyl 3-hydroxy-5-methylthiophene-2-carboxylate (74) and the respective carboxylic acids.

Esterification of Methyl 3-Hydroxythiophene-2-carboxylate (75).

These esters were prepared using the general methods 5 and 6. The results are summarised in the following series of tables. Table 15 contains the yields, melting points/boiling points and microanalytical data; Table 16 shows the proton nmr spectra of the esters ($\delta$ $CDCl_3$); Table 17 gives IR and mass spectroscopic data and finally in Tables 18 and 19 are the $^{13}C$ nmr values for ring carbon atoms and substituent carbon atoms, respectively.

Structures of Prepared Esters.




(120): R=Me
(121): R=Et
(122): R=Ph
(123): R=Th

Table 15.

Yields, m.p./b.p. and microanalytical data:

| No | Yield | M.p./B.p. | Cryst Solv. | Formula | Microanalysis Found | Requires |
|---|---|---|---|---|---|---|
| (120) | 80 | 140/0,9 | --- | $C_8H_8SO_4$ | Lit.[134] =83-85°C/0,03 mm Hg) | |
| (121) | 72 | 130/0,8 | --- | $C_9H_{10}SO_4$ | C,50,2;H,4,9; | C,50,5;H,4,7 |
| (122) | 91 | 63-64 | EtOH | $C_{10}H_{10}SO_4$ | C,59,9;H,3,9; | C,59,5;H,3,8 |
| (123) | 80 | 95-96 | EtOH | $C_7H_6S_2O_4$ | C,49,7;H,3,2; | C,49,2;H,3,0 |

Table 16.

$^1$H NMR Data.

| No | H-1 | H-2 | $Co_2Me$ | Acyl Group Protons |
|---|---|---|---|---|
| (120) | 7.44 (d, 6Hz) | 6.84 (d, 6Hz) | 3.00 | 2.30 ($COCH_3$) |
| (121) | 7.50 (d, 6Hz) | 6.85 (d, 6Hz) | 3.75 | 2.60, qd, 10Hz ($-CH_2-$) |
| (122) | 8.25 (d, 6Hz) | 7.12 (d, 6Hz) | 3.80 | 8.20, m, 7.55, m, 7.50, m; benzene ring |
| (123) | 7.55 (d, 6Hz) | 7.12 (d, 6Hz) | 3.80 | 7.20, m, 7.25, 8.05, m; thiophene ring |

Table 17.

IR and Mass Spectra Data.

| No | Med | C=O cm$^{-1}$ $CO_2Me$ | C=O cm$^{-1}$ OCOR | M+H% | 100% m/e | Other |
|---|---|---|---|---|---|---|
| (120) | a | 1711 | 1755 | --- | --- | --- |
| (121) | a | 1720 | 1775 | 215(30) | 159($C_6H_6SO_3$) | --- |
| (122) | c | 1702 | 1720 | 263(100) | --- | 231(-OMe) |
| (123) | c | 1705 | 1718 | 269(100) | --- | 237(OMe) |

a, liquid film; c, Nujol mull

Tables 18 and 19 - $^{13}C$ NMR Data.

Ring Carbon Values.

| No | C-2 | C-3 | C-4 | C-5 | C-1' | C-2' | C-3' | C-4' | C-5' | C-6' |
|---|---|---|---|---|---|---|---|---|---|---|
| (120) | 118,6 | 151,1 | 123,5 | 129,5 | --- | --- | --- | --- | --- | --- |
| (121) | 118,7 | 151,2 | 123,6 | 129,5 | --- | --- | --- | --- | --- | --- |
| (122) | 118,8 | 151,0 | 123,6 | 129,7 | 129,7 | 130,4 | 128,6 | 133,7 | 128,6 | 130,4 |
| (123) | 119,0 | 150,4 | 123,5 | 129,7 | --- | 132,0 | 135,2 | 128,0 | 133,9 | --- |

Substituent Carbon Values.

| No | OCO | 2-CO | $CO_2Me$ | Others |
|---|---|---|---|---|
| (120) | 168,3 | 160,9 | 51,9 | 20,7($COCH_3$) |
| (121) | 171,7 | 160,9 | 51,8 | 27,6(-$CH_3$-),8,9($CH_3$) |
| (122) | 164,0 | 161,0 | 51,9 | --- |
| (123) | 159,2 | 160,9 | 52,0 | --- |

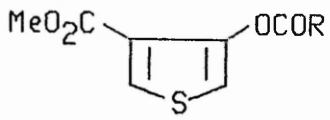
Fries Rearrangement of Esters (120) - (123).

Fries rearrangement of the esters prepared in this series using general method 7 resulted in cleavage in all cases. Methyl 3-hydroxythiophene-2-carboxylate (75) was recovered in all cases and with esters (122) and (123) the respective carboxylic acids were also recovered.

## Esterification of Methyl 3-Hydroxythiophene-4-carboxylate (77).

This series of compounds was prepared using the general methods 5 and 6. The yields and the physical properties of the products are collected in the following Tables. Table 20 gives the yields, melting/boiling points and microanalytical dates; Table 21 shows the proton nmr signals of the esters δ($CDCl_3$); in Table 22 are collected the ir and mass spectroscopic data and $^{13}C$ nmr values (for $CDCl_3$ solutions) are shown in Tables 23 (ring carbon values) and 24 (substituent values).

## Structures of Prepared Esters.




(124): R=Me
(125): R=Cyclohexyl
(126): R=Ph
(127): R=2-Thienyl
(128): R=3-Methyl-2-thienyl
(129): R=3-Methoxy-2-thienyl

Table 20.

Yields, m.p./b/p. and microanalytical data:

| No | Yield % | m.p./b.p. | Cryst. Solv. | Formula | Microanalysis Found | Required |
|---|---|---|---|---|---|---|
| (124) | 85 | 105/0.1 | --- | $C_8H_8SO_4$ | C,48.5;H,4.2; | C,48.0;H,4.0 |
| (125) | 70 | 68-69 | EtOH | $C_{13}H_{16}SO_4$ | C,58.2;H,3.9; | C,58.2;H,6.0 |
| (126) | 77 | 66 | EtOH | $C_{13}H_{10}SO_4$ | C,59.2;H,3.9; | C,59.5;H,3.8 |
| (127) | 87 | 104 | EtOH | $C_{11}H_8S_2O_4$ | C,44.5;H,3.0; | C,44.8;H,3.0 |
| (128) | 90 | 76-77 | EtOH | $C_{12}H_{10}S_2O_4$ | C,51.2;H,3.7; | C,51.0;H,3.5 |
| (129) | 86 | 144-45 | EtOH | $C_{12}H_{10}S_2O_5$ | C,48.6;H,3.5; | C,48.3;H,3.3 |

Table 21.

$^1H$ nmr data ($CDCl_3$) ppm.

| No | $^1H$ | $^2H$ | $CO_2Me$ | Acyl Group Protons |
|---|---|---|---|---|
| (124) | 6.98(d, 4Hz) | 8.03(d, 4Hz) | 3.77 | 2.27(-OCOMe) |
| (125) | 7.00(d, 4Hz) | 8.08(d, 4Hz) | 3.80 | 1.0-3.0(m, $C_6H_{10}$) |
| (126) | 7.18(d, 4Hz) | 8.03(d, 4Hz | 3.71 | 8.2(m,2xH)<br>7.5(m,C6H5) |
| (127) | 7.20(d, 4Hz) | 8.07(d, 4Hz) | 3.75 | 7.1(d,4Hz)<br>8.1(d,4Hz)<br>7.7(m,$C_4H_3CO$) |
| (128) | 7.16(d, 4Hz) | 8.10(d, 4Hz) | 3.78 | 6.98(d,6Hz) Th<br>7.50(d,6Hz) Th<br>2.63(ArMe) |
| (129) | 7.05(d, 4Hz) | 7.95(d, 4Hz) | 3.78 | 6.78(d,8Hz) Th<br>7.42(d,8Hz) Th<br>3.92(OMe) |

Table 22.

Infra-red and mass spectral data.

| No | Med. | C=O cm$^{-1}$ CO2Me | C=O cm$^{-1}$ OCOR | M+H(%) | 100% m/e | Other |
|---|---|---|---|---|---|---|
| (124) | c | 1720 | 1760 | 201(50) | 159 | ($C_6H_6SO_3$) |
| (125) | c | 1710 | 1750 | 269(10) | 129 | ($C_7H_{12}O_2$) |
| (126) | c | 1710 | 1720 | 263(93) | 123 | ($C_7H_6O_2$) |
| (127) | c | 1705 | 1715 | 269(100) | --- | --- |
| (128) | c | 1720 | 1740 | 283(45) | 127 | ($C_6H_6OS$) |
| (129) | c | 1715 | 1730 | 299(25) | 141 | ($C_6H_6O_2S$) |

c = Nujol mull

Tables 23 and 24.

$^{13}C$ data ($CDCl_3$ solutions).

Table 23.

Values for ring carbon atoms.

| No | C-2 | C-3 | C-4 | C-5 | C-1' | C-2' | C-3' | C-4' | C-5' | C-6' |
|---|---|---|---|---|---|---|---|---|---|---|
| (124) | 114,0 | 146,6 | 125,0 | 132,9 | --- | --- | --- | --- | --- | --- |
| (125) | 113,7 | 146,5 | 125,2 | 132,7 | 43,1 | 28,8 | 25,4 | 25,7 | 25,4 | 28,8 |
| (126) | 113,9 | 146,3 | 125,2 | 132,8 | 129,2 | 130,3 | 128,6 | 133,6 | 128,6 | 130,3 |
| (127) | 114,0 | 146,0 | 125,5 | 132,6 | --- | 134,9 | 134,9 | 133,5 | 127,9 | --- |
| (128) | 114,3 | 145,9 | 125,4 | 132,7 | --- | 131,5 | 148,3 | 131,4 | 131,7 | --- |
| (129) | 114,0 | 145,9 | 125,4 | 132,5 | --- | 132,2 | 145,9 | 116,0 | 132,1 | --- |

Table 24.

Values for substituent carbon atoms.

| No | OCO | 4-OCO | $CO_2Me$ | Other |
|---|---|---|---|---|
| (124) | 169,1 | 161,4 | 51,7 | 20,7($COCH_3$) |
| (125) | 173,9 | 161,4 | 51,7 | --- |
| (126) | 164,7 | 161,4 | 51,7 | --- |
| (127) | Unassigned | Unassigned | 51,7 | --- |
| (128) | 161,5 | 160,5 | 51,7 | 15,9($ArOH_3$) |
| (129) | Unassigned | 163,8 | 51,7 | 59,1($OCH_3$) |

Fries Rearrangement Products of Methyl 3-Acyloxythiophene-4-carboxylates:

Methyl 2-Acetyl-3-hydroxythiophene-4-carboxylate

The title compound was prepared in quantitative yield using general method 7, from the ester (124). It had m.p. 118°C (lit.[134] 120-121°C). $^1$H nmr $\delta$($CDCl_3$) 2.53 (3H, s, $COCH_3$) 3.94 (3H, s, -OMe), 8.23 (1H, s, 5-H) and 10.74 (1H, br, OH, $D_2O$ex). Vmax (KBr) 3250 (OH), 1685 ($CO_2Me$) and 1640 (C=0 $cm^{-1}$. $^{13}$C $\delta$($CDCl_3$) and 28.50 ($CH_3$), 52.3 ($CO_2\underline{Me}$), 122.0 (C-2), 138.3 (C-4), C-5), 163.0 (C-3 and 182.0 ($CH_3\underline{C}O$).

Methyl 3-Hydroxy-2-(2'-thenoyl) thiophene-4-carboxylate (131).

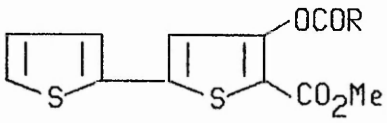
The title ketone was prepared in 55% yield using general method 7 from ester (127). It had m.p. 153°C (from methanol). (Found: C, 49.3; H, 2.9%. $C_{11}H_8O_4S_2$ requires C, 49.3; H, 2.9%). $^1$H nmr $\delta$ ($CDCl_3$) 3.90 (3H, s, $CO_2Me$), 7.20 (1H, m, ArH) and 8.80 (1H, s, ArH). Vmax (Nujol) 3,300 (OH), 1680 ($CO_2Me$) and 1640 (C=0) $cm^{-1}$. M/e 269 )M+H; 100%) and 237 (30%, M-OMe).

Fries Rearrangement of Esters (125)-(126) and (128)-(129):

Fries rearrangement of the above esters using general method 7 resulted in cleavage to the component methyl 3-hydroxy thiophene-4-carboxylate and the respective carboxylic acids.

Esterification of Methyl 4-Hydroxy-2,2'-bithienyl-5-carboxylate (81).

These esters were prepared using the general methods 5 and 6 as appropriate. The yields obtained, melting points and microanalytical data are all summarised in Table 25; Table 26 shows the proton nmr signals of the esters (for $CDCl_3$ solutions): in Table 27 the infra-red and mass-spectroscopic data are collected and finally in Tables 28 and 29 are shown the $^{13}C$ nmr values for bithienyl ring carbon atom and acyl group and substituent carbon atom values, respectively.




R

(132) = Me
(133) = 2"-Thienyl
(134) = 3"-Methyl-2"-thienyl
(135) = 3"-Methoxy-2"-thienyl
(136) = 5"-Methyl-3"-methoxy-2"-thienyl

Table 25.

Yields, m.p./b.p. and microanalytical data:

| No | Yield % | M.p (°C) | Cryst. Solv. | Formula | Microanalysis Found | Required |
|---|---|---|---|---|---|---|
| (132) | 86 | 121 | EtOH | $C_{12}H_{10}S_2O_4$ | C,52.3;H,4.3; | C,51.1;H,3.6 |
| (133) | 84 | 152 | EtOH | $C_{15}H_{10}S_3O_4$ | C,51.7;H,3.9; | C,51.4;H,2.9 |
| (134) | 80 | 96-97 | EtOH | $C_{16}H_{12}S_3O_4$ | C,52.5;H,3.7; | C,52.7;H,3.3 |
| (135) | 84 | 147 | EtOAc | $C_{16}H_{12}S_3O_4$ | C,51.4;H,3.3; | C,50.5;H,3.2 |
| (136) | 76 | 134 | EtOH | $C_{17}H_{14}S_3O_4$ | C,51.0;H,3.6; | C,51.8;H,3.6 |

Table 26.

$^1$H NMR Data.

| No | H-1 | H-2 | H-3 | H-4 | $CO_2Me$ Acyl Group |
|---|---|---|---|---|---|
| (132) | 7.15 | 7.30(m) | 7.30(m) 7.00 | 3.85 | 2.35(-COMe) |
| (133) | 7.05(d,6Hz) | 7.25(m) | 7.25(m) 7.10 | 3.75 | 8.0(d,6Hz,ArH)<br>7.65(m,ArH) |
| (134) | 7.05(d,6Hz) | 7.28(m) | 7.28(m) 7.05 | 3.80 | 7.52(d,6Hz,4-H)<br>6.98(d,6Hz,5-H)<br>2.60(s,3-ArMe) |
| (135) | 7.05(d,6Hz) | 7.25(m) | 7.25(m) 7.00 | 4.00 | 3.80(s,3-OMe)<br>7.55(d,6Hz,4-H)<br>6.90(d,6Hz,5-H) |
| (136) | 7.00(d,6Hz) | 7.20(m) | 7.20(m) 6.60 | 3.90 | 7.20(s,4-H)<br>3.80(s,-OMe)<br>2.40(s,-Me) |

Table 27.

IR and Mass Spectra Data.

| No | Med. | C=Ocm$^{-1}$ | | M+H (%) | 100(%) m/e | Other |
|---|---|---|---|---|---|---|
| | | $CO_2Me$ | OCOR | | | |
| (132) | c | 1702 | 1780 | 283(55) | 241(-$COCH_3$) | |
| (133) | c | 1708 | 1718 | 351(100) | --- | 319(OMe) |
| (134) | c | 1708 | 1720 | 365(55) | 125(-$C_6H_5SO$) | |
| (135) | c | 1708 | 1722 | 381(45) | 141(-$C_6H_5SO_2$) | |
| (136) | c | 1708 | 1715 | 395(40) | 155(-$C_7H_7SO_2$) | |

c = Nujol mull.

Tables 28 and 29.

$^{13}C$ Data for Ring Carbon Atoms.

| No | C-5' | C-4' | C-3' | C-2' | C-2 | C-3 | C-4 | C-5 |
|---|---|---|---|---|---|---|---|---|
| (134) | 126,7 | 128,1 | 125,4 | 135,8 | 141,0 | 119,3 | 168,2 | |
| (135) | 126,7 | 128,1 | 125,4 | 136,0 | 141,0 | 119,3 | 170,0 | |
| (136) | 126,6 | 128,1 | 125,4 | 135,2 | 140,5 | 119,6 | Not identified | 102,5 |
| (137) | 126,5 | 128,1 | 125,3 | 125,3 | 140,7 | 119,7 | 164,1 | 107,4 |
| (138) | 126,5 | 128,1 | 125,2 | 125,2 | 140,6 | 119,7 | 164,1 | 104,6 |

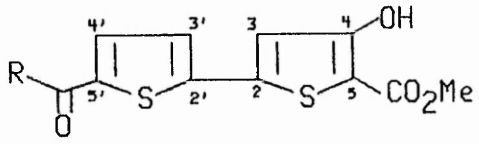
$^{13}C$ Data for Acyl Group and Substituent Carbon Atoms.

| No | C-2 | C-3 | C-4 | C-5 | OCO | 8-CO | $CO_2Me$ | Other |
|---|---|---|---|---|---|---|---|---|
| (134) | --- | --- | --- | --- | 160,8 | 150,9 | 51,9 | $COCH_3$,20,7 |
| (135) | 134,0 | 135,3 | 121,8 | 134,0 | 160,8 | 159,1 | 52,0 | --- |
| (136) | 125,4 | 148,6 | 131,5 | 131,9 | 160,1 | 159,8 | 51,9 | 3'-Me,15,5 |
| (137) | 108,2 | 150,4 | 116,0 | 132,5 | 160,9 | 158,2 | 51,9 | 3'-Ome,59,1 |
| (138) | 104,6 | 150,6 | 114,9 | 148,2 | 160,9 | 158,0 | 51,9 | 5'-Me,16,7; 3'-Ome,59,1 |

Fries Rearrangement of Methyl 4-Acyloxy-2.2'-bithienyl-5-carboxylates.

The esters described in the previous section were Fries rearranged using general method 7. The results are summarised in the following Tables. In Table 30 are the yields, melting points and microanalytical data; Table 31 contains proton nmr signals of the

ketones (for $CDCl_3$ solutions); in Table 32 are collected the infra-red and mass spectroscopic details, whilst Tables 33 and 34 contain the $^{13}C$ nmr data (for $CDCl_3$ solutions), Table 33 showing the values for bithienyl ring carbon atoms, and Table 34 the values for the rearranged acyl groups and substituent carbon atoms.




Where R = (137): Acetyl
(138): 2-Thienyl
(139): 3-Methyl-2-thienyl
(140): 3-Methoxy-2-thienyl
(141): 5-Methyl-3-methoxy-2-thienyl

Table 30.

Yield, m.p./b.p. and microanalytical data:

| No | Yield % | M.p (°C) | Cryst. Solv. | Formula | Microanalysis Found | Required |
|---|---|---|---|---|---|---|
| (137) | 75 | 160 | EtOH | $C_{12}H_{10}S_2O_4$ | C,52.0;H,4.2; | C,51.1;H,3.6 |
| (138) | 92 | 176-178 | EtOH | $C_{15}H_{10}S_3O_4$ | C,51.9;H,2.8; | C,51.3;H,2.8 |
| (139) | 90 | 164 | EtOH | $C_{16}H_{12}S_3O_4$ | C,53.2;H,3.9; | C,52.9;H,3.3 |
| (140) | 62 | 197 | EtOH | $C_{16}H_{12}S_3O_5$ | C,50.5;H,3.2; | C,49.1;H,3.2 |
| (141) | 70 | 188-189 | EtOH | $C_{17}H_{14}S_3O_5$ | C,52.3;H,2.8; | C,51.8;H,3.6 |

Table 31.

$^1H$ nmr Data.

| No | H-1 | H-2 | H-3 | OH* | $CO_2Me$ | Other |
|---|---|---|---|---|---|---|
| (137) | 7.62(d,6Hz) | 7.20(m) | 6.98 | 9.6 | 3.90 | 2.58($COCH_3$) |
| (138) | 7.70(m) | 7.25(m) | 6.95 | 9.7 | 3.90 | 8.0(m,ArH's) |
| (139) | 7.45(d,8Hz) | 7.35(m) | 6.90 | 9.5 | 3.90 | 7.75($H^a$,d,6Hz,ArH)<br>6.95($H^b$,d,6Hz)<br>2.55(3-Me) |
| (140) | 7.30(m) | 7.10(m) | 6.85 | 8.0 | 3.85 | 7.45($H^a$,d,6Hz,ArH)<br>6.90($H^b$,d,6Hz,ArH)<br>3.80(s,3-OMe) |
| (141) | 7.30(m) | 7.15(m) | 6.85 | 9.6 | 3.88 | 7.10(s,$H^b$,ArH)<br>3.80(s,3-OMe)<br>2.50(s,5-Me) |

* All OH groups underwent $D_2O$ exchange.

Table 32.

| No | Med | C=O $CO_2Me$ | C=O RCO | OH $cm^{-1}$ | M+H (%) | 100% m/e | Other |
|---|---|---|---|---|---|---|---|
| (137) | c | 1716 | 1650 | 3700 | 283(100) | --- | 225($CO_2Me$) |
| (138) | c | 1702 | 1655 | 3700 | 351(100) | --- | |
| (139) | c | 1702 | 1660 | 3600 | 365(20) | 125($C_6H_5SO_2$) | |
| (140) | a | 1708 | 1660 | 3200 | 381(63) | 142($C_6H_6SO_2$)) | |
| (141) | c | 1708 | 1660 | 3300 | 395(12) | 157($C_7H_7SO_2$) | |

a, KBr disc; c, Nujol mull.

Tables 33 and 34.

Table 33.

$^{13}C$ Data for Bithienyl Ring Carbon Atoms.

| No | C-5' | C-4' | C-3' | C-2' | C-2 | C-3 | C-4 | C-5 | $CO_2$ |
|---|---|---|---|---|---|---|---|---|---|
| (137) | 143,0 | 132,8 | 125,7 | 150,0 | 147,5 | 116,5 | 164,2 | 105,0 | 166,2 |
| (138) | 145,2 | 132,5 | 125,6 | 149,9 | 146,9 | 116,5 | 164,3 | 103,9 | 166,2 |
| (139) | 145,4 | 137,3 | 125,7 | 149,6 | 146,6 | 116,5 | 164,5 | 103,7 | 166,3 |
| (140) | 145,2 | 132,5 | 125,6 | 149,3 | 146,5 | 116,9 | 164,4 | 103,5 | 166,3 |
| (141) | 145,1 | 133,0 | 125,4 | 145,5 | 145,8 | 117,0 | 164,4 | 103,5 | 166,4 |

Table 34.

$^{13}C$ Data for Rearranged Acyl Groups and Substituent Carbon Atoms.

| No | C-2'' | C-3'' | C-4'' | C-5'' | C=O | $CO_2Me$ | Other |
|---|---|---|---|---|---|---|---|
| (137) | --- | --- | --- | --- | 190,1 | 52,1 | 26,6($COCH_3$) |
| (138) | 141,2 | 136,2 | 129,1 | 133,8 | 180,4 | 52,1 | --- |
| (139) | 140,8 | 143,5 | 130,1 | 133,9 | 179,4 | 52,1 | 16,6(3'-Me) |
| (140) | 109,1 | 158,9 | 1120,2 | 133,0 | Not found | 52,0 | 59,1(3'-OMe) |
| (141) | 114,8 | 164,4 | 128,0 | 134,2 | Not found | 51,8 | 141,1(5''-Me) |

Methyl 3-Hydroxy-5-methyl-4-(2'-thenoyl)-thiophene-2-carboxylate (145).

To one gram ($3.85 \times 10^{-3}$M) of methyl 5-methyl-3-(2'-thenoyl)oxythiophene-2-carboxylate (103) was added anhydrous aluminium (111) chloride (3g) and 1,2-dichloroethane (10ml). The mixture was heated at reflux for 3 h and the allowed to cool before being poured into ice/HCl (25ml). The product was extracted into dichloromethane (25ml) and washed once with water (20ml), dried ($MgSO_4$) and the solvent was removed on the rotary evaporator to give the title compound (0.64g, 64%). It had m.p. 140-141°C (from ethanol). (Found: C, 50.9; H, 4.2% ($C_{12}H_{10}O_4S_2$ requires C,51.5; H,3.6%). $^1$H nmr $\delta$($CDCl_3$) 7.90 (1H, m, 5'-H), 7.55 (1H, m, 4'-H), 9.80 (1H, s, -OH, $D_2O$ex), 3.75 (3H, s, $CO_2Me$) and 2.35 (3H, s, 5-Me). Vmax (Nujol) 3,500-3,000 (br, -OH), 1660 ($CO_2Me$) and 1630 (C=O) $cm^{-1}$. M/e 283 (M+H, 100%), 251 85%, M-OMe) and 199 (72% M-$C_4H_3S$). $^{13}$C $\delta$($CDCl_3$) 15.8 (5-Me), 51.2 ($CO_2\underline{Me}$), 101.0 (C-2(, 128.0 (C-4'), 134.9 (C-2'), 134.9 (C-5'), 135.1 (C-3'), 144.2 (C-4), 150.7 (C-5) and 166.2 (C-3).

## 16.0 Synthesis of Polysubstituted Dithienyl Ketones using the Friedel-Crafts Acylation Reaction.

### Preliminary Investigation:

### 2-Cyclohexanoylthiophene.

Cyclohexane carbonyl chloride (15g, 0.15M) and tin (IV) chloride (16g, 0.06M) were dissolved in anhydrous 1,2-dichloroethane (50ml) then added to a stirred solution of thiophene (8.4g, 0.1M) in 1,2-dichloroethane (50ml), dropwise at $0^{o}C$. The reaction mixture was stirred for 1 h at this temperature then poured into ice/HCl, the organic layer was separated, washed, and dried, and the solvent was removed to give the title compound (16g, 77%) as a white solid. Recrystallisation from ethanol yielded white plates, m.p. $49^{o}C$ (Found: C, 68.1; H, 7.1. $C_{11}H_{14}OS$ requires C,68.0; H,7.2%), $^{1}H$ nmr d($CDCl_3$) 0.8-1.8 (1H, m, cyclohexyl ring protons), 2.90 (1H, m, cyclohexyl ring proton), 6.85 (1H, m, thiophene ring proton) and 7.45 (1H, m, thiophene ring protons). Vmax (Nujol) 1,665 (C=0) $cm^{-1}$. M/e 195 (M+H, 100%), $^{13}C$ d($CDCl_3$) 25.84 (cyclohexyl ring carbons), 29.61 (cyclohexyl ring carbons), 41.53 (cyclohexyl ring carbons), 127.91 (C-4), 131.29 (C-3), 133.17 (C-5, 143.95 (c-2) and 196.61 (C=0).

### 3-Methyl-2-cyclohexanoylthiophene.

This was prepared from 3-methylthiophene as for 2-cyclohexanoyl thiophene, in 90% yield. The product was obtained using vacuum

distillation to give a clear oil b.p. 112-114°C, 0.4mm Hg. (Found: C, 68.8; H, 7.5, $C_{12}H_{10}OS$ requires C,69.2; H,7.7%). $^{1}H$ nmr d($CDCl_3$) 1.00-1.90 (10H, m, cyclohexyl ring protons), 2.50 (3H, s, 3-Me), 2.90 (1H, m, cyclohexyl ring protons), 6.90 (1H, d, J=8Hz, thiophene ring proton), and 7.40 (1H, d, J=8Hz, thiophene ring proton). Vmax (film) 2,950 ($CH_3$) and 1.665 (C=0) $cm^{-1}$. $^{13}C$ d($CDCl_3$) 16.82 ($-CH_3$), 25.78 (cyclohexylring carbons, 29.61 (cyclohexyl ring carbons), 49.93 (cyclohexyl ring carbons), 128.82 (C-4), 132.28 (C-5), 134.60 (C-2), 145.38 (C-3, and 197.45 (C=0).

2-Benzoylthiophene.

This was prepared using the method described for 2-cyclohexanoyl thiophene in 80% yield. The pure product was obtained by recrystallisation from ethanol as off-white needles, m.p. 58%°C (lit. [109] 56.5-57°C). $^{1}H$ nmr d($CDCl_3$) 7.15 (1H, m, thiophene ring proton) and 7.30-7.90 (7H, m, benzene and thiophene ring protons). Vmax (Nujol) 1625 (C=0) $cm^{-1}$. $^{13}C$ d($CDCl_3$) 127.91 (C-2), 128.37 (C-2'), C-5'), 129.14 (C-3', C-5') 132.20 (C-3), 134.15 (C-5), 134.80 (C-4'), 138.17 (C-6'), 143.69 (C-2) and 188.16 (C-0).

Di-2-thienyl Ketone.

Thiophene (4.2g, 0.05M) and thenoyl chloride (8g) were dissolved in anhydrous dichloromethane (2.5ml) containing titanium (IV) chloride (9.4g, 0.05M). The reaction mixture was stirred at room temperature for 1 h then worked up in the usual way to give the required ketone as an off-white powder in 90% yield. It has m.p.

89-91°C (lit. [190] 90-90.5°C). $^{1}H$ nmr $\delta(CDCl_3)$ 7.35 (2H, m, thiophene ring protons). Vmax (Nujol) 1615 (C-O) $cm^{-1}$. $^{13}C$ $\delta(CDCl_3)$ 127.91 (C-4), 133.04 (C-3), 133.37 (C-5) and 142.91 (C-2).

Polysubstituted Dithienyl Ketones.

2-Acetyl-3-methoxy-5-methylthiophene (147).

Method A:

A mixture of 3-methoxy-5-methylthiophene and acetic anhydride (8ml) (85) (5g, 0.05M) was heated to 55°C then orthophosphoric acid (0.3ml) was added; the temperature rose spontaneously to 80°C. The temperature was then maintained at 70°C for 1 h, the mixture was cooled then added to a stirred mixture of dilute hydrochloric acid and ice. After 1 h the organic material was isolated by extraction into dichloromethane, washed with water, 10% sodium carbonate and water, dried ($MgSO_4$) and the solvent was removed on the rotary evaporator. Distillation of the residue gave the unreacted 3-methoxy-5-methylthiophene (85%) (2g), followed by the title ketone (1.0g, 15%), b.p. 150°C/10mm Hg. The product solidified on standing. it had m.p. 94-95°C (from light petroleum). (Found: C, 56.7; H, 6.0. $C_8H_{10}O_2S$ requires C, 56.9; H, 5.9%). $^{1}H$ nmr $\delta(CDCl_3)$ 2.44 (6H, s, Th-5-methyl+MeCO), 3.90 (3H, s, -OMe) and 6.50 (1H, s, 4-H). Vmax (Nujol) 1625 (C=O) $cm^{-1}$. $^{13}C$ $\delta(CDCl_3)$ 16.8 (Th-5-methyl), 29.0 (MeCO), 58.7 (-OMe), 114.9 (C-4), 121.3 (C-2), 148.0 (C-5), 160.2 (C-3) and 189 (MeCO).

Method B:

3-Methoxy-5-methylthiophene (85), (5g, 0.06M) was dissolved in 1,2-dichloroethane (50ml). To this was added tin (IV) chloride (15.6g, 0.06M) and the mixture was cooled to 0°C. A solution of acetyl chloride (4.15g, 0.06M) in 1,2-dichloroethane (25ml) was then added over 30 min being poured and the mixture was stirred at 0°C for a further 1 h before being poured into ice-hydrochloric acid (100ml). The mixture was separated and the organic layer was washed with water, dried ($MgSO_4$) and the solvent was removed on the rotary evaporator to give the title compound in 18% yield. Purification was then carried out as for Method A.

2-Acetyl-3-methoxy-4-methylthiophene (148).

Reaction of 3-methoxy-4-methylthiophene, (90) (3g, 0.023M) and acetic anhydride (15g) in the presence of orthophosphoric acid (0.5ml), as described in Method A above, gave the title compound (2.5g, 64%) as an oil, b.p. 80°C/5mm Hg. $^1H$ nmr $\delta(CDCl_3)$ 2.12 (3H, s, -OMe), 2.50 (3H, s, 4-Me), 28.4 (MeCO), 101.8 (C-2), 125.8 (C-4), 127.8 (C-5) and 159.6 (C-3), COMe). The 2,4-dinitrophenylhydrazone formed red needles from ethanol and had m.p. 204-205°C. (Found: C, 47.8; H, 4.0; N, 16.1. $C_{14}H_{14}N_4O_5$ requires C, 48.0; H, 4.0; N, 16.0%).

Bis (3-methoxy-5-methyl-2-thienyl) Ketone (150).

A solution of 3-methoxy-5-methyl thiophene (85), (3g, 0.023M) and 5-methyl-3-methoxy - thiophene-2-carbonyl chloride (149), (3g, 0.024M) in 1,2-dichloroethane (20ml) was stirred and cooled to 0°C while tin (IV) chloride (2ml) in 1,2-dichloroethane (10ml) was added over 10 min. The mixture was allowed to warm to room temperature and stirred for 2 h, then water (50ml) was added to quench the reaction. The organic layer was separated, combined with an additional 1,2-dichloroethane extract, washed (water, saturated sodium hydrogen carbonate solution), dried ($MgSO_4$) and the solvent was removed on the rotary evaporator. The residue, which crystallised upon trituration with ether, was recrystallised form ethanol to give the title ketone (4.1g, 72%), m.p. 224-254°C. (Found: C, 55.5; H, 5.0%. $C_{13}H_{14}O_3S$ requires C, 55.3; H, 5.0%). $^1H$ nmr $\delta(CF_3CO_2H)$ 2.70 (6H, s, 2x5-Me), 4.30 (6H, s, 2x-OMe) and 6.95 (2H, s, 3- and 3'-H). Vmax (Nujol) 1570 (C=O) $cm^1$, m/e 283 (100%, M+H) and 155 (50%, ArCO).

3-(3'-Methoxy-5'-methyl-2'-thenoyl)-3-methoxythiophene (152).

Application of the procedure used to prepare (150) to 3-methoxythiophene-2-carbonyl chloride (151), (2.8g, 0.01M) and 3-methoxy-5-methyl thiophene (85), (2g, 0.015M) in 1,2-dichloroethane (20ml) with tin (IV) chloride (1.5ml) in 1,2-dichloroethane (10ml) gave the title ketone (2.65g, 65%), m.p. 166-167°C (from ethanol). (Found: C, 53.9; H, 4.5. $C_{12}H_{12}O_3S_2$ requires C, 53.7; H, 4.4%). $^1H$ nmr $\delta(CDCl_3)$ 2.40 (3H, s, 5-Me), 3.75 and 3.85 (6H, both s, -

OMe), 6.45 (1H, s, 4-H), 6.70 (1H, d, J=6Hz, 4'-H) and 7.30 (1H, d, J=6Hz, 5'-H). Vmax (KBr) 1570 (C=O) $cm^{1}$, m/e 3269 (100%, M+H), 155 (15%, ($C_6H_7O_5$) CO), and 141 (11% ($C_5H_5OS$) CO).

2-(3'-Methoxy-5'-methyl-2'-thenoyl)-3-methoxy-4-methylthiophene (153).

3-Methoxy-4-methyl thiophene, (90), (2.2g, 0.02M) and 3-methoxy-5-methyl thiophene-2-carbonyl chloride, (149), (4.5g, 0.02M), were stirred at room temperature in 1,2-dichloroethane (30ml) in the presence of tin (IV) chloride (4.0ml) for a period of 1 h before being poured into ice/water. The solution was acidified with 4M hydrochloric acid (25ml) and stirred for 0.5 h at room temperature before being separated and worked up as previously to give a solid which upon trituration with ether gave the title compound (2.6g, 36%), m.p. 106-108°C (from ethanol). (Found: C, 54.8; H, 4.9. $C_{13}H_{14}O_3S_2$ requires C, 55.3; H, 5.0%). $^{1}H$ nmr $\delta$($CDCl_3$) 2.06 (3H, s, 4-Me), 2.40 (3H, s, 5'-Me), 3.79 (6H, s, 2x-OMe), 6.58 (1H, s, 4'-H) and 6.95 (1H, s, 5-H). Vmax (KBr) 1595 (C-O) $cm^{-1}$, m/e 283 (100%, M+H) and 155 (83%, ($C_6H_7OS$) CO). $^{13}C$ $\delta$($CDCl_3$) 13.05 (4'-OMe), 16.75 (5-Me), 58.83 (3-OMe), 61.68 (3'-OMe) 115.24 (C-2, C-2'), 123.82 (C-4, C-5'), 131.81 (C-4'), 147.72 (C-5) 158.40 (C-3) and 160.83 (C-3') (C=O) not identified.

Methyl 4-Methoxy-3-methyl-5-(3'-methoxy-5'-methyl-2'-thenoyl) thiophene-2-carboxylate (154).

Methyl 4-methoxy-3-methyl thiophene-2-carboxylate (88), (3.9g, 0.02M) and 3-methoxy-5-methyl thiophene-2-carbonyl chloride (149), (3.9g, 0.02M) were dissolved in 1,2-dichloroethane (25ml) and cooled to 0°C with stirring. To this was added tin (IV) chloride (3ml) in 1,2-dichloroethane (10ml) and the mixture was stirred at 0°C for 4 h. The reaction mixture was added to ice/water and the organic layer was separated and combined with a further 1,2-dichloroethane extract, followed by the usual work-up. Trituration of the residue with ether afforded a solid which was dried to give the title compound (2.9g, 48%), m.p. 105°C (from ethanol). (Found: C, 53.0; H, 4.8. $C_{15}H_{16}O_5S_2$ requires C, 52.9; H, 4.8%). $^1H$ nmr $\delta(CF_3CO_2H)$ 2.38 and 2.45 (6H, both s, 2xArMe), 3.80 and 3.82 (6H+3H, all s, 3x-OMe) and 6.56 (1H, d, 4'-H). Vmax (KBr) 1725 ($CO_2Me$) and 1560 (ArCOAr) $cm^{-1}$. M/e 341 (100%, M+H), 213 (5% ($C_8H_9S$) CO) and 155 (19% ($C_6H_7OS$) CO), $^{13}C$ $\delta$ ($CDCl_3$) 12.40 (3-Me), 17.01 (5'-Me), 52.00 ($CO_2\underline{Me}$), 58.96 (3'-OMe), 61.94 (4-OMe), 115.2 (C-2', C-4', C-5) 138.5 (C-3), 148.6 (C-5'), 149.1 (C-2, 166.2 (C-3') and 161.81 (OCO); no signal was observed for C-4.

Methyl 3-Hydroxy-4-propionylthiophene.

Propionyl chloride (4g, 0.02M) and aluminium chloride (9g, 0.07H) were dissolved in dry 1,2-dichloroethane (25ml) and cooled to 0°C. To the stirred solution was added 3.3g (0.02M) of methyl 3-methoxy thiophene-2-carboxylate (86) (3.3g, 0.02M) in 1,2-dichloroethane

(10ml). The reaction mixture was allowed to come to room temperature then stirred for 100 h. The usual work-up gave the title compound (1.3g, 30%), m.p. 141-142°C (from ethanol). (Found: C, 50.4; H, 4.8. $C_9H_{10}O_4S$ requires C, 50.5; H, 3.7%). $^1H$ nmr $\delta$($CDCl_3$) 1.20 (3H, t, J=10Hz, $CH_2\underline{CH_3}$), 2.35 (1H, br, -OH, $D_2O$ ex), 2.90 (2H, qd, J=10Hz, $\underline{CH_2}$ $CH_3$), 3.95 (3H, s, $CO_2Me$) and 1620 ($CO_2Me$) $cm^{-1}$ m/e 215 (M+H, 75%) and 183 (100%, M+H -OMe). $^{13}C$ $\delta$($CDCl_3$) 7.80, 33.83 ($CH_3\underline{CH_2}$), 52.07 ($CO_2\underline{Me}$), 102.20 (C-2), 137.8 (C-4), C-5), 161.54 (C-3), 163.50 ($\underline{CO_2}Me$) and 197.20 (Et$\underline{CO}$). The 2,4-dinitrophenylhydrazone was prepared and gave red needles, m.p. 128-129°C (from ethanol).

Direct Acylation using Phosphorus Pentoxide.

2-Benzoylthiophene (158).

Thiophene (9g, 0.11M) was added to benzene (100ml) followed by phosphorus pentoxide (14.2g, 0.1M). To the vigorously stirred mixture was then added benzoic acid (12.6g, 0.1M) and the mixture was boiled under reflux for 6 h. The benzene layer was decanted and the remaining sludge was stirred with a further portion of benzene (50ml) which was then also decanted and combined with the first decantate. The organic solution was then washed with 10% sodium hydroxide solution (2x25ml), water (4x50ml), dried ($MgSO_4$) and the benzene was removed on the rotary evaporator to give the crude product (4.1g, 22%).

Recrystallisation from ethanol gave the product as white crystals, m.p. 56°C. (Lit. [109] 56.5-57°C), $\delta(CDCl_3)$ 7.15 (1H, m, thiophene ring proton) and 7.30-7.90 (7H, m, benzene and thiophene ring protons). Vmax (Nujol) 1625 (C=0) $cm^{-1}$.

2-(3-Nitrobenzoyl)thiophene (159).

The above procedure was repeated using 3-nitrobenzoic acid (16.7g, 0.1M) to give the title ketone (4.0g, 17%), m.p. 105-106°C (from ethanol). $^1H$ nmr $\delta(CDCl_3)$ 7.23 (1H, m, thiophene ring proton), 7.70 (3H, m, aromatic ring protons) 8.33 (2H, m, aromatic ring protons) and 8.72 (1H, m, benzene ring proton). Vmax (Nujol) 1630 (C=0) and 1350 ($NO_2$) $cm^{-1}$.

## 17.0 Desulphurisation of Polysubstituted Thiophenes and Dithienyl Ketones.

3-Methoxythexanoic acid (160).

Methyl 3-methoxy-5-methyl thiophene-2-carboxylate (83) (4g, 0.02M) was desulphurised using general method 8 to give 1.2g (39%) of the title compound (1.2g, 39%). It had b.p. 81°C/w/p (lit. [191] 74.6°C/25mm Hg), $^1H$ nmr $\delta(CDCl_3)$ 0.80-1.10 (3H, s, $CH_3$), 1.15-1.65 (3H, m, CH and $CH_2$), 2.10-2.62 (4H, m, 2x$CH_2$), 3.38 (3H, s, OMe) and 8.65 (1H, br, $CO_2H$, $D_2O$ ex). Vmax (film) 3,600-3,100 br ($CO_2H$) and 1710 (C=0) $cm^{-1}$.

Methyl 3-Methoxyhexanoate (161).

Methyl 3-methoxy-5-methyl thiophene-2-carboxylate (83) (2g, 0.01M) was desulphurised using general method 9 to give 1.1g (69%) of the title ester (1.1g, 69%). It had $^{1}H$ nmr $\delta(CDCl_3)$ 0.85-1.10 (3H, s, $CH_3$), 1.15-1.65 (3H, m, CH and $CH_2$), 1.12-2.65 (4H, m, 2x$CH_2$), 3.38 (3H, s, OMe) and 3.65 (3H, s, $CO_2Me$). Vmax (film) 2,995 (OMe) and 1695 (C=O) $cm^{-1}$.

11-Hydroxy-6-methyldodecanoic Acid (163).

1-(5-Acetyl-2-thienyl)-1(5-methoxycarbonyl-2-thienyl)ethane (162) (3g, 0.1M) was desulphurised using general method 8 to give the title acid (2.1g, 91%) as a pale yellow oil, b.p. 150°C/0.5mmHg (lit. [185] = 140-145°C/0.11mmHg). $^{1}H$ nmr $\delta(CDCl_3)$ 0.85 (3H, br, d, J=5 Hz, CH-Me), 1.00-2.55 (20H, br, m, 8x$CH_2$; CH-Me), 3.86 (1H, m, J=6Hz, CH-OH), and 6.38 (2H, br, s, $D_2O$ ex OH and $CO_sH$). Vmax (film) 3,650-2,300 (OH and $CO_2H$) and 1410 (C=O) $cm^{1}$.

Methyl 11-hydroxy-6-methyldodecanoate (164).

1-(5-Acetyl-2-thienyl)-1-(5-methoxycarboxyl-2-thienyl)ethane (162) (3g, 0.01M) was desulphurised using general method 9. The usual work-up gave a pale yellow oil (2g, 87%) which was purified by distillation. It had b.p. 121°C/0.2mm Hg (lit. [186] 100-110°C/0.09mm Hg). $^{1}H$ nmr $\delta(CDCl_3)$ 0.85 (3H, br, d, J=5Hz, CH-Me and Me CH [OH]> and 3.45-5.00 (4H, m, CH [OH] and $CO_2Me$). Vmax (film) 3,600-3,100 (br, OH) and 1,740 ($CO_2Me$) $cm^{-1}$.

Methyl 11-Hydroxydodecanoate (166).

1-(5-Acetyl-2-thienyl)-1-(5-methoxycarbonyl-2-thienyl)methane (165) (0.7g, 2.5mM) was desulphurised using general method 9 to give a yellow oil (0.5g, 91%) which solidified upon standing overnight. Recrystallisation from ethanol gave the pure title compound, m.p. 37-39°C. (Found: C, 67.5; H11.0. $C_{13}H_{26}O_3$ requires c, 67.7; H, 11.3%). $^1H$ nmr $\delta(CDCl_3)$ 0.87-1.05 (1H, br, OH, $d_2O$ ex), 1.10-1.68 (21H, m, $1xCH_{31}$ $9xCH_2$), 2.06-2.48 (1H, m, CHOH), and 3.67 (3H, s, $CO_2Me$). Vmax (film) 3,600-3,100 br (OH) and 1,740 ($CO_2Me$) $cm^{-1}$. M/e 231 (M+H, 10%) and 100% m/e 213 (M+H-$H_2O$).

Methyl 4-Ethyl-3,5-dihydroxyhexanoate (167).

Methyl 4-acetyl-3-hydroxy-5-methylthiophene-2-carboxylate (114) (1g; 4.5mM) was desulphurised using general method 9 to give the title compound as an oil in 78% yield. $^1H$ nmr $\delta(CDCl_3$ 0.95-1.68 (9H, m, br, $2xCH_3$ and 3xCH), 2.20-2.40 (4H, m, $2xCH_2$), 3.65 (3H, s, $1xCO_2Me$) and 6.55 (2H, br, OH, $D_2O$ ex). Vmax (film) 3,500-3,100 (br, OH) and 1680 (C=O) $cm^{-1}$.

Methyl 4-Ethyl-5-hydroxy-3-methoxyhexanoate (168).

Methyl 5-methyl-3-methoxy-4-acetyl thiophene-2-carboxylate (115) (0.5g, 2.2mM) was desulphurised using general method 9 to give the title compound as an oil in 78% yield. $^1H$ nmr $\delta(CDCl_3)$ 0.90-1 (9H, m, br, $2xCH_3$ and 3xCH), 2.20-2.40 (4H, m, $2xCH_2$), 3.60 (3H, s, $1xCO_xMe$) and 4.05 (3H, s, -OMe). Vmax (film) 3,500-3,100 (br, OH) and 1680 (C=O) $cm^{-1}$.

Methyl 4-Ethyl-3,5-dihydroxyheptanoate (169).

Methyl 5-methyl-3-hydroxy-4-propionyl thiophene-2-carboxylate (117) (0.8g, 3.7mM) was desulphurised as described in general method 9 to give the title compound as pale yellow oil (0.3g, 67%). $^1H$ nmr $\delta(CDCl_3)$ 1.05 (9H, m, $2xCH_3$, $1xCH_2$ and 1xCH(, 2.42 (5H, m, $2xCH_2$ and 1xCH), 3.68 (3H, s, $-OCH_3$) 4.22 (1H, br, OH, $D_2O$ ex), and 6.10 (1H, br, OH, $d_2O$ ex). Vmax (film) 3,600-3,200 (br, OH), 2950 ($CH_3$ stretch) and 1705 (C=O) $cm^{-1}$. M/e 185 (38% $[M+H-H_2O]$ -2H), 127 (100%; $[M+H-H_2O)-2H]-[CO_2Me]+H$).

Methyl 3,5-Dihydroxy-4-methylheptanoate (170).

Methyl 3-hydroxy-4-propionyl thiophene-2-carboxylate (0.8g, 2.7mM) was desulphurised using general method 9 to give 0.5g (71%) a brown oil (0.5g, 71%). $^1H$ nmr $\delta(CDCl_3)$ 0.95-1.50 (10H, m, 2xCH, $1xCH_2$ and $2xCH_3$), 2.65 (3H, m, $1xCH_2$ 1xCH), 3.75 (3H, s, $CO_2Me$), 4.35 (1H, br, OH, $D_2O$ ex) and 6.00 (1H, br, OH $D_2O$ ex). Vmax (film 3,500-3,200 (br, OH) and 1710 (C=O) $cm^{-1}$.

Methyl 6-Hydroxy-4,8-dimethoxy-3-methylundecanoate (171).

Methyl 4-methoxy-3-methyl-5-(3'-methoxy-5'-methyl-2'-thenoyl) thiophene-2-carboxylate (154) (0.3g, 0.88mM) was desulphurised according to general method 9 to give 0.18g (67%) the title compound (0.18g, 67%) as a white wax, m.p. 31-33°C (from ethanol). (Found: C, 61.1; H, 10.4. $C_{15}H_{16}S_2O_5$ requires C, 59.6; H, 9.9%). $^1$H nmr $\delta$($CDCl_3$) 0.70-1.75 (13H, m, 5x$CH_2$, 1x$CH_3$), 2.03-2.70 (4H, m, 4xCH(, 3.30 (3H, s, $CO_2Me$), 3.65 (3H, s, OMe), 3.85 (3H, s, Me) and 6.40 (1H, br, OH, $D_2O$ ex). Vmax (film 3,600-3,10.0 (br, OH) and 1742 ($CO_2Me$) $cm^{-1}$. M/e 285 (45%, M+H-$H_2O$) and 129 (100%; [($CH_3[CH_2]_2CH[OMe]CHO$).

5-Hydroxy-3,7-dimethoxydecane (172).

2-(3'-Methoxy-5'-methyl-2'-thenoyl)-3-methoxythiophene (152) (1g, 3.7mM) was desulphurised using general method 9 to give the title compound (0.6g, 76%) as a yellow oil. $^1$H nmr $\delta$($CDCl_3$) 0.90-1.05 (9H, br, 2x$CH_3$,1x$CH_2$,1xCH), 1.20-1.60 (9H, m, br, 4x$CH_2$, 1xCH) 2.55 (1H, m, 1xCH) 2.82 (1H, br, OH, $D_2O$ ex), 3.65 (3H, s, OMe), and 3.80 (3H, s, OMe). Vmax (film) 3,500-3,200 (br, OH) and 2,950 (sharp, -$CH_3$ stretch) $cm^{-1}$.

5-Hydroxy-3,7-dimethoxy-2-methyldecane (173).

2-(3'-Methoxy-5'-methyl-2'-thenoyl)-3-methoxy-4-methylthiophene (153) (0.8g, 2.8mM) was desulphurised using general method 9 to give the title compound (0.4g, 61%) as a yellow oil. $^{1}H$ nmr $\delta(CDCl_3)$ 0.85-1.00 (9H, m, br, $3xCH_3$)), 1.20-1.65 (10H, m, br, $4xCH_2$ and 2xCH(, 2.45 (3H, m, br, 1xOH, 2xCH), and 3.30 (6H, s, br, 2xOMe). Vmax (film) 3,600-3,200 (br, OH) and 2,950 (sharp, $-CH_3$ stretch) $cm^{-1}$.

18.0 Stereochemistry of Desulphurisation.

Dimethyl 3,4-Dihydroxythiophene-2,5-dicarboxylate (174).

To one litre of 1M sodium methoxide was added dimethylthiodiacetate (50g, 0.25M) and dimethyl oxalate (60g, 0.50M). The mixture was stirred for 12 hours then poured into ice/water (1L). Acidification with concentrated hydrochloric acid gave a white precipitate, which was obtained by filtration, giving the title compound (79g, 67%). It had m.p. 182°C (lit. [161] 177°C). $^{1}H$ nmr $\delta(CDCl_3)$ 3.90 (6H, s, $2xCO_xMe$) and 5.35 (2H, br 2xOH, $D_2O$ex). Vmax (Nujol) 3,500, 2,300 (br, OH) and 1,690 (C=O) $cm^{-1}$. $^{13}C$ nmr $\delta(CDCl_3)$ 57.0 ($CO_2\underline{Me}$), 112.6 (C-2,C-5), 155.4 (C-3, C-4) and 168.6 ($CO_2$).

Raney Nickel Desulphurisation of (174) to give Dimethyl ß,ß'-dihydroxyadipate (175).

Dimethyl 3,4-dihydroxythiophene-2,5-dicarboxylate (174) (2.3g, 0.01M) was desulphurised using general method 9 to give a yellow powder (0.94g, 46%), m.p. 86-88°C (from EtOAc) (lit.[177] 80°C). $^1$H nmr $\delta$($CDCl_3$) 2.58 (4H, d, 2x-$CH_2$-, 3.75 (2H, br, 2x-OH, $D_2O$ex), 3.80 (6H, s, 2x$CO_2Me$), and 4.15 (2H, m, 2x-CH). Vmax (Nujol) 3,300-3,000 (br, OH) and 1705 (C=O) $cm^{-1}$. $^{13}$C nmr $\delta$($CDCl_3$) 38.8 ($CH_2$), 51.9 ($CO_2Me$), 69.9 (CH) and 172.9 ($CO_2$).

Dimethyl E-Hex-3-ene-1,6-dioate (177).

E-Hex-3-ene-1,6-dioic acid (14.4g, 0.1M) (176) was esterified using methanol (25ml) and concentrated sulphuric acid (5g) to give the title compound (10.6g, 54%) as a clear oil following purification by distillation. It had b.p. 70°C/0.07mm Hg (lit.[178] 82°C/0.2mm Hg). $^1$H nmr $\delta$($CDCl_3$) 3.12 (4H, d, 2x$CH_2$, J=14Hz), 3.65 (6H, s, 2x$CO_2Me$) and 5.70 (2H, m, 2x-CH=). $^{13}$C $\delta$($CDCl_3$) 37.7 ($CH_2$), 51.8 ($CO_2Me$), 125.9 (CH), and 171.8 (CO). Vmax (film) 1710 (C=O) $cm^{-1}$.

Dimethyl (±)-ß,ß'-Dihydroxyadipate (178).

t-Butyl alcohol (100ml) and 30% hydrogen peroxide (25ml) were dried [(a) $Na_2SO_4$ b) $MgSO_4$ and c) $CaSO_4$)] to give a dry solution of 6% t-butyl hydroperoxide. To this was added dimethyl E-hex-3-ene-1,6-dioate (177)) (8g, 0.046M) followed by 15% osmium tetraoxide in t-butanol (15ml). The stirred reaction mixture was then cooled to

$0^{o}C$ and maintained at this temperature for 24 h. The solvent was removed under reduced pressure, the residue triturated with diethyl ether, the ether removed and the residue cooled in ice and left to stand for 12 h. The total compound (0.8g, 8.5%) was obtained as off-white crystals by filtration at the pump. It had m.p. 77-78$^{o}C$ (from EtOAc) (lit. [177] 80$^{o}C$). $^{1}H$ nmr $\delta(CDCl_3)$ 2.58 (4H, d, 2x-$CH_2$-), 3.75 (2H, br, 2x-OH, $D_2O$ ex), 3.80 (6H, s, 2x$CO_2Me$) and 4.15 (2H, m, 2x-CH). $^{13}C$ nmr $\delta(CDCl_3)$ 37.8 ($CH_2$), 51.9 ($CO_2Me$) 69.7 (CH(, and 172.8 ($CO_2$). Vmax (Nujol) 3,350, 3,000 (br, OH0 and 1705 (C=O) $cm^{-1}$.

V,V-Dilactone of (±)-ß,ß'-Dihydroxyadipic acid (179).

A solution of dimethyl (±)-ß,ß'-dihydroxyadipate (60mg) in 1M hydrochloric acid (10ml) was evaporated over 1 h on the steam bath. The residue was crystallised from ethyl acetate to give the dilactone (25mg, 42%) as white crystals, m.p. 129-130$^{o}C$ (lit. [178] 127-128$^{o}C$).

Reductive Desulphurisation of Optically Active Thiophene Derivatives.

2-(3-Nitrobenzoyl)thiophene (159).

3-Nitrobenzoyl chloride (18.5g, 0.1M) was added to 1,2-dichloroethane (75ml). To this was added aluminium chloride (18.5g) then the mixture was cooled to $0^{o}C$. To this thiophene (10g, 0.12ml) was added, dropwise and the reaction was stirred for

1 h at 0°C then quenched by addition to ice-hydrochloric acid (100ml), followed by stirring for a further 0.5 h. Extraction into dichloromethane, drying ($MgSO_4$) and removal of the solvent under reduced pressure gave the title compound (22.5g, 46%) as a pale yellow solid. It had m.p. 106°C (from ethanol), $^1H$ nmr $\delta(CDCl_3)$ 7.24 (1H, m, thiophene ring proton), 7.70 (3H, m, aromatic ring protons), 8.33 (2H, m, aromatic ring protons, 8.72 (1H, m, benzene ring proton). Vmax (Nujol) 1630 (C=O), 1530 and 1350 ($NO_2$) $cm^{-1}$.

2-(3-Aminobenzoyl)thiophene (182).

2-(3-Nitrobenzoyl)thiophene (11g, 0.05M) was added to absolute ethanol (200ml). To this was added a solution of sodium sulphide nonahydrate (24g, 0.15M) in water (50ml) [(to which had been added sodium hydrogen carbonate (10g)]. The solution was then boiled under reflux for 3 h, then allowed to cool. The solvent was removed under reduced pressure and the residue was taken up into dichloromethane, the solution was filtered, washed with water, dried ($MgSO_4$) and the solvent was removed to give an off-white powder (6.8g, 67%), m.p. 115-116°C (from ethanol). (Found: C, 64.5; H, 4.4; N, 6.9. $C_{11}H_9NOS$ requires C, 65.0; H, 4.4; N, 6.9%). $^1H$ nmr $\delta(CDCl_3)$ 7.95 (1H, d, ArH), 7.60 (1H, d, ArH), 7.25 (1H, s, Ar-H), 7.20 (3H, m, ArH's), 6.75 (1H, d, ArH), and 5.35 (2H, br, $NH_2$, $D_2O$ ex). Vmax (Nujol) 3,500 (br, tr, $NH_2$) and 1670 (C=O) $cm^{-1}$. M/e 204 (M+H, 100%).

α-Hydroxy-2-(3-aminobenzyl)thiophene (183).

2-(3-Aminobenzoyl)thiophene (5g, 0.025M) was dissolved in absolute ethanol (50ml) and to this stirred solution was added sodium borohydride (1.5g) in 2M sodium hydroxide (5ml). The mixture was stirred for 12 hours at room temperature, the solvent was removed and the residue dissolved in dichloromethane, the solution was washed with water, dried (MgSO4) and the solvent was removed to leave pale yellow powder (4.4g, 86%), m.p. 89°C (from ethanol). Found: C, 64.1; H5.3; N6.9. $C_{11}H_{11}NOS$ requires C, 64.4; H, 5.4; N, 6.8%). $^1H$ nmr $\delta(CDCl_3)$ 7.35-6.58 (7H, m, aromatic ring protons) 5.85 (1H, s, CH), 3.64 (2H, br, $NH_2$ $D_2O$ ex), 2.90 (1H, br, OH, $D_2O$ ex). Vmax (Nujol 3,500-3,300 (br, OH0, 3,400-3,100 (tr, $NH_2$). M/e 206 (M+H, 65%), 100% m/e 188 ($M-H_2O+H$).

3-Nitrovalerophenone (186).

Valerophenone (16.2g, 0.1M) was dissolved in cold (-10°C) concentrated sulphuric acid (25ml). To this was added, very slowly, dropwise, over a period of 3 h, an ice-cold (0°C) mixture of concentrated sulphuric acid (9ml) and concentrated nitric acid (9ml), the temperature being kept below 5°C at all times. After the addition was complete the mixture was stirred at 0°C for a further h, then allowed to come to room temperature over a period of 1 h then poured into ice-water with vigorous stirring. The product was extracted into dichloromethane and washed with water (50ml), saturated sodium hydrogen carbonate solution (25ml) and again with water (50ml), dried (MgSO4) and the solvent was removed

to give 14g (68%) a pale yellow oil (14g, 68%), b.p. 115-121°C/0.3mm Hg. (Found: C, 63.8; H, 6.3; N, 6.9. $C_{11}H_{13}NO_3$ requires C, 63.8; H, 6.3; N, 6.8%). $^1H$ nmr $\delta(CDCl_3)$ 8.70 (1H, s, 2-ArH's), 8.30-7.50 (3H, m, ArH's), 3.00 (2H, m, $COCH_2$), 1.65 (4H, m, 2x-$CH_2$-), and 1.05 (3H, 1d, -$CH_3$). Vmax (film) 3,000 ($[CH_2]_3CH_3$), 1,700 (C=O), 1,535 and 1,350 ($NO_2$) $cm^{-1}$. M/e 208 (100%) M+H), 163 (45% M+H-$NO_2$).

3-(α-Hydroxy-n-pentyl)aniline (184)-reference compound.

3-Aminovalerophenone (5.4g, 0.03M) was treated with sodium borohydride (1.2g) as described in the preparation of compound (183) to give a pale yellow oil (4.8g, 90%) which was purified by distillation. It had b.p. 180°C/0.5mm Hg. (Found: C, 74.6; H, 9.7; N, 7.9. $C_{11}H_{17}NO$ requires C, 73.7; H, 9.5; N, 7.8%). $^1H$ nmr $\delta(CDCl_3)$ 7.30-7.20 (1H, m, ArH0, 7.10-7.00 (1H, m, ArH), 6.75-6.60 (2H, m, 2xArH) 4.50 (2H, tr, $NH_2$), 3.45 (1H, br, -OH, $D_2O$ ex), and 2.10-0.90 (10H, m, CH-$[CH_2]_3$). Vmax (film 3,500-3,300 (br, -OH) and 2,900 ($[CH_2]_3CH_3$) $cm^{-1}$. M/e 180 (45% M+H) and 162 (100%, [M-$H_2O$]+H).

Preparation and Resolution of (+) (-) α-Hydroxy-2-(3-aminobenzyl)thiophene.

α-Hydroxy-2-(3-aminobenzyl)thiophene (183) (4g, 0.02M) was dissolved in ethanol (20ml). To this was added (+) tartaric acid (3.1g, 0.02M) in ethanol (5ml). The mixture was boiled for 5 min then allowed to stand for 60 h. The precipitate which formed was

obtained by filtration, and was found to have m.p. 52-54°C and was obtained in 92% yield. (Found: C, 49.8; H, 5.1; N, 4.1, $C_{15}H_{17}NO_7S$ requires C, 50.7; H, 4.8; N, 3.9%). M/e 356 (35% M+H), 188 (100%, $C_{11}H_{11}NOS-H_2O$), and 151 (55% $[CHOHCO_2H]_2$). Repeated recrystallisation from acetone gave a constant m.p. of 62°C, and this material showed an optical rotation of [α] -36.0° (for ethanol solution).

Attempted Preparation of (+) (-) 3-(α-Hydroxy-n-pentyl)aniline salt.

Application of the above procedure to 3-(α-hydroxy-n-pentylaniline (184) led to the formation of a syrup which could not be crystallised. Attempts using acetone, ether, ethanol, ethyl acetate and light petroleum, (b.p. 60-80°C) all failed, leaving the same clear, viscous oil. An attempt to measure the optical rotation of the oil showed no rotation and microanalysis indicated the product was impure.

Preparation of 3-(α-Hydroxy-n-pentyl)aniline (184) via Raney Nickel Desulphurisation of "Resolved" α-Hydroxy-2-(3-aminobenzyl) thiophene.

(+) (-) α-Hydroxy-2-(3-aminobenzyl)thiophene (3.6g, 0.01M) was converted to the free base by treatment with 4M sodium hydroxide solution followed by extraction into dichloromethane and removal of the solvent to give α-Hydroxy-2-(3-aminobenzyl)thiophene (183), m.p. 94°C. The optical rotation of the free-base was measured at

[α] -1.4°. High resolution nmr using a chiral shift reagent indicated an enantiomeric excess of 1:2.6. The "resolved" free-base (2.1g, 0.01M) (183) was then desulphurised with Raney nickel using general method 9 to give 3-(α-Hydroxy-n-pentyl)aniline (184) (1.1g, 62%). (Found: C, 74.2; H, 9.6; N, 8.0. $C_{11}H_{17}NO$ requires C, 73.7; H, 9.5; N, 7.8%). $^1H$ nmr δ($CDCl_3$) 7.30-7.20 (1H, m, ArH), 7.10-7.00 (1H, m, ArH), 6.75-6.60 (2H, m, 2xArH's), 4.45 (2H, tr, $NH_2$), 3.45 (1H, br, -OH, $D_2O$ ex), and 2.10-0.90 (10H, m, CH-$[CH_2]_3CH_3$). Vmax (film) 3,500-3,300 (br, OH) and 2,900 $(CCH_2)_3CH_3$) $cm^{-1}$. M/e 180 (45% M+H) and 162 (100%), ([M-$H_2O$]). The optical rotation was measured at [α], -8.3°, and high resolution nmr using the chiral shift reagent indicated an enantiomeric excess of 1:2.2 (68%).

Determination of Enantiomeric Purity Using 360 MHz nmr*

Ten milligrams of each sample was weighed into an nmr tube and dissolved in deutero chloroform (0.5ml). The chiral shift reagent used was europium D-3-hepta fluorobutyryl camphorate in $CDCl_3$ at $1.9x10^{-5}$ molar. Sequential volumes of 20ml, up to a total of 120ml, were added to the substrate and the proton nmr was acquired on a Bruker AM 360 instrument. From observations of the carbinyl proton the enantiomeric purities were determined.

*Courtesy of B. Taylor of Shell, Sittingbourne

Determination of Optical Rotations Using a Perkin-Elmer Digital Polarimeter *

The optical rotations were measured using the sodium-D-line in ethanol solution at $20^{o}C$. The volume of the cell 2 as 2.5ml and the path-length 10cm. The readings were taken and $[\alpha]^{20}$s calculated using the following formula:

$$[\alpha] = \frac{rv}{nl}$$

where v = volume (ml) of solution
n = grammes of active substance
l = path length (1dm)
r = measured rotation

* Courtesy of B. Taylor of Shell, Sittingbourne

Results:-

(a) (+) (-)-α-Hydroxy-2-(3-aminobenzyl)thiophene-(+)-tartrate salt;

Weight of sample = 0.421g

r = -0.302

$\therefore [\alpha]_d^{20} = -36.0^o$

(b) "Resolved" α-Hydroxy-2-(3-aminobenzyl)thiophene-(+)-tartrate (183);

Weight of sample = 0.0396g

r = 0.022

$\therefore [\alpha]_d^{20} = -1.4^o$

(c) 3-(α-Hydroxy-n-pentyl)aniline (184) was prepared via Raney Nickel Desulphurisation of "Resolved" (183);

Weight of sample = 0.0859g

r = -0.77

$\therefore [\alpha]_d^{20} = 4.5^o$

* Courtesy of B. Taylor of Shell, Sittingbourne

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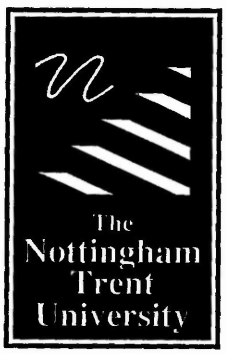


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