Macrocyclisation of Thiophenes via the Mannich Reaction

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Abstract

A number of 3,4-dialkoxythiophene compounds have been synthesised, and their reactivities assessed by the Mannich reaction with secondary amines. These reactivities are discussed in terms of the degree of steric hindrance of the 2 and 5 positions of the thiophene ring. Attempts also have been made to synthesise bis(3,4-alkoxythiophene) polyethers related to dibenzo-18-crown-6 *et al.*, by the Williamson ether synthesis, however under the conditions reported by this author, the [1+1] cyclisation compound was the major product.

Several bis-[2-(thienyl)methyl] amines derived from 3,4-ethylenedioxythiophene are reported, their syntheses being performed under both normal and high dilution conditions. Each synthesis also afforded the trithienylmethylamine oligomers, as well as polymeric material. Attempts to cyclise the bis-[2-(thienyl)methyl] amines with a further moiety of secondary diamine gave as the major product 2-methyl-3,4-ethylenedioxythiophene-5-carboxaldehyde, arising from a 1,6-Hofmann elimination.

Contents

Acknowledgements

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Abbreviations used in this thesis

4-MeO-C_6H_4	4-methoxyphenyl
acac	2,4-pentanedione
AcOH	acetic acid
b.p.	boiling point
BuLi	*n*-butyllithium
Bz	benzyl, (CH_2Ph)
$CDCl_3$	deuterated chloroform
cm	centimetres
d	doublet
DDQ	2,3-dichloro-5,6-cyano-1,4-benzoquinone
DIBAL	diisobutylaluminium hydride
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO-d_6	deuterated dimethyl sulphoxide
EtOAc	ethyl acetate
eq.	equivalent
F.T.I.R.	Fourier transform infrared
G.C.M.S.	gas chromatography-mass spectroscopy
HMPA	hexamethylphosphoramide
^iPr	*iso*-propyl
MCPBA	*meta*-chloroperoxybenzoic acid
Mesyl, Ms	methanesulfonyl
Mol. Wt.	molecular weight
m.p.	melting point
NBS	*N*-bromosuccinamide
nm	nanometre
n.m.r.	nuclear magnetic resonance

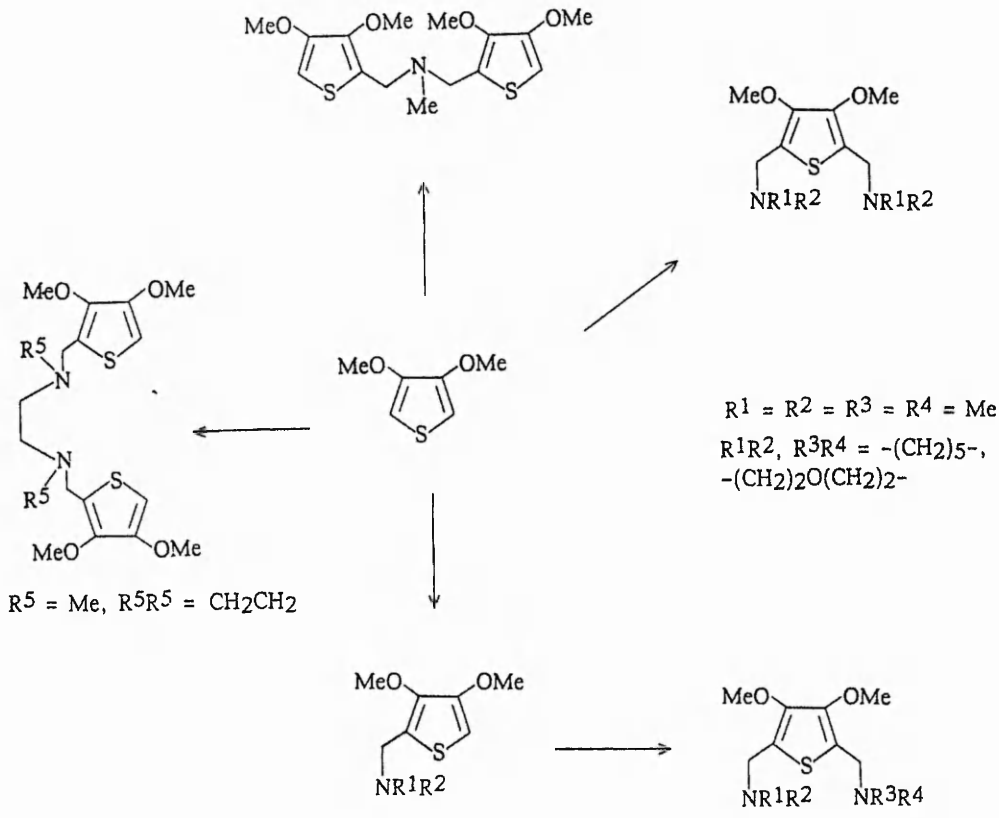
OAc	acetate
OTFA	trifluoroacetate
PBP	pyridinium bromide perbromide
pyr	pyridine
RT	room temperature
s	singlet
S	Siemens, the S.I. unit of electrical conductance
t	triplet
^{t}Bu	*tert*-butyl
$TBAPF_6$	tetrabutylammonium hexafluorophosphate
THF	tetrahydrofuran
THP	tetrahydropyranyl
Ts	toluene-4-sulfonyl

1. Aims of the project

The work reported in this thesis is an extension of some highly successful studies by another member of the group.[96a] In this, a series of α,ω-bis(3'-thienyloxy) alkanes were shown to undergo the Mannich reaction with a range of primary amines or secondary diamines to give a series of compounds related to aza crown ethers, (see Section 2.8.7.2, page 59). One aim of the present author was to apply methodology that had already been developed to a range of 3,4-dioxygenated thiophenes in order to obtain complex cyclic systems.

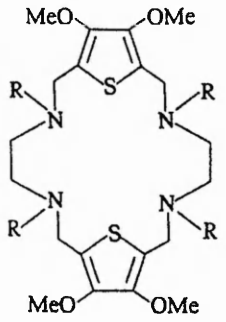
Initially a series of exploratory model syntheses of suitable substrates would be carried out, based on diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate. In addition, some new aspects of the chemistry of 3,4-dimethoxythiophene would be investigated. Some of the proposed work on the latter compound is summarised in Scheme 1.

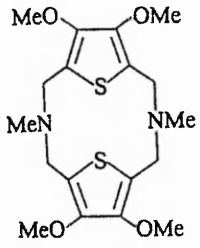
Scheme 1



Further Mannich reactions of the compounds possessing α,ω-bis(3,4-dimethoxy-2-thenyl) functionality would be attempted in the hope of obtaining macrocyclic compounds of the types shown in Figure 1.

Figure 1

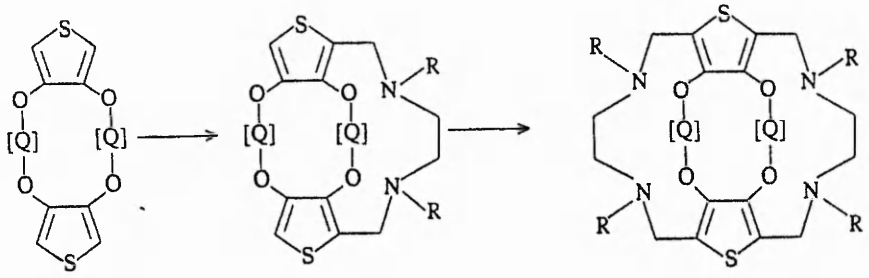




R = Me, RR = CH_2CH_2

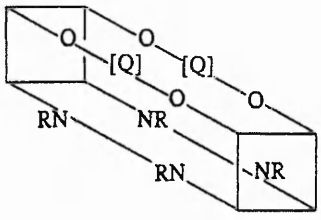
The knowledge gained from this exploratory work would then be applied to 3,4-dioxygenated systems related to Pedersen's crown ethers, the ultimate goal being the formation of box-like structures such as those shown in Scheme 2.

Scheme 2

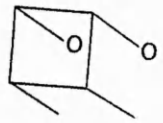


(1)

i.e.



where



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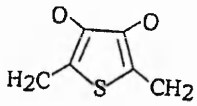


where Q = polyether bridging chain and R = Me or RR = CH_2CH_2

2 Introduction

2.1 Macrocyclic Multidentate Compounds

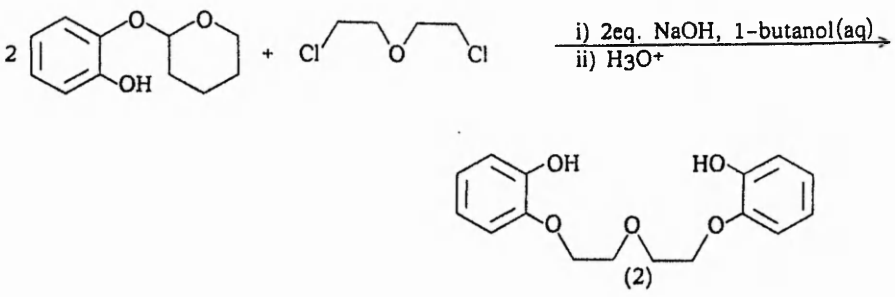
2.1.1 Introduction[6a]

The field of macrocyclic chemistry is concerned with complexation. A complex may be defined as two or more componds held together by hydrogen bonding, van der Waals forces, π-π interactions or metal ion ligation. Typically, the macrocyclic host possesses a cavity into which the guest fits. Since a degree of molecular organisation is involved, a parallel may be drawn with the molecular recognitive processes of enzyme catalysis, immune response and gene expression. Thus, since its awakening in the latter part of the 1960's, macrocyclic chemistry has been studied by many researchers working towards compounds capable of biomimicry, and culminating in the award of the Nobel Prize to Pedersen, Cram and Lehn in 1987. Their contribution has helped enormously in the understanding of the synthesis and physical organic chemistry of macrocycles and their complexes.

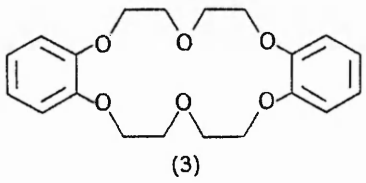
2.1.2 The discovery of Crown Ethers

The area of macrocyclic chemistry featuring polyethers (known as crown ethers) began largely with the work of Charles J. Pedersen of the Dupont Company. He was investigating the vanadyl group, V=O, and it's catalytic polymerisation of alkenes. Specifically, he was preparing bis[2-(*o*-hydroxyphenoxy)ethyl] ether (**2**), by the reaction of mono-tetrahydropyranyl catechol with 2,2'-dichlorodiethyl ether in aqueous 1-butanol in the presence of sodium hydroxide, Equation 1.

Equation 1



Pedersen knew that the mono protected catechol was impure, containing approximately 10% catechol. From the reaction mixture was isolated a small quantity of a white, fibrous crystalline substance which was found to be the cyclic polyether 2,3,11,12-dibenzo-1,4,7,10,13,16-hexaoxacycloocta-2,11-diene.(3).



Such a name was cumbersome. Thus, for brevity Pedersen developed a simpler method which is in common usage today. The system is based on (i) the number and type of carbocycle, (ii) the total number of atoms in the polyether ring, (iii) the generic name, crown and (iv) the number of heteroatoms in the polyether chain. Using these principles, compound (3) is named dibenzo-18-crown-6.[1] Other references to cyclic polyethers with four oxygen atoms exist in the literature which predate Pedersen's work. Lüttringhaus and Ziegler synthesised cyclic polyethers from resorcinol.[2] Adams and Whitehill used a similar procedure with hydroquinone.[3] Lüttringhaus also investigated cyclic polyether systems containing

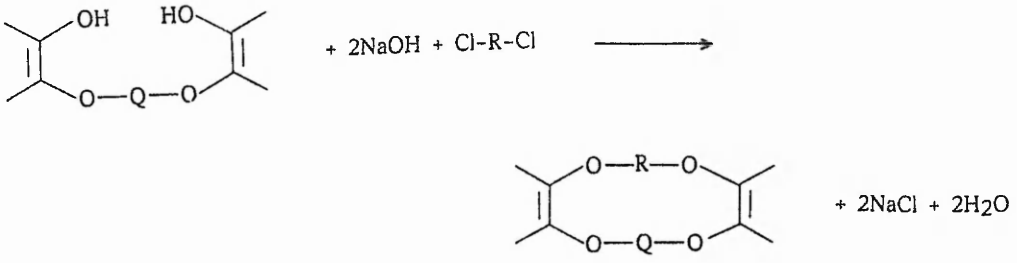
hydroquinone and 1,5- and 1,6-dihydroxynaphthalenes.[4] However, the linking chains used were derived from simple α,ω-dihaloalkanes. As such, the compounds synthesised by Lüttringhaus *et al.* lacked the ability to complex with alkali and alkaline earth metals and the analogous ammonium ion.

2.1.3 Synthetic approaches to Crown Ethers

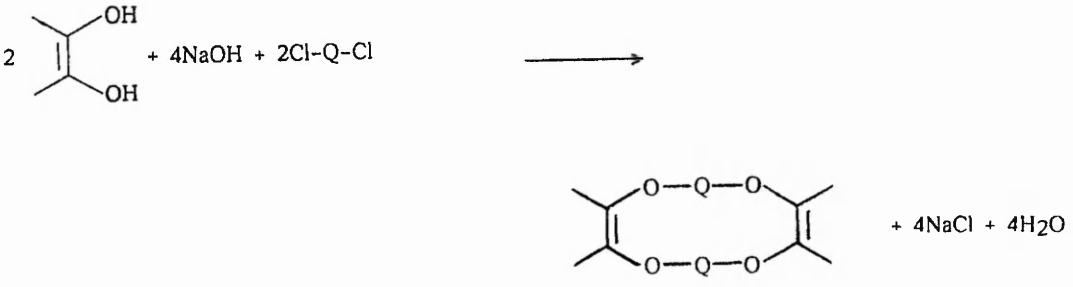
Pedersen reported some 49 crown compounds, prepared by five methods. These methodologies are outlined below; the notations Q and R denote the ether chains where Q and R may or may not be equivalent.

Method A

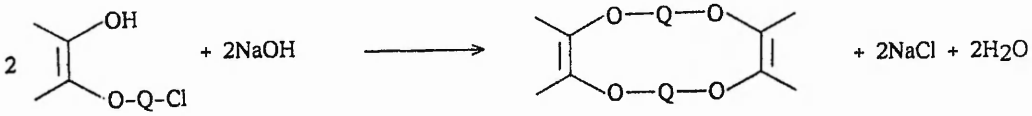
Method B



Method C



Method D



The final method used by Pedersen involved hydrogenation of the benzo and dibenzo crown ethers to give the cyclohexyl and dicyclohexyl derivatives respectively. Methods A to D cover the major synthetic routes used to prepare straightforward crown ethers. The reactions are of an S_N2 type, and most good leaving groups have been utilised, (Cl, Br, OTs, OMs, *etc.*).

Clearly, because macrocyclic synthesis involves the use of divalent organic moieties, polymerisation is an undesirable side reaction. To minimise this, the technique of high dilution has often been employed. First utilised by Ruggli in the condensation of α,ω-diacid chlorides with aromatic diamines,[5] high dilution may take the form of either using a very dilute reaction solution, or by the gradual addition of reagents into the reaction vessel, either by dropping funnels or a syringe pump. By this means, concentrations of reactants are kept low thus reducing polymerisation, whilst avoiding the use of large volumes of solvent. In view of their accuracy and automation, syringe pumps are to be preferred in this technique.

A number of other factors affect the formation of macrocyclic products.[6b] The presence of heteroatoms in the macrocyclic ring can increase yields by reducing transannular interactions. Thus replacement of the methylene group with a less bulky oxygen atom can increase yields significantly.

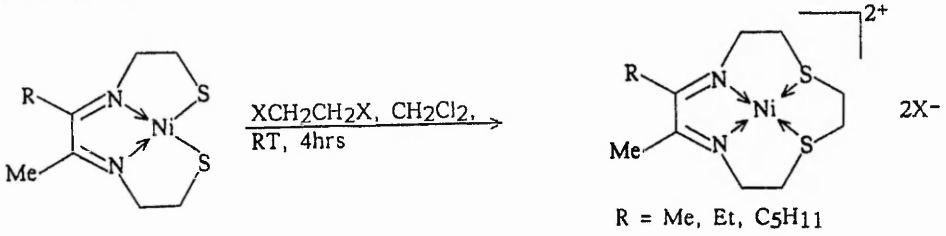
By decreasing the degrees of freedom present in the system prior to ring closure, one increases the probability of an intramolecular reaction as opposed to an intermolecular one. This can be achieved by making the

molecule more rigid, thus decreasing the internal entropy. Rigidity is induced by the presence of aromatic rings, alkenes and alkynes. The internal entropy is also affected by chain length. An increase in chain length leads to more conformations and hence an increase in the degrees of freedom of the system, thereby decreasing the probability of an intramolecular reaction.

2.1.4 The Template Effect

Pertinent to the synthesis of crown ethers is the effect cations in the reaction mixture play in aiding the reactants to hold the correct conformation for macrocyclisation, the "template effect". The operation of the effect had been proposed in the synthesis of a number of nickel(Ⅱ) complexes by Busch and Thompson, Equation 2.[7]

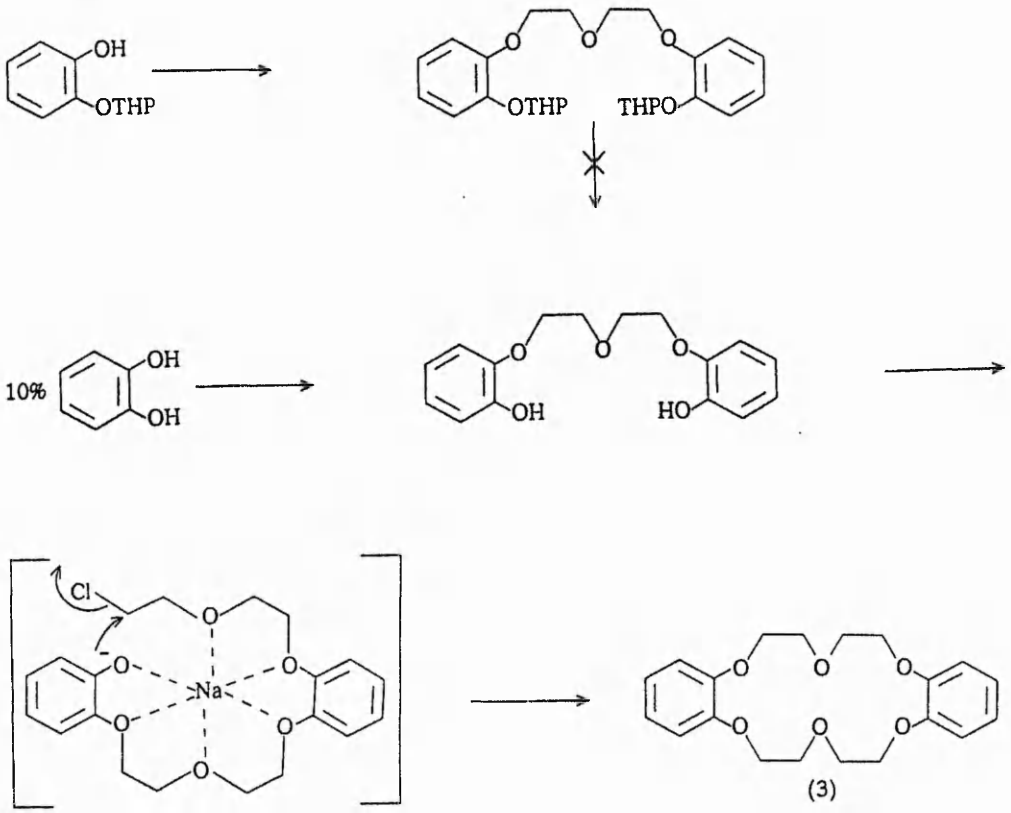
Equation 2



R = Me, Et, C_5H_{11}

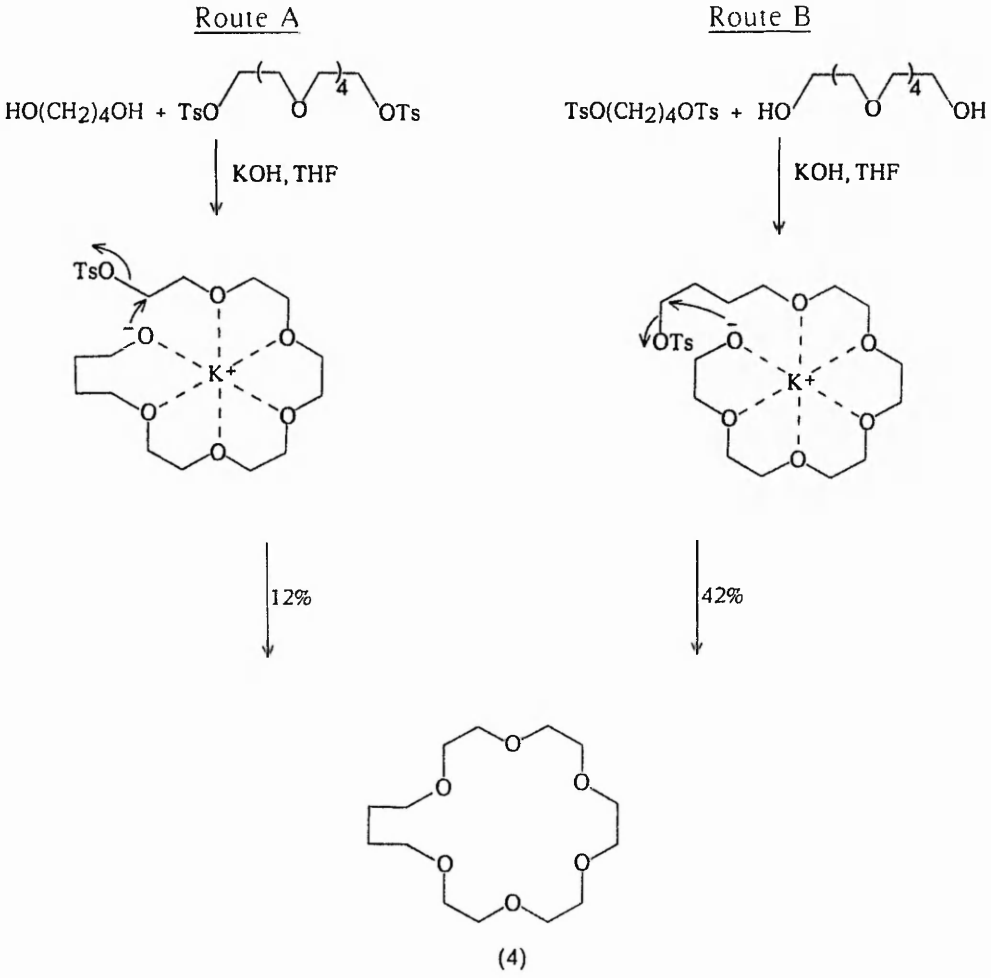
The template effect may be viewed entropically as reducing the internal degrees of freedom leading to preferential intramolecular reaction. In Pedersen's seminal paper, dibenzo-18-crown-6 was obtained in 0.4% yield.[1] This could only have come from the 10% unprotected catechol in the mixture. For an 18 membered ring this was quite high and it was proposed that the sodium ions were acting as a template for cyclisation,[8] Scheme 3.

Scheme 3



Inoue and coworkers reported an excellent example of a template effect in the preparation of 20-crown-6. (**4**).[9] They hypothesised that Route B below, gave higher yields of compound (**4**) due to a more stable orientation in the templated intermediate compared to that of Route A. Scheme 4.

Scheme 4



2.1.5 Complexation Properties of Crown Ethers

Pedersen reported that dibenzo-18-crown-6 showed a base induced shift in the UV: the shift has been associated with the formation of a complex.[10] He was able to isolate 44 stable crystalline complexes of a number of crown ethers with various inorganic salts.[1]

To study complexation, Pedersen used the extraction of metal picrates from aqueous solutions into organic solvents,[11] the degree of complexation being a factor in the transfer of the yellow picrate across the

phase boundary, to be measured by UV spectroscopy. Pedersen was able to show a correlation between the size of the polyether cavity and the cation to which it complexed. The four-oxygen polyethers were selective for lithium, the five-oxygen polyethers for sodium and the six-oxygen polyethers for potassium. However, such simple cavity-cation size correlations are questioned by Gokel and coworkers for more flexible crown ethers.[12]

Potentiometric methods using ion selective electrodes[13] and titration calorimetry[14, 15] have also been used to study complexation and to derive association constants. These two methods use polar solvents whereas crown ethers are used to solubilise salts in apolar solvents. Pedersen's extraction method gives association constants that do not take into account the partition coefficients of the crown, the complex, and the salt between the two phases. Thus Reinhoudt *et al.* investigated complexation between crown ethers and alkali trichloro(ethylene) platinum(Ⅱ) salts in deuterated chloroform using nuclear magnetic resonance.[16, 17] Association constants were derived from the ratio of the integral in the ^{1}H n.m.r. specra of the ethylene protons to the benzylic protons present in their systems. Lockhart and coworkers used n.m.r. to study the chemical shifts of protons in Pedersen's crown ether compounds when complexed.[18] The technique has also been applied to the complexed cation.[19]

In general, the complexes have 1:1 stoichiometry and as such, all oxygens atoms are equidistant from the cation and from each other, and the oxygen atoms and the metal cation are coplanar. In some cases however, where the cation is too large to fit into the crown ether cavity, polyether:cation complexes of stoichiometry 2:1 or 3:2 are formed.[20] The repeating ethyleneoxy unit in crown ethers gives the best conformational fit for complexation. If the carbon portion of the crown were one carbon longer, (propyleneoxy), then unfavourable CH-CH interactions would affect the

conformation of the ring, leading to poorer complexing abilities. The methyleneoxy repeating unit would be acetalic and as such would be susceptible to hydrolysis.

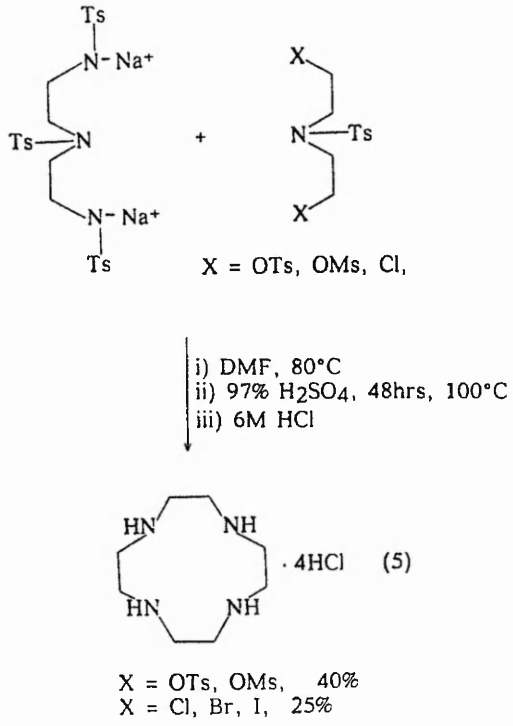
Although complexation involves metal cation-oxygen interactions, some crown ethers derived from *para* substituted benzenes have been reported to show the aromatic ring acting as a π donor to the cation.[21] Metal cations are not the only species complexed by polyether systems. A solid complex between benzo-27-crown-9 and the guanidinium ion has been isolated and evidence for a complex in solution between crown ethers and arenediazonium tetrafluoroborates has been reported.[22] The formation of a complex between 18-crown-6 and acetonitrile has been utilised in the isolation and purification of the crown by Gokel *et al.*[23]

2.2 Structural variation in Crown Ethers

2.2.1 Aza Crown Ethers

Crown ethers containing nitrogen are known as aza crown ethers. A number of approaches have been used to incorporate nitrogen. Lockhart *et al.* used 2-aminophenol and 1,2-phenylenediamine, alkylating with a variety of α,ω-dichloroethers.[24] Richman and Atkins used the disodium salt of *N,N*-bis[2-(4-tolysulfonyloxy)ethyl]toluene-4-sulfonamide to synthesise 1,4,7,10-tetraazacyclododecane tetrahydrochloride, (**5**), Equation 3.[25] Conditions of non-high dilution were found to give good yields of macrocyclic products.

Equation 3



Lehn and coworkers studied macrocyclic amides and their reduction to amines.[26] An α,ω-diamine and a diacyl chloride were condensed under high dilution conditions, and the resulting macrocyclic diamide was reduced to the corresponding diamine. For a more comprehensive account of this topic, attention is drawn to a recent review.[27]

2.2.2 Thia Crown Ethers

The sulfur analogues of crown ethers are called thia crown ethers. The synthetic strategies used fall into two types;

i) reaction of a dithiol and a dihalide in the presence of a base, under high dilution conditions,

ii) reaction of a dihalide with sodium sulfide.

Reagents that are β-halosulfides are severe vesicants and 2-mercaptoethanol is relatively unreactive. Alkylation of the disodium salts of α,ω-

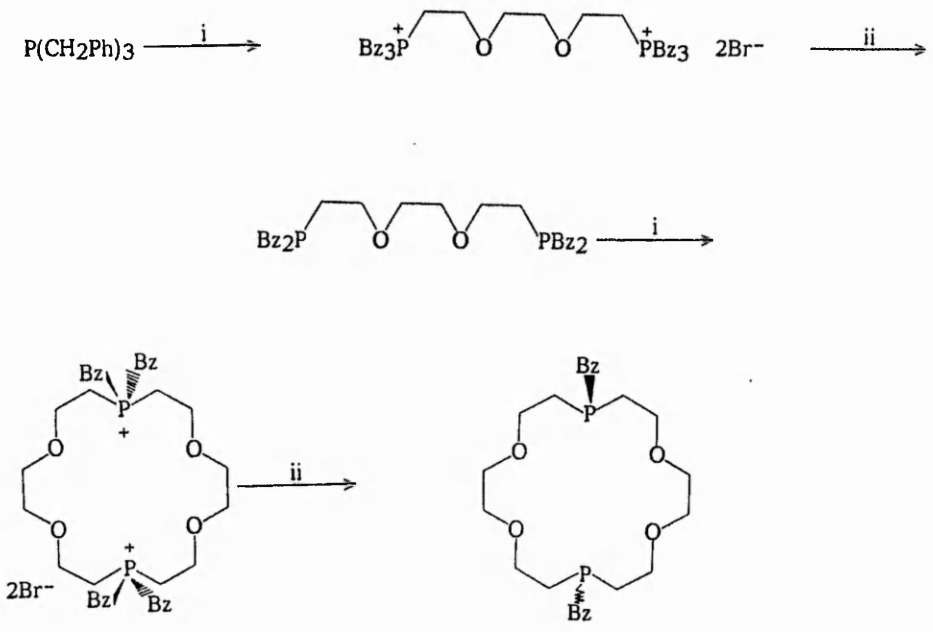
dimercaptosulfides with dibromoalkanes under high dilution in ethanol gave tri- and tetrathiacycloalkanes.[28] Similar methodologies have been used in the synthesis of oxathia crowns,[29] azathia crowns,[30] and oxaazathia crowns.[31] Pedersen applied stategies previously discussed in Section 2.1.3, (page 13), to 2-mercaptophenol and 3,4-dimercaptotoluene.[32]

2.2.3 Crown Ethers containing Phosphorus

Phosphorus containing macrocycles first appeared in the literature as early as 1897. Stokes reported a series of dichlorocyclophosphonitriles of general formula $(PNCl_2)_n$ where n was 5,6 or 7. The related dodeca-(dimethylamido)cyclohexaphosphonitrile, $N_6P_6(NMe_2)_{12}$ has been shown to form stable complexes with copper(II) chloride.[33] The incorporation of phosphorus in crown ethers via nitrogen-phosphorus bonds is a common approach. Hexamethylphosphoramide, (HMPA), and it's derivatives are well known complexing agents. Accordingly, Dutasta and Simon synthesised a number of macrocycles containing HMPA moieties from bis(dimethylamino)-phenylphosphine and a number of open chain polyethers.[34]

A number of analogues of 18-crown-6, containing phosphorus have been reported by Märkl and Hoferer.[35] Two synthetic strategies are described. The first involved a one pot synthesis, reacting dilithiophosphides with α,ω-dihaloethers to give crowns in 8-13% yield. The second method was a multistep process in which tribenzylphosphine and an α,ω-dibromoether were reacted in acetonitrile. The subsequent diphosphonium salt was reduced to the diphosphine with lithium aluminium hydride, Scheme 5.

Scheme 5



(i) $Br(CH_2CH_2O)_2CH_2CH_2Br$. acetonitrile; (ii) Lithium aluminium hydride, THF;

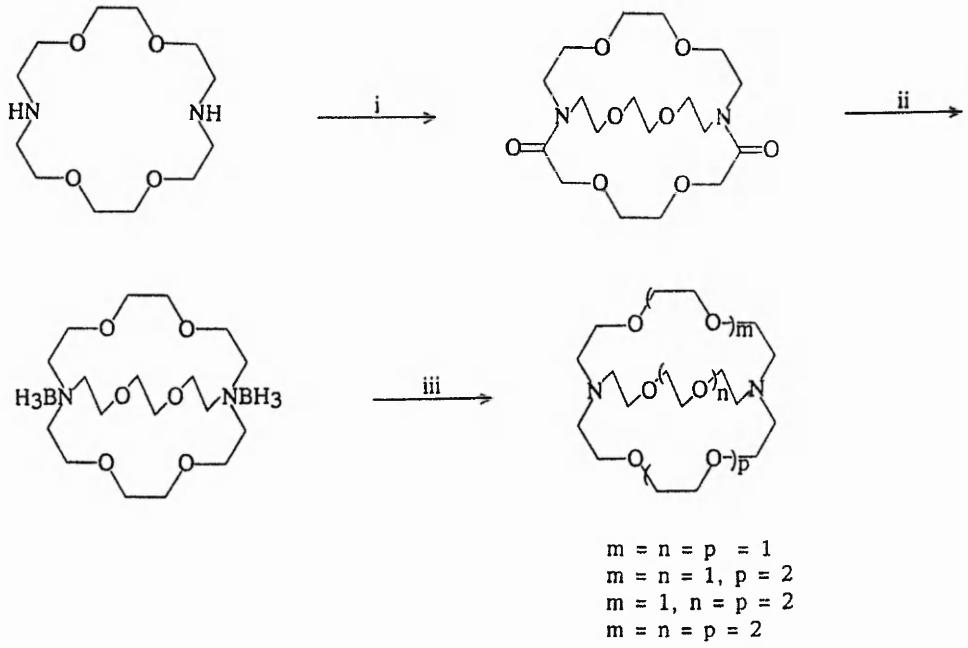
A review of the synthesis of phosphorus containing macrocycles and cryptands has been written by Caminade and Majoral.[36]

2.3 Cyptands, Macrobicycles

2.3.1 Introduction

Soon after the work of Pedersen, Jean-Marie Lehn was working on a series of bicyclic polyether systems which were capped with nitrogen. Aza crown ethers, Section 2.2.1 (page 19), were condensed with an α,ω-diacyl chloride and the product, a macrobicyclic diamide was reduced by the formation of a bis-amine borane. Acid hydrolysis of the latter gave the free bicyclic diamine.[37] The synthetic sequence is outlined in Scheme 6.

Scheme 6



(i)$ClOC(CH_2OCH_2)_2COCl$, high dilution; (ii)B_2H_6, THF; (iii)6M HCl;

A macrotricyclic tetraamide, arising from the 2+2 condensation of an aza crown ether and the α,ω-diacyl chloride was also isolated. Because of their ability to encapsulate a metal cation, the end capped diazabicycles are termed cryptands, (from the Latin *crypta*, meaning cavity), and their complexes are called cryptates.

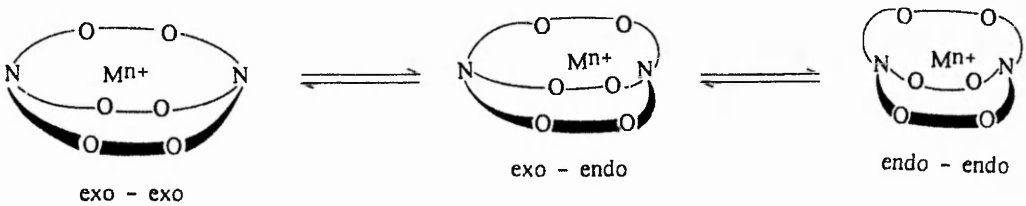
2.3.2 The Nature of the Bridgehead

Cryptands with carbon bridgeheads, (Figure 2), are unaffected by pH and possess high lipophilicity. However, they cannot undergo inversion and exist as diastereoisomers.

Figure 2

Nitrogen bridgeheads can undergo rapid inversion, the so called "in-out" isomerism. The lone pair of electrons on the nitrogen can be directed in or out of the cavity, (Figure 3), and interconversion between the three conformers is rapid.[38]

Figure 3



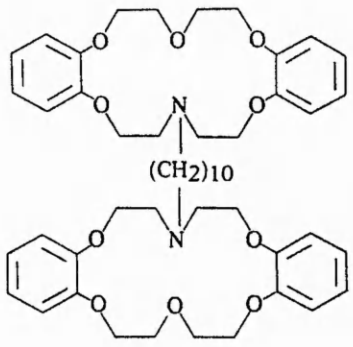
Protonation of the nitrogen bridgeheads affects the complexation properties. 1,11-Diazabicyclo[9.9.9]nonacosane, when mixed with sodium chloride dissolved in 50% deuteriotrifluoroacetic acid and DCl, gave three separate absorptions for the α-CH_2 groups in the proton n.m.r. spectrum, the results being consistent with the encapsulation of the chloride anion. Under similar conditions, the bromide ion was encapsulated to a lesser extent than the chloride ion, and no encapsulation was detected for the iodide ion.

2.3.3 Other Bicyclic Diamines

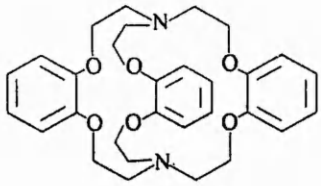
Other bicyclic systems have been developed. The strategy used by Pedersen and Bromels involved lithiation of an aza or diaza crown ether, followed by

N-alkylation with a carbon chain possessing α,ω functionality to give the so called "clam" and "lantern" compounds, Figure 4.

Figure 4



a "clam" compound



a "lantern" compound

2.4 Lariat Ethers

2.4.1 Structure and Terminology of Lariat Ethers

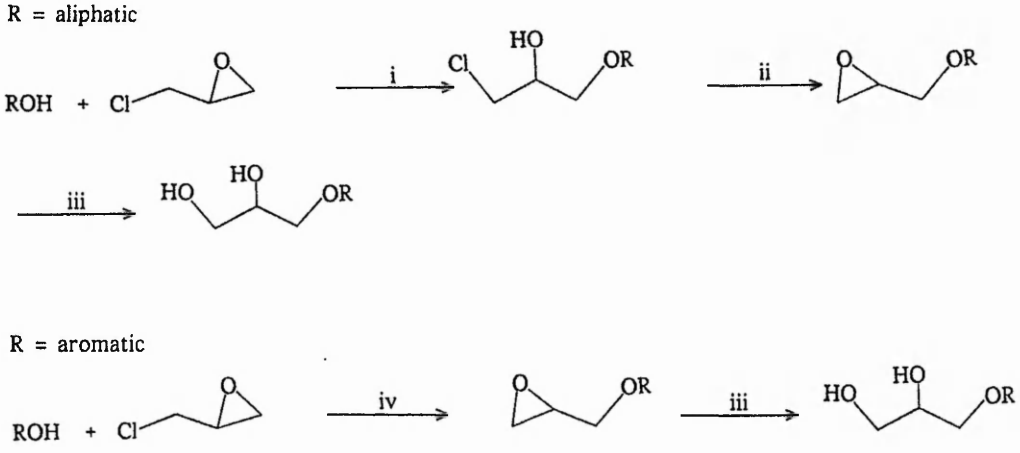
Lariat ethers are crown ethers which possess a side arm or arms capable of complexing to a cation or similar species. The side arm may be attached to either carbon, in which case the compound is termed a C-pivot lariat, or alternatively the side arm may be attached to a heteroatom, typically nitrogen, the compound then being known as an N-pivot lariat. Whilst C-pivot lariats tend to be chemically more stable, N-pivot lariats show greater flexibility due to inversion at nitrogen. Lariat ethers with two arms are termed bibracchial larial ethers, (BIBLE), those with three are called tribracchial lariat ethers, (TRIBLE).

2.4.2 Synthesis of C-Pivot Lariat Ethers

Epichlorohydrin has been used as a precursor to C-pivot lariat ethers in preference to glycerol. Nucleophilic attack by the secondary hydroxyl group and a primary hydroxyl group of glyecrol would give the desirable

ethyleneoxy unit. However, the glycerol may participate in ring closure via both primary hydroxyls, giving the crown ether a three carbon atom structure in the vicinity of the lariat. Typically, epichlorohydrin is reacted with either an aliphatic alcohol, or a phenol, as outlined in Scheme 7; the synthesis of the C-pivot lariat ether is then achieved by the macrocyclisation of the so formed 1,2-diol.[39]

Scheme 7



(i) $BF_3.Et_2O$, 80°C, 15-20hrs; (ii) 50% aqueous NaOH, 1hr; (iii) 72% $HClO_4$, 12hrs; (iv) 50% aqueous NaOH, 80°C 1-2hrs;

2.4.3 Synthesis of N-Pivot Lariat Ethers

Nitrogen pivot lariat ethers have been synthesised by the *N*-alkylation of diethanolamine; macrocyclisation with a polyethylene glycol derivative then afforded the lariat ether.[40] Clearly an alternative is the *N*-alkylation of aza crown ethers, and this has been studied by Gokel and Garcia.[41]

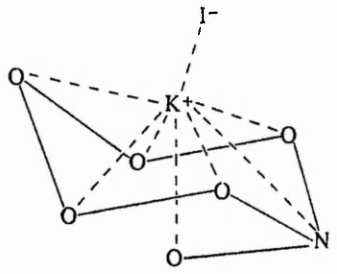
2.4.4 Evidence for Bracchial Participation in Complexation

Relaxation times for the ^{13}C nucleus have been used to study complexation in

both protic and aprotic solvents. The technique relies on the decrease in relaxation times as the motion of the carbon atom is constrained by complexation. Where resonances are resolved, this type of investigation can be carried out on individual carbon atoms. In this way, the carbon atoms of the lariat have been shown to have shorter relaxation times when complexation has occurred, than in the free form.[42]

X-ray crystallographic data have also shown bracchial and bibracchial complexation in the solid state for lariat ethers. Typically, the metal cation did not lie in the same plane as the oxygen atoms of the macrocyclic ring. A complex of potassium iodide and *N*-(2-methoxyethyl)-1,4,7,10-tetraoxa-16-azacyclooctadecane showed the macrocyclic ring in a chair conformation with the potassium ion lying slightly above the plane of the donor atoms of the polyether ring. The lariat complexed to the metal ion from beneath this plane whilst the anion was sited above the cation,[43] Figure 5.

Figure 5



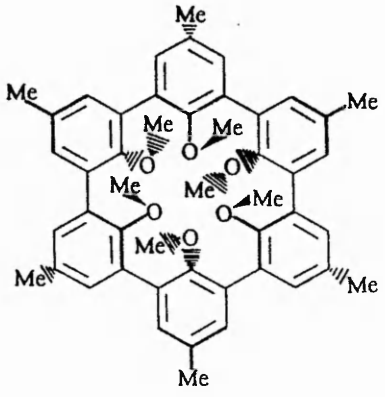
2.5 Spherands, Cavitands and Carcerands

2.5.1 Spherands

Cram and coworkers designed systems whose conformations in both the complexed and uncomplexed forms were identical. Their binding potential relied on the relief of electron-electron repulsion.[44] Based on cyclohexametaphenylene, the first spherands consisted of an inner cavity

containing six methoxy groups whose spacial needs forced an alternate "above and below" plane conformation, Figure 6.

Figure 6

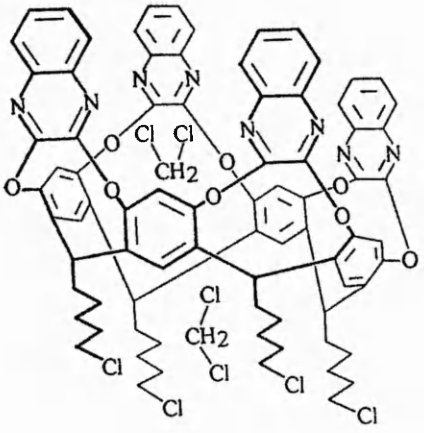


The spherand shown in Figure 6 was found to complex to lithium and to sodium, but not to other alkali and alkaline earth metal cations.

2.5.2 Cavitands and Carcerands

Cavitands are hollow, rigid compounds which have an exposed concave surface capable of forming a complex with neutral organic species. Typically cavitands are saucer shaped, and differ from spherands in that their synthesis is one of self assembly. Cavitands can complex to a variety of solvent molecules, such complexes being termed caviplexes. A typical caviplex is shown in Figure 7

Figure 7



Temperatures in excess of 110°C were necessary to remove the two solvent molecules from this crystalline bis-dichloromethane complex, but despite this, one guest molecule could be replaced by another in solution.

Carcerands, (from the Latin *carcer*, meaning prison or enclosed space), may be considered as two cavitands bonded together by their rims via short chains. Both solvent and solute are thought to act as templates during the shell closure, resulting in entrapment of such molecules by the carcerand to give a carcerplex.[46] Where sufficient gaps in the molecular stucture exist to allow complexed moieties to pass freely, the molecules are termed hemicarcerands and their complexes, hemicarcerplexes.

2.6 Practical Applications of Macrocyclic Systems

2.6.1 Phase Transfer Catalysis

The use of quarternary ammonium salts as phase transfer catalysts, (PTC), is well documented.[47] There is a clear analogy between such salts and the complexes of macrocyclic polyethers with alkali metal ions. Crown ethers can solubilise organic and inorganic metal salts in apolar solvents, which leads to weakly solvated anions which exhibit enhanced nucleophilicity; thus reaction rates for PTC reactions can be very high. Potassium cyanide, acetate and fluoride have all been used as sources of nucleophiles in S_N2 substitutions promoted by 18-crown-6.

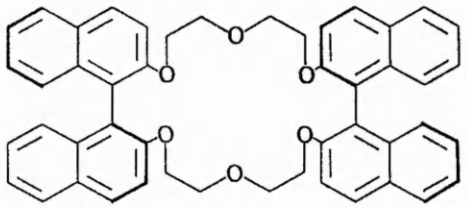
Dicyclohexyl-18-crown-6 was found to enhance the reactivity of the methoxide ion to the extent of promoting an S_NAr mechanism[48] with 1,2- and 1,3-dichlorobenzenes to give *o*- and *m*-chloroanisole respectively.[49] This crown has also been found to solubilise potassium permanganate in benzene, providing a mild but very versatile oxidising agent.

Crown ethers have also been shown to affect the isomer ratios of products in the Wittig olefination of aldehydes.[50]

2.6.2 Chiral Resolution by Optically Active Crown Ethers

Optically pure binapthol has been used to synthesise a number of crowns capable of complexing with partial selectivity to organoammonium salts. Crown ether (**6**), (Figure 8), has been shown to complex to the (*R*) enantiomer of α-methylbenzylamine in preference to the (*S*) enantiomer by a ratio of 2:1.

Figure 8



(6)

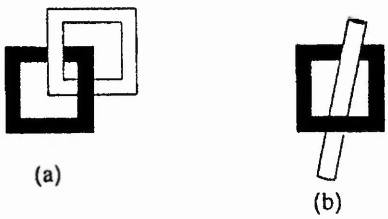
By synthesis of such crown moieties bound to a polystyrene resin, an optically active stationary phase was generated. This was utilised in the chromatographic resolution of amino acids and alkyl ammonium salts.[51]

2.6.3 Molecular Machines

Catenane and rotaxane chemistry has provided some interesting examples of self assembly. A [2]catenane may be considered as two interlocking rings whilst a [2]rotaxane may be viewed as a linear 'rod' threaded through a ring, Figure 9.

Figure 9

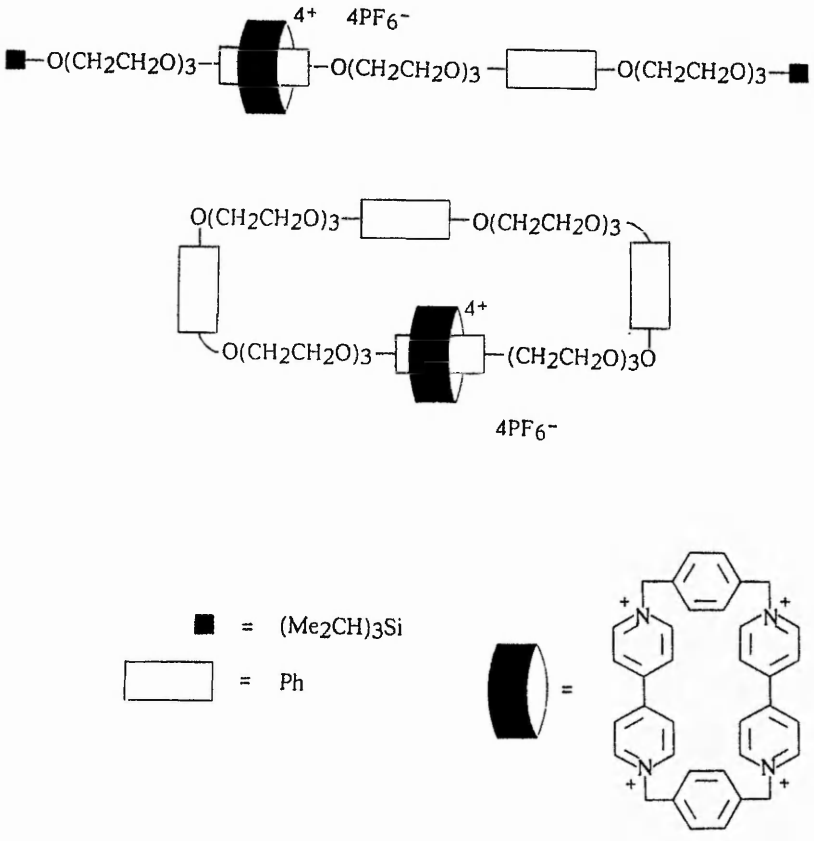
Schematic representation of (a) a [2]catenane, and (b) a [2]rotaxane



(a) (b)

Taking these compounds one stage further, one can envisage a molecular 'shuttle' passing either around a ring, (*cf.* [2] catenanes), or along a molecular chain, (*cf.* [2]rotaxanes). Typically, the shuttle is a polycyclic aromatic and the 'track' consists of alternating polyether chains and aromatic rings, Figure 10.[52]

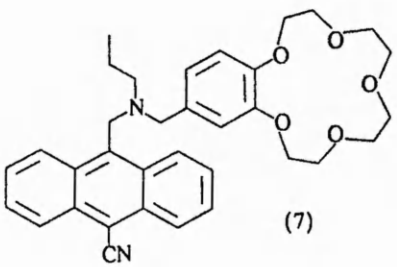
Figure 10



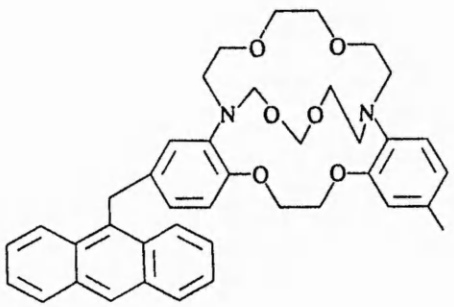
Such phenomena may be used in the future as the basis for molecular computers.

Crown ethers and cryptands have also been studied as potential real time monitors of ion concentration. The anthracene derivative (7) behaves as an AND gate. The benzo-15-crown-5 function binds selectively only to sodium ions whilst the tertiary amine can be protonated. When both criteria are met, the fluorescence output is increased. The presence of other ions does not significantly affect the fluorescence intensity. The cryptand (8) behaves as an OR

gate. The poor selectivity ensures that the cryptand binds to either potassium or rubidium, both being capable of enhancing fluorescence. These species are limited to working in solution, and are thus not suitable for use in integrated circuits.[53a]



(7)



(8)

2.7 Naturally Occurring Macrocycles

Biological systems use osmoregulation as a means of maintaining constant composition of tissue fluids. Solutes like ions of sodium, potassium and calcium play a crucial role in this. There is a parallel between the PTC properties of synthetic crown compounds, (Section 2.6.1, page 29), and the need to transport metal ions through an apolar lipid membrane. Nature has developed a number of systems capable of complexing with high selectivity to metal ions, thus enhancing their lipophilicity.

Valinomycin, a natural macrocyclic depsipetide, was first isolated by Brockmann and Schmidt-Kastner in 1955.[53b] It has been shown to transfer potassium ions through mitochondrial membranes. nonactin, (a macrocyclic depside), and antamanide, (a cyclic decapeptide), both complex strongly to alkali and alkaline earth metal ions. Such compounds show antibacterial properties.

Other large ring systems include the porphyrins and cyclodextrins. Porphyrins are macrocyclic tetrapyrrole systems. In biological organisms a metal ion is complexed to the nitrogen atoms of the four pyrrole rings. Such

metalloporphyrins are used in chlorophyll and cytochromes for elecron transfer during photosynthesis. The cyclodextrins are cyclic oligosaccharides consisting of six (α), seven (β), or eight (γ) glucose units. They are toroid in shape, the cavity being host to a number of organic moieties. As such, they have been studied as biosensors for enantiomeric drugs present in low concentrations in serums. Other sensors in such media are swamped by metal ions present in quite high concentrations.

2.8 Macrocyclic Systems containing Thiophene

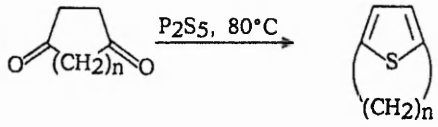
2.8.1 Introduction

Macrocyclic systems containing five membered ring heterocycles are well documented. The strategies used in their syntheses have differed from the benzenoid systems because in general the heterocyclic diols are less stable than catechol *et al.* The presence of a heteroatom in the ring offers the potential for a further coordination site. In this respect, the sulfur atom of the thiophene ring is a poor donor which may account for the preponderance of furan and pyrrole macrocyclic systems in the literature. Thiophene does have the advantage that it may be desulfurised giving aliphatic macrocycles. For comprehensive reviews of macrocyclic systems containing thiophene, attention is drawn to reviews by Meth-Cohn[54] and Newkome and coworkers.[55]

2.8.2 Thiophenophanes

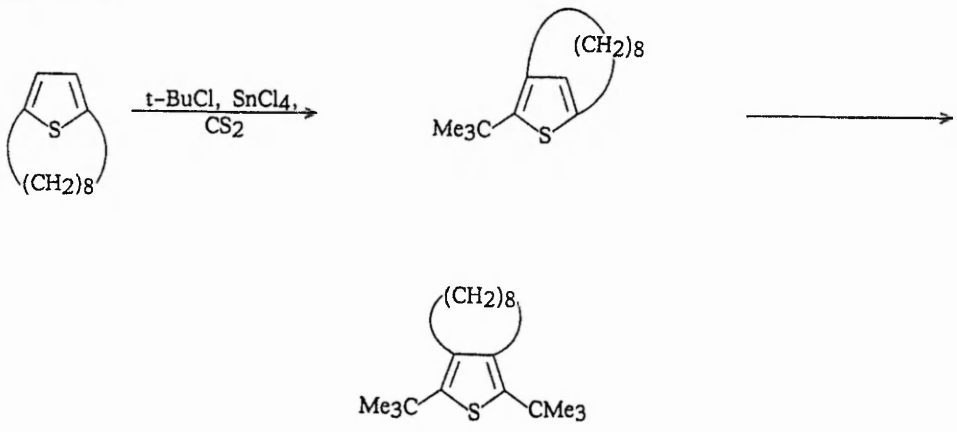
The thiophenophanes represent the largest class of macrocyclic thiophene systems studied. A common strategy for the synthesis of simple 2,5-thiophenophanes has been the Paal-Knorr synthesis where a 1,4-dicarbonyl compound, (here, a macrocyclic 1,4-dicarbonyl compound), is dehydrated in the presence of phosphorus pentasulfide, Equation 4.

Equation 4



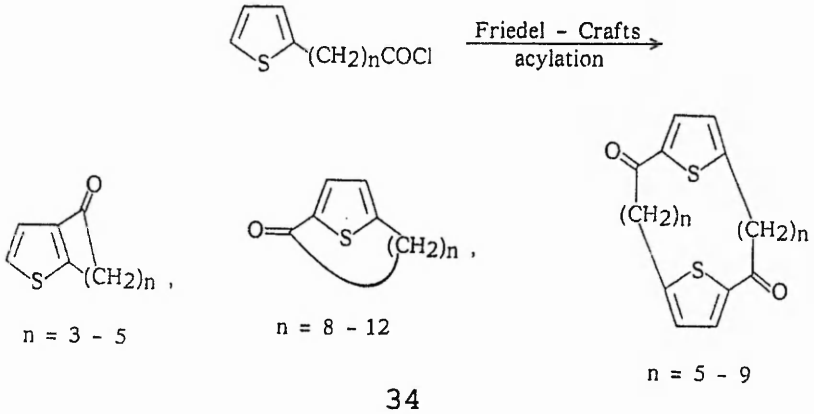
This approach has also been applied to the salts of macrocyclic 1,4-keto acids and 3-acetylcycloalkanones in the synthesis of 2,4-thiophenophanes. The 2,5-thiophenophanes have been shown to undergo a rearrangement to 3,4-thiophenophanes during Friedel-Crafts alkylation with the sterically demanding *tert*-butyl cation, Equation 5.

Equation 5



Gol'dfarb *et al.* have extensively studied Friedel-Crafts acylation with thienyl acid chlorides, using a variety of solvents and Lewis acids. The product was found to depend on the length of the chain between the thiophene ring and the chlorocarbonyl group, Scheme 8.[57]

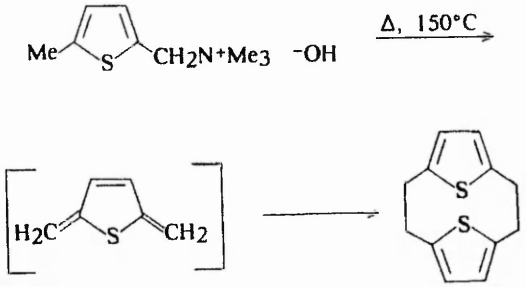
Scheme 8



Gol'dfarb and Taits also studied the synthesis of macrocyclic acyloins, (α-hydroxyketones), under conditions of high dilution. Methyl thiophene-2,5-dialkanoates were added to either sodium or a potassium-sodium alloy in a xylene-diethylether solvent system to give the desired products in yields of 25-30%.

Winberg and coworkers reported an addition product obtained from a 1,6-Hofmann elimination when (5-methyl-2-thienyl)trimethylammonium hydroxide was heated in the presence of a phenothiazine inhibitor, Equation 6.[58]

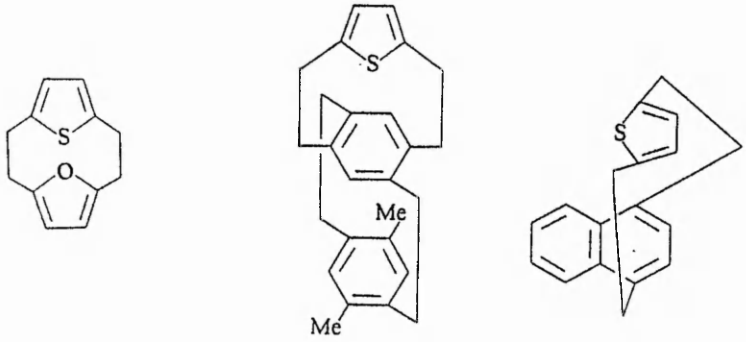
Equation 6



(9)

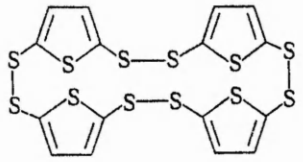
Though not isolated in this case, the 2,5-dimethylene-2,5-dihydrothiophene intermediate (**9**), has been reported at liquid nitrogen temperatures in the pyrolysis of 2-ethyl-5-methylthiophene,. Cross condensation of (**9**) with other reactive dimethylene aryl species has been used to generate a number of heterophanes, Figure 11.[58, 59, 60]

Figure 11



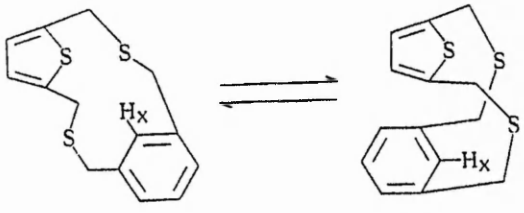
A related synthesis involved the elimination of potassium cyanide from potassium 5-thiocyanato-2-thienylmercaptide to give a trithiomaleic anhydride intermediate. Polymerisation gave a tetrameric disulfide bridged thiophene ring system, albeit in low yield, Figure 12.

Figure 12



Methodology involving *S*-alkylation has also been reported in the construction of heterophanes. The coupling of bis(chloromethyl) and bis(mercaptomethyl) arenes has been usedin the synthesis of dilithia [3]metacyclo[3](2,5)-, (2,4)-, (2,3)- and (3,4)-thiophenophanes. There are similarities between this approach and the strategies used in the synthesis of thia crown ethers, (see Section 2.2.2, page 20). Voegtle and Lichtenthaler showed that in 2,10-dithia[3]metacyclo[3](2,5)thiophenophane, (**10**), there is a high barrier to ring inversion due to the close proximity of the lone pair electrons of the sulfur in the thiophene ring and H_X of the benzene ring, Figure 13.[61]

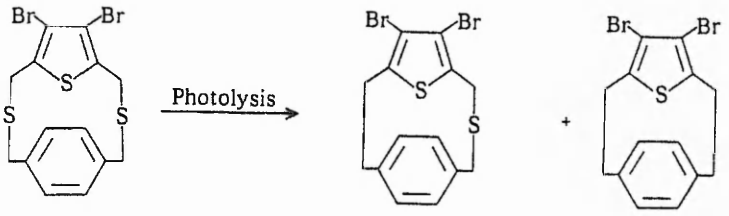
Figure 13



E (10) Z (10)

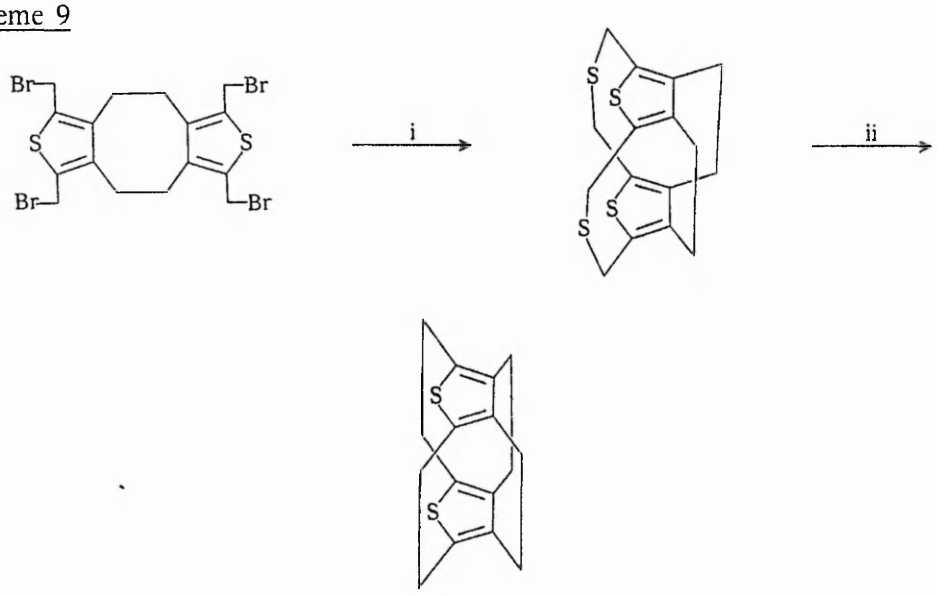
Takeshita *et al.* showed that such thiophenophane derivatives could be selectively desulphurised, removing one or both sulfide atoms by photolysis, Equation 7.

Equaion 7



The authors also reported the oxidation of the sulfide linkages to the corresponding sulfones by 3-chloroperbenzoic acid, (MCPBA), and subsequent pyrolysis at 450-500°C under reduced pressure for several minutes, giving moderate yields of the appropriate desulfurised product. This latter approach was used in the synthesis of the first fully cross linked heterophane, $[2_4](2,3,4,5)$thiophenophane (**11**), Scheme 9.[63]

Scheme 9



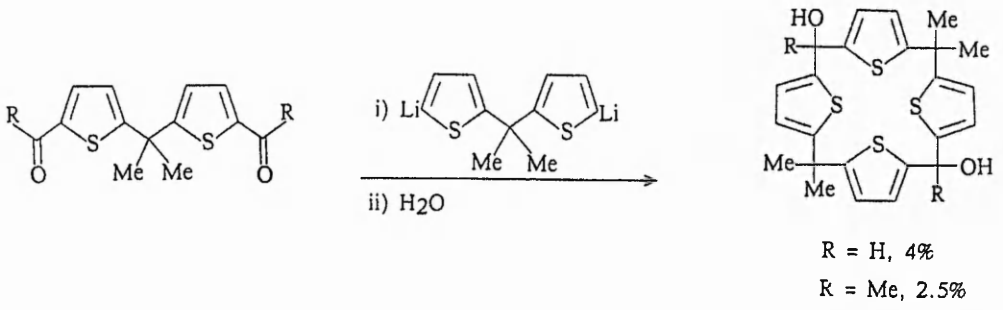
(11)

(i) $Na_2S.9H_2O$, EtOH, (yield, 27%); (ii) MCPBA, then pyrolysis, (yield, 2%)

2.8.3 Porphyrins and Related Analogues

Syntheses of macrocyclic porphyrinogens containing the pyrrole and furan moieties have been known for many years, indeed a porphyrinogen derived from four pyrrole rings was first reported by Baeyer in 1886.[64] The methodology used for both pyrrole and furan involved the acid catalysed condensation of the aromatic ring with acetone. However the reaction failed when applied to thiophene. Ahmed and Meth-Cohn achieved the synthesis of an octamethylthiaporphyrinogen by the condensation of thiophene and acetone in 72% sulfuric acid.[65a] A stepwise approach was reported, in which 2,2-bis(5-lithiothienyl)propane was condensed with either the bis(5-formylthienyl) or bis(5-acetylthienyl) derivatives under high dilution to give dihydroxytetramethyl- and dihydroxyhexamethyl-thiaporphyrinogen, respectively, Equation 8.[65b]

Equation 8

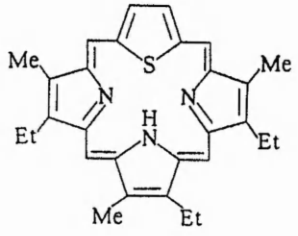


R = H, 4%

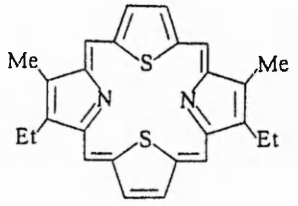
R = Me, 2.5%

Broadhurst and coworkers synthesised a number of porphyrin systems containing the thiophene ring.[66] The approach adopted was an extension of the MacDonald porphin synthesis, (which involves the acid catalysed condensation of a dipyrromethane-5,5'-dicarboxaldehyde with a dipyrromethane or a 5,5'-dicarboxylic acid derivative), using a [3+1] strategy whereby thiophene-2,5-dicarboxaldehyde was condensed with a triaryl-5,5'-dicarboxylic acid, giving a

21-thiaporphyrin, (**12**). By varying the central aromatic ring of the triaryl system, two thiophene rings could be incorporated, giving a 21,23-dithiaporphyrin, (**13**).



(12)



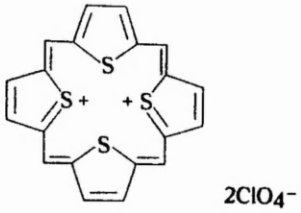
(13)

Armiger and Lash reported the failure of the MacDonald method when applied to the synthesis of a 21,22-dithiaporphyrin.[67] This was attributed to the strain that would arise due to the closeness of the sulfur atoms. However, it was found that dipyrromethane-5,5'-dicarboxylic acid underwent acid based condensation with thiophene-2-carboxaldehydes, oxidation with DDQ then giving porphyrins with extra-annular thiophene rings.

Acid catalysed [2+2] coupling of pyrrole with 2,5-bis(phenylhydroxymethyl)thiophene, to give 5,10,15,20-tetraphenyl-21,23-dithiaporphyrin, was reported by Ulman and Manassen.[68] The yields were highly dependent upon the solvent and acid used, ranging from 10% for a toluene/monochloroacetic acid system to 0.2% for one of methanol-benzene/HBr-acetic acid.

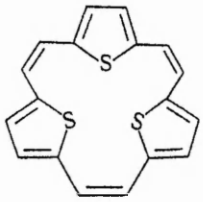
Furfuryl alcohol can be condensed to tetraoxaporphyrinogen by the action of zinc chloride and hydrochloric acid in dichloromethane. Vogel *et al.* used this approach to synthesise tetrathiaporphyrinogen, by treating tetraoxaporphyrinogen with hydrogen sulfide in an acidic medium.[69] The tetrathiaporphyrinogen was then oxidised by the action of a DDQ-AcOH-CH_3NO_2 system, further treatment with perchloric acid then giving the

tetrathiaporphyrin as a dication, (**14**).



(14)

The tetrathia compound (**14**) was stable to sulfuric and perchloric acids as well as liquid sulfur dioxide, but water, nitric acid and common organic solvents led to decomposition. The aromaticity of (**14**) was illustrated by its n.m.r. spectrum, all the protons being deshielded due to the existence of a ring current. This was significant since up until then, no conjugated macrocyclic annulene composed solely of thiophene rings had demonstrated aromaticity. Badger *et al.* synthesised trithia[18]annulene[2,2,2], (**15**) and demonstrated it's lack of aromatic character despite obeying Huckel's (4n+2)π electron rule.[70]



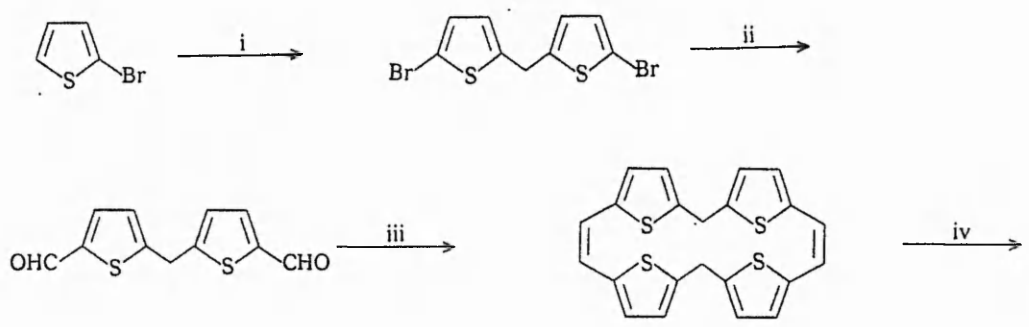
(15)

The lack of a ring current has been attributed to non-planarity, arising from the bulky nature of the sulfur atoms.

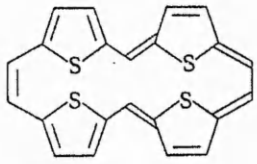
Recent porphyrinoid synthesis has utillised the reductive McMurry coupling of aromatic aldehydes. Using this approach Hu and coworkers synthesised the first neutral aromatic porphyrinoid containing thiophene and

methine moieties, tetrathia[22]annulene[2,1,2,1], (**17**), Scheme 10.[71]

Scheme 10



(16)



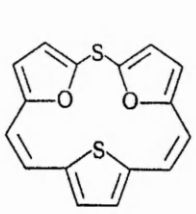
(17)

(i) $CH_2(OMe)_2$, AcOH, H_2SO_4, (yield, 85%); (ii)BuLi, THF, -70°C, then DMF, (yield, 63%); (iii) $TiCl_4$, Zn, Pyridine, THF, reflux, (yield, 75%); (iv) DDQ, hydrazine, (yield, 82%).

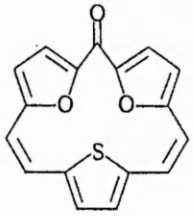
A comparison of the reported proton n.m.r. spectrum of the dihydro-derivative (**16**), and (**17**) is illustrative of the deshielding effect of a ring current. All proton resonances occurred between 6.52 and 6.78ppm for (**16**) whereas the aromatised (**17**) gave signals downfield, between 10.86 and 12.34ppm.

Australian workers have synthesised a number of [17]annulenes which were similar to (**15**) and other related [18]annulenes but a double bond was replaced with either a heteroatom which itself possessed a lone pair of electrons,

or a carbonyl group, (to give a [17]annulone).[72] The compounds were synthesised using Perkin or Wittig reactions, and contained only one thiophene ring, thus reducing steric inhibition of planarity. The [17]heteroannulene, (**18**) and the [17]annulone, (**18**) were shown to be non-aromatic despite being related to the $(4n+2)\pi$ systems.



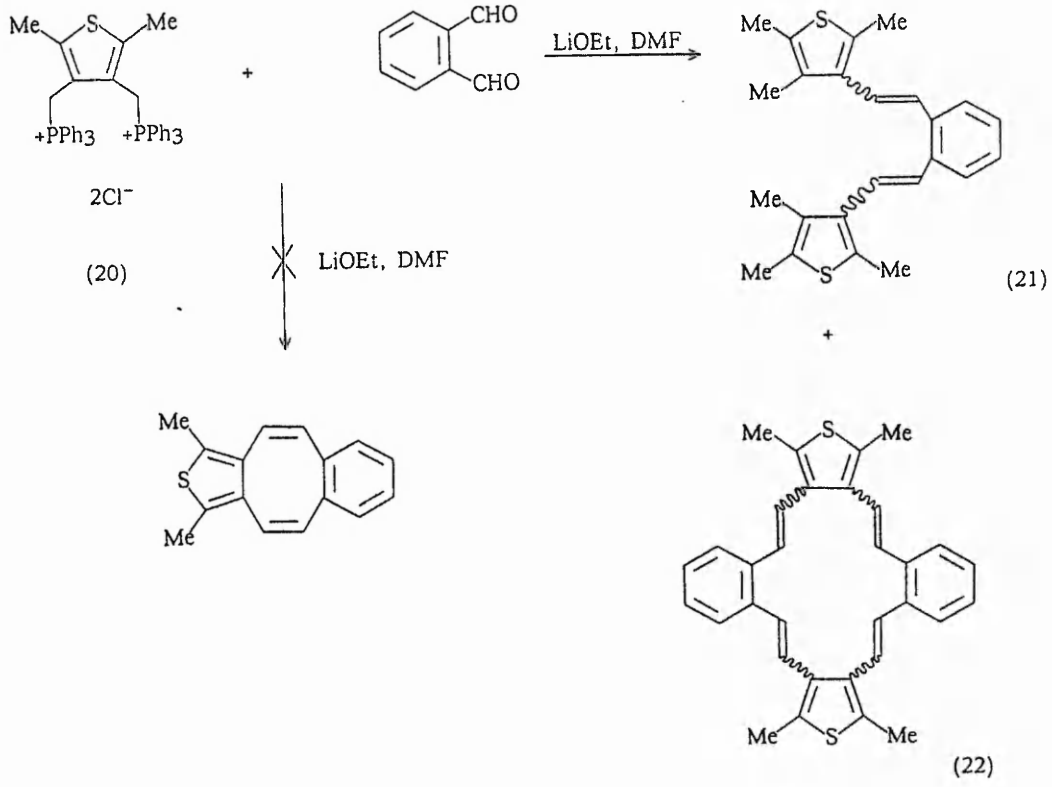
(18)



(19)

A thia[30]annulene has also been synthesised using the Wittig olefination by reaction of 2,5-dimethylthiophene-3,4-diylbis(methylenetriphenylphosphonium chloride, (**20**), with benzene-1,2-dicarboxaldehyde under conditions of high dilution. No [1+1] cyclisation product was isolated, Scheme 11.[73]

Scheme 11

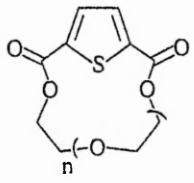


The reaction afforded four separable products; the *trans,trans*, *cis,cis* and *cis,trans* geometric isomers of compound (**21**), as well as the desired macrocycle (**22**). This latter compound was isolated as a mixture of its geometrical isomers and was found to be unstable in the presence of oxygen. Interestingly, only a number of oligomeric alkenes were isolated when 2,5-dimethylthiophene-3,4-dicarboxaldehyde was employed instead of benzene-1,2-dicarboxaldehyde.

2.8.4 Crown Esters and Amides containing Thiophene Rings

A number of heteroaromatic macrocyclic polyether-diesters were synthesised by Bradshaw and coworkers by the nucleophilic substitution at the carbonyl groups of diacyl chlorides by an oxygen nucleophile, under high dilution conditions, Figure 14.[74]

Figure 14



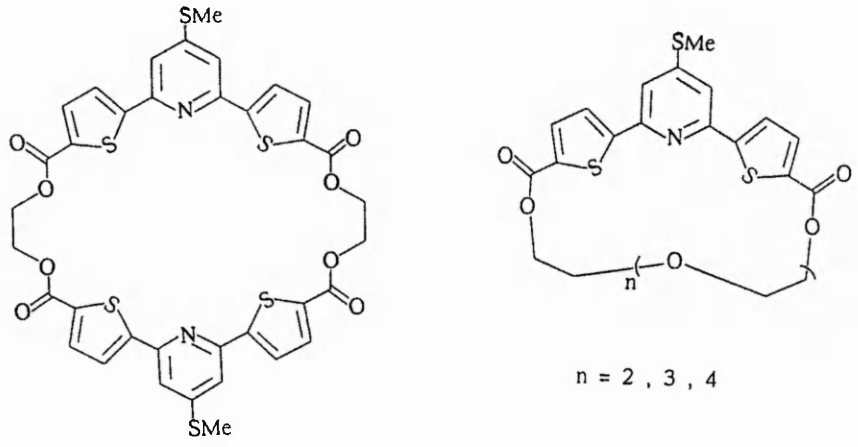
23 a , n = 3 , 17%
23 b , n = 4 , 18%
23 c , n = 5 , 14%

Although the diesters (**23a**) and (**23b**) failed to form complexes with primary alkylammonium cations, the diester (**21c**) was shown to complex by temperature dependent ^{1}H n.m.r. spectroscopy. Interestingly, the analogous furan systems were all found to complex such salts.

In general, such crown ester compounds do not complex cations as strongly as do their crown ether counterparts, although those macrocyclic crown esters derived from pyridine-2,6-dicarboxylic acid are an exception to

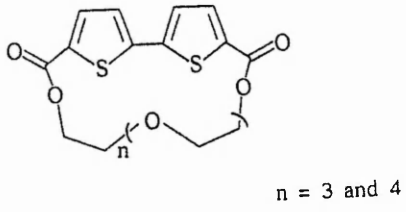
this, *eg.* the pyridyl analogue of (**23a**) forms complexes with stabilities comparable to those of the complexes of 18-crown-6. This observation led Potts and Cipullo synthesise a series of macrocyclic esters incorporating the 2,6-dithienylpyridine moiety.[75] Treatment of the dicesium salt of 2,6-bis(5-carboxy-2-thienyl)-4-(methylthio)pyridine with a series of α,ω-dibromopolyethers yielded a number of crown esters, Figure 15. However, no complexation data was give with these compounds.

Figure 15



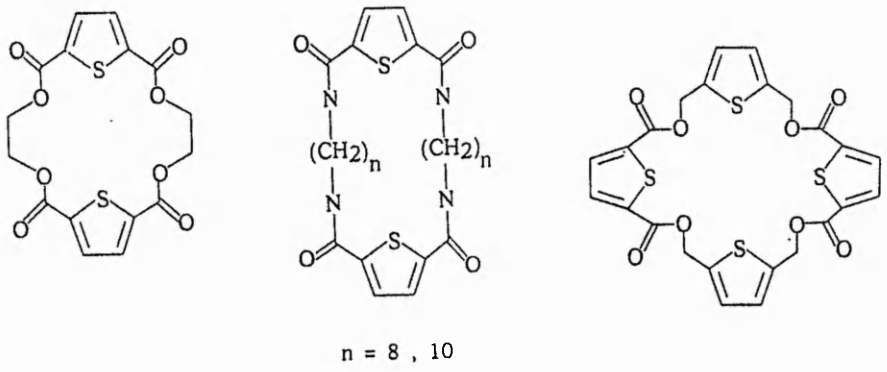
These workers also applied a similar strategy to 2,2'-bithienyl-5,5'-dicarboxylic acid to give the corresponding diester crown ethers, Figure 16.

Figure 16



French workers have recently reported the synthesis of a number of macrocyclic tetraesters and tetraamides from a series of [2+2] cyclisations, Figure 17.[76]

Figure 17



2.8.5 Macrocyclic Schiff Bases derived from Thiophenes

Synthesis of these bases has typically involved the [2+2] condensation of a thiophene-2,5-dicarboxaldehyde with an α,ω-primary diamine to give a macrocyclic tetraimine. As early as 1939, Steinkopf *et al.* assigned macrocyclic structures to a series of compounds, isolated in the condensation of 3,4-dibromothiophene-2.5-dicarboxaldehyde with a number of aliphatic and aromatic diamines.[77] However, the amorphous nature of the products along with the reported high melting points led Meth-Cohn to postulate that these compounds were in fact polymers, rather than discrete molecules.[54]

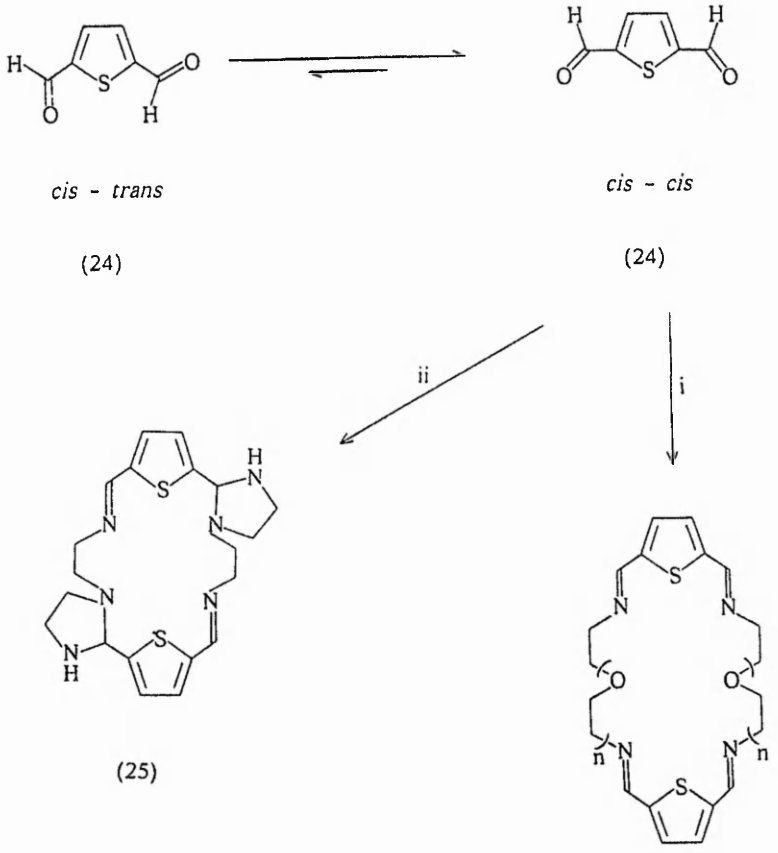
The condensation of pyridine-2,6-dicarbonyls with primary amines yielded macrocyclic products only in the presence of a suitable metal ion template. In the absence of such metal ions oligomerisation and polymerisation predominated. The macrocycles were isolated as complexes with the salt used and attempts to isolate free macrocyces by expulsion of the metal ion failed. This indicates that the metal ion served not only as a template in the macrocyclisation process but also exerted a stabilising effect upon the macrocycle once formed.[78] Bailey and coworkers reported the synthesis of metal free macrocyclic Schiff bases by the reaction of thiophene-2,5-dicarboxaldehyde (**24**), and a series of α,ω-diaminoethers in methanol, Scheme 12.[79] The compounds were shown to be [2+2] cyclisation products by both

their mass spectra and X-ray crystal structure.

Conformational studies showed that (**24**) exists as *cis*, *trans* and *cis*, *cis* conformers, in the ratio 20:80, Scheme 12. The *cis*, *cis* conformer leads most easily to such macrocycles and (**24**) contains a much higher amount of this conformer than either the pyridine or furan analogues.[80]

Subsequently, a number of α,ω-diamino moieties were condensed with (**24**).[81] The reaction utilising bis(2-aminoethyl)amine gave not only the expected [2+2] compound, but also the macrocycle (**25**) comprising of two imidazolidine rings arising from the nucleophilic addition of the secondary amine to the double bond of the imine.

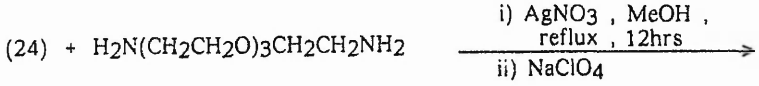
Scheme 12



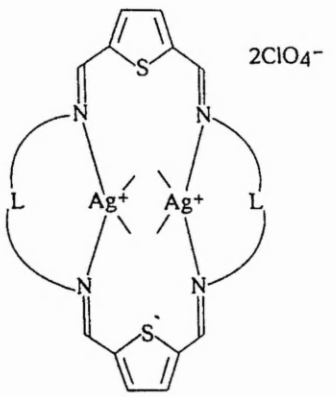
(i) $H_2NCH_2CH_2(OCH_2CH_2)_nNH_2$, MeOH, overnight; (ii) $(H_2NCH_2CH_2)_2NH$, MeOH, overnight:

The products of macrocyclisation were shown to form complexes with silver and barium salts, either by reaction of an ethanolic solution of the free macrocycle with the salt or by using inorganic salts as templates during the macrocyclisation process. The presence of such salts during ring closure was found to have a marked effect upon product formation in certain circumstances. Two products were reported when (**24**) and 3,6,9-trioxaundecane-1,11-diamine, (**26**) were condensed in the presence of silver nitrate. Subsequent treatment with sodium perchlorate led to an anion exchange reaction, Equation 9. One compound was found to be a [2+2] macrocycle complexed to two silver(I) ions, (**27**), and another consisted of two [1+1] macrocycles complexed to one silver(I) ion, (**28**).

Equation 9

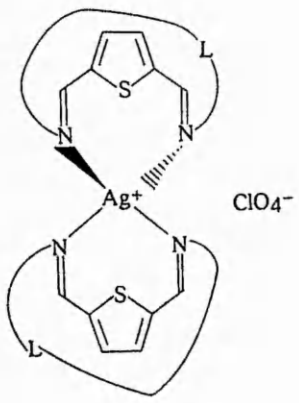


(26)



(27)

+



(28)

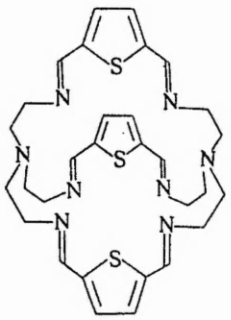
L = $(CH_2CH_2O)_3CH_2CH_2$

It is of interest to note that the same reaction failed to give either a [1+1] or [2+2] macrocycle when barium isothiocyanate was employed. This was attributed to the formation of an intermediate complex in which the oxygen atoms coordinate to the barium(Ⅱ) ion preventing intramolecular reaction of the carbonyl group and primary amine groups.

The extraction abilities of a number of tetraimine Schiff base macrocycles has also been investigated.[82] Using such compounds, Abe and coworkers were able to selectively extract copper(Ⅱ) cations from a weakly acidic solution, allowing it's separation from cobalt(Ⅱ), manganese(Ⅱ), nickel(Ⅱ) and zinc(Ⅱ) cations.

Recently Japanese workers have condensed a number of bis(5-formyl-2-thienyl)alkanes with ethane- and propane-1,2-diamines under high dilution to give 26 and 28 membered macrocyclic tetraimino Schiff bases.[83]

The strategy has been futher extended to [2+3] cyclisations by the reaction of dialdehyde (**24**) with tris(2-aminoethyl)amine, employing a silver(Ⅰ) salt template to give a lantern-like cage molecule, (**29**).



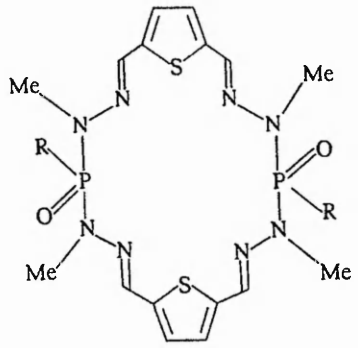
(29)

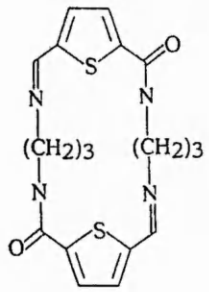
It is worthy of note that whilst this was successful with thiophene-2,5-dicarboxaldehyde only in the presence of a metal cation template, no such template was necessary for furan-2,5-dicarboxaldehyde and pyridine-2,6-dicarboxaldehyde in analogous syntheses.

Oussaid and Garrigues also recently reported the synthesis of a

number of macrocycles derived from (**24**) and 2-formylthiophene-5-carboxylic acid. Figure 18.[76]

Figure 18





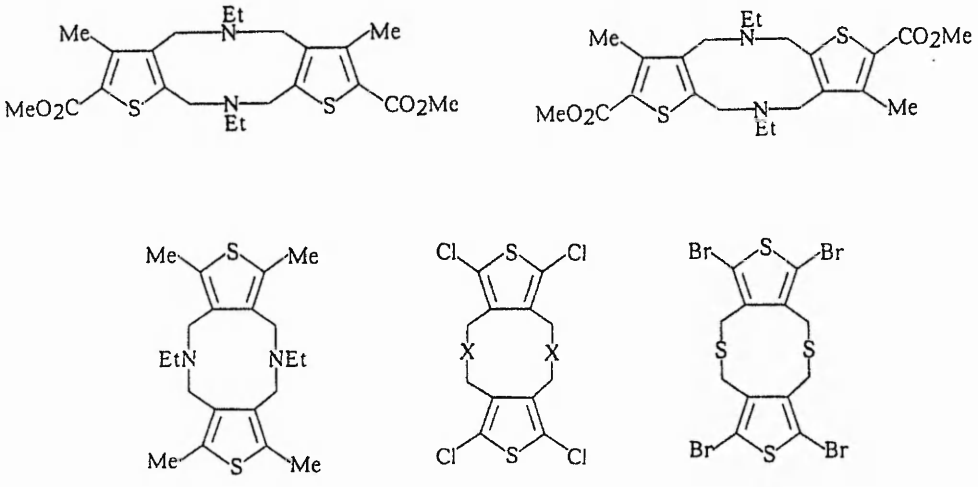
R = Ph , PhO

The reduction of Schiff bases as a route to secondary amines is well documented. Where a tetraimine showed sufficient solubility, Dancey *et al.* accomplished the reduction to a tetraamine using sodium borohydride.[85] reduction *in situ* affording lower yields than isolation and subsequent reduction of the Schiff base.

2.8.6 Macrocycles containing the Thenyl Moiety

In an investigation into the synthesis of a number of fused [2,3-b] and [3,4-c] thiophenes, Zwanberg and Wynberg reported the isolation of a number of thia, aza and oxa macrocycles by the reaction of the appropriate bis(halomethyl)thiophene with an appropriate nucleophile, Figure 19.[86]

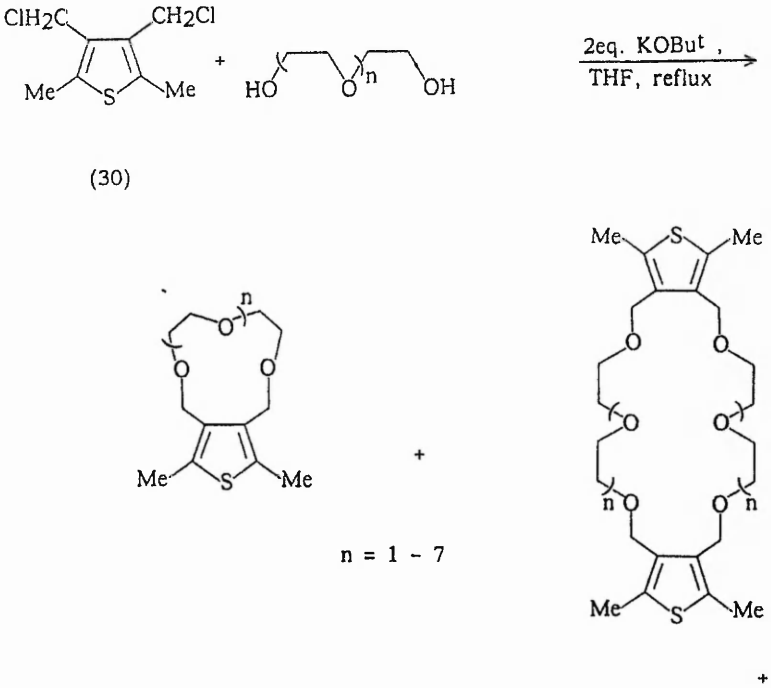
Figure 19



X = NEt , O

Subseqently, Reinhoudt *et al.* investigated the synthesis and complexation properties of a range of crown ethers prepared from 3,4-bis(chloromethyl)-2,5-dimethylthiophene, (**30**), Equation 10.[17, 87]

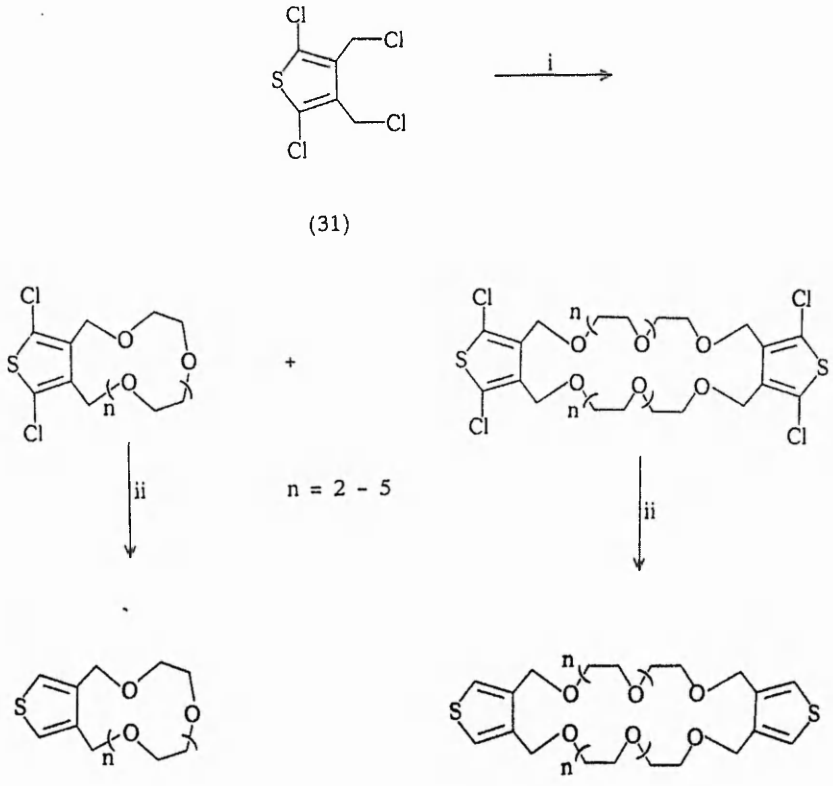
Equation 10



The yields obtained were calculated from integrals in the ^1H n.m.r. spectra. Whilst the [1+1] reaction products were isolated by distillation under reduced pressure, the [2+2] products could not be distilled without decomposition and thus were not isolated. Variations of the Reinhoudt procedure have been used by a number of researchers.

Sone and coworkers reported the synthesis of a series of crown compounds using 3,4-bis(chloromethyl)-2,5-dichlorothiophene, (**31**).[88] They also reported the dechlorination of the crowns by hydrogenation in the presence of palladium on charcoal, the integrity of the polyether and thiophene rings being maintained, Scheme 13.

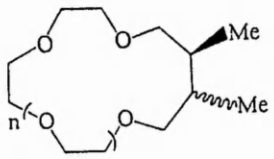
Scheme 13



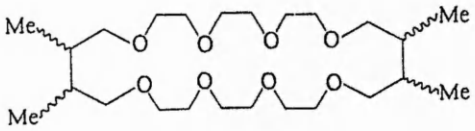
(i) $HO(CH_2CH_2O)_nCH_2CH_2OH$, 2eq. NaH, toluene, reflux, 6hrs; (ii) H_2, 10% Pd-C, KOH, MeOH, RT, 2hrs.

The crowns were desulfurised by treatment with an excess of Raney nickel in ethanol. The ^{1}H and ^{13}C n.m.r. spectra suggested that the products were a mixture of *cis* and *trans* isomers, Figure 20.

Figure 20

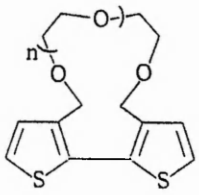


n = 2 - 4

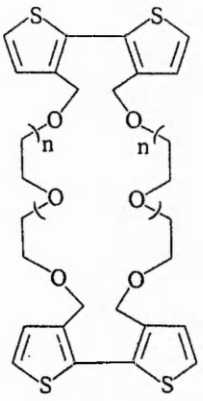


Zimmer *et al.* applied similar methodology to 3,3'-dibromomethyl-2,2'-bithienyl, using a series of α,ω-dialcohols, (employing sodium hydride as a base and THF as a solvent), to synthesise a range of [1+1] and [2+2] crown ethers, although only ethane-1,2-diol and diethylene glycol gave [2+2] adducts, in yields of under 2%, Figure 21.[89]

Figure 21



n = 0 - 4

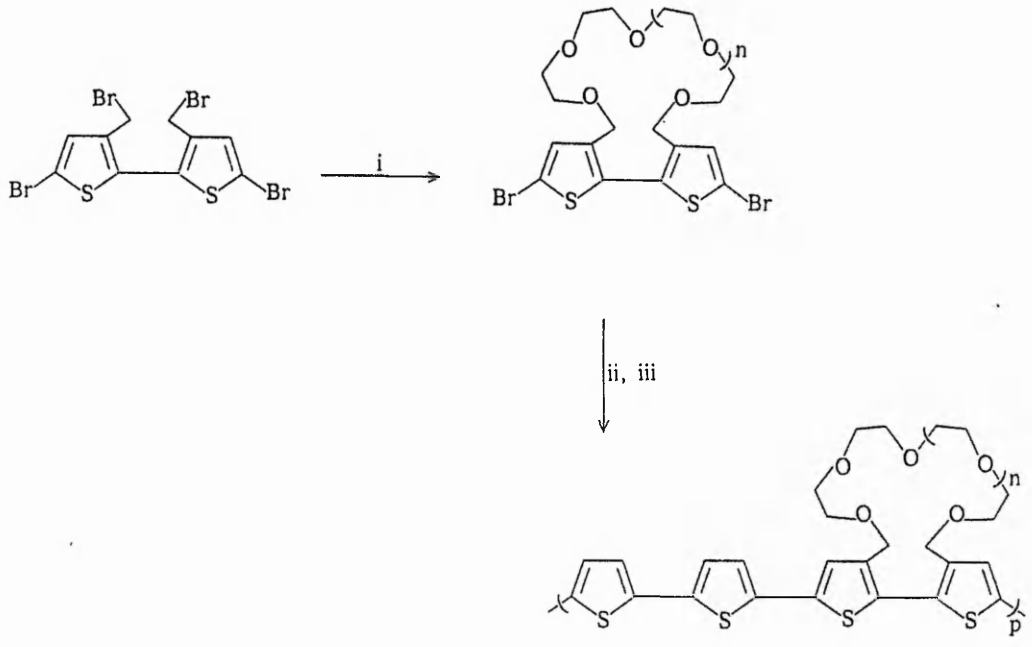


n = 0, 1

A related series of macrocycles was prepared containing crown ether moieties linked to a polythiophene backbone by American researchers. Chemical coupling using the Stille reaction, was employed using a 5,5'-dilithiobithienyl which was

reacted with trimethyl tin chloride and then coupled with 5,5'-dibromo-2,2'-bithienyl in the presence of a palladium catalyst, Scheme 14.[90]

Scheme 14



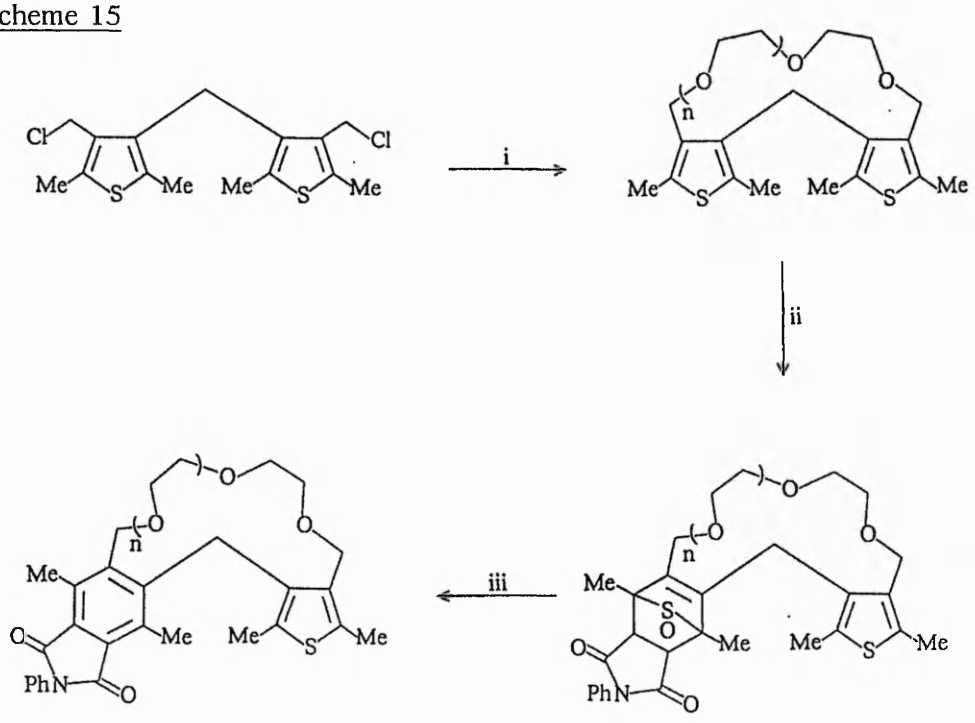
(i) $MOCH_2(CH_2OCH_2)_{n+2}CH_2OM$, for n=1, $M=Na^+$, DME, (yield, 55%); for n=2, $M=K^+$, THF, (yield, 18%); (ii) 2eq. BuLi, THF then Me_3SnCl; (iii) 5,5'-dibromo-2,2'-bithienyl, $PdCl_2(AsPh_3)_2$, Δ.

The electrical conductive properties of certain polythiophenes are well known. Upon complexation the crown ether polythiophenes underwent a conformational change which twisted the polythiophene backbone out of planarity, thereby reducing the π orbital overlap, leading to an increase in the polymer's electrical resistivity.

A number of crown ethers derived from substituted 3,3'-bithienylmethanes were prepared by Li *et al.*[91], using the procedure of Reinhoudt, with the aim of studying their oxidative cycloaddition properties with

N-phenylmaleimide in the presence of MCPBA. Initial oxidation to a reactive thiophene-1-oxide species was followed by a [4+2] cycloaddition. The sulfoxide was further oxidised using PTC to the corresponding phthalimide derivative, Scheme 15

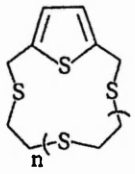
Scheme 15



(i) $HO(CH_2CH_2O)_nCH_2CH_2OH$, 2eq. NaH, THF, (yield, n=3, 61%, n=4, 37%, n=5, 43%); (ii) MCPBA, *N*-phenylmaleimide, CH_2Cl_2, 0°C, (yield, n=3, 37%, n=4, 35%, n=5, 30%); (iii) $KMnO_4$, tetrabutylammonium bromide, CH_2Cl_2, RT, (yield, n=3, 36%, n=4, 42%, n=5, 45%)

Much interest has been shown in polythia crown ethers as mimics of biological complexes in which transition metals are coordinated to a number of sulfur atoms, (the ferrodoxins and the blue copper proteins, for example). Lucas and coworkers reported the synthesis of a variety of polythia crown ethers, Figure 22.

Figure 22

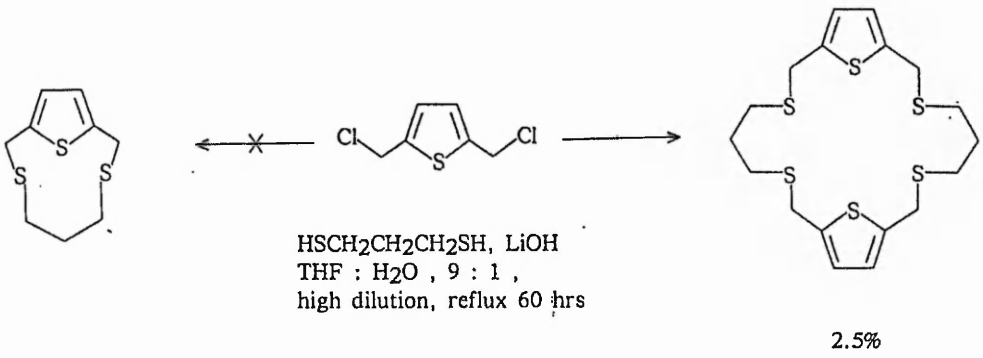


(32a), n = 1
(32b), n = 2
(33c), n = 3

The complexation properties of such systems with copper(Ⅰ), copper(Ⅱ) and silver(Ⅰ) salts was studied, together with the redox properties of the complexes so formed. The thia crown ether **(32a)** formed complexes with copper(Ⅰ) salts of stoichiometry 2 thia crown ethers : 1 metal ion. In contrast, (32a) formed a complex with copper(Ⅱ) chloride whose crystal structure indicated a $[CuCl_2.\text{thia crown}]_2$ molecular structure in which the sulphur atom of the thiophene ring coordinated to each of the copper(Ⅱ) cations.

In an earlier attempt to synthesise 2,6-dithia[7](2,5)-thiophenophane from 2,5-bis(chloromethyl)thiophene and propane-1,3-dithiol, Bhattacharjya and Hortmann reported the isolation of only the [2+2] product, Equation 11.[93]

Equation 11



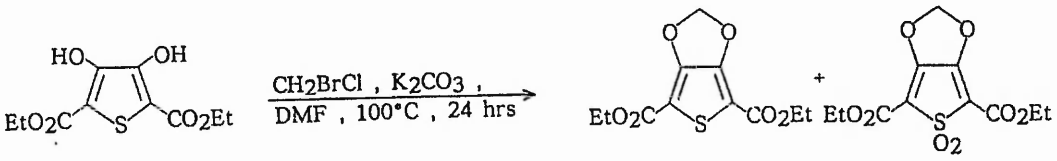
The synthesis of 2,5-bis(methylene)thiophene macrocycles has been reviewed by Voronkov and Knutov.[94]

2.8.7 Macrocycles containing the Thienyloxy Moiety

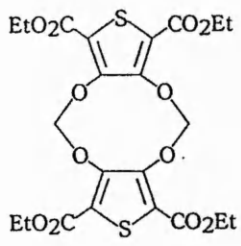
2.8.7.1 Macrocycles derived from 3,4-Dioxythiophenes

The first macrocyclic dioxygenated thiophene was reported in 1975 by Dallacker and Mues.[95] Diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate, (**33a**), underwent *O*-methylation with bromochloromethane to give the corresponding methylenedioxythiophene, (**34a**), (74%), it's *S,S*-dioxide, (**34b**), (15%), and the macrocyclic [2+2] adduct (**35**), although no yield for this compound was given, Equation 12.

Equation 12



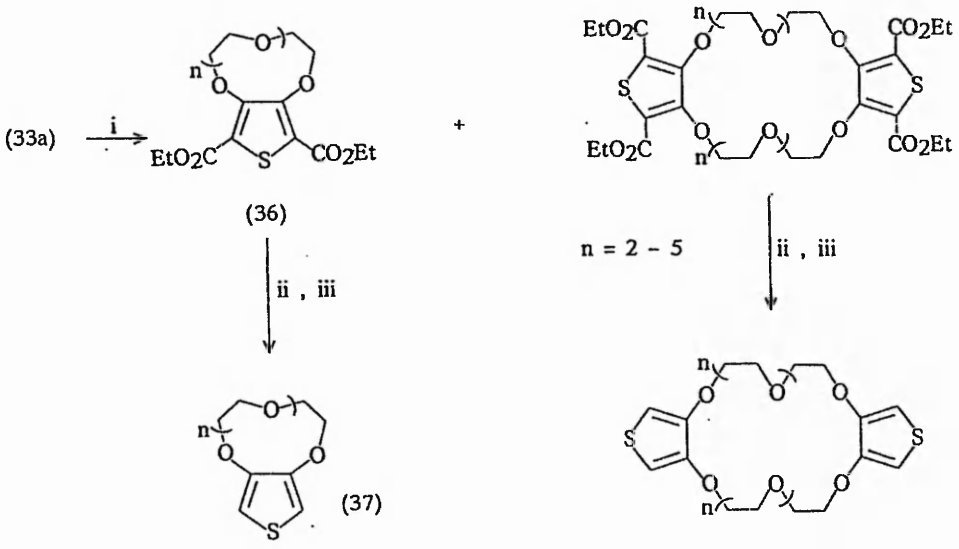
(33a) (34a) 74% (34b) 15%



(35)

Osmotic pressure measurements were used to obtain the molecular masses of (**34a**), (**34b**) and (**35**). The thiophenediol (**33a**) was reported by Sone and coworkers to undergo macrocyclisation with a number of α,ω-ditosylpolyethers in the presence of an excess of either potassium or cesium fluoride in acetonitrile. The resulting di- and tetra-esters were saponified and thermally decarboxylated to yield the respective thiophene crown ethers, Scheme 16.[88]

Scheme 16

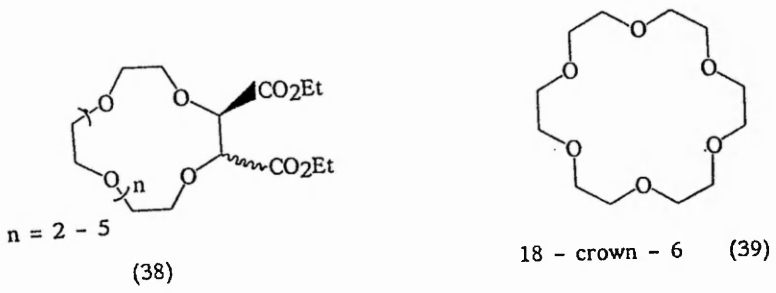


(i) 4eq. CsF, (KF for n=2), $TsO(CH_2CH_2O)_nTs$, MeCN, Δ, 25-30hrs;

(ii) alcoholic NaOH, 60°C, 2hrs, then dilute HCl; (iii) Δ, 200-300°C, 20mmHg, ½-5hrs.

The [1+1] diester adducts, (**36, n=2-5**) were desulfurised by the action of Raney nickel with the products exhibiting *cis* and *trans* isomerism, (*cf.* Section 2.8.6, page 52), Figure 23.

Figure 23



A comparative study was made of the [1+1] diester adducts, (**36, n=2-5**), their decarboxylated analogues, (**37, n=2-5**), and the benzo crown analogues, using Pedersen's extraction method with the alkali metal cations. The extractabilities of compounds (37, n=2-5) were slightly lower than those of their benzo

counterparts, although selectivity was similar. The diesters (**36**, **n**=2–5) showed a much reduced extraction percentage compared to that of (**37**, **n**=2–5).

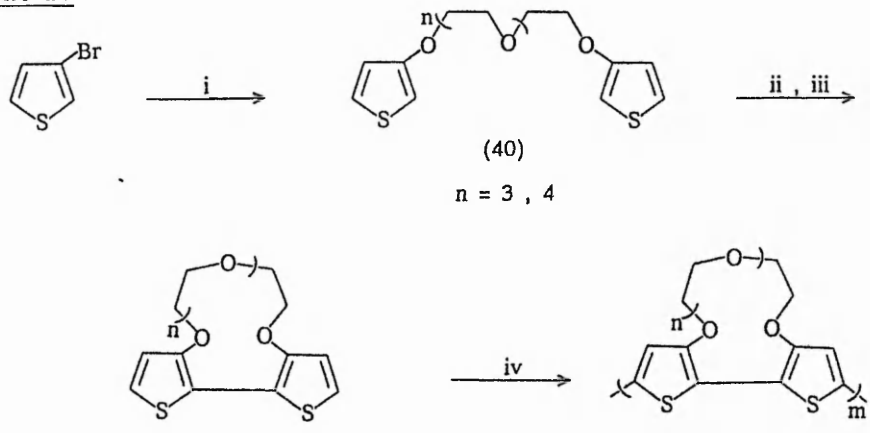
Crown diesters (**38**, **n**=2–5) were compared to 18-crown-6, (**39**), using a similar method; the diesters (**38**, **n**=**4&5**) were comparable to (**39**) in their extractabilities, whilst the values for (**38**, **n**=**2&3**) were typically lower than those of (**39**). Only for sodium ions did (**38**, **n**=**3**) show identical extractability to that of (**39**), again with similar selectivity.

2.8.7.2 Macrocycles derived from 3-Oxygenated Thiophenes

More recent interest has focused on 3-oxygenated thiophenes as potential precursors to macrocyclic systems. The enhanced reactivity of the 2 position of the thiophene ring, due to the +M effect of the neighbouring alkoxy group, affords the opportunity for ring closure reactions.

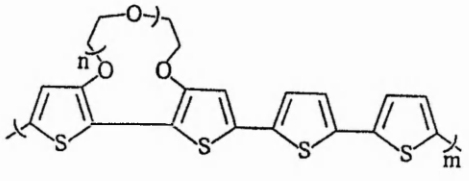
In the design of conducting polymeric sensors, Marsella and Swager investigated the synthesis of 2,2'-bithienyls which were bridged at the 3 and 3' positions by polyether chains, and chemical coupling reactions of the products to produce polymeric material, Scheme 17.[90]

Scheme 17



(i) $CuO(CH_2CH_2O)_nCH_2CH_2OCu$, *tert*-butyl alcohol, lutidine, 80°C, (yield, n=3, 33%, n=4, 36%); (ii) 2eq. BuLi, DME, 0°C; (iii) $CuCl_2$, DME, RT, (yield, n=3, 19%, n=4, 21%); (iv) 2eq. BuLi, THF, then $Fe(acac)_3$;

This route gave much higher yields than the equivalent reaction with 3,3'-dibromo-2,2'-bithienyl with α,ω-copper(I) alkoxides. The use of *n*-butyllithium and $Fe(acac)_3$ as coupling reagents was novel, the advantage of the method over the more traditional $FeCl_3$ approach being the lower solubility of the Fe(III) salt and hence the production of iron free polymeric material. Stille coupling was also used to synthesise polymer (**41**).

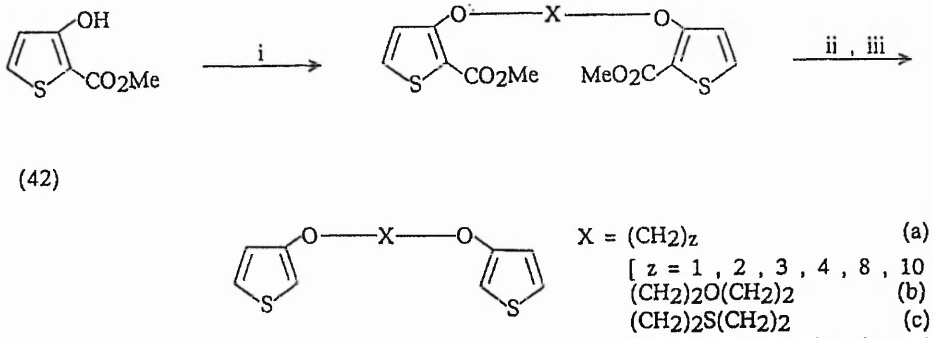


n = 3 , 4 (41)

The effects of complexation led to a reduction in conductivity for reasons previously discussed, (Section 2.8.6, page 53).

In the Nottingham Trent University Chemistry Department, Chaffin synthesised a number of compounds similar to (**40**). The Williamson reaction of methyl 3-hydroxythiophene-2-carboxylate, (**42**) with compounds possessing α,ω-difunctionality was employed, and the bis esters so formed were saponified and decarboxylated to yield a series of bis(3-thienyl)ethers, (**43** a–e), Scheme 18.[96]

Scheme 18



(42)

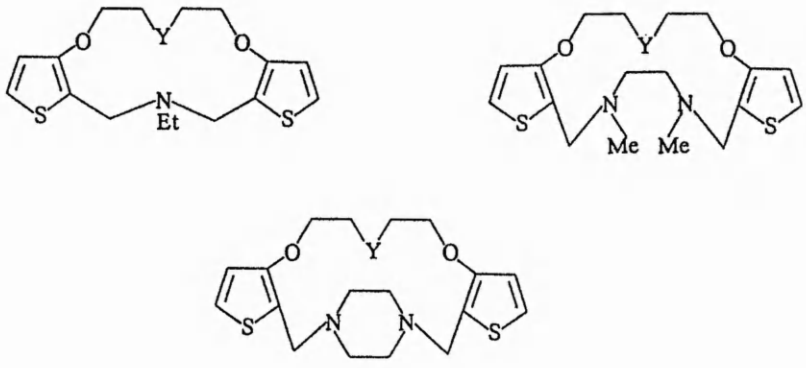
(43)

X = $(CH_2)_z$ (a)
[z = 1 , 2 , 3 , 4 , 8 , 10]
$(CH_2)_2O(CH_2)_2$ (b)
$(CH_2)_2S(CH_2)_2$ (c)
$(CH_2)_2O(CH_2)_2O(CH_2)_2$ (d)
$(CH_2)_2NTs(CH_2)_2$ (e)

(i) Br-X-Br or TsO-X-OTs, K_2CO_3, Me_2CO or DMF; (ii) KOH, $EtOH/H_2O$, then H_3^+O; (iii) Cu_2O, pyridine, Δ.

Compounds (**43 a–e**) were shown to undergo the Mannich reaction with formaldehyde and primary amines or secondary diamines in acetic acid, giving macrocyclic systems related to aza crown ethers, Figure 24.

Figure 24



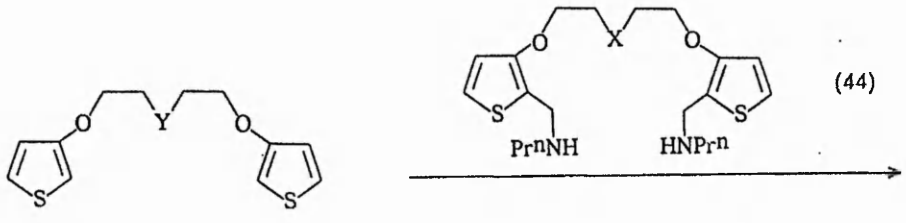
Y = O , S , $O(CH_2)_2O$

Typically yields of macrocyclic material were higher for those compounds whose bridging chain possessed a heteroatom, (**43 b–e**), than for those whose bridging chains were composed solely of alkyl chains, (**43a**). High yields of product were also obtained under normal dilution, though high dilution conditions did improve the yields, affording around 15% more material. These observations led to the postulation of an intramolecular template effect whereby the product of the first Mannich reaction underwent the second, with the heteroatom of the bridging moiety coordinating to the positively charged methylene ammonium ion. This effectively guided the incomming electrophile to the remaining vacant 2 position.

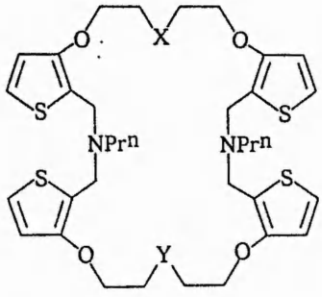
Compounds (**43 a–e**) were shown to undergo the Vilsmeier-Haack formylation in good yield. The subsequent bis(thienyl-2-carboxaldehyde) was converted into a Schiff base by treatment with *n*-propylamine in anhydrous ethanol, and the Schiff base was reduced *in situ* to the bis(*N*-thenylpropylamine), (**44**), by treatment with sodium borohydride. A further bis Mannich reaction with compounds (43), (**44**) and formaldehyde in acetic acid led

to a series of 28, 31 and 34 membered macrocyclic rings, (45), in yields of 20-29%, Equation 13.[96b]

Equation 13



(43)



(45)

X , Y = O , S , $O(CH_2)O$, NTs

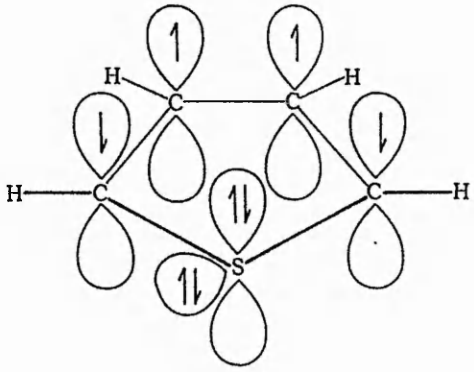
2.9 The Synthesis and Reactions of 3,4-Dialkoxythiophenes

2.9.1 Introduction

Thiophene, C_4H_4S, (bp. 84°C), was first isolated from coal tar derived benzene by Victor Meyer in 1882. The chemistry of thiophenes has been extensively reviewed by H.D. Hartough,[97] and more recently by S. Gronowitz.[98] Thiophene is a planar pentagonal molecule in which the four carbons and the sulfur are sp^2 hybridised. Each atom of the five membered ring forms two σ bonds with its neighbours by the overlap of two sp^2 hybrid orbitals. The remaining sp^2 orbital on each carbon overlaps an s orbital of a hydrogen to form four sp^2-s σ C-H bonds. The remaining sp^2 orbital of the heteroatom contains a lone pair of elecrons in the same plane as the ring. Each ring atom has an unhybridised p orbital orthogonal to the molecular plane, those of the four carbon atoms each contain one electron and form two π bonds, whilst that of the sulphur contain a

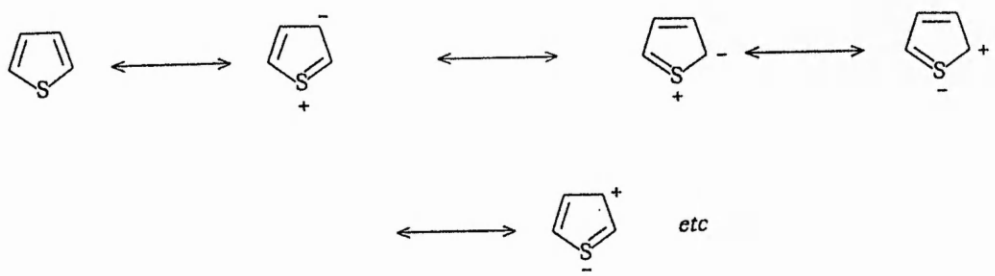
second lone pair of electrons which interact with the π system, creating a six π electron system conforming to Hückel's (4n+2)π electron rule for aromaticity, Figure 25. Since six π electrons are dispersed over five ring atoms, thiophene is said to be π excessive.

Figure25



This simple treatment of five-membered ring heterocycles is applicable to pyrrole and furan too. However, unlike the heteroatoms of these latter two ring systems, the sulfur atom of thiophene possesses d orbitals, which may take part in the hybidisation process. Longuet-Higgins used a model assuming $3p_z$-$3d_{xz}$-$3d_{yz}$ hybridisation of the sulfur orbitals, which led to thiophene being more benzene-like than either pyrrole or furan.[99] However, other workers dispute this, claiming that the 3d orbitals are of too higher energy to participate in the bonding process.[100] Further, the valence bond theory treats thiophene as a resonance hybrid of the canonical forms such as those shown in Figure 26.

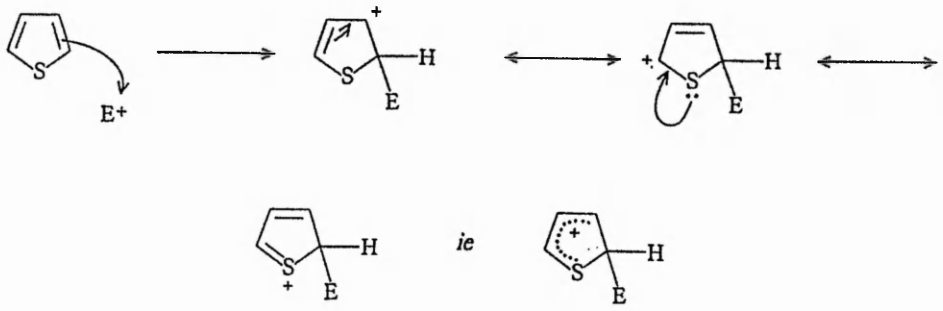
Figure 26



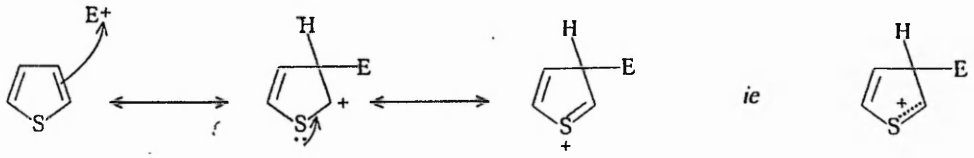
Typically for such an aromatic ring system, electrophilic substitution reactions are important in the chemistry of thiophene. Substitution at the 2 position predominates because of the more extensive delocalisation of the positive charge in the σ complex, than is possible for the equivalent reaction at the 3 position, Figure 27.

Figure 27

(a) Electrophilic substitution at the 2 position



(b) Electrophilic substitution at the 3 position



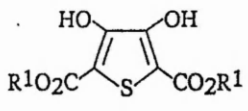
Thiophenes substituted at C-2 undergo further electrophilic substitution. Electron releasing groups like -OMe, -Me, -Br, and -Cl in the 2 position direct further substitution predominantly to the 5 position. Electron withdrawing groups like -CHO and -COR in the 2 position often lead to less selectivity in electrophilic substitution reactions. For example, thiophene-2-carboxaldehyde when nitrated with a mixture of nitric acid and sulfuric acid gives both the 4- and 5-nitrothiophene-2-carboxaldehydes, as well as the 2,4- and 2,5-dinitrothiophenes.

Thiophenes substituted at C-3 by an electron withdrawing group, usually undergo further substitution in the 5 position. Thus 3-acetylthiophene,

when treated with an equivalence of bromine, in a solution of acetic acid and sodium acetate gives 3-acetyl-5-bromothiophene,[101a] 3-amidothiophene is nitrated in the 5 position by the action of a mixture of nitric and sulfuric acids.[101b] Where the 3 position is substituted by a +M group, further substitution occurs at C-2, thus 3-bromothiophene is nitrated by acetyl nitrate to yield 3-bromo-2-nitrothiophene.[102] Since most of the work described in this thesis is concerned with the synthesis and reactions of 3,4-dihydroxy- and 3,4-dialkoxythiophenes, this particular aspect of thiophene chemistry will now be reviewed in more detail.

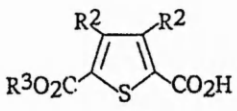
2.9.2 Dialkyl 3,4-dihydroxythiophene-2,5-dicarboxylates

The reaction of a dialkyl thiodiacetate with a 1,2-dicarbonyl compound in the presence of the alkoxide anion to give 3,4-disubstituted thiophene-2,5-dicarboxylic acid derivatives, is known as the Hinsberg reaction.[103] The nature of the 1,2-dicarbonyl component dictates the reaction mechanism and product. The use of a 1,2-diester, (typically diethyl oxalate), in the synthesis leads to a Dieckmann type condensation, affording a dialkyl 3,4-dihydroxythiophene-2,5-dicarboxylate, (**46**). However, employing a 1,2-diketone leads to a mono ester of a 3,4-dialkyl- or 3,4-diarylthiophene-2,5-dicarboxylic acid, (**47**). The use of ^{18}O isotopic labelling supported a Stobbe-type mechanism.[104] The Hinsberg reaction has been extended to the syntheses of a range of symmetrically and unsymmetrically substituted thiophenes.[105]



(46)

a , R^1 = Et
b , R^1 = H



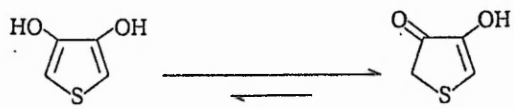
(47)

R^2 , R^3 = alkyl or aryl

Compounds (**46**, R=alkyl) have been investigated for use as chemotherapeutic agents by Indian researchers and found to be active against Yoshida sarcoma and fibrosarcoma.[106] Trichomonacidal [107] and fungicidal [107, 108] properties have also been reported for a number of derivatives of (**46**).

Saponification of the diethyl ester (**46a**) using a melt of sodium acetate dihydrate and sodium hydroxide at 110°C, was reported by Turnbull;[109a] this process was said to reduce concomitant decarboxylation. Subsequent decarboxylation to give 3,4-dihydroxythiophene, (**48a**), was achieved by heating the diacid in pyridine until evolution of carbon dioxide had ceased.[109b] However no definite hydrolysis product could be isolated, nor could the decarboxylation be repeated when the Turnbull syntheses were attempted by Gogte *et al.*[110] They reported that the hydrolysis of (**46a**) using sodium hydroxide (5M), gave (**46b**) in 81% yield, and that thermal decarboxylation of this by heating to 120°C in a vacuum gave an 82% yield of (**48a**). However spectroscopic evidence supplied by Mortensen *et al.* indicated that the product is the 4-hydroxy-3-oxo-2,3-dihydrothiophene tautomer, (**48b**), rather than a true dihydroxythiophene as represented by (**48a**), Figure 28.[111]

Figure 28

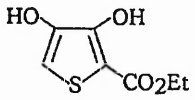


(48a) (48b)

Both compounds (**46b**) and (**48b**) are unstable, (**48b**) particularly so, and darken on exposure to light. This is typical of dihydroxythiophenes, which are stable only when -M groups are appropriately located on the thiophene ring.

Compound (**46a**) was hydrolysed with accompanying decarboxylation under basic conditions to give ethyl 3,4-dihydroxythiophene-2-carboxylate, (**49**).[111, 112] More recently a much improved acid-catalysed

synthesis of (49) was reported; the compound exists as a dihydroxythiophene rather than the keto tautomer.[113]

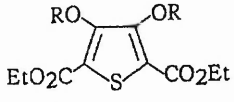


(49)

2.9.3 Alkylation of 3,4-Dihydroxythiophene-2,5-dicarboxylates

The Williamson reaction is an excellent method for the synthesis of both symmetrical and unsymmetrical ethers.[114] An alkylating agent, typically an alkyl halide, sulfate or sulfonic ester, is reacted with a nucleophilic alkoxide or aroxide anion, derived from the corresponding alcohol or phenol.

O-alkylation of compound (**33a**) was achieved by a number of workers by treatment of the disodium salt of the thiophene diol, (**33b**) with the alkylating agent, the latter acting as both reagent and solvent.



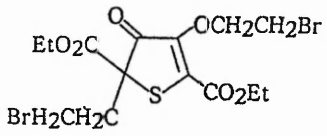
(33)

a , R = H
b , R = Na
c , R = Me
d , R,R = CH_2CH_2
e , R = Et
f , R = CH_2Ph
g , R,R = CH_2

Overberger and Lal treated (**33b**) with dimethyl sulfate to give a 51% yield of diethyl 3,4-dimethoxythiophene-2,5-dicarboxylate, (**33c**).[115] This compound was also prepared more cleanly by the reaction of (**33a**) with a large excess of diazomethane in dioxane.

During an investigation into the synthesis of a naturally occurring tetrahydrofuran derivative, Guha and Iyer synthesised diethyl 3,4-ethylenedioxythiophene-2,5-dicarboxylate, (**33d**), by the action of 1,2-dibromoethane on compound (**33b**).[116] Despite a reaction time in excess of 50 hours the yield was poor, (12%). Recently, Austrian workers isolated a 3-oxo-

2,3-dihydroxythiophene derivative, (**50**), (arising from the *C*-alkylation of position 2 of the thiophene ring), from this reaction.[117]



(50)

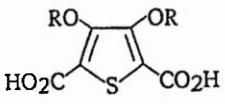
By reaction of (**33b**) with 1,2-dibromoethane or diethyl sulfate, Gogte *et al.* synthesised compounds (**33d**) and (**33e**) respectively, in order to investigate any potential anticancer activity they may have shown.[110]

In recent years polar aprotic solvents have been employed to improve the solubility and nucleophilicity of the aroxide anion, and therefore increase the yields of such reactions. Chadwick and coworkers employed DMF as a cosolvent in the synthesis of compound (**33f**).[118] The use of DMF[95] and acetonitrile[88] as reaction media for such *O*-alkylations of (**33a**) have already been discussed, (Section 2.8.7 page 56)

2.9.4 3,4-Dialkoxythiophene-2,5-dicarboxylic acids

2.9.4.1 Saponification of 3,4-Dialkoxythiophene-2,5-dicarboxylate Esters

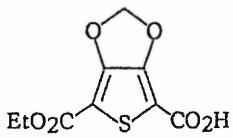
The synthesis of 3,4-dialkoxythiophene-2,5-dicarboxylic acids is accomplished by the alkaline hydrolysis of the corresponding dimethyl- or diethyl- ester. Fager reported the synthesis of 3,4-dimethoxythiophene-2,5-dicaboxylic acid, (**51a**), by reaction of the disodium salt of dimethyl 3,4-dihydoxythiophene-2,5-dicarboxylate with dimethyl sulfate, followed by hydrolysis of the crude dimethyl ester with aqueous sodium hydroxide; no analytical data were recorded.[119]



(51)

a , R = Me
b , R = Et
c , R,R = CH_2CH_2
d , R = CH_2Ph
e , R,R = CH_2

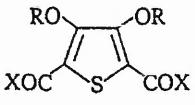
The synthesis of compound (**51a**) was more thoroughly investigated by Overberger and Lal who isolated a pure sample of diethyl 3,4-dimethoxythiophene-2,5-dicarboxylate, (**33c**), and hydrolysed it with a methanolic solution of potassium hydroxide.[115] Similarly, compounds (**51b**), (**51c**)[110] and (**51d**)[118] were prepared by the saponification of the appropriate diethyl ester with ethanolic sodium hydroxide. Dallacker and Mues studied the hydrolysis of diethyl 3,4-methylenedioxythiophene-2,5-dicarboxylate, (**33g**), in some detail.[120] Complete hydrolysis to give (**51e**) in 97% yield was reported, whilst partial hydrolysis using 1 equivalent of alkali gave the mono ethyl ester, (52), (80%).



(52)

2.9.4.2 Nucleophilic Substitution at the Carbonyl Group, Carboxylic Acid Derivatives

The synthesis of 3,4-dialkoxythiophene-2,5-dicarbonyl chlorides, (**53**, **X=Cl**) is most often accomplished either by heating the appropriate dicarboxylic acid with thionyl chloride,[121] or by reaction of the dicarboxylic acid with dimethylformamidinium chloride, the latter formed *in situ* by the action of thionyl chloride on DMF.[120]

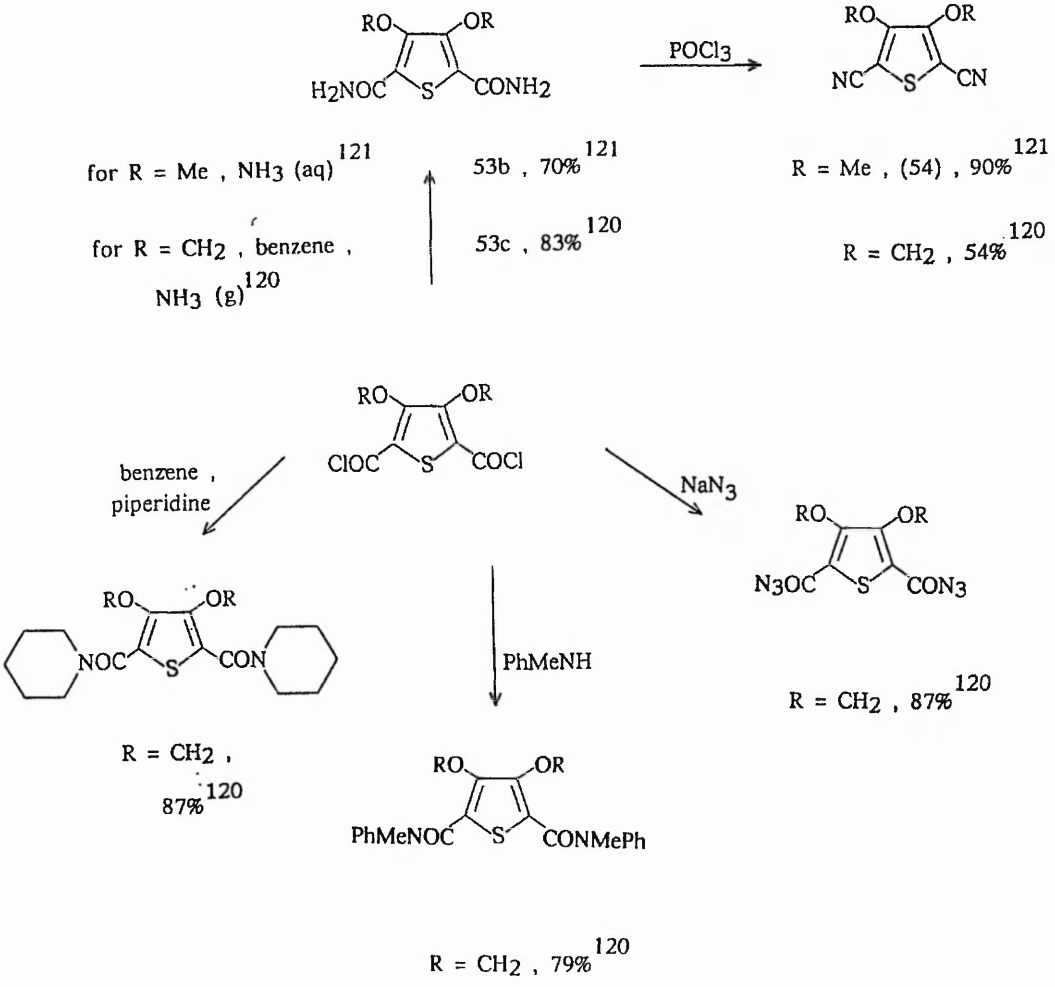


(53)

a , X = Cl , R = Me
b , X = NH_2 , R = Me
c , X = NH_2 , R = CH_2
d , X = $NHNH_2$, R,R = CH_2

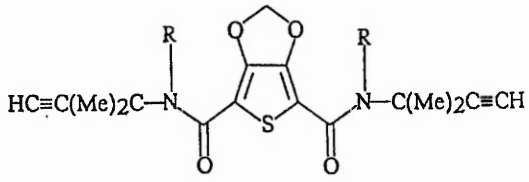
The reacton of acyl halides with nucleophilic nitrogen compounds is a well documented method for the preparation of both unsubstituted and substituted amides, and other compounds containing an acyl-nitrogen bond.[122] Morel and Pastour treated (**53a**) with an aqueous solution of ammonia to give 3,4-dimethoxythiophene-2,5-dicarboxamide, (**53b**).[121] This was dehydrated by the action of phosphoryl chloride to give 2,5-dicyano-3,4-dimethoxythiophene, (**54**), Scheme 19. A number of derivatives of 3,4-methylenedioxythiophene-2,5-dicarboxylic acid were reported by Dallacker and Mues, Scheme 19.[120]

Scheme 19



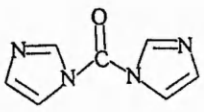
Mues and coworkers also employed a similar strategy in the synthesis of a number of *N,N*-disubstituted amides possessing anti-inflammatory and anti-pyretic activity, Figure 29.[123]

Figure 29

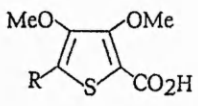


R = alkyl or aryl

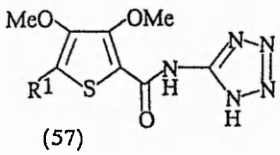
Hydrazones can be prepared from esters by treatment of the latter with hydrazine monohydrate. Compound (**33g**) was reacted in this way to give the corresponding dihydrazide, (**53d**), in 79% yield.[120] Although reaction of carboxylic acids with amines does not give amides directly, the synthesis may be aided by the use of coupling agents. In this manner, 1,1'-carbonyldiimidazole, (**55**), was used to couple 3,4-dimethoxythiophene-2-carboxylic acid, (**56**), and related compounds with a variety of amines to yield the corresponding amides, (**57**) and (**58**).[124]



(55)

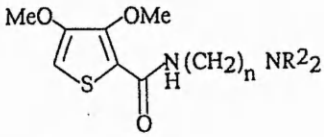


(56)



(57)

R^1 = H , alkyl , alkoxy , aryl or arlyoxy[124a, b]



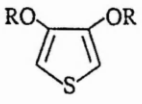
(58)

n = 1 - 3 and R^2 = C_{1-4} alkyl , C_{2-4} alkenyl and CH_2Ph[124c, d, e]

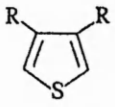
Compounds (57) and (58) were shown to inhibit histamine release, and were also found to possess antiemetic, antidepressant and antipsychotic properties.

2.9.5 Synthesis of 3,4-Dialkoxythiophenes

Turnbull reported the first synthesis of 3,4-dimethoxythiophene, (**59a**), by *O*-alkylation of the proposed 3,4-dihydroxythiophene, (**48a**), with diazomethane.[109b] However by far the most common strategy employed in the synthesis of 3,4-dialkoxythiophenes, (as well as 3,4-dialkyl- and 3,4-diarylthiophenes), is the decarboxylation of the corresponding 2,5-dicarboxylic acid. The method used by Fager is a general one in which the dicarboxylic acid, (**51a**) was heated with copper chromite in quinoline to 180°C for 30 minutes under an atmosphere of nitrogen, giving 3,4-dimethoxythiophene, (**59a**), (58%).



R = alkyl or aryl



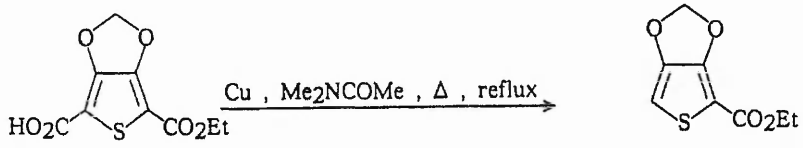
(59) (60)

a ; R = Me
b , R = CH_2CH_2

a , R = Me
b , R = 4-MeO-C_6H_4
c , R = 4-Me-C_6H_4

An identical method was used recently by Pei *et al.* in the synthesis of 3,4-ethylenedioxythiophene, (**59b**);[125] the same compound was also synthesised by Jonas and Heywang, the copper moiety being copper(I) oxide.[126] Quinoline is not the only solvent that has been employed in such reactions. Dallacker and Mues successfully used *N,N*-dimethylacetamide as a reaction medium to decarboxylate the mono ester of 3,4-methylenedioxythiophene-2,5-dicarboxylic acid, (**51**) with copper powder giving ethyl 3,4-methylenedioxythiophene-2-carboxylate, (**61**), Equation 14.[120]

Equation 14

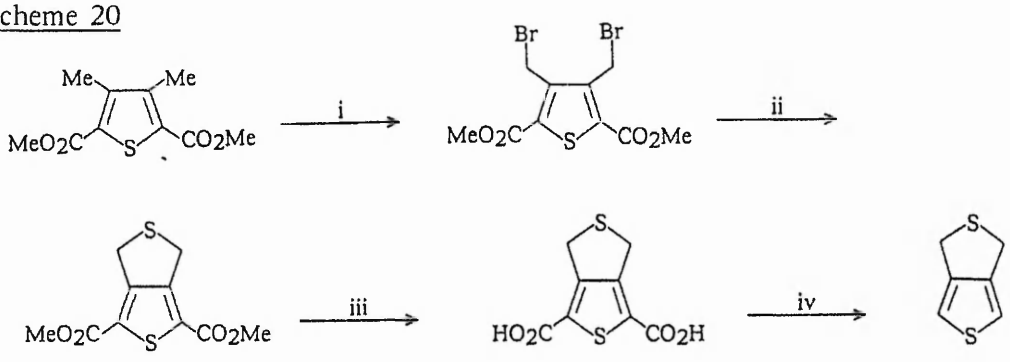


(51) (61)

21%

The decarboxylation of 3,4-disubstituted thiophene-2,5-dicarboxylic acids by heating the aromatic dicarboxylic acid with copper metal or copper bronze in the absence of a solvent has also been reported. Thus Overberger and Lal obtained compound (**59a**), (vacuum, 180-190°C, copper powder; 88%),[115] and Chadwick *et al.* prepared (**59a**), (**60a**) and (**60b**), (copper bronze, 300°C, 1hr).[127] A similar process of copper assisted thermal decarboxylation was earlier reported by Wynberg and Zwanenburg in their synthesis of 1H, 3H-thieno[3,4-c]-thiophene, (**63**).[128] The final step in the sequence involved heating compound (**62**) to 325°C with copper powder in a sublimation apparatus and condensing the crude product on a cold finger, resublimation affording pure (**63**) in a moderate yield, Scheme 20.

Scheme 20



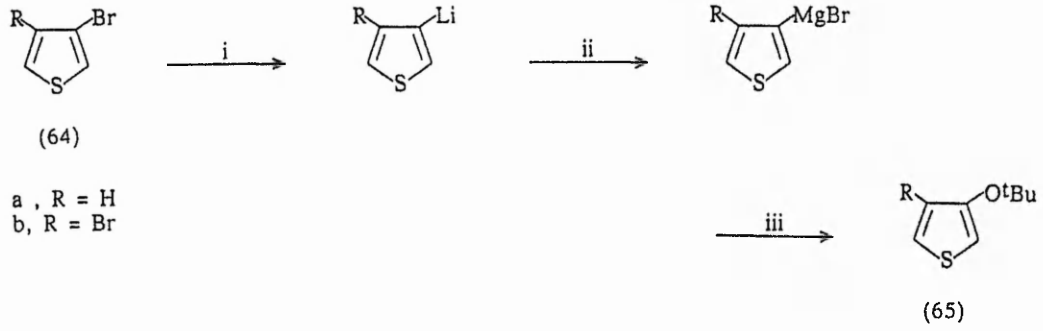
(62) (63)

(i) 2eq. *N*-bromosuccinamide, dibenzoyl peroxide, CCl_4, Δ, ½-1 hr., (yield, 71%); (ii) Na_2S, MeOH, Δ, 1hr, (yield, 58%); (iii) KOH, H_2O/MeOH, Δ, 5hrs, (yield, ~100%); (iv) copper powder, Δ, 325°C, (yield, 31%).

Examples are known of the decarboxylation of a number of substituted thiophene-2,5-dicarboxylic acids by thermal means alone. Sone *et al.* synthesised a series of thienyloxy crown ethers by heating either a di- or a tetracarboxylic acid to 50°C above it's melting point under reduced pressure for a number of hours,[88] (see Section 2.8.7.1, page 56). Earlier Backer and Stevens reported the synthesis of 3,4-di(4'-methylphenyl)thiophene, (**60c**), by heating the corresponding 2,5-dicarboxylic acid to 330°C.[129] Similarly the disodium salt of 3,4-di(2'-furyl)thiophene-2,5-dicarboxylic acid, when heated *in vacuo* with calcium hydroxide led to 3,4-di(2'-furyl)thiophene.

Some strategies are known for the conversion of bromo- and dibromothiophenes into alkoxy- and dialkoxythiophenes. For example, Jakobsen and Lawesson reported the synthesis of 3-*tert*-butoxythiophene, (**65a**), from 3-bromothiophene, (**64a**), via treatment of the Grignard reagent with tert-butyl perbenzoate, Scheme 21.[130]

Scheme 21



(64)

a , R = H
b, R = Br

(65)

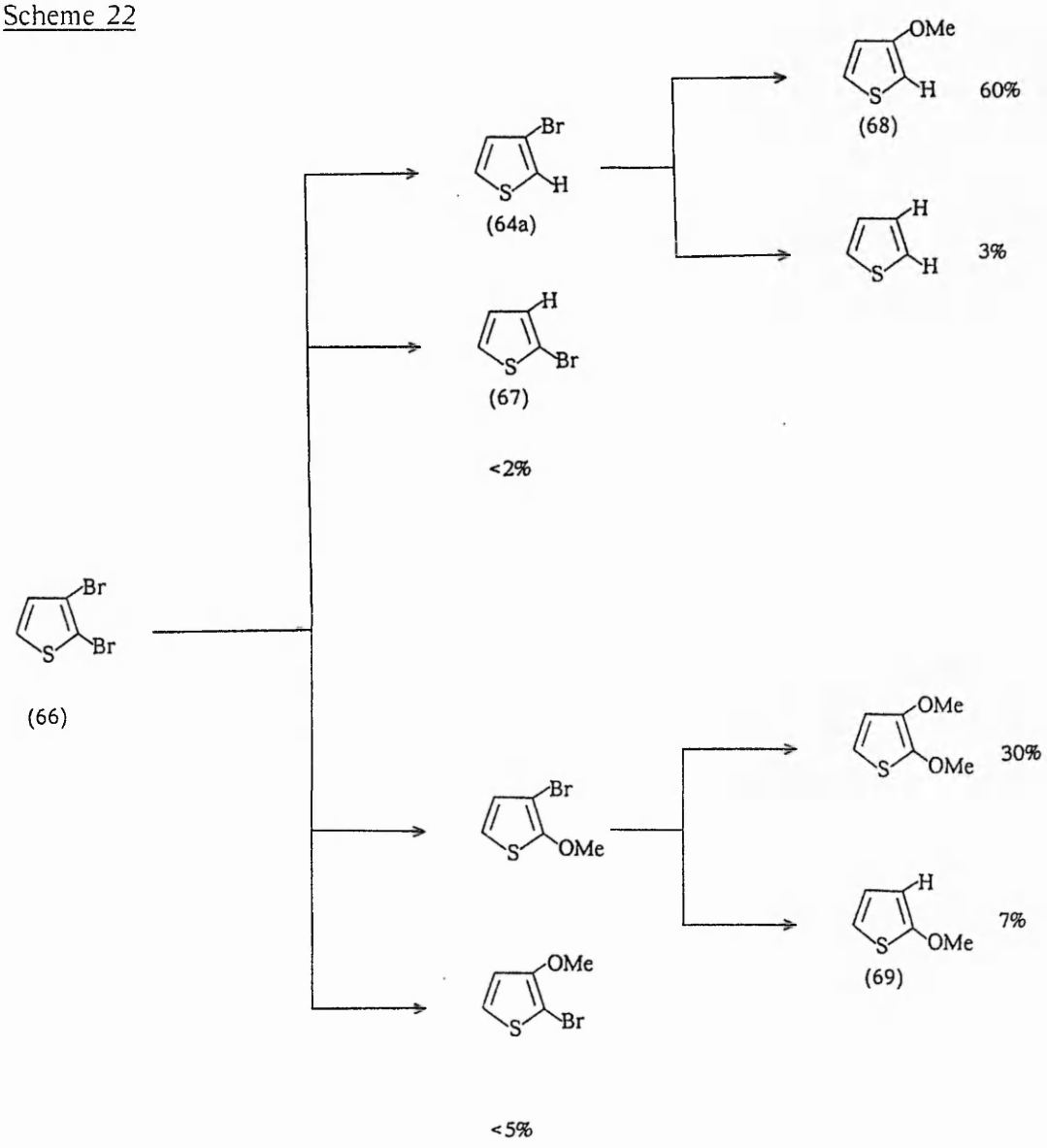
a , R = H
b , R = Br
c , R = OtBu

(i) BuLi, -70°C, THF; (ii) anhydrous magnesium bromide, then -70°C to room temperature; (iii) *tert*-butyl perbenzoate, 0°C, 12hrs then water and HCl.

By a similar route, 3-bromo-4-*tert*-butoxythiophene, (**65b**), was synthesised from 3,4-dibromothiophene, (**64b**), further application of this strategy to

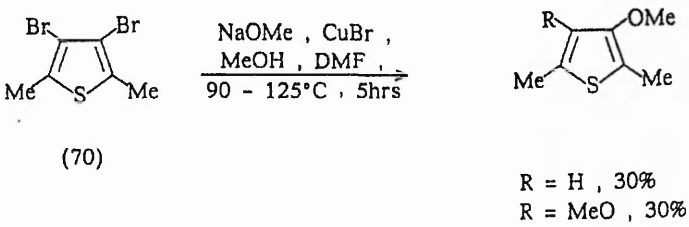
compound (**65b**) gave 3,4-di-*tert*-butoxythiophene, (**65c**).[111] More recently, copper(I)-promoted alkoxy-debromination was used to methoxylate a series of dibromothiophenes.[131] The procedure involved reacting the dibromothiophene with sodium methoxide in the presence of copper(I) bromide in methanol. The reaction proceeded most smoothly with 3,4-dibromothiophene, (**64b**), giving 3,4-dimethoxythiophene, (**59a**), in 74% yield. When similar reaction conditions were applied to the remaining three dibromothiophene isomers, the results were dependent upon the substrate, both the 2,5- and 2,4-dibromothiophenes giving their corresponding dimethoxythiophenes in moderate yields of 49% and 47% respectively. The latter reaction could also be terminated so that the intermediate 2-methoxy-4-bromothiophene could be isolated, the fact that this formed preferentially to 4-methoxy-2-bromothiophene was of interest since under the same reaction conditions 3-bromothiophene was reported to react much faster than 2-bromothiophene. An important side reaction was found to be the debromination of the starting material. In this, the results observed with 2,3-dibromothiophene, (**66**), are illustrative. When employing compound (**66**) in this reaction the first major step was found to be hydro-debromination of the 2 site giving 3-bromothiophene, (**64a**), only a small amount of debromination at the 3 position giving 2-bromothiophene, (**67**) was observed. Methoxylation as a competing reaction occurred to a lesser extent, again preferentially but not exclusively at the 2 position. The second step was one of methoxylation accounting for the high yield of 3-methoxythiophene, (**68**), whilst debromination occurred as a side reaction accounting for the low yields of thiophene and 2-methoxythiophene, (**69**), Scheme 22.

Scheme 22



Using a similar strategy, Peeters *et al.* employed copper(I) bromide/DMF in the methoxylation of 3,4-dibromo-2,5-dimethylthiophene, (**70**); again some debromination was observed. Equation 15.[132]

Equation 15

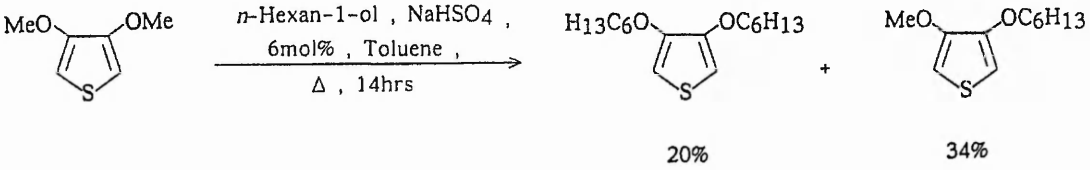


(70)

R = H , 30%
R = MeO , 30%

Transetherification of compound (**59a**) was reported by Wegener *et al.*.[133] A range of 3,4-dialkoxythiophenes were prepared by heating the thiophene moiety with an alcohol and protonic acid catalyst, typically sodium hydrogen sulphate in toluene with removal of the methanol-toluene azeotrope. It was not uncommon for the synthesis to afford both fully and half reacted compounds, Equation 16.

Equation 16



20%

34%

2.10 Aromatic Electrophilic Substitution of 3,4-Dialkoxythiophenes

2.10.1 Introduction

This section will deal predominantly with the substitution reactions of 3,4-dialkoxythiophenes. For a wider review of the reactions of other substituted thiophenes including alkoxythiophenes, the reader's attention is drawn to the recent work by Gronowitz.[134] Unlike other alkoxythiophenes, comparatively little work has been done on the 3,4-dialkoxythiophene series in this area.

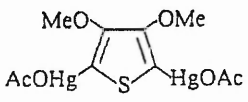
2.10.2 Metallation

Metallated thiophenes are used as intermediates in the preparation of other substituted 3,4-dialkoxythiophenes. Some 2-substituted-3,4-dialkoxythiophenes were prepared by lithiation, whilst mercuration was the method of choice for the

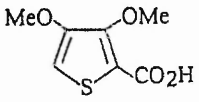
preparation of some 2,5-disubstituted products. Where appropriate, such reactions will be described elsewhere.

The synthesis of 3,4-dimethoxythiophene-2,5-bis(mercuriacetate), (**71**), was first accomplished by the decarboxylative *ipso* substitution of 3,4-dimethoxythiophene-2,5-dicarboxylic acid, (**51a**), by mercury(II) acetate,[121] although no yield was reported. Compound (**71**) was also prepared, (75%), by direct mercuration of 3,4-dimethoxythiophene.[135]

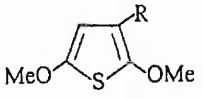
During a study of the synthesis of thiophene analogues of papaverine, Huddleston *et al.* prepared 3,4-dimethoxythiophene-2-carboxylic acid, (**72**), by the addition of 3,4-dimethoxy-2-lithiothiophene to carbon dioxide, however during the work-up, a greater proportion of the starting material, (55%), remained unaltered.[136] In contrast when a similar procedure was applied to 2,5-dimethoxythiophene, (**73a**), much polymeric material was obtained, arising from a ring opening reaction.[137] However the lithiation of 3-bromo-2,5-dimethoxythiophene, (**73b**), at -70°C followed by carboxylation gave 2,5-dimethoxythiophene-3-carboxylic acid, (**73c**), in 60% yield.[138]



(71)



(72)



(73)

a , R = H
b , R = Br
c , R = CO_2H

The synthesis of Grignard reagents from 2-bromo-3,4-dimethoxythiophene is discussed in Section 2.10.3, (below).

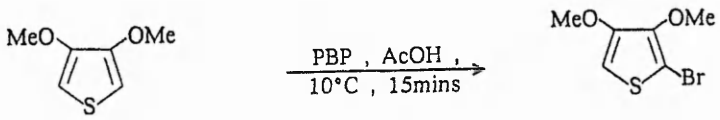
2.10.3 Halogenation

Iodination of 3,4-dimethoxythiophene was achieved by the demercuration of compound (**71**) by treatment with a large excess of iodine in acetic acid. The

yield of 2,5-diiodo-3,4-methoxythiophene was low, (19%).[121] An identical procedure was employed by Dallacker and Mues in the synthesis of 2,5-diiodo-3,4-methylenedioxythiophene, the yield being 12%.[120] Similarly, the corresponding 2,5-dibromo derivative, (79%), was obtained by the decarboxylative bromination of 3,4-methylenedioxythiophene-2,5-dicarboxylic acid at neutral pH. This compound was found to be extremely air and light sensitive.

During the synthesis of thiophene analogues of papaverine, Huddleston and coworkers studied a synthetic route involving the bromination of 3,4-dimethoxythiophene by pyridinium bromide perbromide, (PBP), giving 2-bromo-3,4-dimethoxythiophene, (**74**), as an unstable oil. The corresponding Grignard reagent was prepared and was reacted with the carbonyl group of 1-formyl-6,7-dimethoxyisoquinoline, Scheme 23.

Scheme 23

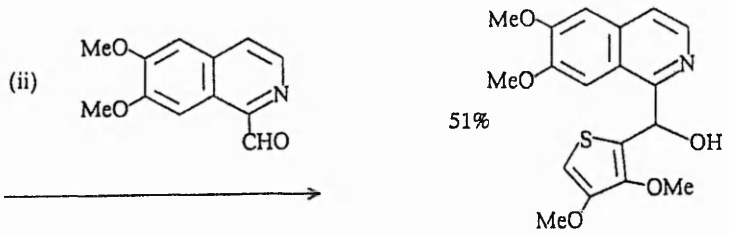


(74)

80%

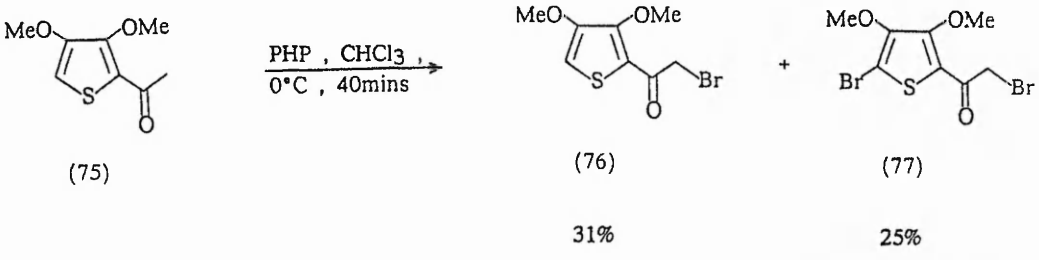
(i) Mg , THF , 1½hrs

(ii)



Interestingly, PBP failed to brominate 2,5-dimethoxythiophene. The preferred method in this case is NBS in carbon tetrachloride, giving 3-bromo-2,5-dimethoxythiophene in 50% yield.[137] Canadian researchers studying thiophene isosters of phenylethanolamines investigated the bromination of 2-acetyl-3,4-dimethoxythiophene. (75).[139] In this case, the use of PBP gave a mixture of products, bromination occurring at the methyl group of the acetyl moiety and to a lesser extent, at the 5 position on the thiophene ring, Equation 17.

Equation 17



(75) (76) (77)

31% 25%

Greater selectivity was obtained by heating compound (75) with copper(Ⅱ) bromide in ethyl acetate, the product (76) being afforded in a yield of 60%.

2.10.4 Formylation

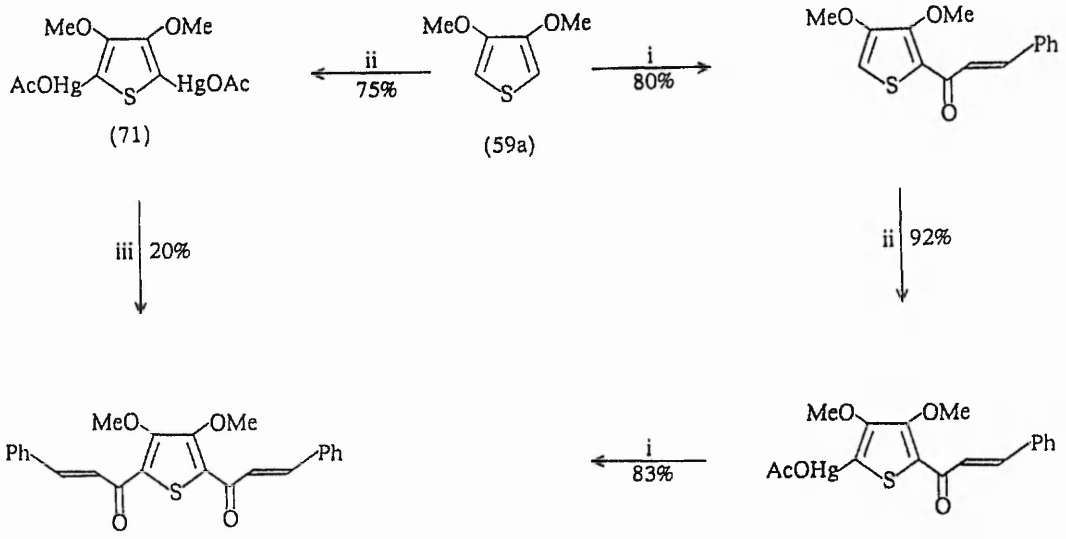
Continuing their studies of derivatives of 3,4-dimethoxythiophene, Morel and Pastour synthesised 3,4-dimethoxythiophene-2,5-dicarboxaldehyde by two routes.[121] The reduction of the previously discussed 2,5-dicyano derivative, (54), by diisobutylaluminium hydride, (DIBAL), afforded the corresponding 2,5-dicarboxaldehyde in 43% yield. The dicarboxaldehyde was also synthesised by the reaction of 2,5-diiodo-3,4-dimethoxythiophene, with n-butyllithium at -78°C, followed by treatment with DMF, (83%).

Requiring a range of substituted thiophene-2-carboxaldehydes, Chadwick *et al.* employed the Vilsmeier-Haack formylation to 3,4-dimethoxythiophene, giving the desired 3,4-dimethoxythiophene-2-carboxaldehyde in 69% yield.[127]

2.10.5 Acylation

By using the lithiation technique outlined in Section 2.10.4, (page 79), 2,5-diacetyl-3,4-dimethoxythiophene was synthesised, (39%), by addition of *N,N*-dimethylacetamide to the dilithio species.[121] However a more general route to such acylthiophenes is the Friedel-Crafts acylation. This method was successfully applied to both methoxythiophenes and their mercurated counterparts. Bagli and Ferdinandi reported the acetylation of 3,4-dimethoxythiophene using tin(Ⅳ) chloride and acetyl chloride in benzene at 0°C giving 2-acetyl-3,4-dimethoxythiophene, though no yield was reported.[139] At the same time Henrio *et al.* were working on the synthesis of flavone-type compounds containing the thiophene ring.[135] The strategy employed was to acylate in either the 2 position or in both 2 and 5 positions, again employing tin(Ⅳ) chloride as the Lewis acid and benzene as the solvent. The bis acylations were carried out in a single step by using the bis(mercuriacetate) derivative, (**71**), or in a multistep approach by acylation of compound (**59a**), followed by mercuration and another acylation reaction. A summary of the acylation reactions involving cinnamoyl chloride is shown in Scheme 24. The synthesis was completed by the bromination of the alkene moiety using bromine in acetic acid, followed by demethylation and cyclisation induced by pyridinium chloride.

Scheme 24



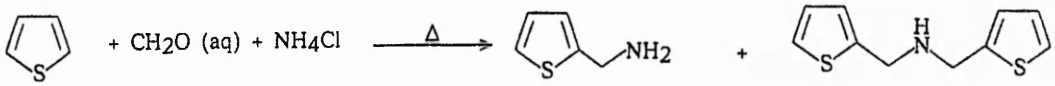
(i) 1eq. PhCH=CHCOCl, $SnCl_4$, benzene; (ii) $Hg(OAc)_2$, $EtOH/H_2O$;

(iii) 2eq. PhCH=CHCOCl, $SnCl_4$, benzene.

2.10.6 Aminomethylation

The aminomethylation of thiophene by formaldehyde and ammonium chloride was much studied by Hartough *et al.* during the latter part of the 1940's;[140] a series of rather complex products were obtained, including the two amines shown in Equation 18.

Equation 18

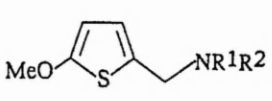


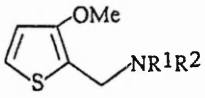
+ Polymeric material , 48%

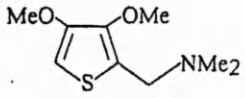
This reaction may be viewed as a modified Mannich reaction but importantly, the reaction failed when hydrochloride amine salts were substituted for ammonium chloride. The first genuine Mannich reaction of a thiophene ring was

reported by Barker *et al.* who used electron rich thiophene compounds, (2-methoxy-, 3-methoxy- and 3,4-dimethoxythiophene),[141] under conditions which were known to be successful for the Mannich reaction of indole.[142] The amine, aqueous formaldehyde and activated thiophene moiety were reacted in glacial acetic acid, affording a number of Mannich bases shown in Figure 30.

Figure 30



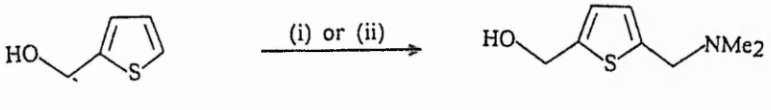




$R^1 = R^2 = Me$
$R^1R^2 = -(CH_2)_5-$
$R^1R^2 = -(CH_2)_2O(CH_2)_2-$

Dowle and coworkers latter showed that 2-hydroxymethylthiophene, (78), underwent a Mannich reaction when formaldehyde gas was passed into a solution of (78) and dimethylamine hydrochloride in acetonitrile, giving (79), (25%), Scheme 25.[143] The yield was significantly improved, (73%), by the use of *N,N*-dimethylmethylene ammonium chloride, (*cf.* Eschenmoser's salt).[144]

Scheme 25



(78) (79)

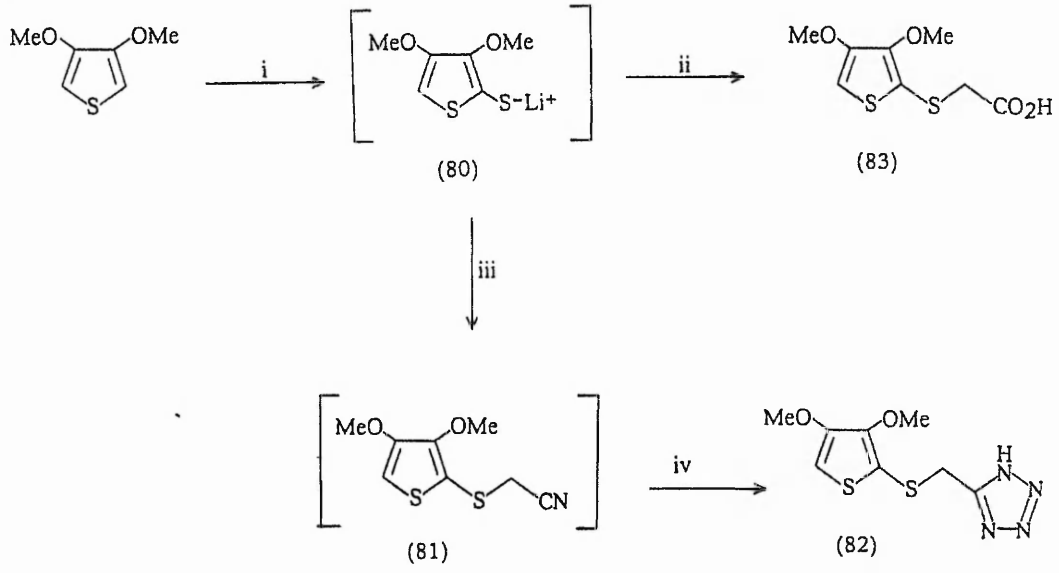
(i) $CH_2O(g)$, $Me_2NH{\cdot}HCl$, MeCN. Δ, 5hrs, (yield, 25%); (ii) $Me_2^+N{=}CH_2Cl^-$, MeCN, Δ, 2-24hrs, (yield, 73%).

2.10.7 Miscellaneous Electrophilic Substitution Reactions

3,4-Dimethoxythiophene, (**59a**), is sufficiently reactive to be nitrated by acetyl nitrate, (formed *in situ* by the reaction of acetic anhydride and fuming nitric acid), giving 3,4-dimethoxy-2,5-dinitrothiophene in 46% yield.[115]

German workers synthesised a range of 2-thienylthioethers, *eg.* compounds (**83**) and (**84**), which were found to reduce the fatty acid concentration in blood serum by inhibition of triglyceride cleavage, (lipolysis), thereby arresting the onset of arteriosclerosis.[145] The strategy used was to lithiate the thiophene moiety at -20°C, and then treat with sulfur. The arylthiolate anion, (**80**), so formed was then reacted with either the potassium salt of chloroacetic acid[145a] or chloroacetonitrile[145b], Scheme 26. In the latter case, the (3,4-dimethoxy-2-thienylthiol)-acetonitrile, (**81**) was converted, without isolation, into the substituted tetraazole, (**82**).

Scheme 26



(i) 1eq. BuLi, Et_2O, -20°C, 1hr at R.T. then -40°C, 1eq. S, 1hr at R.T.; (ii) $ClCH_2CO_2^-$ K^+, overnight then H_3O^+, (yield, 19%); (iii) $ClCH_2CN$, 1½hrs at R.T.; (iv) 4eq. sodium azide, 8eq. formic acid, HMPA, 60°C, 40hrs then aqueous sodium hydroxide, (yield, 67%).

2.11 Conducting Polymers derived from 3,4-Dialkoxythiophenes

2.11.1 Introduction

Much work over the last fifteen years has focussed on the polymerisation of thiophene and substituted thiophenes, and a study of their potential applications as electrical conductors, electrochromic displays and energy stores. Of particular interest has been the 3,4-disubstituted thiophenes since their polymerisation gives constant 2,5-coupling, leading to high conjugation along the polymer chain. Any occasional coupling at vacant 3 or 4 sites is undesirable since this serves to interupt the conjugation by increasing the disorder within the polymer chain, thereby reducing any potential electrical properties the polymer may have.

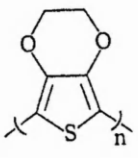
The polymerisation reaction is performed either by chemical or electrochemical means and leads to the incorporation of impurities, (known as dopants), within the polymer lattice during chain propagation. It is the doping phenomenon that is responsible for the conductivity of conjugated thiophene polymers, since in the pure state such materials are insulators. The dopants oxidise the polymer chain leading to a positive charge within the structure, the transfer of this positive charge along the thiophene chain is responsible for the conductivity of the polymer. By semiconductor convention, since it is the apparent movement of a positive charge that carries the current, these materials are called p-type conductors. Clearly the presence of alkoxy groups should stabilise the positive charge of such p doped material by the +M effect.

2.11.2 Chemical Polymerisation of 3,4-Dialkoxythiophenes

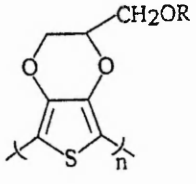
By far the most common reagents used in the chemical polymerisation of thiophenes are iron(Ⅲ) salts. Pei *et al.* polymerised 3,4-ethylenedioxythiophene using anhydrous iron(Ⅲ) chloride in acetonitrile but with disappointing results; the polymer (**84**), Figure 31, was an intractable black powder, insoluble in a range of solvents, (*eg.* dimethylsulfoxide, *N*-methylpyrrolidone and acetic acid),

and was studied no further.[125] Contemperaneous to this work, Jonas and Heywang also synthesised polymer (**84**) by an identical method and concurred with the findings concerning the compound's intractability.[126] Nevertheless, they measured the conductivity and found it to be in the range of 5-10 Scm^{-1}, (such conductivity values for these polymers should be compared with those of other semiconductors, *eg.* germanium $200-10^5$ Scm^{-1}, and silicon $1-10^3$ Scm^{-1}). This could be improved to $31Scm^{-1}$ by performing the polymerisation in benzonitrile heated to 180°C.

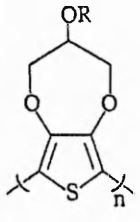
Figure 31



(84)



(85)

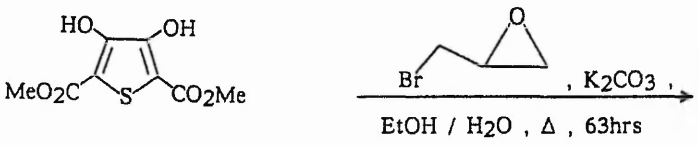


(86)

R = H , $C_{(1\ -\ 18)}$, $-CH_2Ph$

Blohm and coworkers developed an electro-optical device, capable of monitoring light transmittance over a range of 250-2500 nm, that utilised combinations of doped and undoped polymers of types (**85**) and (**86**). The synthesis of such polymers started with the *O*-alkylation of dimethyl 3,4-dihydroxythiophene-2,5-dicarboxylate, (**87**), using epibromohydrin and potassium carbonate in aqueous ethanol heated under reflux, Equation 19.[146]

Equation 19



(87)

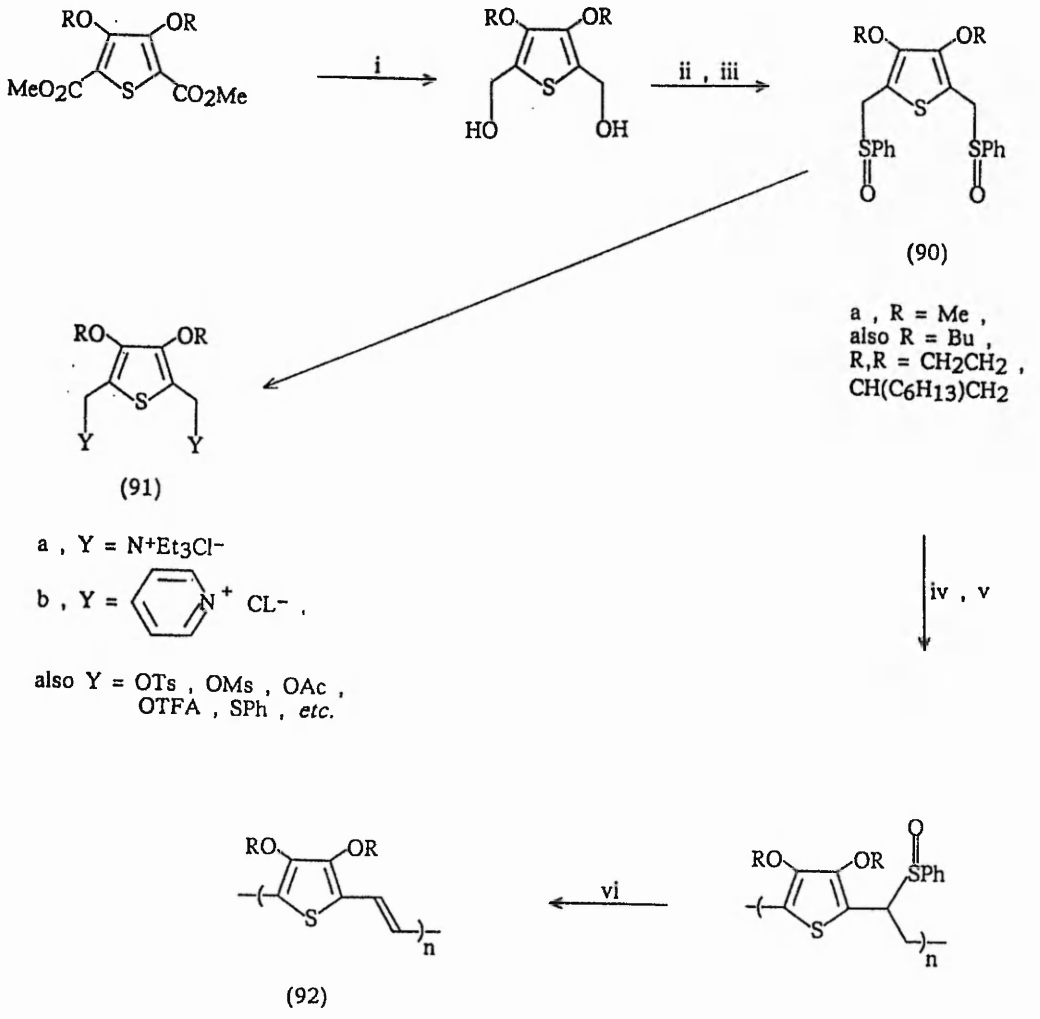
(88) (89)

~70% ~30%

Two products were formed, (**88**) and (**89**), which could be separated by flash chromatography on silica gel though no solvent system was given. In some cases these products were *O*-alkylated (NaH/THF/RBr), the ester groups were then saponified (KOH-EtOH-H_2O) and the product acids were decarboxylated by heating to 220°C with activated copper metal and quinoline, (see Section 2.9.5, page 71), to give the monomers of compounds (**85**) and (**86**). Polymerisation of these was achieved using iron(Ⅲ) p-toluenesulfonate in acetone.

Recently a series of poly(3,4-dialkoxy-2,5-thienylenevinylene)s, (**92**), were prepared by Cheng and Elsenbaumer using the base catalysed polymerisation of (**90**), followed by the facile thermal elimination of the phenylsulphoxide moiety according to Scheme 27.[147]

Scheme 27



(i) Lithium aluminium hydride, MeOH; (ii) PhSH, ZnI_2; (iii) MCPBA, 0°C; (iv)Bu^{t}OK, THF, -78°C; (v) 20°C; (vi) 80°C, reduced pressure.

The elimination involving the bis(phenylsulfoxide), (**90**), was the only one found to succeed. A range of other leaving groups, (Y), was employed but the monomeric unit, (**91**), was either unstable or failed to polymerise. However some polymeric material was obtained with compounds (**91a**) and (**91b**), but these were neither the expected precursory polymer nor the conjugated polymer (**92**). The poly (3,4-dimethoxy-2,5-thienylenevinylene), (**92a**), was described as

being deep blue in colour having a golden lustre. The polymer as isolated was undoped but exposure to air caused some slight doping, giving a maximum conductivity of 10^{-3} Scm^{-1}; this was increased to 25 Scm^{-1} by treatment with iron(Ⅲ) chloride.

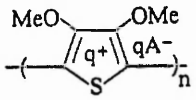
The monomer (**90a**) was polymerised both thermally and by acid catalysis. By heating (**90a**) to a temperature just above the melting point caused rapid polymerisation. Doping this with iron(Ⅲ) chloride gave material of low conductivity, typically in the order of 10^{-3} Scm^{-1}.

Acid catalysed polymerisation involved treating the monomer with trifluoroacetic acid in dichloromethane, the reaction being aided significantly by the addition of acetic anhydride. This was reported to give polymers of high molecular mass and long effective conjugation lengths.

2.11.3 Electrochemical Polymerisation of 3,4-Dialkoxythiophenes

A number of research groups have studied the polymerisation of 3,4-dialkoxythiophenes by electrochemical means, either exclusively or for comparison with polymeric materials prepared chemically. The electrochemical cells used consisted of two electrodes made of an inert material, usually platinum, (to prevent contamination of the system by reaction of the electrode with either the solvent or a solute). A third electrode, the reference electrode, was often employed to give a reference potential for the experiment, but itself passed no current. The solvents were necessarily organic and of high dielectric constant; acetonitrile, propylene carbonate or nitrobenzene were used extensively. The electrolysis proceeded in the presence of a supporting electrolyte, typically a tetraalkylammonium salt, the counteranion of this becomming the dopant in the conducting thiophene polymer, again affording p-doped material. Typically, in the synthesis of poly(3,4-dimethoxythiophene), (**93a**),[149] Yamamoto employed 3,4-dimethoxythiophene in acetonitrile,

platinum electrodes, and tetrabutylammonium hexafluorophosphate as the electrolyte, giving (**93a**) with a conductivity of 1·5 Scm^{-1}.



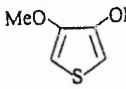
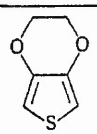
where A is the dopant anion and q is the doping level ; for A = PF_6^- , q = 0·15

(93)

a , A = PF_6^- ,
also A = BF_4^- , TsO^- ,
ClO_4^- *etc.*

By microanalysis the uptake of hexafluorophsphate anions was shown to be 1 anion per 6·7 thiophene rings, leading to a doping level of 0·15. This should be compared to the p-doping of silicon with indium where the dopant : substrate ratio is typically 1 : 10^6! Table 1 summarises the results obtained in the electrochemical polymerisation of 3,4-dimethoxythiophene and 3,4-ethylenedioxythiophene.

Table 1

Substrate	Solvent	Dopant anion	Conductivity/Scm^{-1}
	Acetonitrile	PF_6^-	1·5[149]
	Nitrobenzene	BF_4^-	30[149]
	Propylene carbonate	TsO^-	No polymer formed[150]
	"	HSO_4^-	No polymer formed[150]
	"	ClO_4^-	35[150]
	"	BF_4^-	56[150]
	"	PF_6^-	200[125, 126, 151]

3 Nomeclature of Compounds Involved in the Present Work

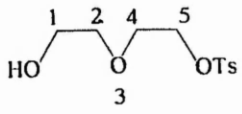
Given the structural complexity of some of the compounds hitherto described, it should be of no surprise that there are several ways in which crown ethers and particularly their precursors can be named. The compounds described in this work fall into three main categories for naming purposes:-

Type A; compounds best named as linear acyclic polyethers.

Type B; compounds best named as derivatives of 3-alkoxy- or 3,4-dialkoxythiophenes.

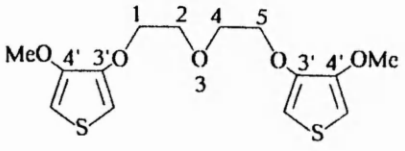
Type C; compounds that are cyclic polyethers.

The approach used for compounds of Type A was to treat the oxygen atoms forming the ether bridges as though they were methylene groups when deciding the parent name of the chain. The oxygen atom's presence was then indicated by the prefix -oxa- accompanied by a number to show the atom's position. Any terminal oxygen atoms were not included in this but were accounted for by either classing terminal -OH groups as alcohols or by suffixing the appropriate functional group with -oxy. Thus the mono tosylate of diethylene glycol, (**94**), was called 5-tosyloxy-3-oxapentan-1-ol. Using this style of nomenclature, compound (**95**), (1,5-bis(4'-methoxy-3'-thienyloxy)-3-oxapentane), was more easily named as a 3-oxapentane derivative, relegating the thiophene moieties to functional groups.



(94)

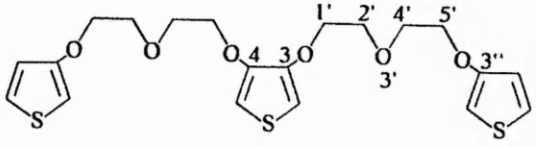
5-tosyloxy-3-oxapentan-1-ol



(95)

1,5-bis(4'-methoxy-3'-thienyloxy)-3-oxapentane

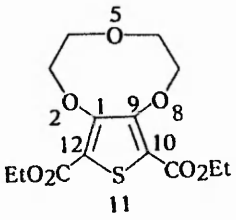
Compounds of Type B were best named by applying the method outlined above to any side chain emanating from the heterocyclic ring. The naming of compound (**96**), illustrates this approach. For further examples of the application of this method attention is drawn to the work of Börjesson and Welch.[152]



(96)

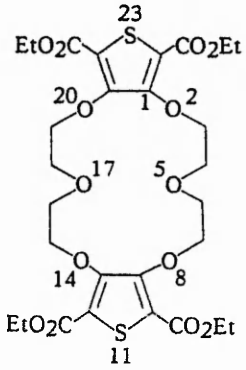
3,4-bis[5'-(3''-thienyloxy)-3'-oxapentyloxy]thiophene

The macrocyclic polyethers, (Type C compounds) reported in this work were named according to the method used by Sone *et al.*[88] The macrocycles were named as polycyclic carbocycles, the number of atoms in the largest ring present forming the parent name. The presence of oxygen atoms in the ring was indicated by the prefix -oxa-, and sulfur and nitrogen were designated the prefixes -thia- and -aza-, respectively. Numbering of the ring commenced at a common bridgehead atom and continued in the direction of the largest ring, the numbers then being used to indicate the location of any heteroatom, as well as other functional groups, present in the molecule. For bicyclic systems the conventional [x,y,z] technique is employed, *eg.* compound (**97**). For tricyclo- and higher systems, further information is required, the numbers of the bridgehead atoms linked by the fourth and higher chains are shown as superscripts to the chain designation, *eg.* compound (**98**).



diethyl 2,5,8-trioxa-11-thiabicyclo[7.3.0]dodeca-1(12),9-dien-10,12-dioate

(97)



tetraethyl 2,5,8,14,17,20-hexaoxa-11,23-dithiatricyclo[19.3.0.0^{9,13}]tetraeicosa-1(24),9,12,21-tetraen-10,12,22,24-tetraoate

(98)

Though it would be possible to name 3,4-ethylenedioxythiophene as a bicyclic system like compound (**97**), it is clearly simpler to employ traditional heterocyclic nomenclature in this case.

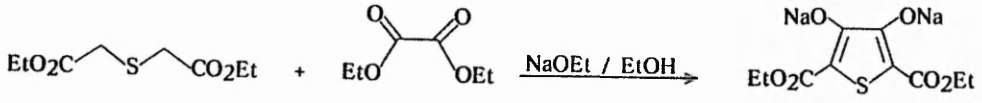
4 Discussion

4.1 Synthesis of Precursors

4.1.1 Diethyl 3,4-Dihydroxythiophene-2,5-dicarboxylate, (33a)

Diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate, (**33a**) was synthesised by the reaction of diethyl thiodiglycolate, (**99**) with diethyl oxalate in the presence of sodium ethoxide, using the procedure of Fager,[119] which gave the product as the disodium salt, (**33b**), Equation 20.

Equation 20



(99)

(33b) , 75 - 89 %

Where the free dihydroxythiophene derivative, (**33a**) was required, the disodium salt was dissolved in distilled water, the solution was filtered to remove any insoluble matter, then acidified with hydrochloric acid.

The synthesis of diethyl thiodiglycolate, (**99**), was accomplished using a two phase system in which an aqueous solution of sodium sulfide was stirred with ethyl chloroacetate in the presence of a quaternary ammonium salt, acting as a phase transfer catalyst. In the absence of such a catalyst the reaction never went to completion despite prolonged reaction times, and large quantities of unreacted ethyl chloroacetate were recovered along with amounts of the mercaptan ethyl thioglycolate, and compound (**99**) was obtained in yields that rarely exceeded 45%. The PTC method for the synthesis of (**99**) was more productive than the much used esterification of thiodiglycolic acid,[153] and was more convenient than the procedure used by Kyrides *et al.*.[154]

4.1.2 The 4-Methylbenzenesulfonate Esters

The 4-methylbenzenesulfonate esters, (**94**) and (**100**)-(**102**), were synthesised according to the appropriate literature procedures in yields comparable to those cited. Throughout this work the 4-methylbenzenesulfonyl group is referred to as the tosyl group, generally abbreviated to Ts, and the esters containing such a group are called tosylates.

(100)

1-tosyloxy-3-oxapentane[155]

(101)

1,5-ditosyloxy-3-oxapentane[156]

(102)

1,8-ditosyloxy-3,6-dioxaoctane[157]

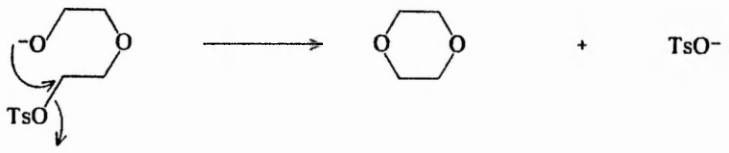
(94)

5-tosyloxy-3-oxapentan-1-ol[152]

The purification of compound (**100**) involved distillation which led to a minimal amount of decomposition, as evinced by the slight darkening of the distillate. The coloured impurity could be removed by washing the distillate with an aqueous solution of sodium hydrogen carbonate, but failure to do so did not appear to affect any subsequent reactions in which the tosylate was employed.

In the tosylation of alcohols, temperature is an important factor in regulating side reactions, since allowing the reaction to become too warm increases the tendency to form quaternary ammonium tosylate salts arising from the reaction of the desired product and the basic solvent, (*eg.* pyridine or triethylamine), employed in such reactions.[155b] Strict temperature control was also necssary to minimise any tendency for oligomerisation, a potential problem

in the synthesis of (**101**), (**102**) and (**94**). Another possible side reaction in the synthesis of (**94**) and (**101**) was an intramolecular substitution occurring in the mono- tosylated species to give dioxan :-



The synthesis of the monotosylate, (**94**), deserves further comment. Initially, a procedure outlined by van Doorn and coworkers for the synthesis of 8-tosyloxy-3,6-dioxaoctan-1-ol was followed for the attempted preparation of the homologous monotosylate, (**94**).[158] Their method involved the reaction of the glycol with a 0·5 equivalent of tosyl chloride in a mixed solvent of triethylamine and dichloromethane, and any ditosylate formed was removed by its crystallisation from the monotosylate derivative. This procedure was applied to diethylene glycol but only gave a 49% yield of the ditosylate (**101**), and none of the monotosylate, compound (**94**) was detected.

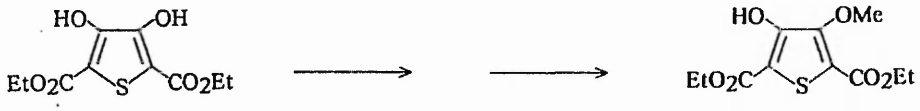
The approach adopted by Börjesson and Welch was to react tosyl chloride in the presence of a very large excess of the glycol, again employing a triethylamine-dichloromethane solvent, and to separate the di- and monotosylates by chromatography.[152] Any unreacted glycol was previously removed during the washing procedure. This synthesis was reproduced to give a 63% yield of (**94**) when carried out with *ca.* 10g of tosyl chloride. Column chromatography was used in the final purification of (**94**), since unlike (**100**), distillation caused severe decomposition of the product.

4.2 Synthesis and Reactions of a Bridged Methoxythiophene System

4.2.1 Introduction

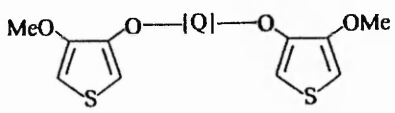
Given that the ultimate goal of this project was to synthesise compounds resembling closed boxes, as a preliminary investigation, compounds with a partial box-like structure, *eg.* compounds of type (**105**) were to be synthesised. This would be accomplished by firstly bridging two molecules of diethyl 3-hydroxy-4-methoxythiophene-2,5-dicarboxylate, (**103**), by their free hydroxy groups employing the Williamson ether sythesis with a compound possessing suitable α,ω-difunctionality. Saponification and decarboxylation would then give compounds of type (**104**) which would be expected to then undergo two consecutive Mannich reactions with a primary amine or secondary diamine, since both the 2 and 5 positions of the thiophene ring should be activated to such an electrophilic substitution by the +M effect of the alkoxy groups. This, it was hoped, would lead to the linking of the 2 and 5 positions of one thiophene ring to their counterparts on the other ring, Scheme 28.

Scheme 28



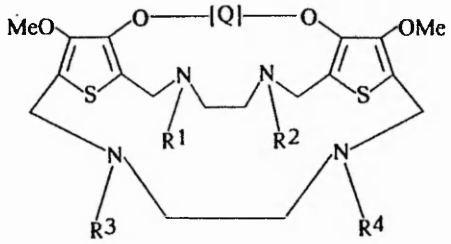
(33a) (103)

i) Willamson ether synthesis
ii) Saponification
iii) Decarboxylation



(104)

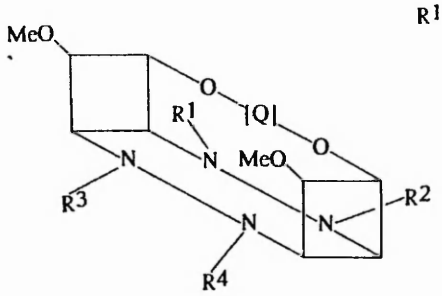
Two Mannich reactions



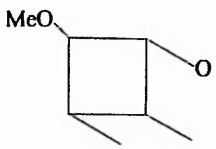
(105)

where Q = alkyl , (CH_2CH_2) , $(CH_2CH_2O)_2CH_2CH_2$ *etc*
$R^1 = R^2 = R^3 = R^4 = Me$
$R^1R^2 = R^3R^4 = CH_2CH_2$

ie



where



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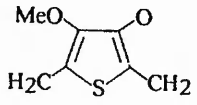
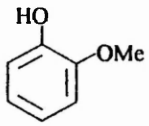
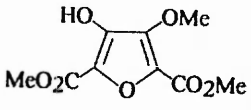


Thus a synthesis of (**103**) was required. A search of the literature for examples of compounds which could be derived from a methylation of only one hydroxy group, where two were present in an identical environment gave two compounds worthy of further study, guaiacol, (2-methoxyphenol), (**106**), and dimethyl 3-hydroxy-4-methoxyfuran-2,5-dicarboxylate, (**107**).



(106)



(107)

By far the most cited compound was guaiacol, the synthesis of which was accomplished by three strategies. Clearly an obvious route to compound (**106**) was the incomplete methylation of catechol, (1,2-dihydroxybenzene), and this was exploited by a number of groups. Matsuzaki *et al.* successfully synthesised guaiacol in high yield by the vapour phase methylation of catechol by methanol at a temperature of 290°C in the presence of kaolin.[159] Similar conditions were employed by Shiomi and coworkers using a series of metal and non-metal oxides as catalysts.[160] The lack of volatility of the thiophene analogue of (**107**) make this vapour phase approach unattractive for the present work.

A number of research groups studied the catalytic hydroxylation of methoxybenzene by hydrogen peroxide, the catalyst being either a transition metal[161] or a titanium(Ⅳ) silicon(Ⅳ) silicate lattice.[162] Such a reaction would be unsuitable for the purpose here required, due to the propensity of the thiophene moiety to oxidise to a thiophene-1,1-dioxide derivative in the presence of hydrogen peroxide. The third common method is the reductive ring opening of the cyclic acetal 1,2-methylenedioxybenzene.[163] This too was deemed unsuitable for the present work due to the presence of ester groups on the thiophene ring.

The synthesis of compound (**107**) was reported by Hoehn, and involved the incomplete methylation of dimethyl 3,4-dihydroxyfuran-2,5-dicarboxylate.[164] The exact experimental conditions were not given but it was reported that (**107**) was obtained as a minor product, (*ca.* 10%), in the synthesis of dimethyl 3,4-dimethoxyfuran-2,5-dicarboxylate.

4.2.2 The Mono-*O*-alkylation of Diethyl 3,4-Dihydroxythiophene-2,5-dicarboxylate, (**33a**)

In view of the unsuitability of the methods just described, the approach used in the synthesis of diethyl 3-hydroxy-4-methoxythiophene-2,5-dicarboxylate, (**103**), was to try to partially methylate compound (**33a**) and find the optimum conditions, for the preparation. Numerous reactions were performed towards this goal in this respect, the results of which are summarised in Table 2, (page 103)

Initial attempts to synthesise (**103**) centred on the monomethylation of the disodium salt, (**33b**), in a ketonic solvent, either acetone, 2-butanone or cyclohexanone, heated under reflux in the presence of 0·5 equivalents of the methylating agent, dimethyl sulfate, (preferred to methyl iodide because of its lower volatility). Despite extended reaction times, no reaction was noted and work up only returned the starting material as the free dihydroxythiophene derivative, (**33a**). Equal lack of success was observed when compound (**33a**) and potassium carbonate were heated together in the solvents mentioned above. This lack of reactivity was attributed to a lack of solubility of the metal aroxide salt in such solvents.

To overcome this solubility problem, the polar aprotic solvents DMF and DMSO were studied as possible reaction media. Methylation of either the sodium or potassium salt of (**33a**) gave the fully methylated diethyl 3,4-dimethoxythiophene-2,5-dicarboxylate, (**33c**) in low yields, (typically 15-21%);

no monomethylation product could be detected.

The attempts outlined above all involved the reaction of a large excess of the fully deprotonated 3,4-dihydroxythiophene derivative with an insufficiency of methylating agent. The next strategy employed was to synthesise the monopotassium salt of (**33a**) *in situ* and attempt to methylate this. Thus two equivalents of (**33a**) were stirred with potassium carbonate in either DMF or DMSO at room temperature. Treatment of these solutions with dimethyl sulfate again only yielded small quantities of the completely methylated material, (**33c**). A more successful approach was to use elevated temperatures in these reactions. Thus by stirring two equivalents of compound (**33a**) with potassium carbonate and dimethyl sulfate in DMF at 100°C, the desired compound (**103**) was obtained in a 19% yield, accompanied by (**33c**), (14%), and unreacted starting material, (43%). Similar results were obtained when the base potassium *tert*-butoxide was used in 1·0 mole equivalence with the dihydroxythiophene moiety under identical reaction conditions. Given the small scale on which these experiments were conducted, (*ca.* 1g of thiophene moiety), separations could be achieved by column chromatography which, whilst separating the dihydroxy compound, (**33a**) from the blend, failed to separate the monomethoxy derivative, (**103**), from its dimethoxy counterpart, (**33c**). The separation of the latter two compounds was accomplished by centrifugal chromatography.

At this juncture in the synthesis of (**103**), a different approach was adopted: rather than relying on the formation of the mono alkali metal salt of (**33a**) *in situ*, attempts were made to form and isolate the monosodium salt. This was done by dissolving (**33a**) in a 1:1 mixture of ethanol and diethyl ether, and adding to this rapidly stirred solution 1·1 equivalents of sodium ethoxide in ethanol. The solvents were removed under reduced pressure, leaving dark orange crystals of the proposed monosodium salt. During the removal of the solvent it was observed that should any prolonged heating occur, an olive green

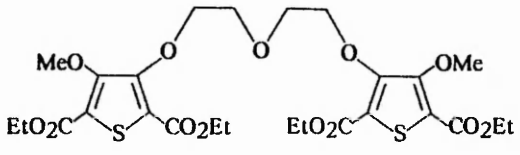
rather than orange residue was obtained, to the detriment of any subsequent reactions.

When a methylation of this proposed monosodium salt was performed in hot DMF, as outlined above, a moderate yield, (26%), of (**103**) was obtained though, again, it was accompanied by the dimethoxythiophene derivative, (**33c**), (33%), and unreacted starting material, (**33a**), (28%). One attempt was made to solubilise the organic salt in acetone using a molar equivalent of a phase transfer reagent, (tri-*n*-butylbenzylammonium bromide). However, stirring this solution vigorously under reflux and treating with dimethyl sulfate, effected no improvment, only 17% of compound (**103**) being obtained.

Next, a similar approach to that used by Fager in the synthesis of dimethyl 3,4-dimethoxythiophene-2,5-dicarboxylate was adopted,[119] *ie.* to treat the monosodium salt directly with a very large excess of dimethyl sulfate in the absence of any other solvent. The reaction was initially performed on a scale involving *ca.* 1g of thiophene moiety, and the residue from this was shown by thin layer chromatography, (TLC), to be composed of (**33c**) and the desired product, (**103**), as well as polar material. Separation by centifugal chromatography showed the mixture to contain 32% of compound (**103**). Given that previous attempts to separate (**103**) from (**33c**) by column chromatography had failed, and the application of centrifugal chromatography was only feasible for small scale separations, it was envisaged that the separation of large quantities of the dimethoxy- and hydroxymethoxy-thiophene derivatives would have to be done by virtue of the latter's free OH group. This involved washing an ethyl acetate solution of the two thiophene derivatives with an aqueous base, the idea being to transport the hydroythiophene into the aqueous phase and leave the dimethoxythiophene species in the organic layer. However washing with solutions of sodium carbonate, ammonia or disodium hydrogen phosphate only served to produce dense unyielding emulsions which were resistant to

attempts to break them down.

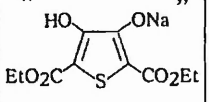
Thus a further Williamson reaction was performed in which the total product from the last approach just described, was stirred in hot DMF with potassium carbonate and 1,5-ditosyloxy-3-oxapentane, (**101**), to give *inter alia* the methoxythiophene derivative (**108**), in a yield of 21%. Separation of (**108**) from the dimethoxythiophene moiety, (**33c**) was easily achieved by column chromatography.

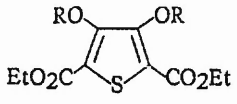


(108)

This was the preferred method for the generation of thiophenes containing both a methoxy group and a different alkoxy substituent.

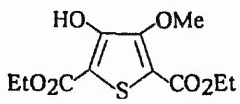
Table 2 Summary of the Attempted syntheses of Diethyl 3-hydroxy-4-methoxythiophene-2,5-dicarboxylate, (103)

Thiophene Moiety	Base	Solvent	Reaction Conditions	Products
1eq. (33b)	not applicable	acetone 2-butanone cyclohexanone	0·5 eq. Me_2SO_4, reflux	No reaction
1eq. (33a)	1eq. K_2CO_3	as above	as above	No reaction
1eq. (33b)	not applicable	DMF	0·5eq. Me_2SO_4, RT	(33c), 15%
1eq. (33b)	not applicable	DMSO	as above	(33c), 18%
1eq. (33a)	1eq. K_2CO_3	DMF	as above	(33c), 19%
1eq. (33a)	1eq. K_2CO_3	DMSO	as above	(33c), 21%
2eq. (33a)	1eq. K_2CO_3	DMF	Me_2SO_4, RT	(33c), 13%
as above	as above	DMSO	as above	(33c), 17%
1eq. (33a)	1eq. K^tBuO	DMF	Me_2SO_4, 100°C	(33c), 19% (33a), 51% (103). 23%
"  "	not applicable	DMF	as above	(33c), 33% (33a), 28% (103), 26%
as above	not applicable	acetone	Me_2SO_4, 1eq. PTC reflux	(103), 17%
as above	not applicable	none	large excess of Me_2SO_4	(33c), 48% (103), 32%



(33)

a , R = H
b , R = Na
c , R = Me

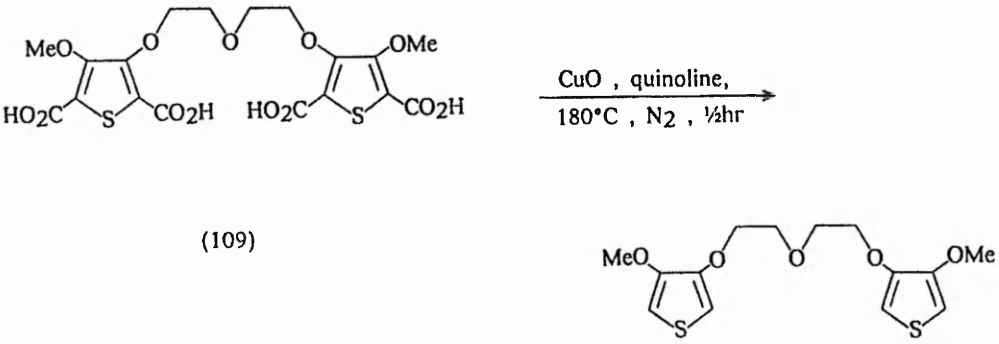


(103)

4.2.3 Synthesis and Reactions of 1,5-bis(4'-methoxy-3'-thienyloxy)-3-oxapentane, (95)

The conversion of the tetraethyl ester, (**108**), into the corresponding tetracarboxylic acid, 1,5-bis(2',5'-dicarboxy-4'-methoxy-3'-thienyloxy)-3-oxapentane, (**109**), was done by hydrolysis, using aqueous sodium hydroxide in ethanol. There was found to be a significant difference in the microanalytical results between the percentage obtained and the percentage expected for the carbon and hydrogen content of compound (**109**), the most likely explanation for this being that the tetracarboxylic acid had been isolated as a complex hydrate. Further drying did induce some weight loss from (**109**), and this material was decarboxylated in good yield when treated with copper(I) oxide in quinoline at 180°C under nitrogen, Equation 21.

Equation 21



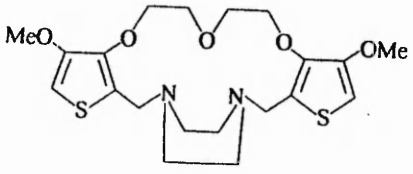
(109)

(95)

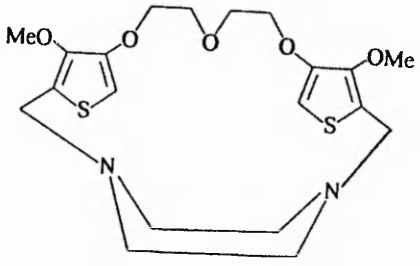
65%

A proton n.m.r. spectrum of (**95**) showed sets of signals at 6·17 and 6·24ppm associated with the protons on carbons 5 and 2 of the thiophene ring, respectively. The carbon-13 n.m.r. spectrum was consistent with a nearly symmetrically substituted ring, with signals at 96·2 and 97·8 ppm, and at 146·7 and 148·1 ppm.

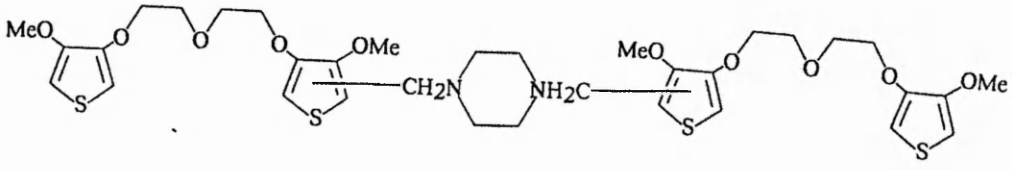
The next step was to study the way in which (**95**) underwent the Mannich reaction. Because of the relatively small amounts of material obtained, it was decided to proceed with a macrocyclisation reaction involving the secondary diamine, piperazine. This base was chosen because of its proven reactivity under well studied conditions,[96] and because of its spectroscopic simplicity, by virtue of possessing only NCH_2 moieties. The assembly of the box-like structure was to be done in a stepwise fashion, so that by reaction of one equivalent of (**95**) with one equivalent of piperazine, (in the presence of formaldehyde), two possible desirable Mannich bases might be formed, (**110a**) and (**110b**).



(110a)



(110b)



(110c)

Either (**110a**) or (**110b**) would have been of use in further experiments to generate compounds of type (**105**). Clearly polymerisation posed a serious problem, given the range of active sites and the numerous possible cross-linkages that could occur. Thus the reaction was performed under high dilution conditions. TLC analysis suggested that the majority of the thiophene moiety

had reacted after stirring for 18 hours; on work up a small amount, (*ca.* 18%) of unreacted (**95**) was obtained, but the main bulk of material had undergone a reaction. Three spots were observed on TLC which had R_f values of 0·33, 0·18 and 0·11, (Al_2O_3/1:1 ethyl acetate-light petroleum bp. 40°-60°C). However, the three products could not be separated by column or by centifugal chromatography.

Both proton and carbon-13 n.m.r. spectra were obtained for the mixture; they were very complex, and, in the abscence of spectroscopic data for any pure material it was difficult to draw conclusions as to whether any cyclisation had occurred. However, the proton n.m.r. spectrum did show that a Mannich reaction had taken place between the thiophene moiety, formaldehyde and piperazine; a very complex set of signals at *ca.* 3·6 ppm corresponds to those usually observed for $ArC\underline{H}_2N$.

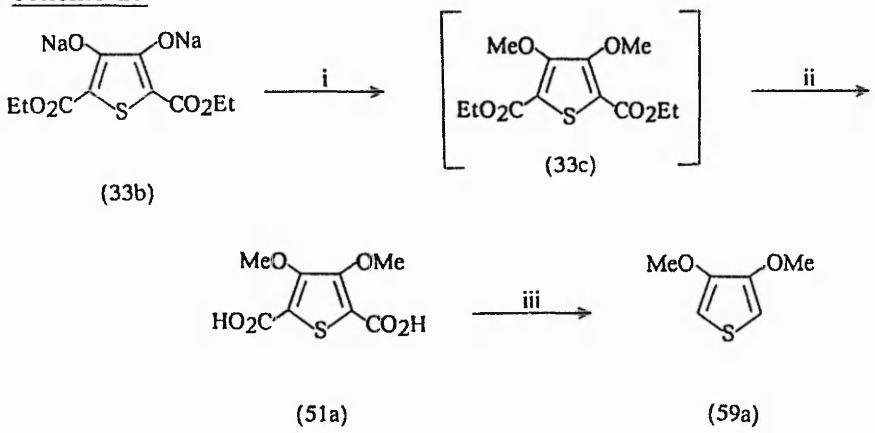
Both proton and carbon-13 spectra showed evidence of a thiophene ring that was unsubstituted in either the 2 or 5 positions, suggesting that at least one of the products may have been that arising from the bridging of two molecules of (**95**) by a 1,4-dimethylenepiperazine moiety, (**110c**). Due to the limited amounts of compound (**103**) available and the small quantities of methoxyalkoxythiophene obtained subsequently from it, the study of the reaction of such systems was reluctantly abandoned.

4.3 A Study of the Reactions of 3,4-Dialkoxythiophenes

4.3.1 Synthesis of 3,4-Dimethoxythiophene, (**59a**)

In accordance with the aims of the project a quantity of 3,4-dimethoxythiophene, (**59a**), was required. It was prepared essentially by the literature method, Scheme 29.[119]

Scheme 29



(33b) (33c) (51a) (59a)

(i) Me_2SO_4, Δ, ½hr; (ii) 6M NaOH (aq), Δ, 1hr, then H_3O^+, (yield, 74%); (iii) Cu_2O, quinoline, Δ, ½hr, N_2, (yield, 74%).

However in order to obtain a reference sample of diethyl 3,4-dimethoxythiophene-2,5-dicarboxylate, (**33c**), in one instance the intermediate diethyl ester was isolated. Further preparations of 3,4-dimethoxythiophene-2,5-dicarboxylic acid, (**51a**) were done without isolation of (33c).

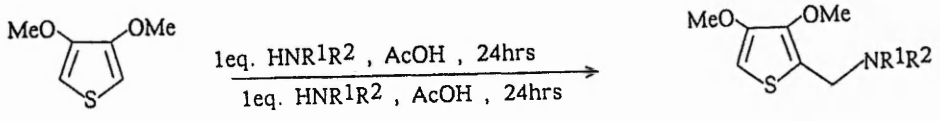
Decarboxylation of the dicarboxylic acid, (**51a**) was attempted using the procedure of Overberger and Lal,[115] but with limited success. Their route was experimentally quite elegant, relying on the thermal decarboxylation of the diacid derivative in the presence of copper metal under reduced pressure, giving 3,4-dimethoxythiophene as a distillate. Attempts to reproduce this work only gave low yields, (*ca.* 5-10%), and replacing the copper metal with copper(I) oxide gave only a moderate improvement, (21%)

4.3.2 Application of the Mannich Reaction to 3,4-Dimethoxythiophene, (59a)

Barker *et al.* observed an apparent lack of reactivity of 3,4-dimethoxythiophene in their study of the Mannich reaction of electron rich thiophene systems.[141] However only the reaction of 3,4-dimethoxythiophene with formaldehyde and

dimethylamine in glacial acetic acid was studied, the bulk of this paper dealing with the Mannich reactions of 2- and 3-methoxythiophene. The aim of the present work was to broaden our understanding of the nature of (**59a**), as well as to employ the system as a model for later work. An extension of the published study, employing one equivalent of aqueous formaldehyde and one equivalent of either dimethylamine, piperidine or morpholine, was undertaken. In order to standardise the reaction conditions so that comparisons could be made, all reactions were carried out at room temperature for a period of 24 hours, (Equation 22).

Equation 22



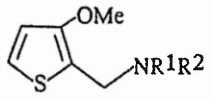
(59a) (111)

a , $R^1 = R^2 = Me$, 5%
b , $R^1,R^2 = -(CH_2)5-$, 5%
c , $R^1,R^2 = -(CH_2)2O(CH_2)2-$, 53%

The Mannich bases (**111a**) and (**111b**) were isolated in very low yields as oils, although that derived from morpholine, (**111c**), was formed in much higher yields. Purification of these amines was achieved by extracting the basic components into an aqueous solution of hydrochloric acid, followed by basification. The residue obtained from this was purified further by column chromatography, since none of the Mannich bases derived from 3,4-dimethoxythiophene withstood distillation. The n.m.r. spectra of material obtained by distillation showed the presence of approximately 50% of (**59a**), indicating that some of the crude material had undergone a thermal retro-Mannich reaction. Methiodides of the above Mannich bases were formed very readily by their treatment, in diethyl ether, with methyl iodide; the salts were

used in conjunction with the free amine to obtain microanalytical data, particularly for those Mannich bases isolated as oils.

For a direct comparison of the reactivity of 3,4-dimethoxythiophene with that of 3-methoxythiophene, the latter was subjected to the reaction shown in Equation 22. This gave the Mannich bases (**112a**), (**112b**) and (**112c**) in yields of 62, 75 and 87% respectively.



a , $R^1 = R^2 = Me$, 62%
b , $R^1,R^2 = -(CH_2)_5-$, 75%
c , $R^1,R^2 = -(CH_2)_2O(CH_2)_2-$, 87%

(112)

Why should 3,4-dimethoxythiophene exhibit such a lack of reactivity when compared to 3-methoxythiophene? Clearly electronic influences cannot explain this phenomenom. This effect has been attributed by the author to the spatial requirements of the adjacent methoxy groups, this is such that the two groups are forced away from each other and towards the 2 and 5 positions of the thiophene ring, thus inhibiting any attack by the immonium electrophile. There is no bulky substituent on the 4 position of 3-methoxythiophene so that the 2 position is more open to attack by the incomming electrophile.

4.3.3 Synthesis and Mannich Reactions of Other 3,4-Dialkoxythiophene Systems

Two further compounds were prepared in order to test the theory that steric hindrance is responsible for the lack of reactivity of 3,4-dimethoxythiophene, (**59a**), in the Mannich reaction.

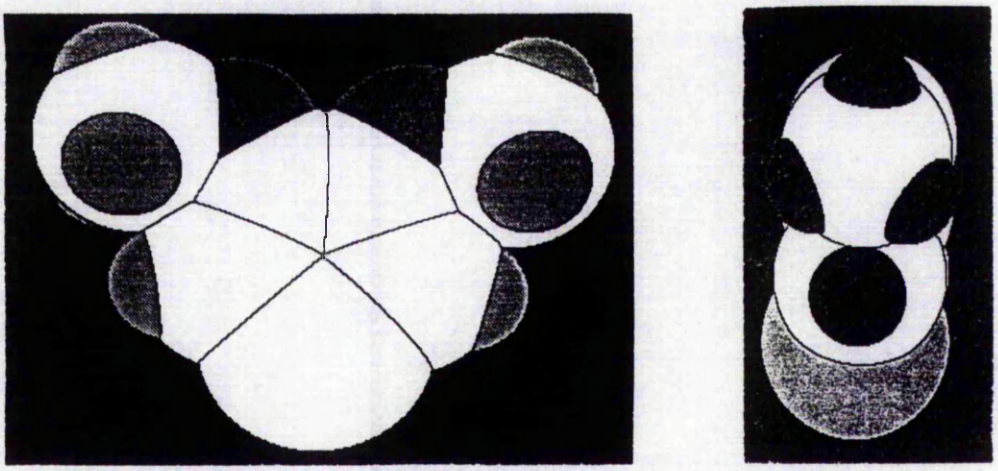
The first was 3,4-ethylenedioxythiophene, (**59b**), which, it was believed, might be more reactive than (**59a**); the replacement of $-OCH_3$ by $-OCH_2-$, and the constraints on the latter imposed by their presence in a ring might be expected to give greater access to C-2/C-5 by an electrophile. The

relative crowding of these sites in 3,4-ethylenedioxythiophene and 3,4-dimethoxythiophene, shown in Figure 32, lends support to this view.

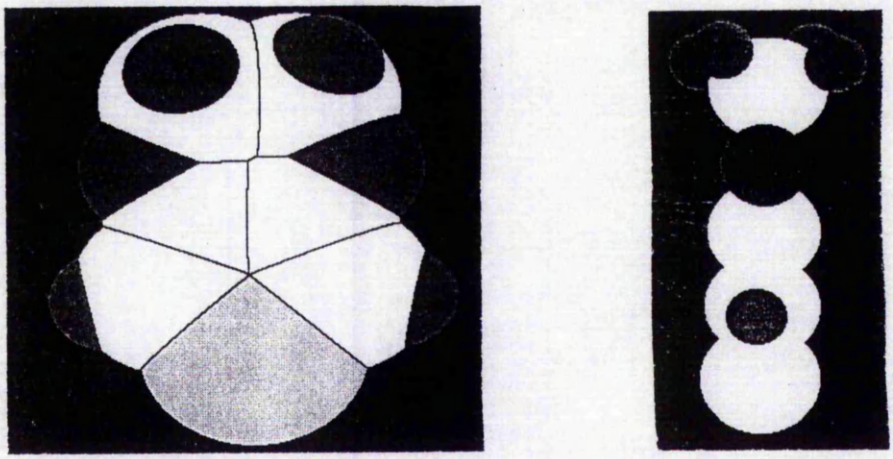
Figure 32

Computer generated Corey-Pauling-Koltun, (C.P.K.)* models of :-

(a) 3,4-dimethoxythiophene, (**59a**)



(b) 3,4-ethylenedioxythiophene, (**59b**)

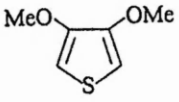


* Kindly supplied by Synthetic Chemicals Limited, Wolverhampton, U.K.

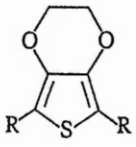
Contemporaneous to this work, several papers appeared concerning the synthesis of 3,4-ethylenedioxythiophene, and it's polymerisation to highly stable conducting polymers.[125, 126] The methodology employed the alkylation of the disodium salt, (**33b**), by prolonged treatment with 1,2-dibromoethane.[116] With

respect to quantities of material for subsequent reactions, this was the limiting step, giving at most 27% of diethyl 3,4-ethylenedioxythiophene-2,5-dicarboxylate, (**33d**). However, the author found that, by employing the alkylation procedure used by Dallacker and Mues,[120] which employed DMF and potassium carbonate as the solvent and base, and by substituting 1,2-dibromoethane for bromochloromethane, yields of (**33d**) were significantly improved, (78%). Subsequent saponification and decarboxylation gave 3,4-ethylenedioxythiophene in sufficient quantities to allow purification by distillation.

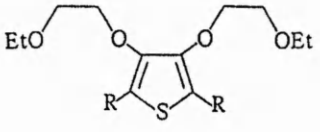
The second compound used in this study was 3,4-bis(3'-oxa-pentyloxy)thiophene, (**59c**), which, it was believed, might show intermediate reactivity between (**59a**) and (**59b**), since like 3,4-ethylenedioxythiophene, (**59c**) possesses OCH_2CH_2O groups, but they lack the constraints that are imposed by a ring. By using the productive method, with 1-tosyloxy-3-oxapentane as the alkylating agent, (**33h**) was obtained in good yield. Similarly saponification followed by decarboxylation with copper(I) oxide and quinoline gave (**59c**) in 70% yield.



(59a)



R = CO_2Et , 33d
R = H , 59b

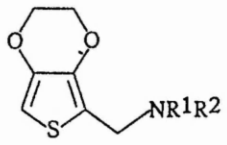


R = CO_2Et , 33h
R = H , 59c

The performances of these compounds in the Mannich reaction were assessed using the standard reaction conditions developed earlier. As predicted, the yields of the Mannich bases derived from 3,4-ethylenedioxythiophene, (**59b**), were generally higher than those derived from (**59a**); dimethylamine and piperidine gave 72% and 82% yields of the expected tertiary amines (**113a**) and (**113b**),

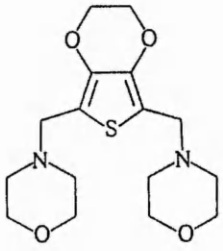
respectively. The Mannich base (**113a**) was tolerant of distillation, the distillate showing no trace of (**59b**). Interestingly the reaction employing morpholine gave a mixture of two products, the expected mono Mannich base (**113c**), (52%), and the bis Mannich base (**114**), (13%). This particular reaction was exceedingly exothermic, requiring prolonged cooling to attain a steady ambient temperature. The fact that some (**113c**) underwent further substitution, indicates that the remaining 5 position must be relatively unhindered. Column chromatography of the mixture gave some pure bis Mannich base, and a fraction containing both products; the latter was separated by centrifugal chromatography.

The compound (**59c**) gave low yields of the Mannich base (**115a**), (12%), the yields of (**115b**) were moderate, and the results obtained with morpholine again indicated the presence of both the mono- and bis Mannich bases (**115c**) and (**116**). The latter two compounds showed similar chromatographic properties to those of their 3,4-ethylenedioxythiophene counterparts. From these results it may be seen that, where dimethylamine and piperidine are used, (**59c**) is intermediate in reactivity between (**59a**), (the least reactive) and (**59b**), (the most reactive). The yields of those Mannich bases derived from morpholine were generally higher than those yields obtained with the other secondary amines.



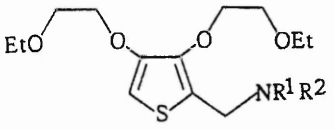
(113)

a , $R^1 = R^2$ = Me , 72%
b , R^1,R^2 = $-(CH_2)_5-$, 82%
c , R^1,R^2 = $-(CH_2)_2O(CH_2)_2-$, 52%*



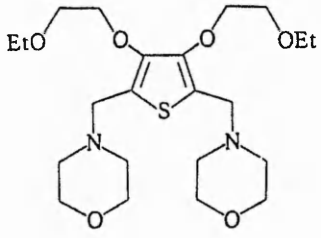
(114)

* including a 13% yield of (114)



(115)

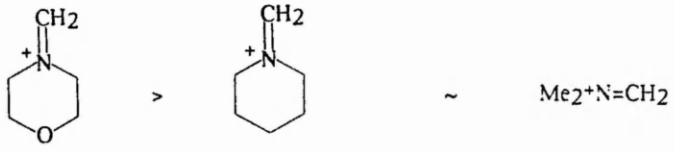
a , $R^1 = R^2 = Me$, 12%
b , $R^1,R^2 = -(CH_2)_5-$, 42%
c , $R^1,R^2 = -(CH_2)_2O(CH_2)_2-$, 46% †



(116)

† including a 24% yield of (116)

From these data conclusions about the reactivity of the immonium electrophiles may be drawn. Under the conditions employed here, the *N,N*-dimethylmethyleneammonium ion, (**117**), is similar in reactivity to the 1-methylenepiperidinium ion, (**118**). The most reactive of these is the 4-methylenemorpholiium ion, (**119**).



(119) (118) (117)

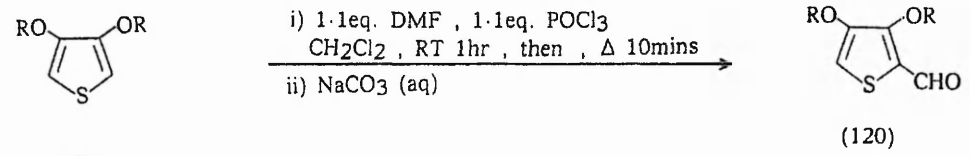
Some corroboration of the reactivity of the 4-methylenemorpholinium ion is afforded by Jasor *et al.* [165] They observed that in the reaction of unsymmetrical ketones with immonium salts, the salt 4-methylenemorpholinium trifluoroacetate exhibited enhanced reaction rates.

Though methiodides could be formed from those Mannich bases derived from 3,4-ethylenedioxythiophene, attempts to form methiodide salts from Mannich bases obtained from (**59c**) routinely failed, giving only gelatinous brown material.

4.3.4 The Vilsmeier-Haack Formylation of Activated Thiophene Systems

A comparison was made between the previously discussed dioxygenated thiophenes in their behaviour in the Vilsmeier-Haack formylation reaction. The chloroimmonium electrophile generated in this reaction bears an obvious similarity to the electrophile formed in the Mannich reaction. The conditions used were those given by Chadwick and coworkers in their synthesis of 3,4-dimethoxythiophene-2-carboxaldehyde, (**120a**), Equation 23.[127]

Equation 23



(59)

a , R = Me
b , R = CH_2CH_2
c , R = CH_2CH_2OEt

(120)

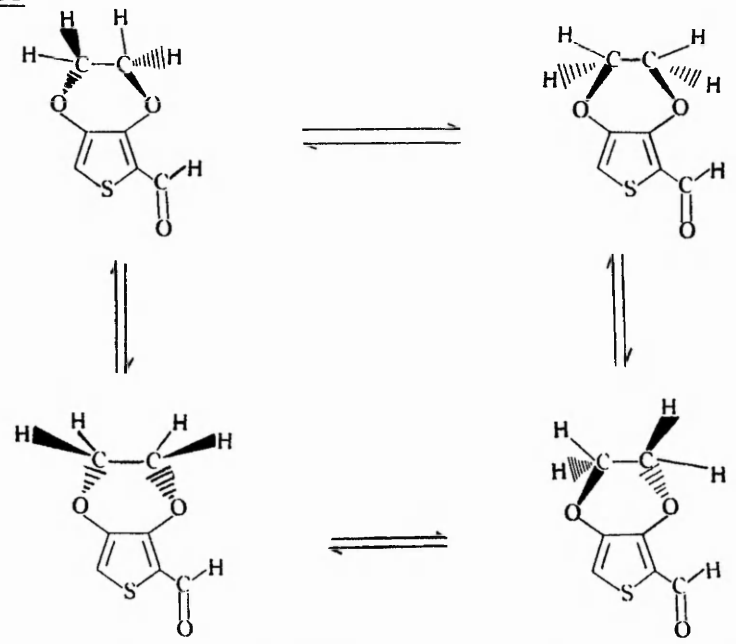
a , R = Me , 62%
b , R,R = CH_2CH_2 , 82%
c , R = CH_2CH_2OEt , 70%

Under the same conditions, 3-methoxythiophene gave 3-methoxythiophene-2-carboxaldehyde, (**121**), in 42% yield. Spectroscopically these compounds were interesting. In the proton n.m.r. spectra, the aldehydic proton and aromatic proton were indicated by doublets centred on 10 ppm and *ca.* 6·6-6·9 ppm respectively, with a coupling constant of 0·99-1·32 Hz. This coupling is a known phenomenom, and arises from the long range coupling between H-5 and -CHO, across the conjugated system [166]

Splitting of the protons attached to the alkoxy carbon atom was also observed. Compound (**120a**) showed two signals at 3·87 ppm and 4·12 ppm arising from the protons of the now non-equivalent methoxy groups. In compound (**120b**) the protons of the ethylene group were represented by a complex signal best described as a doublet of multiplets. The complexity of the signal is due to the various conformers that are possible within the ethylenedioxy ring, which lead to magnetic non-equivalence of the four protons

in the ethylene bridge, (Figure 33).

Figure 33

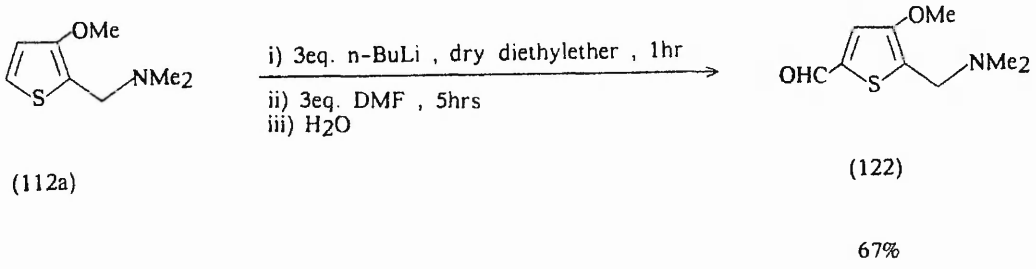


The splitting paterns for the ethoxy protons in (**120c**) were very complex over the range of 3·7–3·8 ppm, as one would expect, given the composition of the side chain.

The formylation of the Mannich base (**112a**) was studied next. Attempts to use the Vilsmeier-Haack procedure failed to give any isolable products, the intractable residue obtained from such experiments show little evidence of any formylation having occurred. In an alternative approach, lithiation was attempted after the method of Slocum and Gierer.[167] After the period of metallation, the degree of lithiation was assessed by the addition of deuterium oxide to the metallated species, and calculating the ratio of the ^{1}H and ^{2}H isotopes from the integral of the proton n.m.r. spectrum of the residue obtained. This showed that about 60% of the amine had undergone deuteration at the expected C-5 of the aromatic ring. The carbon-13 n.m.r. spectrum showed an intense signal at 122·5 ppm surrounded by three peaks of approximately one tenth the intensity at 121·9, 122·3 and 122·7 ppm with a J value of 28·7 Hz. This triplet relates to those carbon atoms bonded to

deuterium and the reduced intensity may be attributed to the absence of any Nuclear Overhauser Effect, (N.O.E.). Using this information as a guide, (**112a**), was lithiated with three equivalents of *n*-butyllithium, then treated with DMF. Subsequent hydrolysis of the intermediate afforded the aldehyde, (**122**), in good yield, (Equation 24).

Equation 24



(112a)

(122)

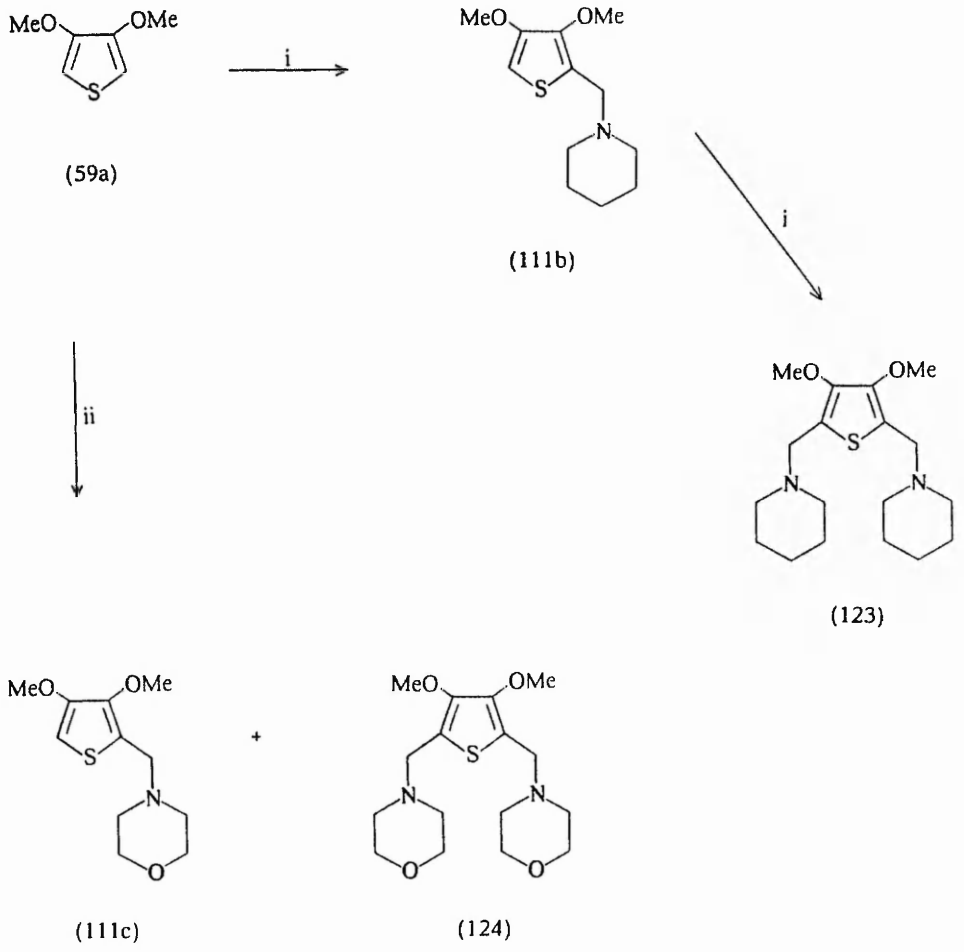
67%

4.3.5 Further Mannich Reactions Involving 3,4-Dimethoxythiophene, (**59a**), and 3,4-Bis(3'-oxapentyloxy)thiophene, (**59c**)

Given that the 3,4-dimethoxythiophene, (**59a**), was somewhat unreactive under the conditions hitherto employed, a study was embarked upon to see under what conditions it might be forced to react.

By reaction of the compound with the reagents used thus far, but employing elevated temperatures, *eg.* 100°C, some reasonable yields of Mannich bases were obtained. In this manner 3,4-dimethoxythiophene gave a 53% yield of the Mannich base (**111b**), which in turn was further reacted under identical conditions to give the bis Mannich base, (**123**), (27%), (Scheme 30). Because of the innate high reactivity of the methylenemorpholinium electrophile (**119**), it was felt unnecessary to use high reaction temperatures in a synthesis of the mono Mannich base, (**111c**). At higher temperatures an excellent yield of the bis Mannich base, (**124**), was obtained, some mono-substituted product also being isolated.

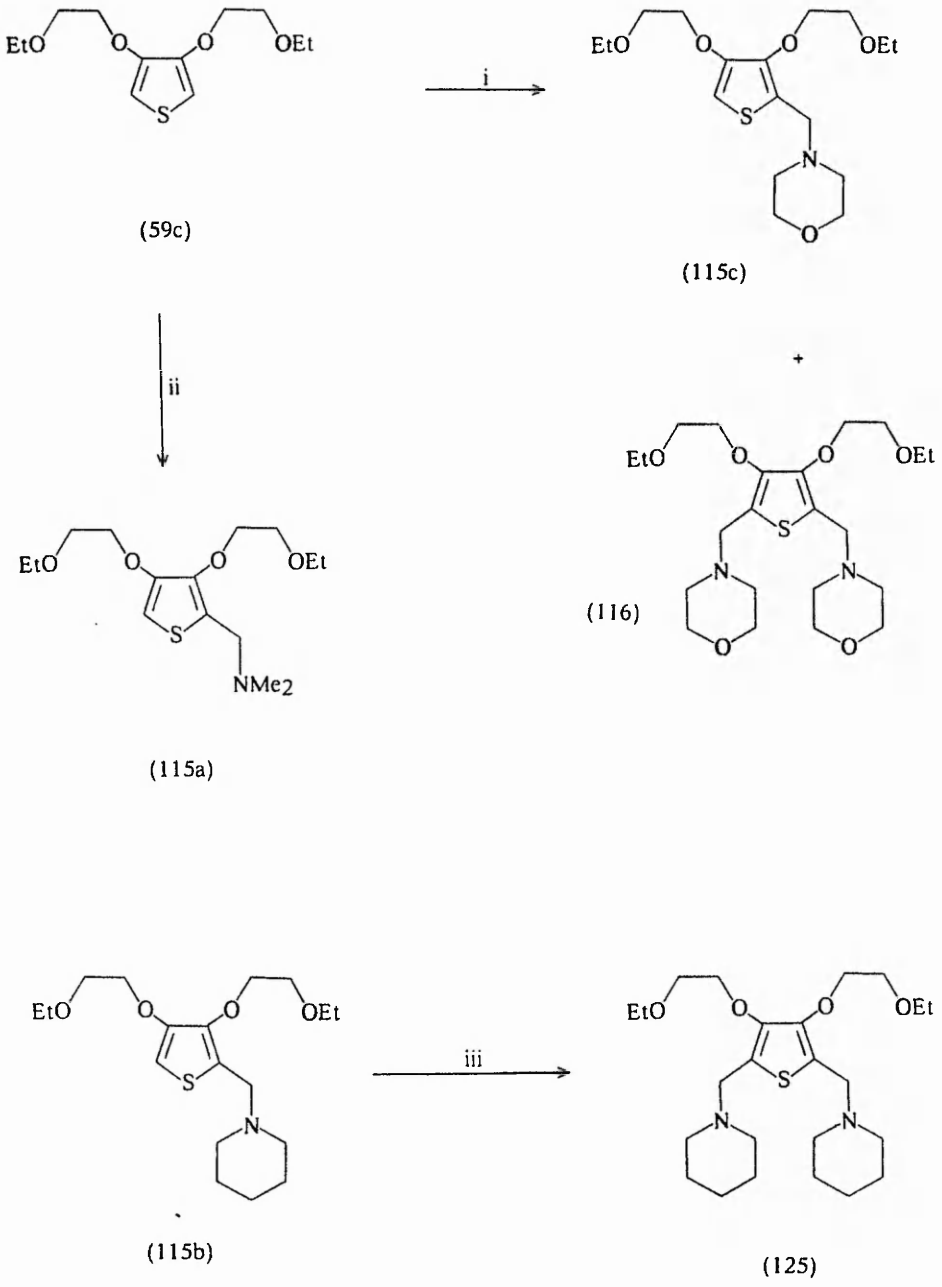
Scheme 30



(i) 1eq. 37% HCHO(aq), 1eq. piperidine, AcOH, 100°C, 4hrs, (yields, (**111b**), 53%, (**123**), 27%); (ii) 2·2eq. 37% HCHO(aq), 2·2eq. morpholine, AcOH, 100°C, 4hrs, (yields, (**111c**), 21%, (**124**), 78%).

The dialkoxythiophene, (**59c**) was also found to give a number of Mannich bases in improved yields when the reactions were carried out at 100°C, (Scheme 31).

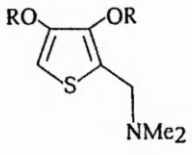
Scheme 31



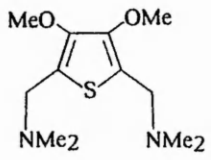
(i) 2·2eq. HCHO(aq), 2·2eq. morpholine, AcOH, 100°C, 4hrs, (yields, (**115c**), 52%, (**116**), 16%); (ii) 1eq. HCHO(aq), 1eq. Me_2NH(aq), AcOH, 100°C, 4hrs, (yield, 37%); (iii) 1eq. HCHO(aq), 1eq. piperidine, AcOH, 100°C, 4hrs, (yield, 35%).

4.3.6 Other Approaches to the Synthesis of Thienylmethylamines

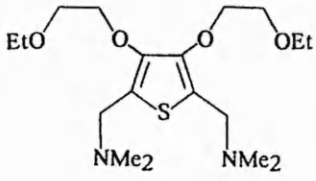
An alternative route was used to synthesise the tertiary amines (**111a**) and (**115a**), starting from the appropriate dialkoxythiophene. The latter was treated with *N,N*-dimethylmethyleneammonium chloride in dry acetonitrile under an atmosphere of nitrogen.[143] Careful control of the reaction conditions is very necessary, given the highly reactive nature of the preformed intermediate immonium chloride salt. In this fashion the Mannich bases (**111a**) and (**115a**) were isolated in yields of 54% and 84%, respectively.



R = Me , 54% , (111a)
R = CH_2CH_2OEt , 84% , (115a)



(126)



(127)

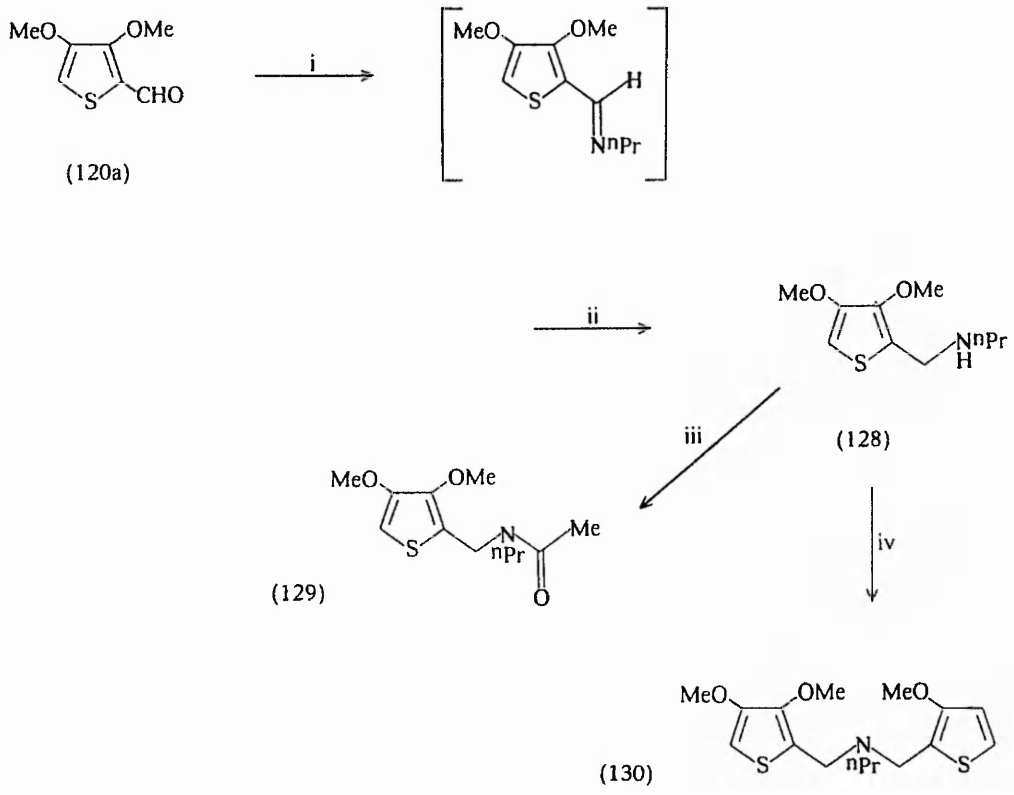
From these products, further attempts to synthesise the bis Mannich bases (**126**) and (**127**) were made, by reaction with another equivalent of the immonium chloride salt.

These reactions failed to give any definite products, although the n.m.r. spectra of the resulting oils showed the possible presence of 2,5-disubstituted material. Attempts to purify these oils by chomatographic means failed and, when the material was examined by TLC some hours later, the presence of further spots was noticed; after 12 hours the oils had darkened and degraded completely.

Another synthetic route to thienylmethylamines derived from 3,4-dimethoxythiophene, which would circumvent it's apparent lack of reactivity in the Mannich reaction would be to generate a Schiff base from 3,4-dimethoxy-thiophene-2-carboxaldehyde, (**120a**), reduce this to a secondary amine which

could then be further employed in a Mannich reaction with a more responsive thiophene moiety, such as 3-methoxythiophene. The aldehyde, (**120a**) was reacted with *n*-propylamine in boiling dry ethanol under reflux.[80] *n*-Propylamine was chosen because of it's ease of handling; both methylamine and ethylamine were available either as aqueous solutions or in gaseous state from cylinders, neither of which forms was experimentally convenient. The Schiff base so formed was not isolated but was reduced *in situ* by the action of sodium borohydride, to afford the secondary amine *N*-[(3,4-dimethoxy-2-thienyl)methyl]-propylamine, (**128**), in quantitative yields, (Scheme 32). For the purposes of obtaining a microanalytically pure sample, (**128**) was converted into the less polar ethanamide derivative by treatment with acetic anhydride, when purification by column chromatography gave an analytically pure sample of the amide, *N*-[(3,4-dimethoxy-2-thienyl)methyl]-*N*-propylethanamide, (**129**). The n.m.r. spectra of (**129**) were interesting in so far as all peaks in both the proton and carbon-13 n.m.r. spectra appeared as two signals, a phenomenom arising from the restricted rotation about the nitrogen-carbonyl bond of amides. By employing the Mannich reaction to 3-methoxythiophene with the secondary amine, (**128**), the bis thienylmethyl Mannich base, *N,N*-[(3,3',4-trimethoxy-2,2'-dithienyl)dimethyl]-propylamine, (**130**), was obtained in a yield of 80%, (Scheme 32). Further work in this area was not pursued, since it was difficult to envisage this route leading to macrocyclic products.

Scheme 32

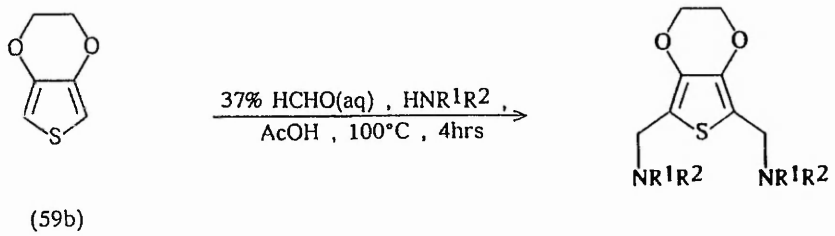


(i) 1eq. *n*-$PrNH_2$, dry EtOH, Δ, 1hr; (ii) 1eq. $NaBH_4$, dry EtOH, Δ, 1hr, (yield, ~100%); (iii) Ac_2O, overnight, (yield, 95%); (iv)1eq. HCHO(aq), 1eq. 3-methoxythiophene, AcOH, RT, (yield. 80%).

4.3.7 The Synthesis of Bis Mannich Bases Derived from 3,4-Ethylenedioxy-Thiophene, (**59b**), and Secondary Amines

A more detailed study of the Mannich reaction of 3,4-ethylenedioxythiophene, (**59b**), now undertaken because of it's proven responsiveness under conditions that were now well established. The bis Mannich bases (**131**) and (**133**) were synthesised directly by the treatment of the thiophene moiety with 2·2 equivalents of both formaldehyde and secondary amine, giving excellent yields of the desired products, (Equation 25).

Equation 25

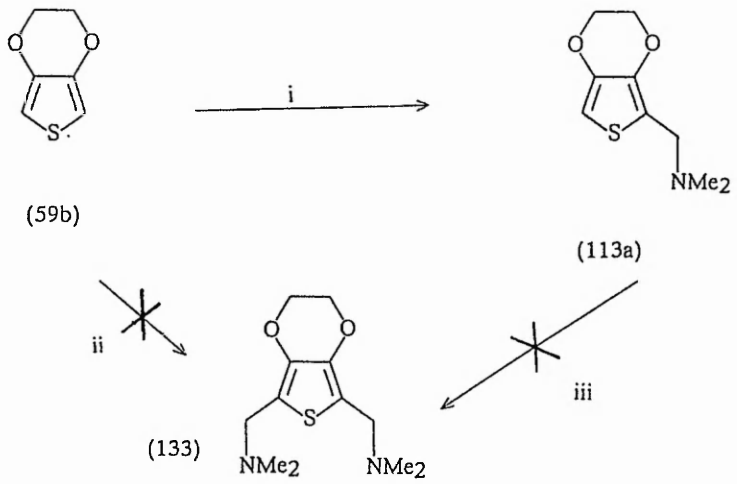


(59b)

$R^1,R^2 = -(CH_2)_5-$, 86% , (131)
$R^1,R^2 = -(CH_2)_2O(CH_2)_2-$, 91% , (114)

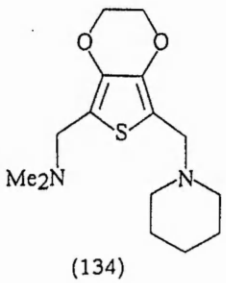
A successful synthesis of the bis Mannich base (**133**) was not achieved, whether starting from the thiophene moiety (**59b**) or from the mono Mannich base, (**113a**). Treatment of (**59b**) with two equivalents of formaldehyde and dimethylamine gave high yields of (**113a**) only. Reaction of either (**59b**) or (113a) with two or one equivalents of *N,N*-dimethylmethyleneammonium chloride, respectively, gave a complex mixture of products which was found to be unstable, darkening over a period of time, (Scheme 33).

Scheme 33



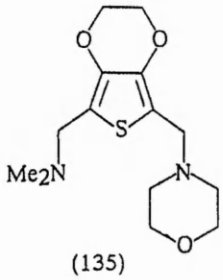
(i) 2·2eq. 37% HCHO(aq), 2·2eq. 40% $HNMe_2$(aq), AcOH, 100°C, 4hrs, (yield, 84%); (ii) 2eq. $Me_2^+N{=}CH_2$ Cl^-, MeCN, Δ, 4hrs; (iii) 1eq. $Me_2^+N{=}CH_2$ Cl^-, MeCN, Δ, 4hrs.

Synthesis of "mixed" bis Mannich bases (**134**), (**135**) and (**136**) were also attempted. The general strategy used here was to substitute the vacant 5 position of a mono Mannich base with the more reactive immonium moiety. Thus, (**113a**) was reacted at elevated tempratures with formaldehyde and either piperidine or morpholine in acetic acid to give the bis Mannich bases (**134**) and (**135**) in yields of 54% and 74%, respectively. However, both were unstable and although satisfactory n.m.r. spectra were obtained, no microanalytically pure samples of (**134**), (**135**), or their methiodide salts were given. Compound (**136**) was synthesised by the reaction of (**113b**) with formaldehyde and morpholine to give a 91% yield of the desired bis Mannich base, (**135**).



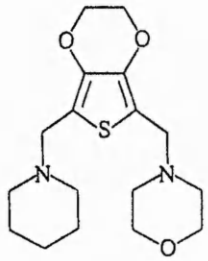
(134)

54%



(135)

74%



(136)

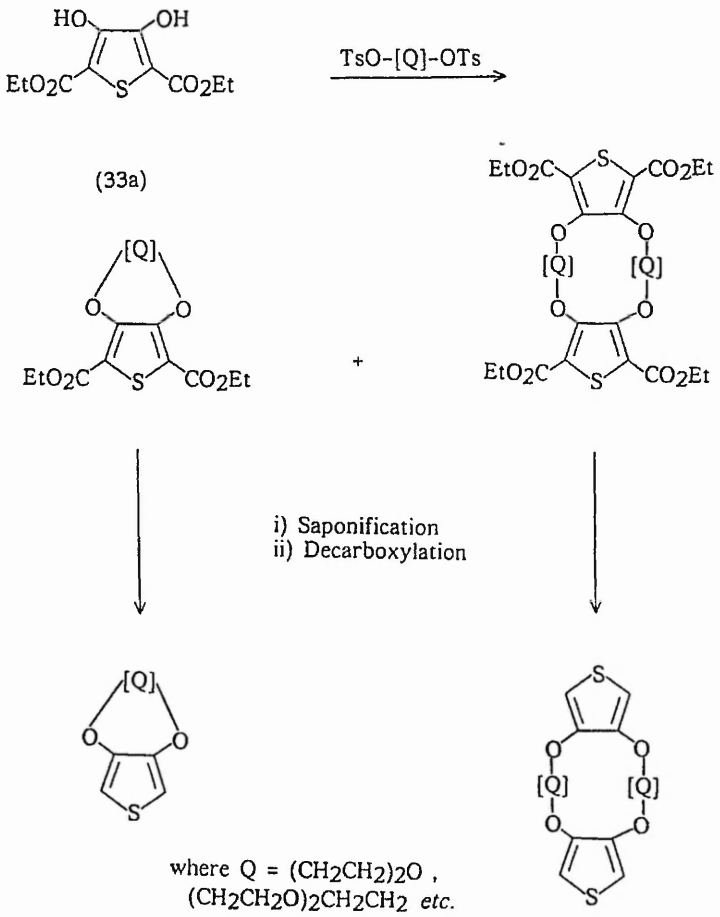
91%

4.4 Synthesis of More Complex 3,4-Dialkoxythiophene Systems

4.4.1 Introduction

The next stage in the study was to investigate the synthesis of the thiophene analogues of Pedersen's crown ethers. Again the general strategy envisaged was one of alkylation of the dihydroxythiophene derivative, (**33a**), this time with an alkylating agent possessing α,ω-functionality, followed by saponification and decarboxylation, as outlined in Scheme 34.

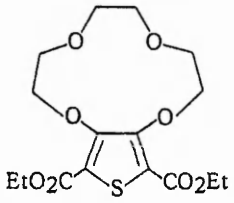
Scheme 34



4.4.2 The Synthesis of Crown Ether-Like Thiophene Moieties

A search of the literature revealed that the general approach outlined above had been used by Sone *et al.* to give reasonable yields of both the [1+1] and [2+2] alkylation products.[88] Their procedure involved the reaction of (**33a**) with ditosylate esters in the presence of a base, (either potassium or cesium fluoride), the reaction solvent being acetonitrile, (see Scheme 16, page 57). The procedure given by Sone and coworkers was followed, employing 1,8-ditosyloxy-3,6-dioxaoctane, (**102**). The material obtained from this reaction had a melting point in agreement with that given for the [1+1] macrocyclic product, (**137**), and such a structure was further supported by the mass spectrum, which showed a molecular ion peak at 374(M^+, 14). Attempts to reproduce the other

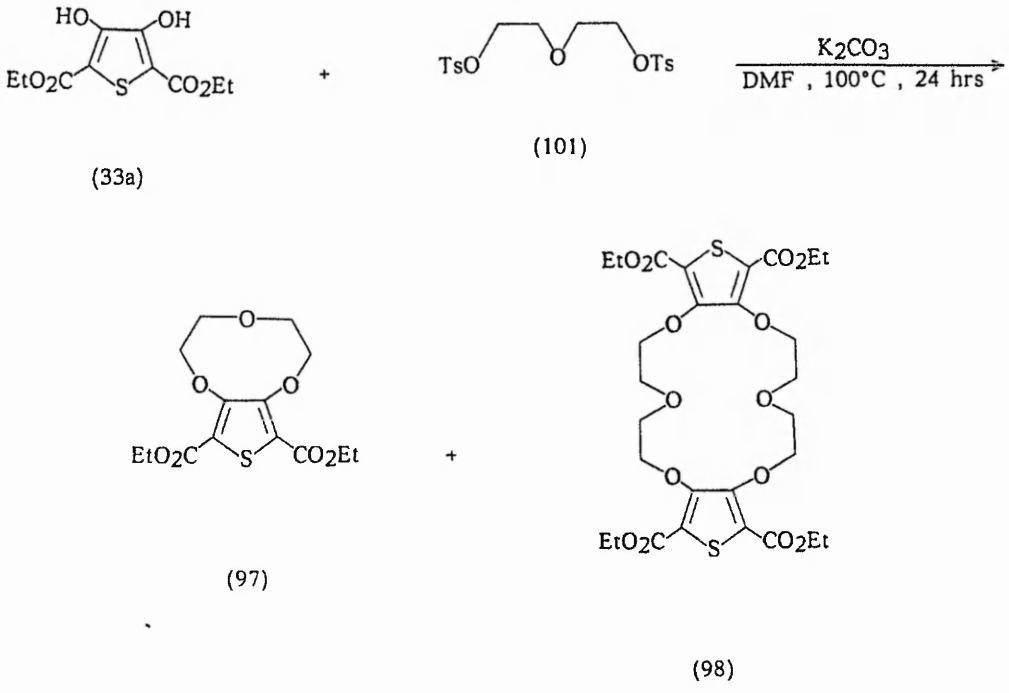
results reported in this paper failed to yield any [2+2] material.



(137)

Because no [2+2] macrocyclic material could be isolated from the above reaction, a different approach was needed; the synthetic method given by Dallacker and Mues,[95] substituting 1,5-ditosyloxy-3-oxapentane, (**101**), for bromochloromethane, was employed, (Equation 26, *cf.* Equation 12, page 56).

Equation 26



(33a)

(101)

(97)

(98)

Two distinct compounds were obtained, after column chromatography of the products, one melting at 120-2°C, (15%), and the other at 172-5°C, (7%). The microanalytical data for both compounds were consistent with the same empirical formula, $C_{14}H_{18}O_7S$, so almost certainly these were the [1+1] and [2+2] products, (**97**) and (**98**); the question was, which compound was which?

As expected, the proton n.m.r. spectra of the two compounds were similar and of little use in distinguishing between them. Similarly, the carbon-13 n.m.r. spectra of both compounds served merely to support the existence of a symmetrically substituted thiophene ring, with ester moieties in the 2 and 5 positions and alkoxy groups in the 3 and 4 positions. The infrared spectra of the two compounds were very different, in so far as the lower melting compound possessed two intense signals relating to the carbonyl stretching frequency at 1719 and 1683 cm^{-1}, whilst the higher melting compound had a single intense, peak again corresponding to the carbonyl stretching frequency at 1722 cm^{-1}. Although this difference would prove useful later, it did not serve to distinguish between the components. Both were subjected to mass spectroscopic analysis, but both compounds gave ions of 330 as the highest m/e value; for the lower melting compound the signal had an intensity of 100%, whereas for the higher melting compound the intensity was 41%. Both spectra contained other common fragments, *eg.* at m/e = 73 (CO_2Et) and m/e = 45 (OEt). Also apparent were small peaks at an m/e of 332 corresponding to the presence of the ^{34}S isotope. Since mass spectrometry had failed to resolve the identities of the compounds, as a final resort, Rast's camphor method was employed, which, though lacking the pin-point accuracy mass spectrometry, was ideal in this case since one was trying to differentiate between two compounds with widely differing molecular weights, 330 versus 660.[168] The determination revealed that the lower melting compound had a molecular weight of 312, and therefore was the [1+1] alkylation product, (**97**). The value for the higher melting compound was 632, corresponding to the [2+2] product, (**98**).

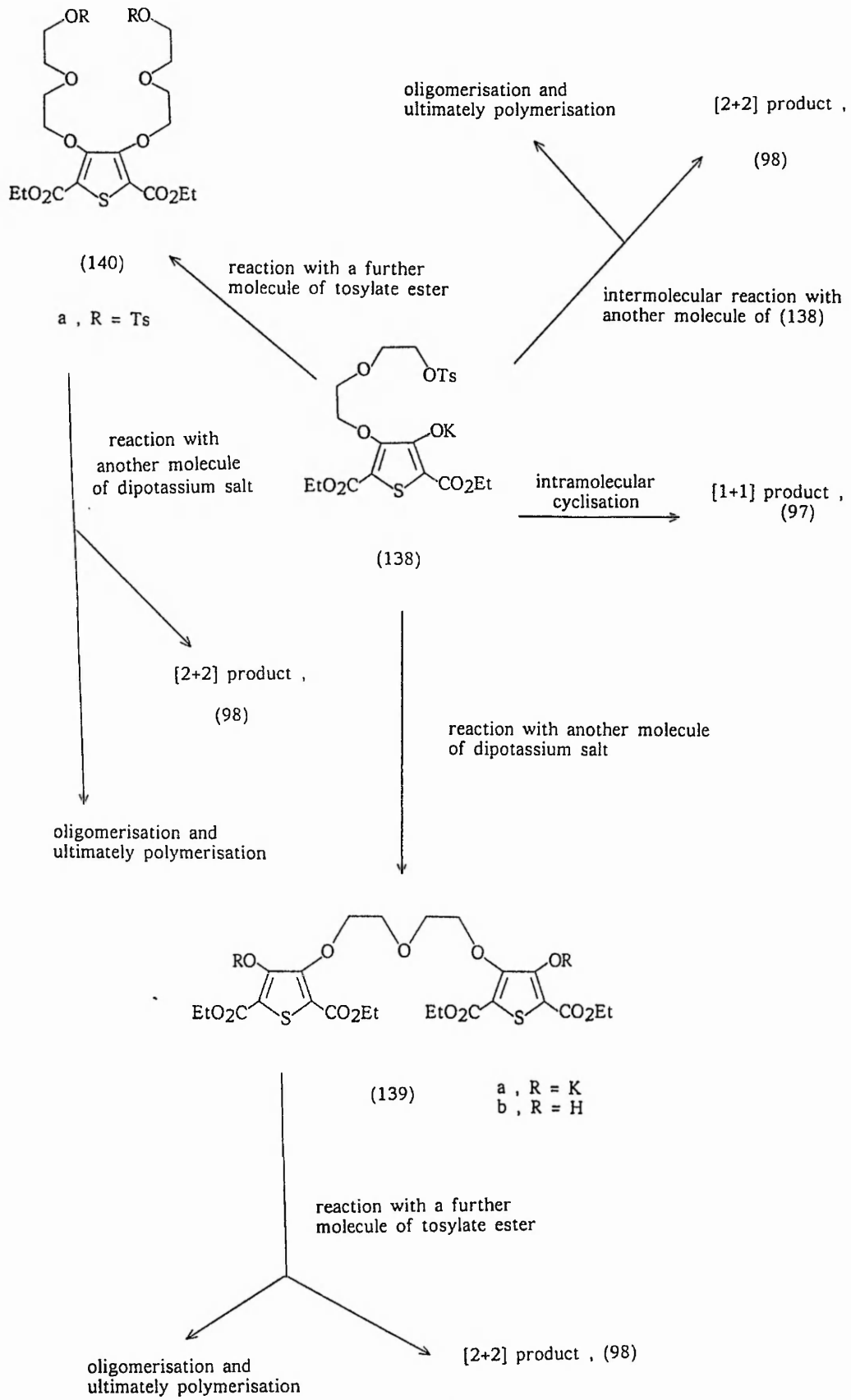
This experiment had given very little isolable, identifiable material, because it had been performed under fairly concentrated reaction conditions, [1·8 M with respect to the dihydroxythiophene component, (**33a**)]. The next stage of the study involved performing a high dilution experiment, where

solutions of (**33a**), and the ditosylate ester, (**101**), in DMF were fed independently into a rapidly stirred, hot suspension of potassium carbonate in DMF; the addition was perfomed at a rate of 2 $mmolh^{-1}$. Polymerisation was reduced, whilst a 7% yield of (**98**) was given, (a similar yield to that obtained under non-high dilution conditions), and a 36% yield of the [1+1] product, (**97**) was afforded, (*cf.* 15% obtained under non-high dilution conditions). Interestingly, when the ditosylate ester, (**102**), was substituted for the compound (**101**), no [2+2] crown ether was isolated; rather, small amounts of the [1+1] cyclisation compound, (**137**), and anomalously compound (**97**), were given, (15%, and 2%, respectively).

Why should the [1+1] bicyclic compounds predominate in such reactions? The rationale for this is quite straightforward, if one considers the fate of the product formed from the first alkylation reaction between (**101**) and the dipotassium salt of (**33a**), that is, intermediate, (**138**), (Scheme 35).

Scheme 35

Scheme 35


OR
RO
O
O
O
O
EtO2C
S
CO2Et
(140)
a , R = Ts
oligomerisation and
ultimately polymerisation
[2+2] product ,
(98)
reaction with a further
molecule of tosylate ester
intermolecular reaction with
another molecule of (138)
OTs
O
O
OK
EtO2C
S
CO2Et
(138)
reaction with
another molecule
of dipotassium salt
intramolecular
cyclisation
[1+1] product ,
(97)
[2+2] product ,
(98)
oligomerisation and
ultimately polymerisation
reaction with another molecule
of dipotassium salt
RO
O
O
O
OR
EtO2C
S
CO2Et
EtO2C
S
CO2Et
(139)
a , R = K
b , R = H
reaction with a further
molecule of tosylate ester
oligomerisation and
ultimately polymerisation
[2+2] product , (98)

Clearly the chances of the intermediate (**138**) following a pathway leading to polymerisation are very much increased if one uses very concentrated reaction conditions, and it should be of no surprise that under the conditions of high dilution the chances of an intramolecular reaction, between the nucleophilic phenoxide anion and the terminal tosylate ester of (**138**) are very much increased, thus giving higher yields of the [1+1] product, (**97**). So how could yields of the desired crown ether-like [2+2] compound, (**98**), be improved upon? Three stategies were felt worthy of further study:

i) the employment of a suitable template ion,

ii) synthesis of compound (**139b**), (Scheme 35, page 128), followed by further reaction with a ditosylate ester, *eg.* (**101**), to give the tricyclic [2+2] compound, (**98**).

iii) synthesis of compounds related to (**140**), (Scheme 35), followed by further reaction with a dipotassium salt of a dihydroxythiophene derivative to give compound (**98**).

Given the structural similarity between dibenzo-18-crown-6, (a compound with a cavity size of the order of the potassium ion), and the dithienyloxy crown compound (**98**), it was felt that the potassium ion would be of a suitable size around which to assemble the crown ether. Thus the reaction shown in Equation 26, (page 125) was carried out under high dilution conditions in the presence of a high concentration of a lipophilic potassium salt, *eg.* potassium tosylate or potassium perchlorate. Again the [1+1] cyclisation product was obtained as the major product in yields of a similar order to those already reported. The desired [2+2] crown ether was obtained in yields of 12% and 9%. Though an improvement on the yields obtained in the absence of such salts, this approach was abandoned in favour of investigating the other two strategies.

The second approach involved the synthesis of (**139b**) as illustrated in Scheme 35. Given the problems encountered in the synthesis of other mono

methylated species, previously discussed in Section 4.2.2, (page 99), the isolation of 1,5-bis(2',5'-diethoxycarbonyl-4'-hydroxy-3'-thienyloxy)-3-oxapentane, (**139b**), was not envisaged. Conditions were employed which would maximise the probability of an encounter between one moiety of α,ω-ditosylate, and two moieties of the dipotassium salt of (**33a**), leading to the formation of (**139a**) rather than undergoing a cyclisation process that would lead to the [1+1] product. It was hoped that a greater quantity of (**139a**) in the reaction mixture would lead to higher yields of the [2+2] product because of the improved probability of a reaction between the dipotassium salt (**139a**) and a further molecule of ditosylate ester, (**101**). The reaction was performed by the gradual addition of compound (**101**) to a solution of the dihydroxythiophene derivative, (**33a**), and potassium carbonate in DMF; several experiments being carried out, each of which the initial concentration of the thiophene moiety was different.

The results are summarised in Table 3 and the associated graph. It will be seen from these data that at high concentrations of (**33a**), fairly constant yields of both the [1+1] and [2+2] products was obtained, probably due to the saturation of the DMF with the dipotassium salt, thus providing a constant concentration of the latter with which the ditosylate ester, (**101**), can react. As expected, as the solutions become more dilute, the probability of an intramolecular cyclisation reaction increases, leading to high yields of the bicylic [1+1] product, (**97**). Yields of the desired tricyclic [2+2] compound (**98**), remained near constant and only exceeded 10% when an initial 0·0625 M solution of (**33a**) was employed. The base used in the above work was potassium carbonate, though one experiment was performed with tetrabutylammonium hydroxide and the dihydroxythiophene derivative in acetonitrile, and this gave yields of the [1+1] and [2+2] products comparable to those obtained with the inorganic base in DMF.

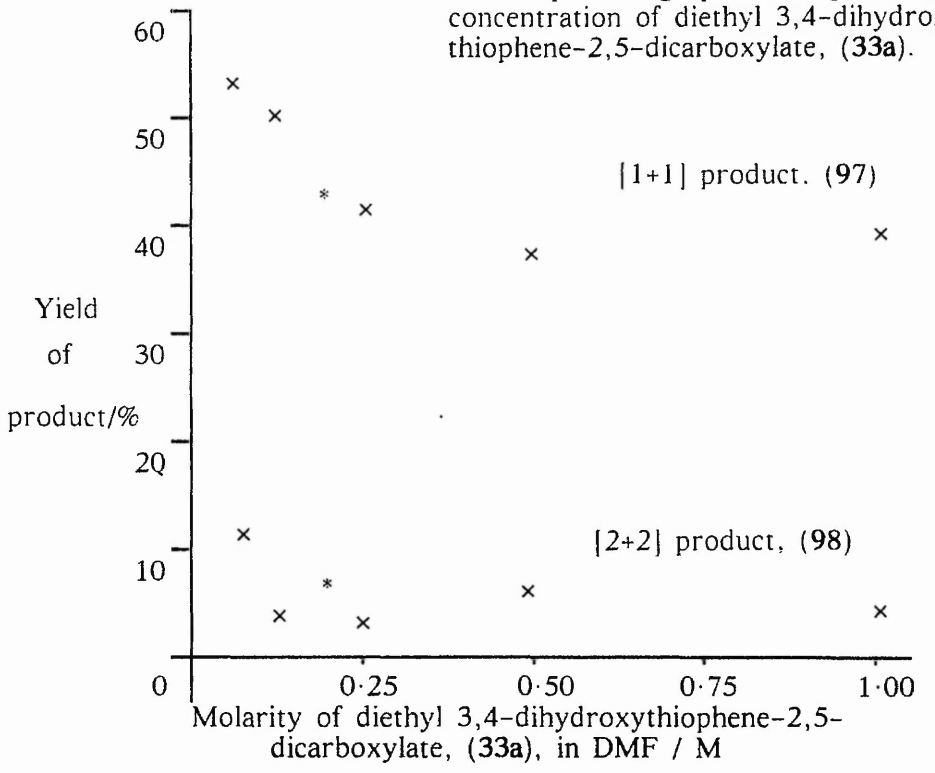
Table 3

Molarity of (**33a**) in DMF	Base	Percentage [1+1] product obtained	Percentage [2+2] product obtained
1·0	K_2CO_3	39	4
0·5	"	37	7
0·25	"	41	3
0·125	"	50	3
0·0625	"	53	11
0·2*	Bu_4NOH	43	7

* in this case the solvent used was acetonitrile

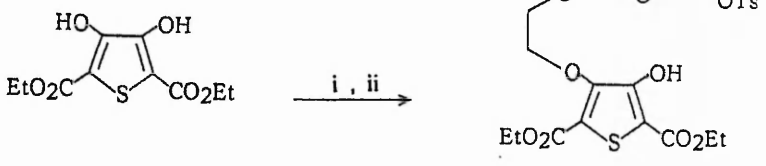
Figure 34

Plot of percentage product against initial concentration of diethyl 3,4-dihydroxy-thiophene-2,5-dicarboxylate, (**33a**).



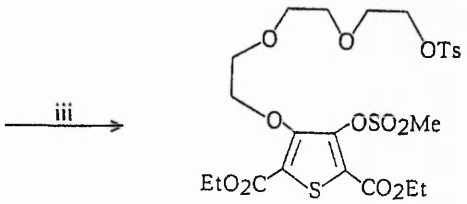
One further experiment was performed, which was a variation on the method used by Sone *et al.*,[88] in which the thiophene derivative, (**33a**) and anhydrous potassium fluoride were stirred together in acetonitrile, heated to boiling under reflux for several hours, to generate the desired dipotassium salt. This was treated with the ditosylate ester (**102**), in the same solvent. The addition was carried out in a gradual manner as outlined above and upon completion, the mixture was heated for a further forty hours. From this was isolated mainly the unreacted thiophene derivative, (**33a**), although the mono alkylation product, diethyl 3-hydroxy-4-(8'-tosyloxy-3',6'-dioxaoctanyloxy)-thiophene-2,5-dicarboxylate, (**141**), was isolated in a 24% yield, (Scheme 36). Compound (**141**) was identified in part by the very sharp peak in the proton n.m.r. spectrum at 9·37 ppm, corresponding to the proton of the phenolic hydroxy group, in conjuction with the complex series of peaks at *ca.* 3·5–4·4ppm arising from the protons of the numerous CH_2O moieties. The carbon-13 n.m.r. spectrum showed four signals in the aromatic region arising from the unsymmetrically substituted thiophene ring, those peaks at 106·8, 120·1, 148·6 and 155·1 ppm related to C-2, C-5, C-4, and C-3, respectively. The hydroxyalkoxythiophene derivative was further reacted with methanesulfonyl chloride in triethylamine,[169] to afford the mesylate ester, (**142**), in a yield of 75%, (Scheme 36).

Scheme 36



(33a)

(141)

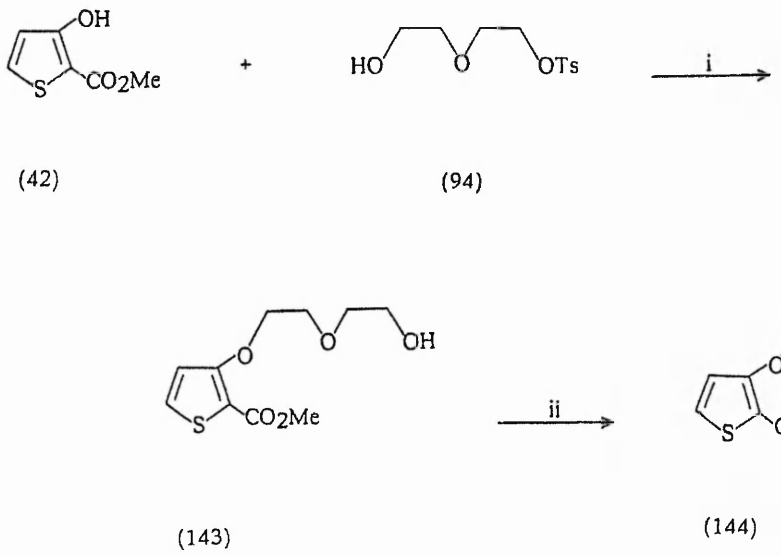


(142)

(i) 4eq. KF, acetonitrle, N_2, Δ, 1hr; (ii) $TsO(CH_2O)_3Ts$, Δ, 40hrs, (yield, 24%); (iii) excess MsCl, Et_3N, 0°C, (yield, 75%).

The final strategy employed in the synthesis of the crown ether, (**98**), (Scheme 35, page 128), was the preparation of compounds of a type (**140**). A pilot reaction, which involved the alkylation of methyl 3-hydroxythiophene-2-carboxylate, (**42**), with 5-tosyloxy-3-oxapentan-1-ol, (**94**), (Scheme 37), was carried out. Compound (**42**) was chosen in this preliminary study because of its similarity to the dihydroxythiophene derivative, (**33a**), whilst being chemically more simple and readily available. Conversion of the alcohol, (**143**) to it's tosylate ester derivative, (**144**), gave the desired compound, albeit in only moderate yield, (Scheme 37).

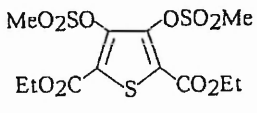
Scheme 37



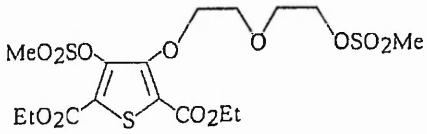
(i) 1·2eq. K_2CO_3, DMF, Δ, 12hrs, 100°C, (yield, 64%); (ii) 1·1eq. TsCl, pyridine, 0°C, (yield, 58%).

With the experience gained in this model experiment, synthesis of the alcohol, diethyl 3,4-bis(5'-hydroxy-3'-oxapentyloxy)thiophene-2,5-dicarboxylate, (**140b**), was embarked upon, using the usual slow addition technique. This approach was used in order to minimise any intermolecular Williamson reaction between two molecules of the tosylate ester. A small quantity of the residue from the reaction was subjected to column chromatography, affording the desired bis alcohol, (**140b**), in a yield of 56%. The polar nature of (**140b**) was problematic, causing the compound to adhere strongly to the column. in order to speed up the purification process, conversion of (**140b**) into the corresponding bis methanesulfonyl ester derivative, (**140c**), was envisaged, as this would have several advantages. Given the disappointing yield obtained in the synthesis of the tosylate ester derivative (**144**), it was felt that mesylation might be a more efficient process, as well as providing a derivative with much simplified n.m.r. spectra. Most important, however, were the effects on

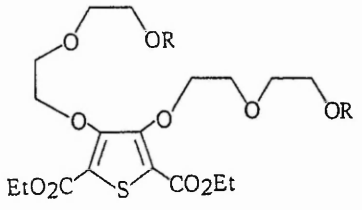
solubility and molecular weight. Previous high dilution experiments had indicated that the ditosylate derivatives (**101**) and (**102**), could on occasion, recrystallise out of solution during the slow addition process; this problem did not occur with the bis methanesulfonyl derivative (**140c**). Clearly, in this respect, a reduction in the molecular weight of the leaving group is beneficial. The crude mixture obtained in the synthesis of the bis alcohol (**140b**) was dissolved in a solution of dichloromethane and triethylamine, and treated with methanesulfonyl chloride.[169] Purification afforded three methanesulfonyl derivatives, (**33i**), (**145**) and (**140c**).



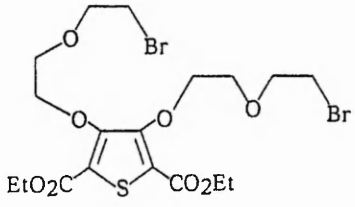
(33i)



(145)



(140) b , R = H
c , R = SO_2Me



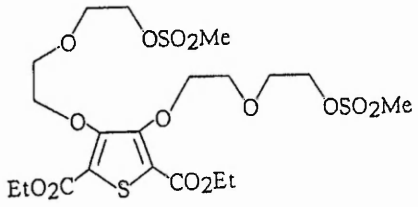
(146)

Also, by treating an ethereal solution of a small amount of the alkylation residue and pyridine with phosphorus tribromide, the bis bromoalkane, (**146**), was obtained in a yield of 28%. The low yield associated with this experiment may be attributed to the acid sensitivity of the ether linkages in the side chains; similar results have been reported by Chaffin.[96b]

The next step involved the use of (**140c**) in the synthesis of crown ether (**98**), the idea being to react (**140c**) and the dihydroxythiophene derivative

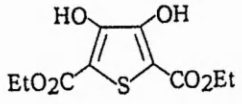
(33a), under high dilution conditions in the presence of a base. This type of approach, although not often employed, was not novel and had been used most notably by Chen *et al.* in the synthesis of a number of substituted dibenzo-14-crown-4 derivatives. When separate solutions of (**140c**) and (**33a**) were fed at a rate of 0·12 mmolhr^{-1} into a hot suspension of potassium carbonate in DMF, the only product isolated was the crown ether (**98**), in low yield, (7%). The experiment was repeated, this time including two equivalents of potassium tosylate to act as a template, but this effected only a slight improvement, giving (**98**) in 10% yield, (Equation 27).

Eqation 27



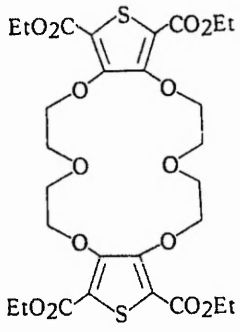
(140c)

+



(33a)

1.2eq. K_2CO_3 , DMF , 100°C →



(98)

7% without a potassium tosylate template

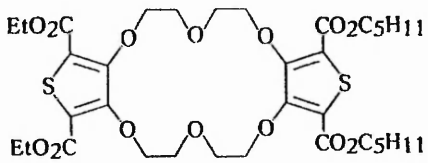
10% with a potassium tosylate template

Although the yields were disappointing, these experiments did confirm the assignment of the [2+2] structure to the higher melting product, both compounds having identical melting points and infrared spectra. Could the yields mentioned above be improved by using a more lipophilic dianion? To answer this question, the synthesis of an analogue of (**33a**) was attempted. This would then permit the use of a range of solvents which would offer potentially higher yields of crown ether material. Thus various approaches to the synthesis of dipentyl 3,4-dihydroxythiophene-2,5-dcarboxylate, (**147a**), were studied.

Initially the transesterification of (**33a**) by heating it with pentan-1-ol under reflux, in the presence of a catalytic amount of 4-toluenesulfonic acid was attempted. However, when a very large excess of the solvent alcohol was used, or when any displaced ethanol was removed azeotropically, no transesterification reaction was detected. In another approach, reaction of an ethereal solution of pentan-1-ol and chloroacetyl chloride in the presence of pyridine very readily yielded pentyl chloroacetate; the latter was reacted with sodium sulfide in the presence of a PTC to give dipentyl thiodiglycollate, (**148**). Application of the Hinsberg reaction to (**148**) and diethyl oxalate in a solution of sodium in pentan-1-ol, led to the desired dihydroxythiophene derivative, (**147a**). Interestingly, compound (**147a**) was also given if one reacted diethyl thiodiglycollate and diethyl oxalate in the above solution.[107] In order to test the hypothesis that the dianion of (**147a**) was more lipophilic than it's diethyl ester counterpart, compound (**147a**) was methylated using dimethyl sulfate in acetone employing potassium carbonate as base, giving dipentyl 3,4-dimethoxythiophene-2,5-dicarboxylate, (**147b**), (70%).

Replacement of compound (**33a**) with (**147a**) in the reaction shown in Equation 27, under high dilution conditions and in the presence of a template, (potassium tosylate), led to the desired crown ether, (**149**). There was some variation in yield with the solvent employed, (DMF, 15%; acetone or

acetonitrile, 12%).



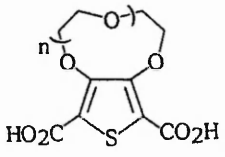
(149)

From the information presented above it is clear that the tendency of (**140c**) to react with a dihydroxythiophene moiety, (**33a** or **147a**), in such a way as to give a crown ether is quite low. Though the use of a lipophilic dianion like the dipotassium salt of (**147a**) did a give higher yield of [2+2] type crown compound, the low yield of crown ether-like material obtained using the method given in Equation 27 and subsequent variations would indicated that the problem lay in the conformations adopted by compound (**140a**) and its derivatives, rather than any poor solubilities of the dianions of the dihydroxythiophene compounds. The lengths of the side chains give rise to a large number of degrees of freedom within compound (**140c**), leading to a dominance of polymerisation. Templation overcomes this a little, by enforcing a favourable conformation for cyclisation on any intermediate, but this does not reduce polymerisation to any great extent.

4.4.3 Further Reactions of the Crown Ether-Like Moieties, (97), (98) and (137)

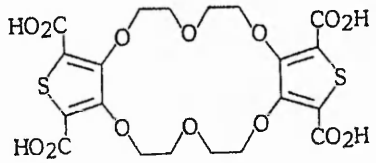
The carboxylic acids (**150a**) and (**150b**), and the tetracarboxylic acid, (**151**) were synthesised by the facile hydrolysis of their corresponding ethyl ester derivatives, (97), (98) and (137), respectively, according to the method given by Sone and coworkers.[88] The yields were high for the [1+1] type dicarboxylic acids, but that for the [2+2] tetracarboxylic acid, (**151**), was only moderate, similar results were obtained when the bis pentyl bis ethyl ester, (**149**), was employed instead of compound (**98**). Microanalysis showed that tetracarboxylic

acid (**151**) had been isolated as a mono hydrate.



(150)

a , n = 1 , 90%
b , n = 2 , 73%



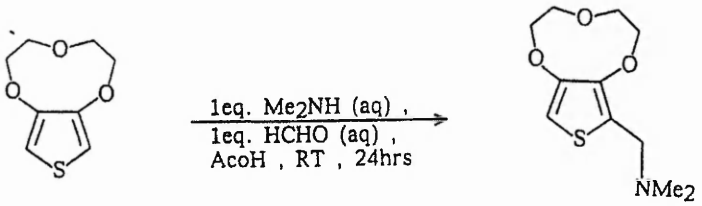
(151)

52%

No further work was done on compound (**151**) due to the lack of material, a situation arising from the disappointing yields obtained in the initial cyclisation step, compounded by the yields given by the subsequent hydrolysis of the tetra ester.

Decarboxylation of the dicarboxylic acid derivative, (**150a**), by treatment with copper(I) oxide and quinoline as discussed in Section 4.3.1, (page 106), gave the desired [1+1] dialkoxythiophene, 2,5,8-trioxa-11-thiabicyclo[7.3.0]dodeca-1(12),9-diene, (**59d**), as an oil in a yield of 74%. This was employed in the Mannich reaction, using the standard conditions given in Section 4.3.2, (page 107), and gave high yields of the desired Mannich base, (**152**), (Equation 28).

Equation 28



(59d)

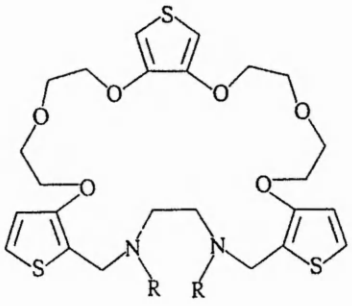
(152)

89%

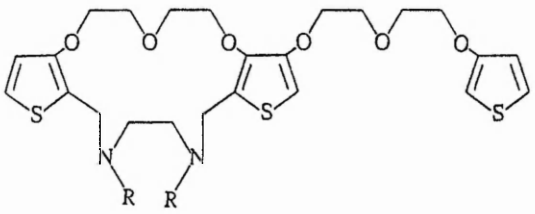
The high yields of the tertiary amine, (**152**), in this reaction indicates a lack of steric hindrance about the 2 and 5 positions of compound (**59d**).

4.4.4 The Synthesis and Mannich Reaction of 3,4-Bis[5'-(3''-thienyloxy)-3'-oxapentyloxy]thiophene, (**96**)

The Mannich reaction of the title compound, (**96**), posed an interesting question; since the molecule possesses both a 3,4-dialkoxythiophene moiety and two 3-alkoxythiophene moieties, how would it undergo the Mannich reaction with 1equivalent of a secondary diamine? Would it give the product arising from the electrophilic substitution at the two 2 positions of the 3-alkoxythiophene units, (**153a**), or would the substitution occur so as to bridge the 3-alkoxy- and 3,4-dialkoxythiophene units, (**153b**).



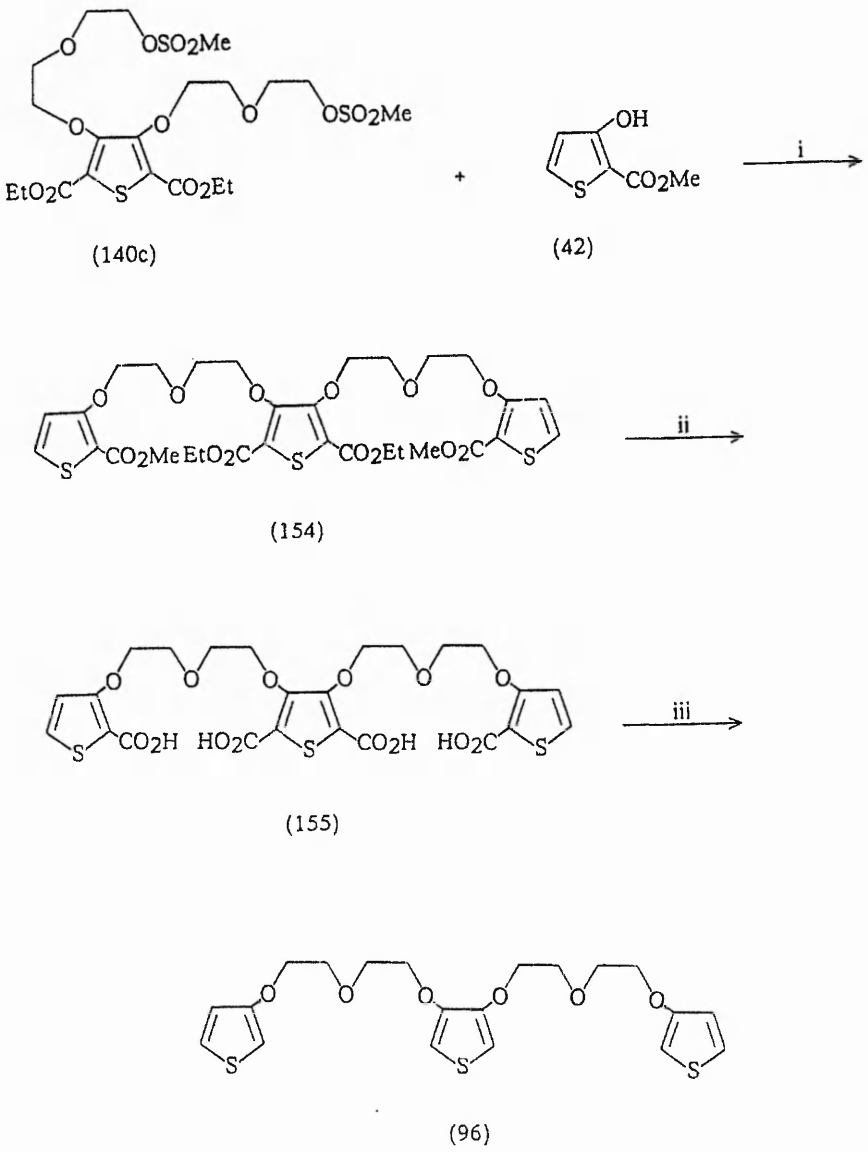
(153a)



(153b)

Application of the techniques already developed in this work led to the desired trithienyloxy derivative (**96**), *via* the steps illustrated in Scheme 38.

Scheme 38



(140c) (42) (154) (155) (96)

(i) K_2CO_3, DMF, Δ, 100°C, 12hrs, (yield, 75%); (ii) NaOH, H_2O, EtOH, Δ, 1hr, (yield, 92%); (iii) Cu_2O, quinoline, Δ, 180°C, ¾hr, N_2, (yield, 81%).

Reaction of (**96**) with aqueous formaldehyde and piperidine in acetic acid afforded only one isolable product, in a yield of 49%. N.m.r. spectroscopy was invaluable in the identification of this product; the essential features were:-

i) singlet (2H) at 6·25 ppm associated with protons in the 2 and 5

positions of a 3,4-dialkoxythiophene,

ii) doublet (2H) centred on 6·79 ppm, (J, 5·28 Hz), associated with protons in the 4 position of a 2-substituted 3-alkoxythiophene,

iii) doublet (2H) centred on 7·08 ppm, (J, 5·60 Hz), associated with protons in the 5 position of a 2-substituted 3-alkoxythiophene.

iv) two peaks at 98·2 ppm, (C-2/5), and 147·0 ppm, (C-3/4), associated with an unsubstituted 3,4-dialkoxythiophene.

v) four peaks at 117·7 ppm, (C-4), 118·0 ppm, (C-2), 122·4 ppm, (C-4), and 154·1 ppm, (C-3), associated with a 2-substituted 3-alkoxythiophene.

Clearly, with such a symmetrical pattern, the product isolated was (**153a**). The n.m.r. spectra for a compound with a structure like that shown by compound (**153b**), would be very different, the salient features of this compound would be:-

i) three peaks at *ca.* 6·1, 6·7, and 7·10 ppm, associated with the protons of a 3-alkoxythiophene.

ii) two peaks at *ca.* 6·8 and 7·1 ppm associated with the protons of a 2-substituted 3-alkoxythiophene.

iii) one peak at *ca.* 6·1 ppm associated with the proton of a 2-substituted 3,4-dialkoxythiophene.

iv) four peaks at *ca.* 97 ppm, (C-2), 120 ppm, (C-4), 125 ppm, (C-5), and 158 ppm, (C-3), associated with a 3-alkoxythiophene.

v) four peaks at *ca.* 116 ppm, (C-4), 117 ppm, (C-2), 123 ppm, (C-5), and 155 ppm, (C-3), associated with a 2-substituted 3-alkoxythiophene.

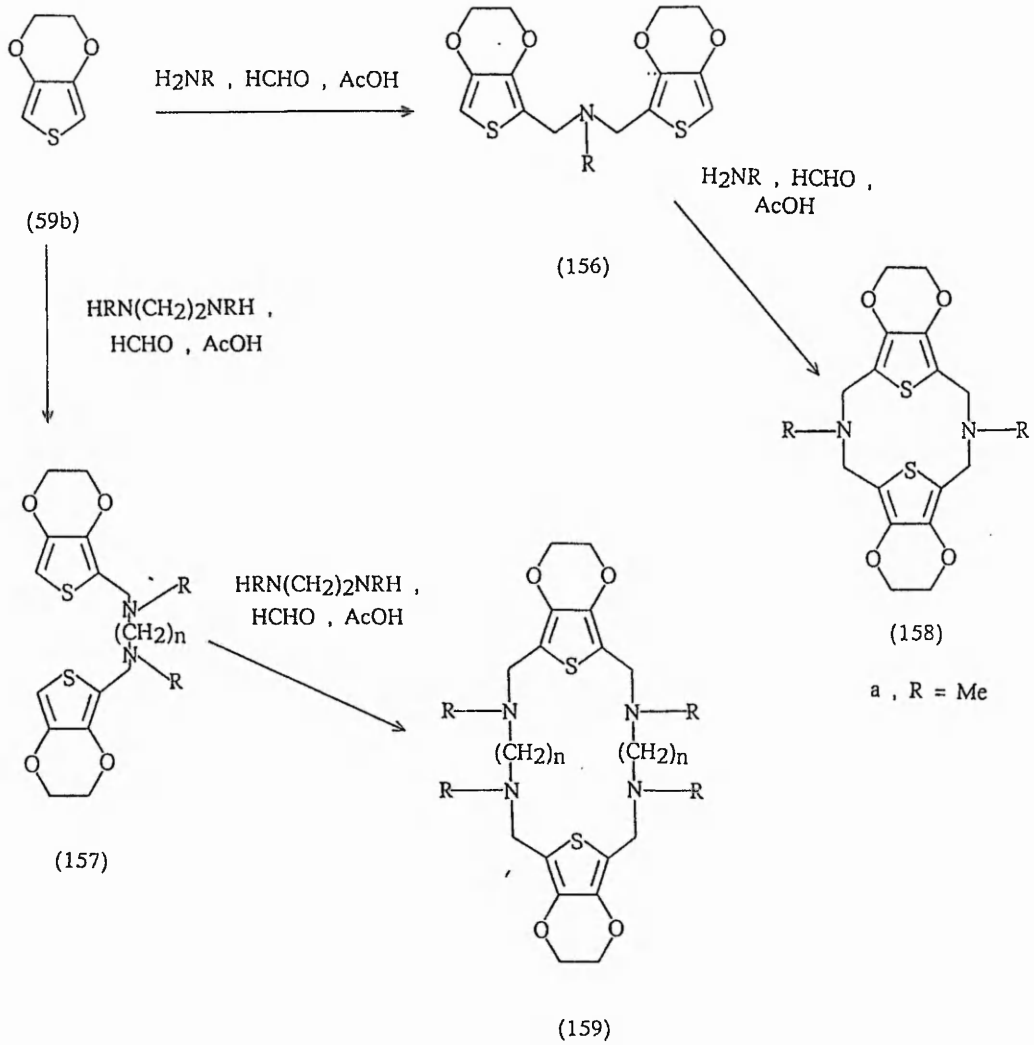
vi) four peaks at *ca.* 94 ppm, (C-5), 124 ppm, (C-2), 145 ppm, (C-3), and 150 ppm, (C-4), associated with a 2-substituted 3,4-dialkoxythiophene.

4.5 The Macrocyclisation of 3,4-Dioxygenated Thiophene Systems using the Mannich Reaction

4.5.1 Introduction

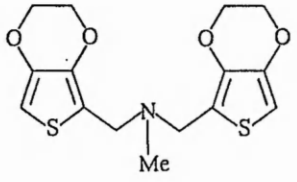
This work centred on the use of reactive 3,4-dioxygenated thiophene compounds, in the Mannich reaction with primary amines and secondary diamines using the conditions described previously. Initially, because of it's accessibility, exploratory work focused on 3,4-ethylenedioxythiophene, (**59b**), as a model compound. By the various successions of Mannich reactions illustrated in Scheme 39, it was hoped that the bis- and tetra-aza macrocycles (**158**) and (**159**) might be obtained.

Scheme 39



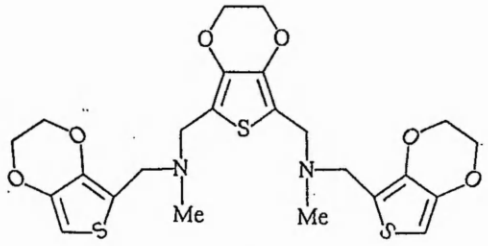
4.5.2 Synthesis of the Bis 2-Thienylmethyl Mannich Bases

The work described in Section 4.3.3, (page 109), suggested that a combination of 3,4-ethylenedioxythiophene and primary or secondary amine would give a series of bis 2-thienylmethyl Mannich bases at room temperature, with a minimum of polymerisation. Thus, the reaction of methylamine and two equivalents of 3,4-ethylenedioxythiophene was initially performed under non-high dilution conditions, which, with two equivalents of formaldehyde gave the desired Mannich base, (**156a**), (37%), accompanied by the oligomeric tri 3,4-ethylenedioxythiophene compound, (**160**), (21%). The latter was easily identifiable, since it's carbon-13 n.m.r. spectrum showed six peaks in the aromatic region, two peaks arising from a symmetrically substituted 3,4-ethylenedioxythiophene moiety, and four peaks ascribed to a 3,4-ethylenedioxythiophene ring substituted in the 2 position.



(156a)

37%

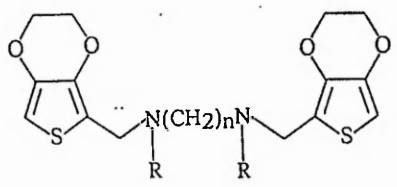


(160)

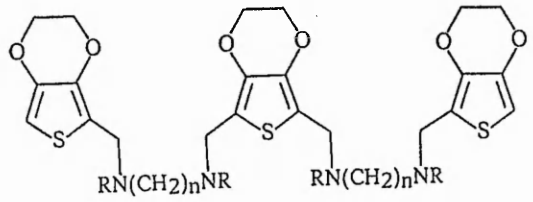
21%

Unfortunately, under these reaction conditions with the secondary diamines *N,N'*-dimethylethylenediamine and piperazine, polymerisation was extensive. The former diamine gave a polymeric oil which was highly unstable, darkening rapidly in the air. Piperazine afforded high yields, (>80%), of an amorphous white solid, possessing high thermal stability, not decomposing until *ca.* 300°C. In view of these disappointing results, a series of high dilution Mannich reactions were performed in which separate glacial acetic acid solutions of 3,4-ethylenedioxythiophene and the diamine, together with two equivalents of

aqueous formaldehyde were fed at a rate of 2·2 mmolhr^{-1} into a further small volume of glacial acetic acid The same two secondary diamines were employed in this study, and a third, (*N,N'*-dimethyl-1,3-propanediamine), was also used. Under these conditions polymerisation was still the dominating reaction, although this tendency was at its lowest with *N,N'*-dimethylethylenediamine, which gave the highest yield, (45%), of the desired bis (2'-thienylmethyl) derivative, (**157a**). the homologous *N,N'*-dimethyl-1,3-propanediamine showed the greatest tendency to polymerise, with the result that only a 12% yield of compound (**157b**) was obtained. 1,4-Bis(3',4'-ethylenedioxy-2'-thienylmethyl)piperazine, (**157c**), was given in a yield intermediate between the previous two, (22%). The nature of compounds (**157a–c**) was clear from their n.m.r. spectra and mass spectra. In all cases, the bis(2'-thienylmethyl) derivatives were accompanied by small quantities of the oligomer corresponding to the tri 3,4-ethylenedioxythienyl species, (**161a–c**).



(157)



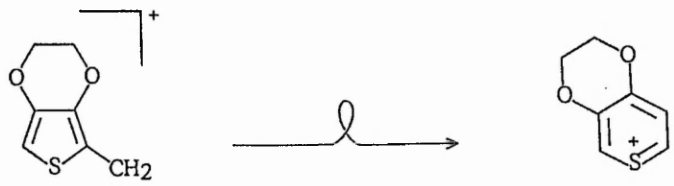
(161)

	(157)	(161)
a , R = Me , n = 2	45%	7%
b , R = Me , n = 3	12%	6%
c , R,R = CH_2CH_2 , n = 2	22%	9%

Neither of the oligomers (**161a**) nor (**161b**) were sufficiently stable when isolated to obtain microanalytical data or mass spectra. The mass spectra of (**157c**) and (**161c**) are worthy of further discussion. In common with all the 2-thienylmethyl Mannich bases, compound (**157c**) gave an intense peak with an m/e value of 155, (89%). This was attributed to a 3,4-ethylenedioxy-2-methylenethiophene

fragment, (**162a**), which by comparison with what is known about 2-alkylthiophenes in mass spectroscopy, may be assumed to undergo a rearrangement to a thiopyrylium ion, (**162b**), (Figure 35). This is comparable with the cycloheptatriene cation, (the tropylium ion), obtained when toluene is subjected to mass spectoscopic analysis. The only other peak of any note was that with an m/e value of 239, (100%) corresponding to the loss of fragment (**162a**) from the molecule (**157c**).

Figure 35

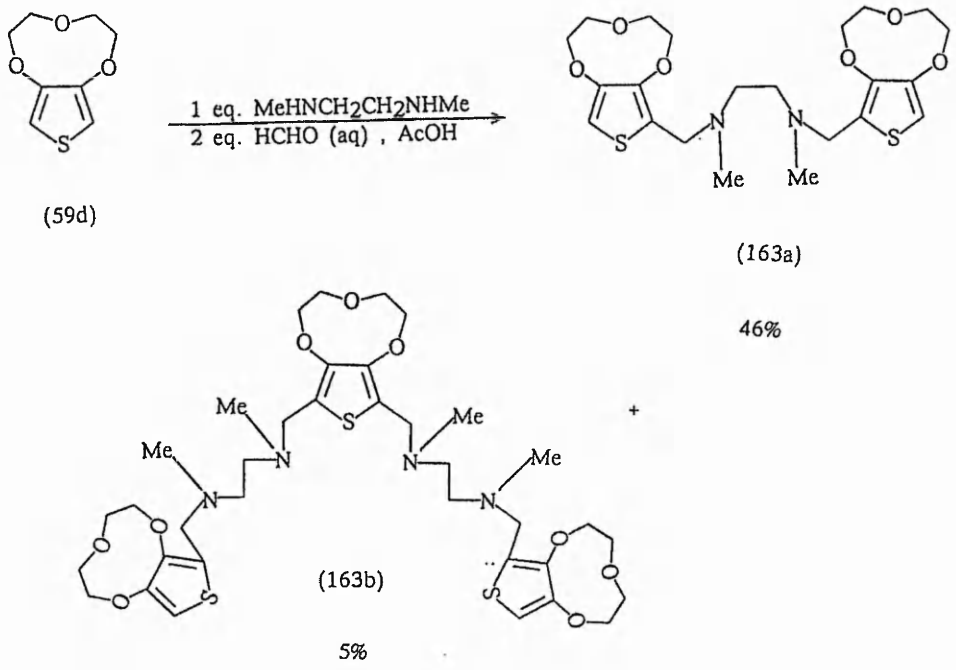


(162a) (162b)

In comparison, (**161c**) showed two main peaks, one at m/e 143, (95%) and the other with m/e 221, (100%), the peak m/e 155 having an intensity of only 3% in this case.

The reactive thiophene macrocycle, (**59d**), was also used in the synthesis of a bis 2-thienylmethyl compound, by the reaction with *N,N'*-dimethylethylenediamine and two equivalents of formaldehyde under high diution conditions just described. This gave compound (**163a**), (46%), accompanied by the complex tetraamine, (**163b**), (5%), (Equation 29). Compound (**163b**), like the related compounds (**161a–c**), was not sufficiently stable to permit mass spectroscopic analysis or microanalysis, but n.m.r. spectroscopy supported the structural assignment given.

Equation 29



(59d)

(163a)

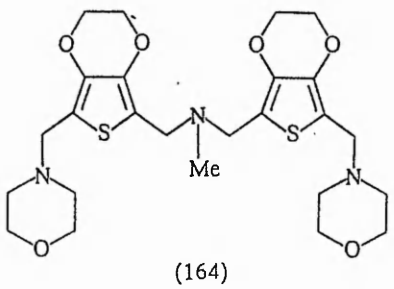
46%

(163b)

5%

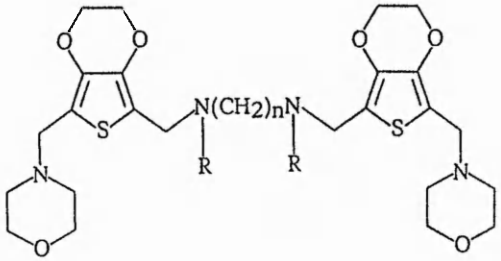
4.5.3 Macrocyclisation of the 2-Thienylmethyl Mannich Bases

In a preliminary study of the behaviour towards a further Mannich reaction of the 2-thienylmethyl Mannich bases, (Section 4.5.2, page 144), (**156a**) and (**157a–c**), the bases were treated with morpholine and two equivalents of formaldehyde as described in Section 4.3.7, (page 121). In this way, a series of bis 4-[(3',4'-ethylenedioxy-2'-thienyl)methyl]-morpholine derivatives, (**164**) and (**165a–c**) were prepared in excellent yields.



(164)

97%



(165)

a , R = Me , n = 2 , 97%
b , R = Me , n = 3 , 92%
c , R,R = CH_2CH_2 , n = 2 , 83%

These compounds were stable enough to provide microanalytical data, although they darkened on very prolonged exposure to daylight. Their stability was however, much greater than those bis Mannich bases obtained by further reaction of *N*-[(3,4-ethylenedioxy-2-thienyl)methyl]-dimethylamine, (**113a**), (Section 4.3.3, page 109).

In the initial synthesis of the bis 2-thienylmethyl Mannich bases (**156a**) and (**160a-c**), much polymeric material was obtained even though the reaction was performed at room temperature. This fact, and the results from the syntheses of the bis 4-[(3',4'-ethylenedioxy-2'-thienyl)methyl]-morpholine derivatives reported above, gave weight to the idea that, by reaction under high dilution conditions of the bis 2-thienylmethyl compounds (**156a**) or (**157a-c**), with a further moiety of primary amine or secondary diamine, and the required amounts of formaldehyde, the desired macrocyclic polyamine, (**158**) or (**159**), would be obtained. Because the Mannich bases (**156a**) and (**157a**) were afforded in the greatest yields, initial macrocyclisation work centred on their further Mannich reactions with methylamine and *N,N'*-dimethylethylenediamine, respectively.

When the Mannich base, (**156a**) was reacted with methylamine and two equivalents of formaldehyde under high dilution conditions at room temperature, no macrocyclic material, (**158a**), was obtained, instead much polymer and some starting material, (**156a**), (21%), was returned. Similarly, the Mannich base (**157a**) and *N,N'*-dimethylethylenediamine gave solely polymeric material.

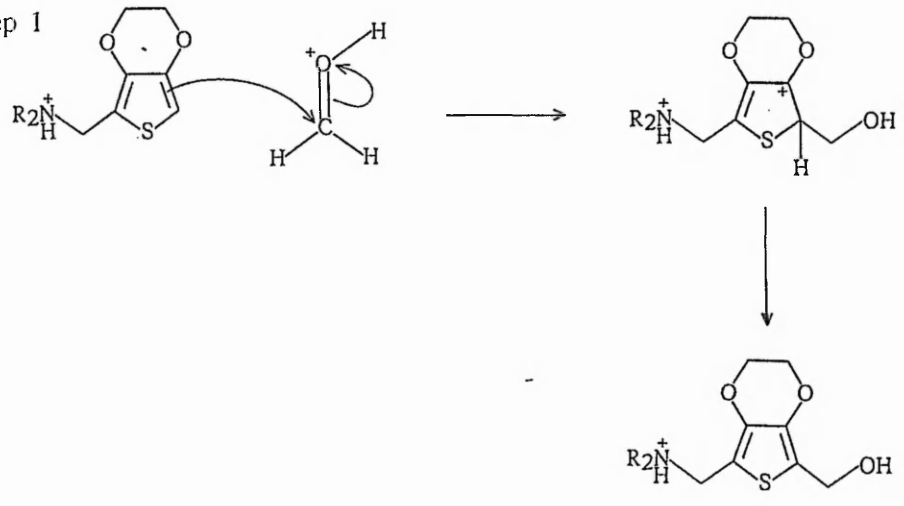
The fact that the former reaction gave some unreacted starting material may be rationalised if one considers that 3,4-ethylenedioxythiophene, formaldehyde and methylamine reacted under non-high dilution conditions to give some of the Mannich base (**156a**), whereas under identical conditions, the secondary diamines yielded only polymers. It may be concluded therefore that methylamine is less reactive under these conditions than those secondary

diamines here employed, thus explaining why, when compound (**156a**) was further treated with another portion of methylamine, some of it was recovered.

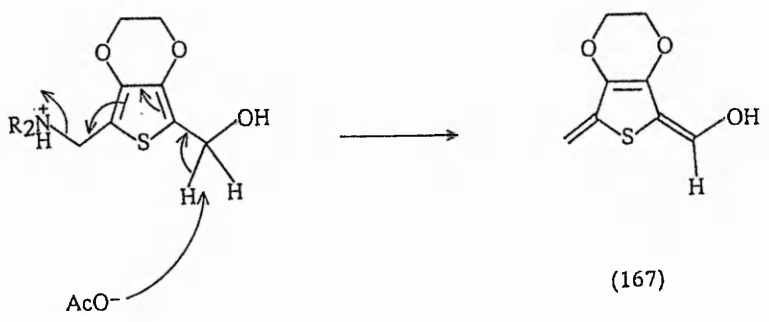
A common problem encountered in high dilution experiments is that when the rate of addition of the reagents exceeds their rate of reaction, predominantly polymeric material is produced. In order to discover if this was the case here, the above experiments were repeated using the same rate of addition, this time to a suspension of nickel(Ⅱ) acetate in acetic acid at 100°C. However, neither compounds (**156a**) or (**157a**) afforded the macrocycles (**158a**) or (**159a**), instead the only material isolated was the compound 3,4-ethylenedioxy-5-methylthiophene-2-carboxaldehyde, (**166**), in yields of 14% and 19%, respectively. The production of the aldehyde is easily explained, bearing in mind that glacial acetic acid was used as a solvent. Given the acidic nature of the solvent, it is reasonable to assume that both the tertiary amine of the starting material, and any formaldehyde not already reacted to form the immonium electrophile of the Mannich reaction, are in protonated states. Initially, the electrophilic protonated formaldehyde substitutes at the vacant 5 position of the thiophene ring, (Scheme 40). This is followed by a 1,6-Hofmann-like elimination, giving a 3-thiolene derivative, (**167**), which rearranges to the methylthiophene derivative, (**166**).

Scheme 40

Step 1

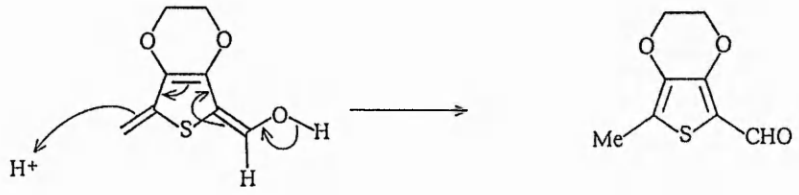


Step 2



(167)

Step 3



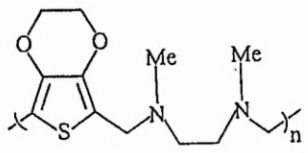
(166)

No further work was done in the synthesis of the macrocycle (**158a**), since on reflection, it was felt that such a cyclisation reaction would be unfavourable due to the nearness of the lone pairs of electrons on the sulfur atoms of the thiophene rings to each other. Thus, further work focused on the synthesis of the macrocycles (**159a–c**), derived from secondary diamines.

Since only polymeric material had been isolated thus far, the next line of investigation involved the use of a template cation, the idea being to enforce a favourable conformation on the reagents for a macrocyclic reaction to occur, as opposed to simple polymerisation. A host of macrocycles similar to those proposed in the work presented here, have been prepared by employing a nickel(Ⅱ) salt as a template; typically, these were isolated as complexes of that salt.[7, 171] By repeating the high dilution work described above, with the Mannich base (**157a**) and *N,N'*-dimethylethylenediamine, the Mannich reaction was performed in the presence of nickel(Ⅱ) acetate in acetic acid at 100°C. This process also afforded 3,4-ethylenedioxy-5-methylthiophene-2-carboxaldehyde,

(166), (23%) as the major product; however this was accompanied by a pale brown solid, (6%), which was of some interest.

The carbon-13 n.m.r. spectrum of this material was commensurate with a symmetrically substituted thiophene ring, the aromatic region of the spectrum showing two peaks, one at 112·7 ppm corresponding to carbons 2 and 5, the other peak at 138·4 ppm pertaining to the carbons at positions 3 and 4 of the heterocyclic ring. These values were consistent with those found for other bis Mannich bases derived from 3,4-ethylenedioxythiophene. However neither the carbon-13 nor proton n.m.r. spectra showed any evidence of the existence of a complex between any macrocycle and the nickel(Ⅱ) salt. The unitary nature of this compound is in doubt since the n.m.r. spectra would not distinguish between the macrocycle (**159a**) and the polymer (**168**). Upon removal of the deuterated chloroform used as an n.m.r. solvent, the material had undergone severe degradation, thus preventing mass spectroscopic analysis. Repetition of this experiment, whilst always providing aldehyde (**166**), failed to yield any further such Mannich base.



(168)

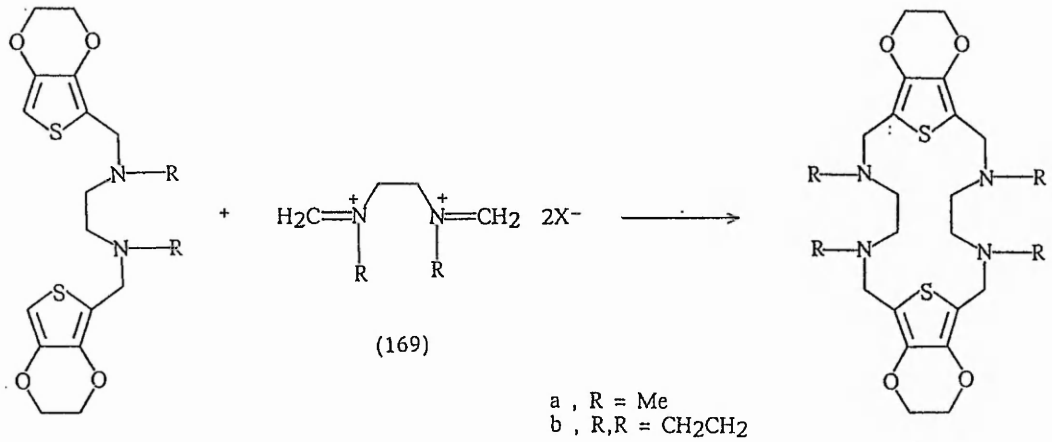
Irrespective of whether nickel(Ⅱ) acetate was used as a template or not, when such conditions were applied to the bis 2-thienylmethyl Mannich bases (**157b**) and (**157c**), and the secondary diamines *N,N'*-dimethyl-1,3-propanediamine and piperazine, respectively, the only isolable product was again the aromatic aldehyde, (**166**).

4.6 Attempted Synthesis of Bis Immonium Salts derived from Tertiary Amines

4.6.1 Introduction

Given the greater reactivity of *N,N*-dimethylmethyleneammonium chloride than to it's acetate counterpart, (formed *in situ* in the Mannich reactions involving dimethylamine employed earlier), the final strategy employed, was the attempted synthesis of bis immonium ions, (**169**). One may assume that these are formed as intermediates in Mannich reactions involving *N,N'*-dimethylethylenediamine and piperazine; if these preformed bis immonium salts were also more reactive than their *in situ* equivalents, then reaction with the Mannich bases (**157a**) or (**157c**) under suitable conditions should afford the macrocycles (**159a**) or (**159c**), Equation 30.

Eqation 30



(157) (169) (159)

The common procedure for the synthesis of such immonium salts is the reaction of the aminal *N,N,N',N'*-teraalkylmethylenediamine with carboxylic acid derivatives[165, 172] or with other reactive species.[173] However, with the diamines employed in the present work, such a strategy is not practical, and others were investigated.

4.6.2 The Action of Trifluoroacetic Anhydride on *N,N'*-Dioxides

A synthesis which could be applied to this work was reported by Ahond *et al.*,[174] who reported the simple cleavage of the nitrogen-oxygen bond of trimethylamine *N*-oxide by the action of trifluoroacetic anhydride, to afford *N,N*-dimethylmethyleneammonium trifluoroacetate. It was decided to apply a similar process to the *N,N*-dioxides of *N,N,N',N'*-tetramethylethylenediamine and 1,4-dimethylpiperazine.

Whilst the synthesis of 1,4-dimethylpiperazine *N,N'*-dioxide was easily accomplished,[175] that of *N,N,N',N'*-tetramethylethylenediamine *N,N'*-dioxide was less straightforward, requiring more forceful conditions in which the diamine was treated with a large excess of hydrogen peroxide for a prolonged period of time. The product of this reaction was isolated as a dihydrate,[176] and attempts to remove the two molecules of water led to complete degradation of the material.

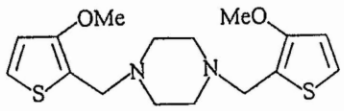
Both these *N,N'*-dioxides, on treatment with trifluoroacetic anhydride afforded a purple residue, which, (because of the highly reactive nature of such salts),was used immediately. In order to ascertain the reactivity of any bis immonium salt that may have been formed, each residue was treated with a solution of 3-methoxythiophene in acetonitrile under nitrogen. However, no Mannich base was detected in either case, much of the thiophene component, (*ca.* 80%), being recovered. Spectroscopic analysis of the reisdue pointed to decomposition having occurred. No better results were obtained when the reaction was carried out at lower temperatures, so this approach was not pursued.

4.6.3 The Action of Triphenylcarbenium Tetrafluoroborate on Tertiary Diamines

A number of research groups had some success in reacting a range of dialkylmethylamines with triphenylcarbenium perchlorate, to generate *N,N*-dialkyl-

methyleneammonium perchlorate salts,[165, 177] and the behaviour of the salts towards unsymmetrical ketones was studied.[165] The present author felt that any procedure involving such perchlorate salts would work equally well where the counter ion was the tetrafluoroborate anion. Thus the reactions of *N,N,N',N'*-tetramethylethylenediamine and 1,4-dimethylpiperazine with triphenylcarbenium tetrafluoroborate was performed according to the procedure given by Voltz and Kiltz.[177]

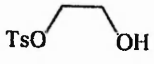
Whilst no isolable salt was given with the former amine, 1,4-dimethylpiperazine afforded a hygroscopic orange powder which was not soluble in a range of solvents, and could not therefore be subjected to n.m.r. analysis. However, reaction of this residue with 3-methoxythiophene in acetonitrile did give 1,4-bis[(3'-methoxy-2'-thienyl)methyl]-piperazine, (**170**), in very low yields, (9%). Compound (**170**) was prepared more efficiently, (84%), by the reaction of 3-methoxythiophene, formaldehyde and piperazine in acetic acid, using conditions previously developed by Barker *et al.*[141]



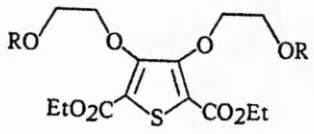
(170)

5. Work for Further Investigation

The aim of this project was to sythesise compounds with a box-like structure, using the Mannich reaction, and the work done thus far has been limited because of the low yields obtained for the [2+2] macrocycle, (**98**). The synthesis of this compound was problematic because of the competing reactions of polymerisation and [1+1] cyclisation. Using the procedure described by Börjesson and Welch,[152] it should be possible to synthesise the mono tosylate ester of ethane-1,2-diol, *ie.* 2-tosyloxyethan-1-ol, (**171**). Reaction of this with diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate, (**33a**), according to the method developed earlier, (page 133), would be expected to give the bis alcohol, (**172a**); such a compound, and its bis methane sulfonyl ester, (**172b**), potentially offer three routes, A, B, and C, to macrocyclic material, (Scheme 41).



(171)



(172)

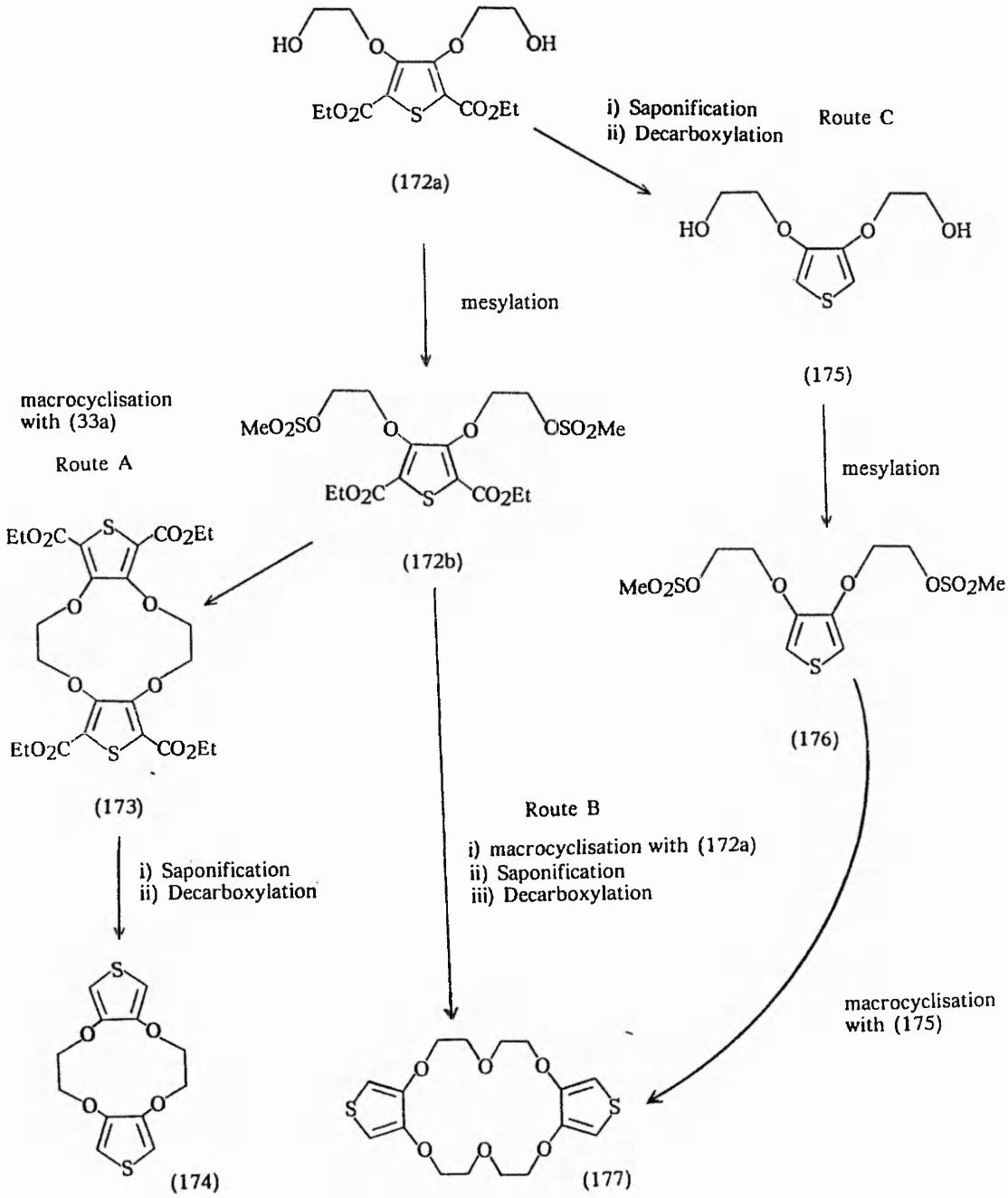
a , R = H
b , R = $MeSO_2$

By the [1+1] reaction of (**172b**) and (**33a**), using the conditions given in Equation 27, (page 136), it should be possible to synthesise macrocycle (**173**), (Route A). The properties of this compound and it's decarboxylated homologue, (**174**), could then be compared with those of their 3,4-ethylenedioxythiophene counterparts. Also using similar reaction conditions to those illustated in Equation 27, one could prepare (**98**) by the [1+1] condensation of (**172a**) and (**172b**), as shown by Route B.

However, of most interest would be the strategy shown by Route C. In this, (**172a**) is saponified and then decarboxylated, to afford 3,4-bis(2'-hydroxyethoxy)thiophene, (**175**). Mesylation of this to give (**176**),

3,4-bis(2'-hydroxyethoxy)thiophene, (175). Mesylation of this to give (176), followed by a [1+1] cyclisation reaction with (175) would then afford macrocycle (177). The clear advantage of this route over Route B is that material suitable for study in a Mannich reaction is given directly; the macrocyclisation reaction, (likely to be the least efficient step), is performed last, thus obviating the need to saponify and decarboxylate potentially small quantities of material.

Scheme 41



6. Experimental

6.1 General

All reagents and solvents were used as supplied unless otherwise stated. In experiments where potassium fluoride is used, the laboratory grade anhydrous salt was finely ground, and heated to constant weight at 180°C, then stored in a desiccator. Before use, the salt was dried at 180°C for three hours and re-ground in a warm mortar. In general, organic solutions of products were dried ($MgSO_4$), filtered, and the solvent was removed by rotary evaporation. Solvents for chromatographic analysis were distilled prior to use. Unless otherwise stated, light petroleum refers to the fraction b.p. 40–60°C.

6.2 Chromatographic Analysis

For thin layer chromatography, (t.l.c.), 250 μm silica gel 60A MK 6F plates were used, purchased from Whatman International Limited. Alumina plates were aluminium oxide $150F_{254}$, neutral (type T), layer thickness 0·2mm, purchased from Merck.

For column chromatography, silica gel 0·06–0·2 mm, pore diameter *ca.* 4 nm was employed, obtained from Acros Limited. Alumina was neutral Brockmann Grade 1 for chromatographic analysis purchased from B.D.H. Limited.

For centrifugal chromatography, a Chromatotron Model 7924 T was used, purchased from T.C. Research, Norwich, UK. The adsorbents used to coat the rotors were silica gel $60PF_{254}$, containing gypsum and aluminium oxide, $60PF_{254}$, Type E, both purchased from Merck. The coatings with alumina were glue bound to the rotors, using Unibond™ PVA Adhesive, added at a rate of 1·5 cm^3 per 60 g of adsorbent, to the initial slurry.

6.3 Instrumentation

Where a syringe pump was used, the type was a model A pump fitted with motors colour coded yellow, manufactured by Razel Scientific Instruments Inc., Stamford, Connecticut, USA. These motors gave flow rates of 0·661, 1·179 and 2·412 cm^3hr^{-1} with 10, 20, and 50 cm^3 syringes, respectively.

Melting points were taken on a Gallenkamp apparatus model 3A 5120, and are reported uncorrected.

Infrared spectra were taken on either a Perkin-Elmer model 782 or a Perkin-Elmer 1600 series F.T.I.R. Spectrophotometer. Nuclear magnetic resonance spectroscopy, (n.m.r.) was performed with a Jeol EX 270 MHz machine; solvents used were deuterated chloroform or deuterated dimethyl sulfoxide. The solvent is specified in the experimental section in parenthesis before the n.m.r. data.

Mass spectroscopy and gas chromatography-mass spectra were provided by the Analytical Chemistry section of Nottingham Trent University, and microanalyses were carried out by the University of Nottingham analytical services department.

6.4 Synthesis of the Oxygenated Thiophene Systems

6.4.1 Synthesis of Dialkyl 3,4-Dihydroxythiophene-2,5-dicarboxylates

6.4.1.1 Synthesis of the Precursors

Pentyl chloroacetate

To a cooled stirred solution of pentan-1-ol (20·95 g, 0·24 mols) and dry pyridine (20 cm^3) in dry diethyl ether (100 cm^3), was added chloroacetyl chloride (28·36 g, 0·25 mols), dropwise over a period of 1 hour. Stirring was continued for a further 2 hours. The ethereal solution was washed with water (3×30 cm^3), after removal of the solvent, the residue was distilled at 66-8°C at 2 mmHg, (Lit.[178], 90-2°C at 18 mmHg) to give the required ester as a

colourless liquid, (33·15 g, 84%).

Diethyl thiodiglycollate, (**99**)

To ethyl chloroacetate (229·08 g, 1·87 mols), and benzyl-tri-*n*-butylammonium bromide (3·21 g, 9mmols) was added a solution of sodium sulfide nonohydrate (224·63 g, 0·94 mols) in the minimum volume of water, over a period of 2 hours, with mechanical stirring. Stirring was continued for a further 4 hours, the organic layer was separated, dried ($MgSO_4$) and distilled, to give the desired product as a colourless liquid, (150·36 g, 78%), b.p. 140–2°C/13 mmHg, (Lit.[153] 135–6°C/10 mmHg).

Dipentyl thiodiglycollate, (**148**)

This was prepared as described above from pentylchloroacetate (20·26 g, 0·12 mols), sodium sulfide nonohydrate (16·33 g, 0·07 mols) and benzyl-tri-*n*-butylammonium bromide (0·40 g, 1·1 mmols). In this case, the mixture was stirred at room temperature for 20 hours. Work-up as before gave the title ester as a pale yellow oil, (12·70 g, 73%), b.p. 177–8°C/3·5 mmHg, (Lit.[154] 202°C/18 mmHg).

6.4.1.2 Synthesis of the Thiophene Ring Systems

Diethyl 3,4-Dihydroxythiophene-2,5-dicarboxylate, (**33a**)

To sodium metal (49·91 g, 2·17 mols) was added freshly dried absolute ethanol (1 dm^3), with ice cooling. When the sodium ethoxide solution had cooled, a mixture of diethyl oxalate (119·74 g, 0·82 mols) and diethyl thiodiglycollate (140·21 g, 0·68 mols) was added, with efficient stirring. The reaction mixture was allowed to stand for 48 hours, then the bright yellow disodium salt, (**33b**) was filtered off and washed with diethyl ether. In subsequent experiments, requiring use of the disodium salt, this material was

employed without further purification.

The disodium salt was dissolved in water, the solution was filtered and the filtrate was acidified with hydrochloric acid (4M). The precipitate was filtered off and recrystallised from ethanol to give the dihydroxythiophene, (**33a**), as an off-white crystalline solid, (134·37 g, 76%), m.p. 133-5°C, (Lit.[154] 134·5-5°C).

Dipentyl 3,4-Dihydroxythiophene-2,5-dicarboxylate, (**147a**)

Method A

Sodium metal (0·92 g, 0·04 mols) was dissolved in pentan-1-ol (50 cm^3), then a mixture of dipentyl thiodiglycollate (4·07 g, 14·14 mmols) and diethyl oxalate (2·22 g, 10·68 mmols) was added with stirring. The reaction was stirred for 12 hours, whereupon a gelatinous orange precipitate had developed. This was filtered off, the filtrate was evaporated *in vacuo* to yield a further portion of an orange waxy solid. The two solids were combined and added to hydrochloric acid (4M, 30 cm^3), the mixture was warmed on a steam bath and any solid matter broken up. Once all organic matter had melted, the solution was cooled. The precipitate was filtered off and recrystallised from aqueous ethanol, to give the desired product, as an orange waxy solid, (2·24 g, 46%), m.p. 70-1°C, (Lit.[107] 71-2°C).

Method B

The title compound was also synthesised in essentially the same yield, by replacing dipentyl thiodiglycollate with diethyl thiodiglycollate.

6.5 Synthesis of the 4-Methylbenzenesulfonate Esters

1,5-Ditosyloxy-3-oxapentane, (**101**)

Diethylene glycol (45·44 g, 0·43 mols) and dry pyridine (300 cm^3) were stirred mechanically at 5°C. 4-Methylbenzenesulfonyl chloride (179·20 g, 0·94 mols)

was added at such a rate that the temperature did not rise above 10°C; the addition took 2 hours. The mixture was stirred for a further 3 hours, then poured onto crushed ice (1 dm^3) and concentrated hydrochloric acid (50 cm^3). The mixture was further acidified with dilute hydrochloric acid (4M, 150 cm^3) followed by ice cold water (150 cm^3). The product was recrystallised from methylated spirits to give fine white needles of the desired compound, (136·03 g, 76%), m.p. 88-9·5°C, (Lit.[156] 88-9°C).

The following comounds were synthesised in the manner just described:

1,8-Ditosyloxy-3,6-dioxaoctane, (**102**)

The product was recrystallised from methylated spirits to give a fine white powder, (80%), m.p. 78-80°C, (Lit.[157] 81-2°C).

1-Tosyloxy-3-oxapentane, (**100**)

Upon acidification the crude product separated out as an oil. This was removed and the aqueous portion was extracted with dichloromethane (2 × 30 cm^3). The combined organic phases were worked up as usual and the combined oils were distilled to give the desired product, (61%), b.p. 152-5°C/0·3 mmHg, (Lit.[155b] 122°C/0·1 mmHg).

5-Tosyloxy-3-oxapentan-1-ol, (**94**)

4-Methylbenzenesulfonyl chloride (9·53 g, 0·05mols) in dichloromethane (200 cm^3) was added dropwise to a stirred solution of diethylene glycol (20·16g, 0·19 mols), triethylamine (18·91 g, 0·19 mols) and 4-dimethylaminopyridine (0·31 g, 2·46 mmols) in dichloromethane (750 cm^3) over a 2 hour period with efficient ice cooling throughout.

When the addition was complete, the solution was allowed to warm to

room temperature and stirred for a further 3 hours. The reaction mixture was then concentrated to half its volume at the rotary evaporator. The organic phase was washed with saturated sodium bicarbonate solution (3 × 50 cm^3) followed by citric acid solution (10%, 3 × 100 cm^3). Removal of the solvent left an oil, which was purified by column chromatography (silica; dichloromethane–ethanol 0–5%). The desired product was isolated as a pale yellow oil, (8·19 g, 63%). The proton n.m.r. spectrum was in accordance with that cited.[152]

6.6 Synthesis of Dialkyl 3,4-Dimethoxythiophene-2,5-dicarboxylates

Diethyl 3,4-Dimethoxythiophene-2,5-dicarboxylate, (33c)

Method A[119]

To the disodium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate (6·08 g, 0·02 mols) was added dimethyl sulfate (15 cm^3). The mixture was heated on a steam bath for 30 minutes with occasional stirring. The excess of dimethyl sulfate was removed *in vacuo*, the residue was treated with sodium carbonate solution (10%, 10 cm^3) and stirred for 15 minutes. Upon cooling, a solid formed; it was collected by filtration and recrystallised from aqueous methanol to give white crystals (3·11 g, 54%), m.p. 51–3°C, (Lit.[115] 52–3°C).

Method B

To a stirred mixture of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate (0·99 g, 3·85 mmols) and anhydrous potassium carbonate (0·60 g, 4·35 mmols) in DMF (10 cm^3) was added dimethyl sulfate (0·4 cm^3, 4·21 mmols). The reaction was maintained in an oil bath at 100°C overnight. Moisture was excluded by means of a calcium chloride guard tube. The cold reaction mixture was filtered and the inorganic residue was washed with acetone (20 cm^3). The solvents were removed *in vacuo* to give a brown solid which was recrystallised from aqueous methanol to give an identical product to that produced in Method A, (0·70 g, 64%).

Dipentyl 3,4-dimethoxythiophene-2,5-dicarboxylate, (**147b**)

Dipentyl 3,4-dihydroxythiophene-2,5-dicarboxylate (0·44 g, 1·28 mmols) and anhydrous potassium carbonate (0·35 g, 2·54 mmols) were stirred mechanically in acetone (20 cm^3). To this was added dimethyl sulfate (0·24 cm^3, 2·54 mmols). The mixture was heated under reflux for 5 hours, whereupon the dihydroxythiophene moiety appeared to have reacted (t.l.c., silica; light petroleum-EtOAc, 5:1). The desired *dipentyl 3,4-dimethoxythiophene-2,5-dicarboxylate* was isolated as a pale yellow oil, (0·32 g, 70%); ν_{max}(film) 2980, 2920, 2860 and 1710 cm^{-1}; $\delta_H(CDCl_3)$ 0·90-0·96 (6H, m, CH_3), 1·36-1·42 (8H, m, protons in alkyl chain), 1·75 (4H, quintet, J 6·93 Hz, protons in alkyl chain), 4·02 (6H, s, OCH_3), 4·29 (4H, t, J 6·6 Hz, OCH_2); $\delta_C(CDCl_3)$ 14·0, 22·3, 28·1, 28·3, (alkyl chain), 61·9 (OCH_3), 65·5 (OCH_2), 119·5 (C_2/C_5), 154·0 (C_3/C_4), 160·7 (C=O); (Found C, 57·80; H, 7·69. $C_{18}H_{28}O_6S$ requires C, 58·04; H, 7·58%).

6.7 Synthesis and Reactions of Diethyl 3-Hydroxy-4-methoxythiophene-2,5-dicarboxylate, (**103**)

Diethyl 3-Hydroxy-4-methoxythiophene-2,5-dicarboxylate, (**103**)

Method A

To diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate (1·30 g, 5·00 mmols) in dry ethanol (300 cm^3) was added a solution of sodium ethoxide in ethanol (0·56M, 9·1 cm^3, 5·10 mmols) with constant vigorous stirring. After 15 minutes, the ethanol was removed *in vacuo*. To the orange solid was added dimethyl sulfate (5 cm^3). After standing overnight, the excess of dimethyl sulfate was removed *in vacuo* and the residue was partitioned between water and dichloromethane. The organic phase was treated as usual to give a brown solid, which was purified by centrifugal chromatography (silica; light petroleum-EtOAc, 7:1), to give diethyl 3,4-dimethoxythiophene-2,5-dicarboxylate (0·69 g,

48%) followed by *diethyl 3-hydroxy-4-methoxythiophene-2,5-dicarboxylate*, (0·44 g, 32%), m.p. 105-7°C; ν_{max}(KBr) 3320, 2990, 2940 and 1690 cm^{-1}; $\delta_H(CDCl_3)$ 1·37 (3H, t, J 7·26 Hz, $CH_2\underline{CH_3}$), 1·39 (3H, t, J 7·26 Hz, $CH_2\underline{CH_3}$), 4·08 (3H, s, OCH_3), 4·35 (2H, q, J 7·26 Hz, OCH_2), 4·39 (2H, q, J 7·26 Hz, OCH_2), 9·50 (1H, s, ArOH); $\delta_C(CDCl_3)$ 14·2 (CH_3), 61·2 (OCH_3), 61·5, 61·8 (OCH_2), 106·5 (C_2), 119·4 (C_5), 149·6 (C_4), 155·5 (C_3), 160·8 and 160·8 (C=O); (Found: C, 48·75; H, 5·34. $C_{11}H_{14}O_6S$ requires C, 48·17; H, 5·14%).

Method B

To diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate (0·99 g, 3·85 mmols) in dry ethanol (300 cm^3) was added a solution of sodium ethoxide in ethanol (0·56M, 6·8 cm^3, 3·81 mmols) with constant vigorous stirring. After removal of the ethanol *in vacuo*, the solid was heated under reflux in acetone with mechanical stirring. Benzyl-tri-*n*-butylammonium bromide (1·35 g, 3·81 mmols) was added, followed by dimethyl sulfate (0·4 cm^3, 4·24 mmols). The reaction mixture was heated under reflux for 3 hours. The cooled mixture was filtered and the solvent removed. Purification was achieved by column chromatography (silica; light petroleum-EtOAc, 7:1), followed by centifugal chromatography (silica; light petroleum-EtOAc, 7:1) to give the title compound (0·18 g, 17%).

Diethyl 3-Methoxy-4-(3'-oxapentyloxy)thiophene-2,5-dicarboxylate

To the mixture (7·13 g) of diethyl 3,4-dimethoxythiophene-2,5-dicarboxylate and diethyl 3-hydroxy-4-methoxythiophene-2,5-dicarboxylate obtained from the experiment describded in Method A, (page 163), dissolved in DMF (50 cm^3), was added anhydrous potassium carbonate (4·14 g, 0·03 mols) and 1-tosyloxy-3-oxapentane (7·32 g, 0·03 mols). The reaction was stirred mechanically and heated for 10 hours in an oil bath set at 100°C. Moisture was excluded by means of a calcium chloride guard tube. When cool, the mixture

was filtered and the solvent was removed *in vacuo*. The residue was partitioned between EtOAc and water, and the organic phase was worked up as usual. The resultant oil was purified by column chromatography, (silica; light petroleum-EtOAc, 5:1), to give diethyl 3,4-dimethoxythiophene-2,5-dicarboxylate (2·53 g, 8·78 mmols) and *diethyl 3-methoxy-4-(3'-oxapentyloxy)thiophene-2,5-dicarboxylate* (1·20 g, 13%) as a colourless oil; ν_{max}(film) 2980, 2930, 2870 and 1717 cm^{-1}; $\delta_H(CDCl_3)$ 1·20 (3H, t, J 6·93 Hz, $CH_2OCH_2C\underline{H}_3$), 1·38 (6H, t, J 7·26 Hz, $CO_2CH_2C\underline{H}_3$), 3·56 (2H, q, J 6·93 Hz, $CH_2OC\underline{H}_2CH_3$), 3·75-3·78 (2H, m, $EtOC\underline{H}_2$), 4·03 (3H, s, $ArOCH_3$), 4·35 (4H, q, CO_2CH_2), 4·31-4·39 (2H, m, $ArOCH_2$); $\delta_C(CDCl_3)$ 14·2 ($CO_2CH_2C\underline{H}_3$), 15·1 ($CH_2OCH_2C\underline{H}_3$), 61·4 ($CO_2\underline{C}H_2$), 61·9 ($ArOCH_3$), 66·6, 69·6 and 73·9 ($CH_2O$), 119·3 and 119·9 ($C_2/C_5$), 153·1 and 154·2 ($C_3/C_4$), 160·6 (two signals, C=O); (Found: C, 52·08; H, 6·64. $C_{15}H_{22}O_7S$ requires C, 52·01; H, 6·40%).

1,5-Bis(2',5'-ethoxycarbonyl-4'-methoxythienyloxy)-3-oxapentane, (**108**)

The *title compound* was prepared in a similar manner to that desciribed above, from the mixture of diethyl 3,4-dimethoxythiophene-2,5-dicarboxylate and diethyl 3-hydroxy-4-methoxythiophene-2,5-dicarboxylate (7·04 g), obtained from the work described in Method A, (page 163), anhydrous potassium carbonate (4·14 g, 0·03 mols) and 1,5-ditosyloxy-3-oxapentane (5·80 g, 14·01 mmols). The oil obtained after work-up was purified by column chromatography (silica; light petroleum-EtOAc, 3:1). This gave diethyl 3,4-dimethoxythiophene-2,5-dicarboxylate, (0·08 g). Continued elution gave the tetraethyl ester, as a white crystalline solid, (1·72g, 21%), m.p. 83-84°C; ν_{max}(KBr) 2984, 2940 and 1717 cm^{-1}; $\delta_H(CDCl_3)$ 1·37 (6H, t, J 7·26 Hz, $CH_2C\underline{H}_3$), 1·38 (6H, t, J 7·26 Hz, $CH_2C\underline{H}_3$), 3·86-3·90 (4H, m, $ArOCH_2C\underline{H}_2$) 4·02 (6H, s, $ArOCH_3$), 4·30-4·39 (12H, m, OCH_2 of both the ester groups and $ArOCH_2$); $\delta_C(CDCl_3)$ 14·2 ($CH_2\underline{C}H_3$), 61·4 ($CO_2\underline{C}H_2$), 61·9 (OCH_3), 70·3 and 73·8 (OCH_2), 119·3 and

119·8 (C_2/C_5), 153·1 and 154·2 (C_3/C_4), 160·6 (C=O); (Found: C, 50·67; H, 5·60. $C_{26}H_{34}O_{13}S_2$ requires C, 50·48; H, 5·54%).

6.8 Alkylation Procedures

6.8.1 General Synthetic Methods

Method A[95]

Diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate (1 eq.) and anhydrous potassium carbonate (1·2 eq.) were stirred mechanically in DMF (0·5 cm^3mmol^{-1}), for 1 hour. The mixture was heated by means of an oil bath set at 100°C, (calcium chloride guard tube). To the mixture was added the alkylating agent (1·2 eq.) and heating was continued for a further 12 hours. The solvent was removed *in vacuo*, the resultant syrup was partitioned between water and dichloromethane, (EtOAc where tosylate, ditosylate and mesylate esters were employed). The organic layer was washed repeatedly with water and then worked up in the usual way to give the crude product.

Method B

Diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate (1 eq.) and anhydrous potassium carbonate (1·2 eq.) were stirred mechanically in DMF (1·0 cm^3mmol^{-1}) for 1 hour. The mixture was heated by means of an oil bath set at 100°C. The alkylating agent (1·2 eq.) was dissolved in DMF (0·5 cm^3mmol^{-1}), and the solution was fed into the reaction flask by means of a syringe pump, (the rate of addition depended upon the volume of syringe employed, see page 157). When the syringe had emptied, heating was continued for a further 12 hours. The solvent was removed *in vacuo* and the crude mixture was partitioned between water and EtOAc, the organic layer was then worked up in the usual manner.

In the above procedures, the purification techniques have been omitted; these are given with the individual compounds.

6.8.2 Diethyl 3,4-Dialkoxythiophene-2,5-dicarboxylates

Diethyl 3,4-Ethylenedioxythiophene-2,5-dicarboxylate, (**33d**)

The title compound was synthesised according to Method A, employing 1,2-dibromoethane as the alkylating agent. The crude product was recrystallised from ethanol to give the required compound, (78%), m.p. 149·5-151·5°C, (Lit.[116] 148-150°C).

Diethyl 3,4-Bis(3'-oxapentyloxy)thiophene-2,5-dicarboxylate, (**33h**)

The *title compound* was synthesised according to Method A using 2·2 eqivalents of 1-tosyloxy-3-oxapentane. The dark green syrup was purified by column chromatography (silica; light petroleum-EtOAc, 4:1), affording diethyl 3,4-bis(3'-oxapentyloxy)thiophene-2,5-dicarboxylate as a pale green oil; (73%), ν_{max}(film) 2980, 2930, 2870 and 1715 cm^{-1}; δ_H($CDCl_3$) 1·20 (6H, t, J 6·93 Hz, $CH_2OCH_2C\underline{H}_3$), 1·38 (6H, t, J 7·26 Hz, $CO_2CH_2C\underline{H}_3$), 3·56 (4H, q, J 6·93 Hz, $CH_2OC\underline{H}_2CH_3$), 3·75-3·79 (4H, m, $EtOC\underline{H}_2$), 4·35 (4H, q, J 7·26 Hz, CO_2CH_2), 4·35-4·39 (4H, m, $ArOCH_2$); δ_C($CDCl_3$) 14·3 ($O_2CH_2\underline{C}H_3$), 15·2 ($CH_2OCH_2\underline{C}H_3$), 61·3 ($CO_2\underline{C}H_2$), 66·5, 69·7 and 73·8 ($OCH_2$), 119·8 ($C_2/C_5$), 153·3 ($C_3/C_4$), 160·6 (C=O); (Found: C, 53·15; H, 7·31. $C_{18}H_{28}O_8S$ requires C, 53·45; H, 6·98%).

Diethyl 3,4-Bis(5'-hydroxy-3'-oxapentyloxy)thiophene-2,5-dicarboxylate, (**140a**)

The *title compound* was prepared according to Method B using 2·2 equivalents of 5-tosyloxy-3-oxapentane. The crude brown oil was purified by column chromatography (silica; EtOAc) to give the bis alcohol, (56%), as a pale brown oil; ν_{max}(film) 3426, 2937, 2872 and 1717 cm^{-1}; δ_H($CDCl_3$) 1·37 (6H, t, J 7·26 Hz, CH_3), 3·63-3·65 (4H, m, OCH_2), 3·80-3·84 (4H, m, OCH_2), 4·35 (4H, q, CO_2CH_2), 4·39-4·41 (4H, m, $ArOCH_2$); δ_C($CDCl_3$) 14·2 (CH_3), 61·5

($CO_2\underline{C}H_2$), 61·7 (CH_2OH), 70·2, 72·9 and 74·1 (OCH_2), 119·7 (C_2/C_5), 153·2 (C_3/C_4), 160·5 (C=O); (Found: C, 48·71; H, 6·72. $C_{18}H_{28}O_{10}S$ requires C, 49·53; H, 6·47%).

6.8.3 Methyl 3-Alkoxythiohene-2-carboxylates

Methyl 3-Methoxythiophene-2-carboxylate

A mixture of methyl 3-hydroxythiophene-2-carboxylate (60·10 g, 0·38 mols), anhydrous potassium carbonate (61·51 g, 0·45 mols) and dry acetone (600 cm^3) was stirred mechanically under reflux. Dimethyl sulfate (56·00 g, 0·45 mols) was added; after 6 hours no hydroxythiophene remained (t.l.c., chloroform). The cooled mixture was filtered and the inorganic salts were washed with acetone (100 cm^3). The combined filtrate and washings were heated under reduced pressure to remove the solvent. The residue was a mobile brown oil which solidified on standing. It was recrystallised from methanol, (53·60 g, 82%), m.p. 54·4-56·4°C, (Lit.[179] 54°C).

Methyl 3-(5'-hydroxy-3'-oxapentyloxy)thiophene-2-carboxylate, (**143**)

The title *alcohol* was prepared according to Method B, from methyl 3-hydroxythiophene-2-carboxylate and 5-tosyloxy-3-oxapentan-1-ol. The crude brown oil was purified by column chromatography (silica; EtOAc) to give the compound, (62%), as an oil; ν_{max}(film) 3450, 3110, 2950, 2870 and 1705 cm^{-1}; $\delta_H(CDCl_3)$ 3·16 (1H, broad, dissappears on D_2O shake, OH), 3·68-3·78 (4H, m, OCH_2), 3·82 (3H, s, O_2CH_3), 3·88-3·91 (2H, m, OCH_2), 4·26-4·30 (2H, m, $ArOCH_2$), 6·86 (1H, d, J 5·61 Hz, ArH on C_4), 7·42 (1H, d, J 5·61 Hz, ArH on C_5); $\delta_C(CDCl_3)$ 51·7 (O_2CH_3), 61·6 (CH_2OH), 69·3, 71·4 and 72·7 (OCH_2), 109·8 (C_2), 117·1 (C_4), 130·8 (C_5), 161·2 (C=O), 162·2 (C_3); (Found: C, 48·63; H, 5·92. $C_{10}H_{14}O_5S$ requires C, 48·77; H, 5·73%).

6.9 Derivatives of the Oxyethoxy Alcohols

Methyl 3-(5'-tosyloxy-3'-oxapentyloxy)thiophene-2-carboxylate, (**144**)

To methyl 3-(5'-hydroxy-3'-oxapentyloxy)thiophene-2-carboxylate (1·96 g, 8·00 mmols) in dry pyridine (20 cm^3) maintained at 5°C, was added portionwise 4-methylbenzenesulfonyl chloride (1·67 g, 8·01 mmols). The mixture was stirred for 3 hours at room temperature, then poured onto a mixture of crushed ace (100 cm^3) and concentrated hydrochloric acid (10 cm^3). The whole was extracted with dichloromethane (3 × 30 cm^3), the organic phase was washed with hydrochloric acid (4M, 4 × 20 cm^3), water (2 × 20 cm^3), and saturated sodium hydrogen carbonate solution (2 × 20 cm^3). The oil was obtained by the usual method from the extract, and purified by column chromatography, (silica; light petroleum-EtOAc, 1:1), to give the desired *tosylate ester derivative*, (1·76 g, 55%) as a white crystalline solid, m.p. 59-60°C; ν_{max}(KBr) 3081, 2954, 2883, 1698 and 1597 cm^{-1}; δ_H($CDCl_3$) 2·42 (3H, s, $ArCH_3$), 3·79-3·83 (7H, m, O_2CH_3 and OCH_2), 4·16-4·22 (4H, m, OCH_2), 6·84 (1H, d, J 5·61 Hz, ArH on C_4 of thiophene ring), 7·30-7·33 (2H, m, ArH on C_2/C_6 of benzene ring), 7·40 (1H, d, J 5·61 Hz, ArH on C_5 of thiphene ring), 7·75-7·80 (2H, m, ArH on C_3/C_5 of benzene ring); δ_C($CDCl_3$) 21·6 ($ArCH_3$), 51·5 ($CO_2\underline{C}H_3$), 69·1, 69·5, 69·7 and 71·7 (OCH_2), 110·0 (C_2 of thiophene ring), 117·3 (C_4 of thiophene ring), 127·9 (C_2/C_6 of benzene ring), 129·8 (C_3/C_5 of benzene ring), 130·6 (C_5 of thiophene ring) 132·9 (C_1 of benzene ring), 144·8 (C_4 of benzene ring), 160·9 (C=O), 162·0 (C_3 of thiophene ring); (Found: C, 51·02; H, 5·06. $C_{17}H_{20}O_7S_2$ requires C, 50·99; H, 5·03%).

Diethyl 3,4-Bis(5'-methanesulfonyloxy-3'-oxapentyloxy)thiophene-2,5-dicarboxylate, (**140c**),

To the crude mixture obtained in the synthesis of diethyl 3,4-bis(5'-hydroxy-3'-oxapentyloxy)thiophene-2,5-dicarboxylate (5·10 g), in dry dichloromethane

(45 cm^3) and triethylamine (10 cm^3), was added methanesulfonyl chloride (8·04 g, 0·07 mols) with ice cooling. The mixture was stirred at room temperature for 10 minutes, then poured into water (100 cm^3). The organic layer was washed with water (2 × 100 cm^3), dried ($NaSO_4$), filtered, and evaporated. The resultant oil was purified by column chromatography, (silica; EtOAc–light petroleum, 2:1), to give diethyl 3,4-di(methanesulfonyloxy)thiophene-2,5-dicarboxylate, (**33i**),[180] (0·50 g), as an oil and identified by its proton and ^{13}C n.m.r. spectra. Second to be eluted was *diethyl 3-methanesulfonyloxy-4-(5'-methanesulfonyloxy-3'-oxapentyloxy)thiophene-2,5-dicarboxylate*, (0·94 g), m.p. 88–90°C; ν_{max}(KBr) 2980, 2940, 2900, 1730 and 1715 cm^{-1}; δ_H($CDCl_3$) 1·38 (3H, t, J 7·26 Hz, $O_2CH_2C\underline{H}_3$) 1·39 (3H, t, J 7·26 Hz, $O_2CH_2C\underline{H}_3$), 3·07 (3H, s, $CH_2OSO_2C\underline{H}_3$), 3·43 (3H, s, $ArOSO_2CH_3$), 3·80–3·88 (4H, m, OCH_2), 4·34–4·45 (8H, m, CO_2CH_2 and OCH_2); δ_C($CDCl_3$) 14·1 and 14·2 ($O_2CH_2\underline{C}H_3$) 37·6 ($CH_2OSO_2\underline{C}H_3$), 40·3 ($ArOSO_2CH_3$), 61·9 and 62·2 ($CO_2\underline{C}H_2$), 68·9, 69·1, 70·3 and 74·8 (OCH_2), 119·7 (C_5), 124·6 (C_2), 140·4 (C_3), 152·4 (C_4), 159·4 and 159·8 (C=O); (Found: C, 38·50; H, 5·02. $C_{16}H_{24}O_{12}S_3$ requires C,38·09; H, 4·79%); third to be eluted was the desired *bis-methanesulfonyl ester* as an oil, (3·22 g, 47%); ν_{max}(film) 2960, 2910 and 1710 cm^{-1}; δ_H($CDCl_3$) 1·37 (6H, t, J 7·26 Hz, $O_2CH_2C\underline{H}_3$), 3·06 (6H, s, SO_2CH_3), 3·80–3·87 (8H, m, OCH_2) 4·34 (4H, q, J 7·26 Hz, CO_2CH_2), 4·36–4·39 (8H, m, OCH_2); δ_C($CDCl_3$) 14·2 ($CH_2\underline{C}H_3$), 37·5 (SO_2CH_3), 61·4 ($CO_2\underline{C}H_2$), 68·9, 69·3, 70·5 and 73·7 (OCH_2), 119·6 (C_2/C_5), 153·0 (C_3/C_4), 160·4 (C=O); (Found: C, 40·62; H, 5·49. $C_{20}H_{32}O_{14}S_3$ requires C, 40·53; H, 5·44%).

Diethyl 3,4-Bis(5'-bromo-3'-oxapentyloxy)thiophene-2,5-dicarboxylate, (**146**)

To the crude mixture obtained in the synthesis of diethyl 3,4-bis(5'-hydroxy-3'-oxapentyloxy)thiophene-2,5-dicarboxylate (1·03 g) in dry diethyl ether (10 cm^3) was added dry pyridine (0·5 cm^3), with stirring; external cooling was

provided by an ice/salt bath. To this was added phosphorus tribromide (0·51 g, 1·85 mmols) dropwise. The mixture was stirred for 3 hours at room temperature, whereupon it was poured onto cruched ice (20 cm^3). The diethyl ether layer was washed with aqueous hydrochloric acid (4M, 2 × 10 cm^3), followed by saturated sodium hydrogen carbonate solution (2 × 10 cm^3). The usual work-up left an oil, which was purified by column chromatography, (silica; light petroleum-EtOAc, 4:1), to give the required *bis-bromo compound*, (0·37g, 28%), as a pale brown oil; ν_{max}(film) 2930 and 1710 cm^{-1}; $\delta_H(CDCl_3)$ 1·38 (6H, t, J 7·26 Hz, $O_2CH_2C\underline{H}_3$), 3·47 (4H, t, J 6·27 Hz, CH_2Br), 3·85 (4H, t, J 6·27 Hz, $OC\underline{H}_2CH_2Br$) 3·84-3·87 (4H, m, $ArOCH_2C\underline{H}_2$), 4·35 (4H, q, J 7·26, CO_2CH_2), 4·36-4·40(4H, m, $ArOCH_2$); $\delta_C(CDCl_3)$ 14·3 ($CH_2\underline{C}H_3$), 30·3 (CH_2Br), 61·4 ($CO_2\underline{C}H_2$), 70·3, 71·2, and 73·6 (OCH_2), 119·7 (C_2/C_5), 153·0 (C_3/C_4), 160·5 (C=O); (Found: C, 39·28; H, 4·92. $C_{18}H_{26}Br_2O_8S$ requires C, 38·45; H, 4·66%).

Diethyl 3,4-Bis[5'-(2''-methoxycarbonyl-3''-thienyloxy)-3'-oxapentyloxy]-thiophene-2,5-dicarboxylate, **(154)**

A suspension of methyl 3-hydroxythiophene-2-carboxylate (1·25 g, 8·23 mmols) and potassium carbonate (1·50 g, 10·87 mmols) in DMF (50 cm^3) were stirred mechanically for 1 hour in an oil bath at 100°C. To the result was added diethyl 3,4-bis(5'methanesulfonyloxy-3'-oxapentyloxy)thiophene-2,5-dicarboxylate (2·14 g, 3·64 mmols). The reaction mixture was stirred for a further 12 hours at 100°C. Upon cooling, the inorganic material was filtered off and the filtrate was evaporated to dryness *in vacuo*. The oil was dissolved in EtOAc (75 cm^3) and washed with water (3 × 25 cm^3). The usual treatment of the organic solution gave an oil, which was subjected to column chromatography, (silica; EtOAc-light petroleum, 3:1), to give the required *tetra ester*, (1·93 g, 75%) as a pale yellow-green oil; ν_{max}(film) 3110, 2980, 2950

and 1710 cm^{-1}; $\delta_H(CDCl_3)$ 1·36 (6H, t, J 7·26 Hz, $O_2CH_2C\underline{H}_3$) 3·81 (6H, s, CO_2CH_3), 3·87–3·92 (8H, m, OCH_2), 4·24–4·39 (12H, m, CO_2CH_2 and OCH_2), 6·85 (2H, d, J 5·61 Hz, ArH on C_4), 7·37 (2H, d, J 5·61 Hz, ArH on C_5); $\delta_C(CDCl_3)$ 14·2 ($O_2CH_2\underline{C}H_3$), 51·6 ($CO_2\underline{C}H_3$), 61·4 ($CO_2\underline{C}H_2$), 69·6, 70·8, 71·7 and 73·8 (OCH_2), 110·0 ($C_{2'}$), 117·5 ($C_{4'}$), 119·5 (C_2/C_5), 130·5 ($C_{5'}$), 153·2 (C_3/C_4), 160·6 ($\underline{C}O_2Et$), 161·1 ($\underline{C}O_2Me$), 162·0 ($C_{3'}$); (Found: C, 50·62; H, 4·91. $C_{30}H_{36}O_{14}S_3$ requires C, 50·27; H, 5·06%).

6.10 General Syntheses of Crown Ethers and Related Compounds

6.10.1 General Synthetic Methods

Method A, (*O*-alkylation under high dilution conditions)

The dialkyl 3,4-dihydroxythiophene-2,5-dicarboxylate (1·0 eq.) was dissolved in a solvent (7 cm^3mmol^{-1}). The alkylating agent (1·0 eq.) was dissolved in a separate portion of the same solvent, and the solution made up to a volume equal to that of the former solution. The solutions were fed separately by means of a syringe pump, into a stirred suspension of potassium carbonate (1·2 eq.), solvent (7 cm^3mmol^{-1}), (and where a template is specified, 2·0 eq. of that salt). The reaction flask was heated to reflux, (in the case where DMF was the solvent, heating by means of an oil bath set at 100°C was employed), during the addition. When the addition was complete, heating was continued for a further 12 hours. The solvent was then removed *in vacuo* and the residue partitioned between EtOAc (50 cm^3) and water (50 cm^3). The organic phase was then treated in the usual manner. The residue was purified by column chromatography, (silica; light petroleum–EtOAc, 2:1).

Method B[88]

To a stirred solution of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate (3·90 g, 15·00 mmols) in dry acetonitrile (250 cm^3), was added anhydrous potassium fluoride[181] (3·48 g, 0·06 mols). The mixture was stirred for 1 hour under

nitrogen, whereupon a yellow precipitate had formed. To this was added the alkylating agent (1·0 eq.) in dry acetonitrile (100 cm^3). The mixture was heated to reflux under nitrogen for 30 hours, then filtered while hot, and the precipitate was washed with acetonitrile (50 cm^3). When the precipitate was treated with aqueous hydrochloric acid (2M), some unreacted thiophene moiety was returned. The combined filtrate and washings were evaporated to dryness. Further purification was by column chromatography, (silica; light petroleum-EtOAc, 2:1).

6.10.2 Synthesis of the Bis and Tetrakis Ethyl Esters

Diethyl 2,5,8-Trioxa-11-thiabicyclo[7.3.0]dodeca-1(12),9-dien-10,12-dioate, (97)

The title *bis-ester* was synthesised according to Method A, with DMF as the solvent, from diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate and 1,5-ditosyloxy-3-oxapentane in 27% yield. The bis ester was a white solid, m.p. 120-122°C; ν_{max}(KBr) 2982, 2947, 2900, 1719 and 1683 cm^{-1}; $\delta_H(CDCl_3)$ 1·37 (6H, t, J 7·26 Hz, $O_2CH_2C\underline{H}_3$), 3·92-3·95 (4H, m, $ArOCH_2C\underline{H}_2$), 4·34 (4H, q, J 7·26 Hz, CO_2CH_2), 4·44-4·48 (4H, m, $ArOCH_2$); $\delta_C(CDCl_3)$ 14·2 ($O_2CH_2\underline{C}H_3$), 61·2 ($CO_2\underline{C}H_2$), 73·4 and 74·4 (OCH_2), 117·8 (C_2/C_5), 153·7 (C_3/C_4), 160·7 (C=O); (Found: C, 50·92; H, 5·50. $C_{14}H_{18}O_7S$ requires C, 50·90; H, 5·49%); Mol. wt. 312 (Rast's method).[182]

Second to be eluted from the column was *tetraethyl 2,5,8,14,17,20-hexaoxa-11,23-dithiatricyclo[19.3.0.0^{9,13}]tetraeicosa-1(24),9,12,21-tetraen-10,12,22,24-tetraoate* in 2% yield; ν_{max}(KBr) 2981, 2926 and 1722 cm^{-1}; $\delta_H(CDCl_3)$ 1·37 (12H, t, J 7·26 Hz, $O_2CH_2C\underline{H}_3$), 3·92-3·95 (8H, m, $ArOCH_2C\underline{H}_2$), 4·34 (8H, q, J 7·26 Hz, CO_2CH_2), 4·40-4·43 (8H, m, $ArOCH_2$); $\delta_C(CDCl_3)$ 14·2 ($O_2CH_2\underline{C}H_3$), 61·4 ($CO_2\underline{C}H_2$), 70·3 and 74·1 (OCH_2), 119·8 (C_2/C_5), 153·4 (C_3/C_4), 160·6 (C=O); (Found: C, 50·65; H, 5·50.

$C_{28}H_{36}O_{14}S_2$ requires C, 50·90; H, 5·49%); Mol. wt. 632 (Rast's method).[182]

Diethyl 2,5,8,11-Tetraoxa-14-thiabicyclo[10.3.0]pentadeca-1(15),12-dien-13,15-dioate, (**137**)

The title compound was prepared according to Method A, from diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate and 1,8-ditosyloxy-3,6-dioxaoctane, emplying DMF as a solvent, to give the desired diester (15%), m.p. 122-124°C, (Lit.[88] 122-3°C). Second to elute from the column was diethyl 2,5,8,-trioxa-11-thiabicyclo[7.3.0]dodeca-1(12),9-10,12-dioate (2%).

The title compound was also prepared according to Method B giving the required diethyl ester, (0·66 g, 12%).

Tetraethyl 2,5,8,14,17,20-Hexaoxa-11,23-dithiatricyclo[19.3.0.$0^{9,13}$]tetraeicosa-1(24),9,12,21-tetraen-10,12,22,24-tetraoate, (**98**)

The title compound was prepared according to Method A from diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate and diethyl 3,4-bis(5'-methanesulfonyloxy-3'-oxapentyloxy)thiophene-2,5-dicarboxylate, using DMF as a solvent to give the desired teraethyl ester (7%). When carried out in the presence of potassium tosylate (2·0 eq.), a yield of 10% was obtained.

6.10.3 The Bis Ethyl-Bis Pentyl Crown Ether System

Dipentyl, Diethyl 2,5,8,14,17,20-Hexaoxa-11,23-dithiatricyclo[19.3.0.$0^{9,13}$]-tetraeicosa-1(24),9,12,21-tetraen-10,12,22,24-tetraoate, (**149**)

The title *tetra ester* was prepared from dipentyl 3,4-dihydroxythiophene-2,5-dicarboxylate and diethyl 3,4-bis(5'-methanesulfonyloxy-3'-oxapentyloxy)-thiophene-2,5-dicarboxylate using Method A, with DMF as a solvent in the presence of potassium tosylate (2·0 eq.), to give the desired compound (15%), m.p. 138-140°C; ν_{max}(KBr) 2960, 2937 and 1720 cm^{-1}; $\delta_H(CDCl_3)$ 0·93 (6H,

t, J 6·93 Hz, $CH_2CH_2C\underline{H}_3$), 1·26–1·42 (14H, m, $O_2CH_2C\underline{H}_3$ and CH_2 of pentyl group), 1·69–1·79 (4H, m, CH_2 of pentyl group), 3·92–3·95 (8H, m, $ArOCH_2C\underline{H}_2$), 4·20–4·38 (8H, m, CO_2CH_2), 4·40–4·44 (8H, m, $ArOCH_2$); $\delta_C(CDCl_3)$ 14·0 and 14·2 (CH_3), 22·3, 28·1 and 28·3 (CH_2 groups of pentyl chain), 61·4 ($CO_2\underline{C}H_2CH_3$), 65·6 ($CO_2\underline{C}H_2CH_2$), 70·4 (OCH_2), 74·0 and 74·1 (OCH_2), 119·9 (two peaks, C_2/C_5), 153·3, 153·4 (C_3/C_4), 160·6, 160·7 (C=O); (Found: C, 54·87; H, 6·66. $C_{34}H_{48}O_{14}S_2$ requires C, 54·83; H, 6·50%).

The title compound was also synthesised in a similar manner employing acetone and acetonitrile as solvents. In each case, a 12% yield of the desired compound was obtained.

6.10.4 The Incomplete *O*-Alkylation of Diethyl 3,4-Dihydroxythophene-2,5-dicarboxylate

Diethyl 3-Hydroxy-4-(8'-tosyloxy-3',6'-oxaoctyloxy)thiophene-2,5-dicarboxylate, (**141**)

The title *4-methylbenzenesulfonyl ester derivative* was synthesised according to general Method B. However the solution of 1,8-ditosyloxy-3,6-dioxaoctane in acetonitrile (20 cm^3) was introduced by a syringe pump over a period of 17 hours. The reaction mixture was maintained at reflux for a further 24 hours, when work up and purification afforded unreacted the unreacted ditosylate ester (3·84 g) and the title compound (1·32 g, 24%) as a colourless oil; ν_{max}(film) 3300, 2980, 2930, 2870, 1720 and 1670 cm^{-1}; $\delta_H(CDCl_3)$ 1·36 and 1·38 (6H, t, J 7·26 Hz, $O_2CH_2C\underline{H}_3$), 2·43 (3H, s, $ArCH_3$), 3·56–3·70 (8H, m, OCH_2), 3·78–3·81 (2H, m, OCH_2), 4·12–4·18 (2H, m, OCH_2), 4·29–4·42 (6H, m, $ArOCH_2$ and $O_2C\underline{H}_2CH_3$), 7·34 (2H, d, J 8·25 Hz, ArH on C_2/C_6 of benzene ring), 7·79 (2H, d, J 8·25 Hz, ArH on C_3/C_5 of benzene ring), 9·37 (1H, s, ArOH); $\delta_C(CDCl_3)$ 14·2 ($O_2CH_2\underline{C}H_3$) 21·6 ($ArCH_3$), 61·4 and 61·7 ($CO_2\underline{C}H_2$), 68·7, 69·3, 70·3, 70·6, 70·7 and 73·1 (OCH_2), 106·8 (C_2 of thiophene ring),

120·1 (C_5 of thiophene ring), 127·9 (C_2/C_6 of benzene ring), 129·8 (C_3/C_5 of benzene ring), 132·9 (C_1 of benzene ring), 144·9 (C_4 of benzene ring), 148·6 (C_4 of thiophene ring), 155·1 (C_3 of thiophene ring), 160·7 ($C_5C{=}O$), 165·1 ($C_2C{=}O$); (Found: C, 50·66; H, 5·24. $C_{23}H_{30}O_{11}S_2$ requires C, 50·54: H, 5·53%).

Diethyl 3-Methanesulfonyloxy-4-(8'-tosyloxy-3',6'-oxaoctyloxy)thiophene-2,5-dicarboxylate, (**142**)

To the foregoing 4-methylbenzenesulfonyl ester (0·40 g, 0·73 mmols) in dry dichloromethane (1·0 cm^3) and triethylamine (1·0 cm^3), was added methanesulfonyl chloride (1·0 cm^3), dropwise with stirring. After 10 minutes, water (10 cm^3) was added. The aqueous layer was extracted with dichloromethane (3 × 10 cm^3). The washings were combined and treated in the usual way. The red-brown oil was purified by centrifugal chromatography, (silica; EtOAc-light petroleum, 1:1) to give the *methanesulfonyl ester* as a brown oil, (0·34 g, 75%); ν_{max}(film) 3100, 2980, 2940, 2870 and 1710 cm^{-1}; $\delta_H(CDCl_3)$ 1·38 and 1·39 (6H, t, J 7·26 Hz, $O_2CH_2C\underline{H}_3$), 2·44 (3H, s, $ArCH_3$), 3·39 (3H, s, OSO_2CH_3), 3·58-3·70 (6H, m, OCH_2), 3·77-3·80 (2H, m, OCH_2), 4·12-4·18 (2H, m, OCH_2), 4·32-4·43 (6H, m, $ArOCH_2$ and $O_2C\underline{H}_2CH_3$), 7·28-7·36 (2H, m, ArH on C_2/C_6 of benzene ring), 7·78-7·81 (2H, m, ArH on C_3/C_5 of benzene ring); $\delta_C(CDCl_3)$ 14·1 and 14·2 ($O_2CH_2\underline{C}H_3$), 21·6 ($ArCH_3$), 40·3 (OS_2CH_3), 61·9 and 62·2 ($CO_2\underline{C}H_2$), 68·7, 69·3, 70·1, 70·4, 70·7 and 74·9 (OCH_2), 119·9 (C_5 of thiophene ring), 125·1 (C_2 of thiophene ring), 128·0 (C_2/C_6 of benzene ring), 129·9 (C_3/C_5 of benzene ring), 132·9 (C_1 of benzene ring), 140·4 (C_3 of thiophene ring), 144·9 (C_4 of benzene ring), 152·3 (C_4 of thiophene ring), 159·6 and 159·9 (C=O); (Found: C, 46·07; H, 5·33. $C_{24}H_{32}O_{13}S_3$ requires C, 46·15; H, 5·16%).

6.11 Synthesis of the Thiophene Carboxylic Acids

6.11.1 General Synthetic Procedure

The ester, diester or teraester was stirred with a 30% excess of sodium hydroxide solution (2M) and an equal volume of ethanol at 60°C for 1 hour. The cooled solution was acidified with hydrochloric acid (4M), and the subsequent slurry was stirred for a further hour. The ethanol was removed *in vacuo* and the precipitate filtered off, and recrystallised from the given solvent to afford the corresponding acid, diacid or tetraacid as a white solid.

6.11.2 3,4-Dialkyloxythiophene-2,5-dicarboxylic acids

3,4-Dimethoxythiophene-2,5-dicarboxylic Acid, (**51a**)

Recrystallisation from methanol gave the title compound (74%), m.p. 260°C, (decomp.), [Lit.[115] 260°C, (decomp.)].

3-Methoxy-4-(3'-oxapentyloxy)thiophene-2,5-dicarboxylic Acid

Recrystallisation from aqueous methanol gave the title *dicarboxylic acid* (72%), m.p. 173-174°C; ν_{max}(KBr) 2975, 2872, 2549, 1684, 1654 and 1545 cm^{-1}; δ_H($CDCl_3$/DMSO-d_6) 1·17 (3H, t, J 6·93 Hz, $OCH_2C\underline{H}_3$), 3·54 (2H, q, J 6·93 Hz, $OC\underline{H}_2CH_3$), 3·70-3·73 (2H, m, $EtOCH_2$), 3·99 (3H, s, $ArOCH_3$), 4·30-4·33 (2H, m, $ArOCH_2$), (no signal observed for CO_2H); δ_C($CDCl_3$/DMSO-d_6) 15·1 ($OCH_2\underline{C}H_3$), 61·6 (OCH_3), 66·1, 69·2 and 73·5 (OCH_2), 120·0 and 120·4 (C_2/C_5), 152·3 and 153·5 (C_3/C_4), 162·0 and 162·1 (C=O); (Found: C, 43·63; H, 4·62. $C_{11}H_{14}O_7S$ requires C, 45·51; H, 4·86%).

1,5 Bis(2',5'-dicarboxy-4'-methoxy-3'-thienyloxy)-3-oxapentane, (**109**)

Recrystallisation from aqueous methanol gave the title *tetracarboxylic acid* (78%), m.p. 234°C,(decomp.); ν_{max}(KBr) 2940, 2560, 1690 and 1545 cm^{-1}; δ_H($CDCl_3$/DMSO-d_6) 3·86-3·87 (4H, m, CH_2OCH_2), 4·00 (6H, s, $ArOCH_3$),

4·34–4·45 (4H, m, $ArOCH_2$), (no signal observed for CO_2H); $\delta_C(CDCl_3/DMSO\text{-}d_6)$ 61·7 (OCH_3), 69·9 and 73·6 (OCH_2), 120·1 and 120·5 (C_2/C_5), 152·3 and 153·5 (C_3/C_4), 162·1 and 162·2 (C=O); (Found: C, 36·05; H, 3·33. $C_{18}H_{18}O_{13}S_2$ requires C, 42·44; H, 3·56%).

3,4-Ethylenedioxythiophene-2,5-dicarboxylic Acid, (**51c**)

Recrystallisation from methanol afforded the title dicarboxylic acid (93%), m.p. 315°C, (decomp.), [Lit.[110] 323°C, (decomp.)].

3,4-Bis(3'-oxapentyloxy)thiophene-2,5-dicarboxylic Acid

Recrystallisation from water gave the title *dicarboxylic acid* (66%), m.p. 128–129°C; ν_{max}(KBr) 2990, 2870, 2640, 1690, and 1550 cm^{-1}; $\delta_H(CDCl_3/DMSO\text{-}d_6)$ 1·23 (6H, t, J 6·93 Hz, $OCH_2\underline{CH_3}$), 3·59 (4H, q, J 6·93 Hz, $O\underline{CH_2}CH_3$), 3·73–3·76 (4H, m, $EtOCH_2$), 4·47–4·50(4H, m, $ArOCH_2$), 11·50 (CO_2H); $\delta_C(CDCl_3/DMSO\text{-}d_6)$ 14·9 ($OCH_2\underline{C}H_3$), 66·9, 68·6 and 73·8 (OCH_2), 121·5 (C_2/C_5), 151·6 (C_3/C_4), 162·9 (C=O); (Found: C, 48·31; H, 5·87. $C_{14}H_{20}O_8S$ requires C, 48·27; H, 5·79%).

6.11.3 Compounds with the 3-Alkoxythiophene-2-carboxylic Acid Moiety

3-Methoxythiophene-2-carboxylic Acid

Recrystallisation from aqueous ethanol afforded the carboxylic acid (96%), m.p. 180–181°C, (decomp.), [Lit.[183] 178·5–179·5°C, (decomp.)].

3,4-Bis[5'-(2''-carboxy-3''-thienyloxy)-3'-oxapentyloxy]thiophene-2,5-dicarboxylic Acid, (**155**)

Recrystallisation from water gave the desired *teracarboxylic acid* (92%), m.p. 150–152°C; ν_{max}(KBr) 3100, 2920, 2600, 1690 and 1710 cm^{-1}; $\delta_H(CDCl_3/DMSO\text{-}d_6)$ 3·84–3·88 (8H, m, CH_2OCH_2), 4·26–4·30 (4H, m,

$ArOCH_2$), 4·36–4·40 (4H, m, $ArOCH_2$), 6·90 (2H, d, J 5·61 Hz, ArH on C_4'), 7·45 (2H, d, J 5·61 Hz, ArH on C_5'), (no signal observed for CO_2H); $\delta_C(CDCl_3/DMSO\text{-}d_6)$ 69·3, 70·3, 71·4 and 73·5 (OCH_2), 111·0 (C_2'), 117·6 (C_4'), 120·6 (C_2/C_5), 130·7 (C_5'), 152·3 (C_3/C_4), 160·4 (C_3'), 162·1 and 163·2 (C=O); (Found: C, 43·25; H, 4·09. $C_{24}H_{24}O_{14}S_3$ requires C, 45·57; H, 3·82%).

6.11.4 Di- and Tetracarboxylic Acids of Crown Ethers and Related Compounds

2,5,8-Trioxa-11-thiabicyclo[7.3.0]dodeca-1(12),9-diene-10,12-dicarboxylic Acid, (**150a**)

Recrystallisation from water gave the title *dicarboxylic acid* (90%), m.p. 260°C, (decomp.); ν_{max}(KBr) 2930, 2640, 1675, and 1540 cm^{-1}; $\delta_H(CDCl_3/DMSO\text{-}d_6)$ 3·89–3·92 (4H, m, CH_2OCH_2), 4·40–4·44 (4H, m, $ArOCH_2$), (no signal observed for CO_2H); $\delta_C(CDCl_3/DMSO\text{-}d_6)$ 73·1 and 74·2 (OCH_2), 118·5 (C_2/C_5), 153·3 (C_3/C_4), 162·1 (C=O); (Found: C, 43·80; H, 3·77. $C_{10}H_{10}O_7S$ requires C, 43·79; H, 3·68%).

2,5,8,14,17,20-Hexaoxa-11,23-dithiatricyclo[19.3.0.$0^{9,13}$]tetraeicosa-1(24),9,12,21-tetraene-10,12,22,24-tetracarboxylic Acid, (**151**)

The title *tetracarboxylic acid* was recrystallised from water (52%), m.p. 215°C, (decomp.); ν_{max}(KBr) 2926, 2604, 1701, and 1546 cm^{-1}; $\delta_H(CDCl_3/DMSO\text{-}d_6)$ 3·71–3·82 (4H, m, CH_2OCH_2), 4·33–4·46 (4H, m, $ArOCH_2$), (no signal observed for CO_2H); $\delta_C(CDCl_3/DMSO\text{-}d_6)$ 70·5 and 74·2 (OCH_2), 121·6 (C_2/C_5), 152·6 (C_3/C_4), 162·9 (C=O); (Found: C, 43·32; H, 3·91. $C_{20}H_{20}O_{14}S_2$ requires C, 43·79; H, 3·68%).

2,5,8,11-Tetraoxa-14-thiabicyclo[10.3.0]pentadeca-1(15),12-diene-13,15-dicarboxylic Acid, (**150b**)

Recrystallisation from water gave the title dicarboxylic acid (73%), m.p. 262-264°C, (decomp.), [Lit.[88] 263-264°C, (decomp.)].

6.12 Decarboxylation of the Thiophene Carboxylic Acids

6.12.1 General Synthetic Procedure

The acid, diacid or tetraacid was heated under nitrogen to 180°C, with quinoline (3 cm^3g^{-1}) and copper(I) oxide (0·25 mols per mole of CO_2 expected), for 45 minutes. Upon cooling, the mixture was filtered through 'HYFLO' and the residue was washed with diethyl ether. The combined filtrate and ethereal washings were extracted with hydrochloric acid (4M), water and sodium carbonate solution (10%). The diethyl ether layer was dried ($NaSO_4$), filtered and the solvent was removed under reduced pressure. The purification of the products is described individually below.

6.12.2 3,4-Dialkoxythiophenes

3,4-Dimethoxythiophene, (**59a**)

The crude material was distilled to give the title compound, (74%), b.p. 115-118°C/20 mmHg, (Lit.[115] 110°C/17 mmHg).

1,5-Bis(4'-methoxy-3'-thienyloxy)-3-oxapentane, (**95**)

The crude material was purified by centrifugal chromatography, (silica; light petroleum-EtOAc, 2:1), to give the title *bis thiophene compound* as a white solid, (65%), m.p. 112-113°C; ν_{max}(KBr) 3120, 3110, 2920, 2900, and 1570 cm^{-1}; $\delta_H(CDCl_3)$ 3·83 (6H, s, $ArOCH_3$), 3·89-3·93 (4H, m, CH_2OCH_2), 4·14-4·18 (4H, m, $ArOCH_2$), 6·17 (2H, d, J 3·30 Hz, ArH), 6·24 (2H, d, J 3·30 Hz, ArH); $\delta_C(CDCl_3)$ 57·5 (OCH_3), 69·6 and 69·8 (OCH_2), 96·2 (C_2),

97·8 (C_5), 146·7 (C_3), 148·1 (C_4); (Found: C, 51·03; H, 5·65. $C_{14}H_{18}O_5S_2$ requires C, 50·89; H, 5·49%).

3,4-Ethylenedioxythiophene, (**59b**)

Distillation afforded the title compound, (71%), b.p. 110-112°C/20 mmHg. The spectroscopic data was in accordance with the literature values;[125] (Found: C, 50·98; H, 4·34. $C_6H_6O_2S$ requires C, 50·69; H, 4·25%); m/e 142 (M^+).

3,4-Bis(3'-oxapentyloxy)thiophene, (**59c**)

Distillation gave the title *aromatic ether* (70%), b.p. 162-164°C/2 mmHg; ν_{max}(film) 3110, 2980, 2930, 2870 and 1565cm^{-1}; δ_H($CDCl_3$) 1·22 (6H, t, J 6·93 Hz, $OCH_2\underline{CH_3}$), 3·58 (4H, q, J 6·93 Hz, $O\underline{CH_2}CH_3$), 3·76-3·80 (4H, m, $EtOCH_2$), 4·11-4·17 (4H, m, $ArOCH_2$), 6·23 (2H, s, ArH); δ_C($CDCl_3$) 15·1 and 15·2 (CH_3), 66·8, 68·7 and 69·9 (OCH_2), 97·7-98·5 (C_2/C_5), 147·2 (C_3/C_4); (Found: C, 55·53; H, 7·97. $C_{12}H_{20}O_4S$ requires C, 55·36; H, 7·74%).

6.12.3 Compounds with the 3-Alkoxythiophene Moiety

3-Methoxythiophene

The crude material was distilled to give the title compound, (83%), b.p. 75-77°C/25 mmHg, (Lit.[183] 80-82°C/65 mmHg).

3,4-Bis[5'-(3''-thienyloxy)-3'-oxapentyloxy]thiophene, (**96**)

Purification by centrifugal chromatography, (silica; light petroleum-EtOAc, 1:1), gave the desired *trithiophene compound*, as a white solid (81%), m.p. 98·5-100°C; ν_{max}(KBr) 3100, 3090, 2920, 2895, 2850 and 1575 cm^{-1}; δ_H($CDCl_3$) 3·87-3·92 (8H, m, CH_2OCH_2), 4·09-4·18 (8H, m, $ArOCH_2$), 6·23-6·25 (4H, m, ArH on C_2/C_5 and $C_{2'}$), 6·75-6·78 (2H, m, ArH on $C_{4'}$), 7·14-7·17 (2H, m, ArH on $C_{5'}$); δ_C($CDCl_3$) 69·6, 69·7, 69·9 and 70·0 (OCH_2), 97·6 ($C_{2'}$),

98·1 (C_2/C_5), 119·6 ($C_{4'}$), 124·7 ($C_{5'}$), 147·1 (C_3/C_4), 157·5 ($C_{3'}$); (Found: C, 52·33; H, 5·35. $C_{20}H_{24}O_6S_3$ requires C, 52·61; H, 5·30%).

6.12.4 The Crown-like Compound

2,5,8-Trioxa-11-thiabicyclo[7.3.0]dodeca-1(12),9-diene, (**59d**)

Purification by column chromatography, (silica; light petroleum-EtOAc, 3:1) gave the title *aromatic ether* as a colourless oil (74%); ν_{max}(film) 3100, 2940, 2860 and 1550 cm^{-1}; $\delta_H(CDCl_3)$ 3·87-3·90 (4H, m, CH_2OCH_2), 4·27-4·30 (4H, m, $ArOCH_2$), 6·56 (2H, s, ArH); $\delta_C(CDCl_3)$ 72·4 and 74·2 (OCH_2), 107·8 (C_2/C_5), 150·0 (C_3/C_4); (Found: C, 51·50; H, 5·58. $C_8H_{10}O_3S$ requires C, 51·60; H, 5·41%).

6.13 Formylation of the Thiophene Systems

6.13.1 General Synthetic Procedure

To a stirred solution of DMF (1·1 eq.) in dry dichloromethane (0·50 cm^3mmol^{-1}) at 0°C was added phosphoryl chloride (1·1 eq.), dropwise over a period of 10 minutes. To this mixture was added the thiophene moiety (1·0 eq.), the reaction mixture was stirred for 1 hour at room temperature with the exclusion of moisture, then heated to boiling under reflux on a steam bath for a further 10 minutes. When cool, the mixture was poured onto crushed ice, and neutralised with aqueous sodium carbonate solution (10%). The crude product was isolated with dichloromethane; the method of purification is described individually, below.

3-Methoxythiophene-2-carboxaldehyde, (**121**)

Recrystallisation from aqueous methanol gave the title compound (45%), as white crystalline plates, m.p. 80-82°C, (Lit.[185] 82-84°C).

3,4-Dimethoxythiophene-2-carboxaldehyde, (**120a**)

Recrystallisation from methanol gave the desired product (62%), as a white crystalline solid, m.p. 66·5-68·5°C, (Lit.[127] 69-69·5°C).

3,4-Ethylenedioxythiophene-2-carboxaldehyde, (**120b**)

Purification by recrystallisation from methanol gave the title *aromatic carboxaldehyde* as fine white needles, (82%), m.p. 142-144°C; ν_{max}(KBr) 3110, 2930 and 1650 cm^{-1}; δ_H($CDCl_3$) 4·26-4·29 (2H, m, $ArOCH_2$), 4·35-4·39 (2H, m, $ArOCH_2$), 6·80 (1H, d, J 1·32 Hz, ArH), 9·91 (1H, d, J 0·99 Hz, ArCHO); δ_C($CDCl_3$) 64·4 and 65·3 ($ArOCH_2$), 110·8 (C_5), 118·5 (C_2), 141·8 (C_4), 148·5 (C_3), 180·1 (ArCHO); (Found: C, 49·35; H, 3·34. $C_7H_6O_3S$ requires C, 49·40; H, 3·55%).

3,4-Bis(3'-oxapentyloxy)thiophene-2-carboxaldehyde, (**120c**)

Purification by column chromatography, (silica; light petroleum-EtOAc, 2:1), gave the title *aromatic carboxaldehyde* (70%), as a green oil; ν_{max}(film) 3095, 2973, 2869 and 1659 cm^{-1}; δ_H($CDCl_3$) 1·20 (3H, t, J 6·93 Hz, $OCH_2C\underline{H}_3$), 1·22 (3H, t, J 6·93 Hz, $OCH_2C\underline{H}_3$), 3·54 (2H, q, J 6·93 Hz, $OC\underline{H}_2CH_3$), 3·58 (2H, q, J 6·93 Hz, $OC\underline{H}_2CH_3$), 3·70-3·73 (2H, m, $EtOCH_2$), 3·76-3·79 (2H, m, $EtOCH_2$), 4·12-4·16 (2H, m, $ArOCH_2$), 4·47-4·50 (2H, m, $ArOCH_2$), 6·73 (1H, d, J 1·32 Hz, ArH), 10·02 (1H, d, J 0·99 Hz, ArCHO); δ_C($CDCl_3$) 15·2 and 15·2 ($OCH_2\underline{C}H_3$), 66·6, 66·8, 68·6, 69·3, 70·3 and 72·4 (OCH_2), 108·0 (C_5), 125·0 (C_2), 149·3 (C_4), 153·2 (C_3), 182·3 (ArCHO); (Found: C, 54·16; H, 7·26. $C_{13}H_{20}O_5S$ requires C, 54·15; H, 6·99%).

6.14 The Mannich Reaction Applied to 3-Methoxythiophene

6.14.1 Synthesis of a Secondary Amine by Reduction of a Schiff Base

N-[(3,4-Dimethoxy-2-thienyl)methyl]-propylamine, (**128**)

To 3,4-dimethoxythiophene-2-carboxaldehyde (1·00 g, 5·81 mmols) in dry ethanol (10 cm^3), was added *n*-propylamine (0·58 cm^3, 7·01 mmols).The mixture was heated to boiling under reflux for 1 hour, ($CaCl_2$ guard tube). Upon cooling, sodium borohydride (0·26 g, 6·87 mmols) was added along with a further portion of dry ethanol (10 cm^3). The mixture was again boiled under reflux for a further hour. The ethanol was removed *in vacuo*, water was then added and the mixture extracted with dichloromethane (3 × 25 cm^3). The organic phase was worked up in the usual manner to give *N-[(3,4-dimethoxy-2-thienyl)methyl]-propylamine* as a pale green oil (1·22g, 98%); ν_{max}(film) 3320, 3110, 2960 and 1505 cm^{-1}; $\delta_H(CDCl_3)$ 0·90 (3H, t, J 7·26 Hz, $CH_2\underline{CH_3}$), 1·51 (2H, sextet, J 7·26 Hz, $CH_2\underline{CH_2}CH_3$), 2·59 (2H, t, J 7·26 Hz, $NCH_2\underline{CH_2}$), 3·80 (3H, s, $ArOCH_3$), 3·81 (3H, s, $ArOCH_3$), 3·84 (2H, s, $ArCH_2N$), 6·05 (1H, s, ArH); $\delta_C(CDCl_3)$ 11·8 ($CH_2\underline{CH_3}$), 23·1 ($CH_2\underline{CH_2}CH_3$), 44·8 ($N\underline{CH_2}CH_2$), 50·9 ($ArCH_2N$), 57·0 ($ArOCH_3$ on C_4), 60·8 ($ArOCH_3$ on C_3), 93·7 (C_5), 125·7 (C_2), 143·9 (C_3), 150·5 (C_4).

N-[(3,4-Dimethoxy-2-thienyl)methyl]-*N*-propylethanamide, (**129**)

The foregoing secondary amine (0·48 g, 2·23 mmols) was stirred overnight with acetic anhydride (5 cm^3). The mixture was basified with aqueous sodium hydroxide (2M), and the liberated oil was isolated by extraction into dichloromethane (3 × 25 cm^3). The oil obtained after treatment in the usual way was purified by column chromatography, (silica; light petroleum-EtOAc, 3:1) to give the desired *amide* as a pale green oil, (0·54 g, 95%); ν_{max}(film) 3110, 2970, 1645 and 1505 cm^{-1}; $\delta_H(CDCl_3)$ 0·91 (3H, t, J 7·26 Hz, $CH_2\underline{CH_3}$), 1·51-1·68 (2H, m, $CH_2\underline{CH_2}CH_3$), 2·11 and 2·20 (3H, s, $COCH_3$), 3·20 and

3·31 (2H, t, J 7·26 Hz, $NC\underline{H}_2CH_2$), 3·81–3·84 (6H, m, $ArOCH_3$), 4·50–4·60 (2H, s, $ArCH_2N$), 6·09 and 6·12 (1H, s, ArH); $\delta_C(CDCl_3)$ 11·2 and 11·4 ($CH_2\underline{C}H_3$), 20·6 and 21·3 ($CO\underline{C}H_3$), 21·7 and 21·8 ($CH_2\underline{C}H_2CH_3$), 39·6 and 44·0 ($N\underline{C}H_2CH_2$), 47·0 and 49·6 ($ArCH_2N$), 57·1 and 57·2 ($ArOCH_3$ on C_4), 60·6 and 61·0 ($ArOCH_3$ on C_3), 94·5 and 95·1 (C_5), 121·9 and 122·7 (C_2), 144·5 and 144·8 (C_3), 149·9 and 150·5 (C_4), 170·3 and 170·6 (C=O); (Found: C, 55·53; H, 7·62; N, 5·58. $C_{12}H_{19}NO_3S$ requires C, 56·00; H, 7·44; N, 5·44%).

6.15 The Synthesis of 3-Methoxythiophene Mannich Bases

N-(3-Methoxy-2-thienyl)methyl-*N*,*N*-dimethylamine, (**112a**)

The title Mannich base was synthesised according to the literature procedure, (74%), b.p. 110°C/20 mmHg, (Lit.[141] 103°C/14 mmHg).

N,*N*-[(3,3',4-Trimethoxy-2,2'-dithienyl)dimethyl]-propylamine, (**130**)

To glacial acetic acid (4 cm^3) was added *N*-(3,4-dimethoxy-2-thienyl)methyl]-propylamine (1·33 g, 6·18 mmols) and aqueous formaldehyde (37%, 0·55 cm^3, 6·78 mmols). To this was added 3-methoxythiophene (0·78 g, 6·80 mmols). The solution was stirred for 24 hours at room temperature, then basified (4M NaOH) and extracted with diethyl ether (3 × 20 cm^3). The ether layer was extracted with hydrochloric acid (4M, 3 × 20 cm^3), dried ($MgSO_4$), filtered and evaporated to give unreacted 3-methoxythiophene, (0·27 g, 2·37 mmols). The acidic fraction was basified (4M NaOH) and the oil which formed was isolated by extraction into dichloromethane (3 × 30 cm^3). After the usual work-up the crude product was purified by column chromatography, (alumina; light petroleum-EtOAc, 1:1), to give the title *Mannich base*, (1·47 g, 80%), as a colourless oil; ν_{max}(film) 3110, 2940 and 1505 cm^{-1}; $\delta_H(CDCl_3)$ 0·87 (3H, t, J 7·26 Hz, $CH_2C\underline{H}_3$), 1·54 (2H, sextet, J 7·26 Hz, $CH_2C\underline{H}_2CH_3$), 2·43 (2H, t, J

7·26 Hz, $NCH_2\underline{C}H_2$), 3·72 (2H, s, $ArCH_2N$), 3·74 (2H, s, $ArCH_2N$), 3·79 (9H, s, $ArOCH_3$), 6·05 (1H, s, ArH on C_5), 6·78 (1H, d, J 5·27 Hz, ArH on $C_{4'}$), 7·08 (1H, d, J 5·27 Hz, ArH on $C_{5'}$); $\delta_C(CDCl_3)$ 11·8 ($CH_2\underline{C}H_3$), 20·3 ($CH_2\underline{C}H_2CH_3$), 48·2 ($N\underline{C}H_2CH_2$), 49·1 ($ArCH_2N$ on $C_{2'}$), 54·8 ($ArCH_2N$ on C_2), 56·9 ($ArOCH_3$ on C_4), 58·7 ($ArOCH_3$ on $C_{3'}$), 60·8 ($ArOCH_3$ on C_3), 94·1 (C_5), 116·1 ($C_{4'}$), 119·3 ($C_{2'}$), 122·5 ($C_{5'}$), 125·9 (C_2), 144·2 (C_3), 150·2 (C_4), 154·8 ($C_{3'}$); (Found: C, 56·17; H, 6·98; N, 4·38. $C_{16}H_{23}NO_3S_2$ requires C, 56·27; H, 6·79; N, 4·10%).

1,4-Bis[3'-methoxy-2'-thienyl)methyl]piperazine, (**170**)

To a mixture of piperazine (2·15 g, 0·025 mols) and aqueous formaldehyde (37%, 3·80 cm^3, 0·047 mols) in acetic acid (7 cm^3), was added 3-methoxythiophene (5·68 g, 0·05 mols). The mixture was stirred for 24 hours, then basified with aqueous sodium hydroxide (4M). The solid precipitate was collected by filtration, and recrystallised from methanol to give off-white crystals of the title *Mannich base*, (7·1 g, 84%), m.p. 121-123°C; ν_{max}(KBr) 3010, 2940, 2820 and 1570 cm^{-1}; $\delta_H(CDCl_3)$ 2·53 (8H, s, NH_2), 3·64 (4H, s, $ArCH_2N$), 3·78 (6H, s, $ArOCH_3$), 6·78 (2H, d, J 5·28 Hz, ArH on C_4), 7·08 (2H, d, J 5·28Hz, ArH on C_5); $\delta_C(CDCl_3)$ 52·3 ($ArCH_2N$), 52·5 (CH_2N), 58·8 ($ArOCH_3$), 116·2 (C_4), 117·3 (C_2), 122·5 (C_5), 155·1 (C_3); (Found: C, 56·72; H, 6·74; N, 8·34. $C_{16}H_{22}N_2O_2S_2$ requires C, 56·77; H, 6·55; N, 8·27%).

6.16 Formylation of a Mannich Base

N-(5-Formyl-3-methoxy-2-thienyl)methyl-*N,N*-dimethylamine, (**122**)

N-(3-Methoxy-2-thienyl)methyl-*N,N*-dimethylamine (1·05 g, 6·13 mmols) was dissolved in dry diethyl ether (60 cm^3) at room temperature, under nitrogen. To this stirred solution was added *n*-butyllithium (2·5M in hexane, 7·36 cm^3, 18·39 mmols), and the whole was stirred for 1 hour. To the resulting dark

brown solution was added DMF (2·0 cm^3, 25·83 mmols) dropwise to minimise the exotherm. The mixture was stirred for 5 hours then water (50 cm^3) was added. From the dried ($MgSO_4$) ether layer, a deep red tarry mass was obtained. It was subjected to column chromatography, (alumina; light petroleum-EtOAc, 1:1), to give the desired *aromatic aldehyde*, (0·82 g, 67%); ν_{max}(film) 2940, 1670 and 1555 cm^{-1}; $\delta_H(CDCl_3)$ 2·30 (6H, s, $N(CH_3)_2$), 3·61 (2H, s, $ArCH_2N$), 3·88 (3H, s, $ArOCH_3$), 7·49 (1H, s, ArH), 9·75 (1H, s, ArCHO); $\delta_C(CDCl_3)$ 45·2 (NCH_3), 54·1 ($ArCH_2N$), 58·7 ($ArOCH_3$), 122·5 (C_4), 131·1 (C_2), 138·5 (C_5), 155·7 (C_3) 182·2 (C=O); (Found: C, 54·39; H, 6·96; N, 6·92. $C_9H_{13}NO_2S$ requires C, 54·25; H, 6·58; N, 7·03%).

6.17 The Mannich Reaction Applied to 3,4-Dioxygenated Thiophene Systems

6.17.1 Synthesis of mono-Mannich Bases from Secondary Amines[141]

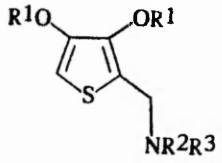
The amine, (40% aqueous solution, for dimethylamine), (1·1 eq.) and aqueous formaldehyde (37%, 1·1 eq.) were added to glacial acetic acid (0·3 cm^3mmol^{-1}) with ice cooling. The thiophene moiety (1·0 eq.) was added and the reaction was stirred for 24 hours. Basification with aqueous sodium hydroxide (4M) and extraction with diethyl ether (3 × 30 cm^3) gave the free organic components. The ethereal solution was extracted with aqueous hydrochloric acid (2M, 3 × 50 cm^3), the ethereal layer was treated in the usual fashion to give any unreacted thiophene moiety.

The aqueous acidic layer was basified with sodium hydroxide solution (4M) and extracted with dichloromethane (3 × 30 cm^3). The organic phase was treated in the usual way, to give the crude Mannich base. Purification was by centrifugal chromatography, (alumina; light petroleum-EtOAc, 6:1), unless stated otherwise. Yields, variations in purification procedure and microanalyses are presented in Table 4.

The methiodides were prepared by the addition of methyl iodide to an

ethereal solution of the tertiary amine, followed by recrystallisation from ethanol. Details of the methiodides are shown in Table 5, and Tables 6-8 give respectively, proton n.m.r., carbon-13 n.m.r. and mass spectroscopic data for the Mannich bases; the compounds synthesised in this work are identified in Figure 37.

Figure 37



	R^1 or R^1,R^1			
	Me	CH_2CH_2	CH_2CH_2OEt	$(CH_2CH_2)_2O$
$R^2=R^3=Me$	**111a**	**113a**	**115a**	**152**
$R^2,R^3=-(CH_2)_5-$	**111b**	**113b**	**115b**	N/A
$R^2,R^3=-(CH_2CH_2)_2O$	**111c**	**113c**	**115c**	N/A

Table 4 Yields and Microanalytical Data for the Mono-Mannich Bases

Compound	Yield, %	Molecular Formula	Found, %			Required, %		
			C	H	N	C	H	N
111a	5[a]	$C_9H_{15}NO_2S$	53·63	7·75	6·75	53·70	7·51	6·96
111b	5	$C_{12}H_{19}NO_2S$	60·18	8·22	5·81	59·72	7·94	5·80
111c	53	$C_{11}H_{17}NO_3S$	54·29	7·20	5·74	54·30	7·04	5·76
113a	72[b]	$C_9H_{13}NO_2S$	53·96	6·77	6·88	54·25	6·58	7·03
113b	82	$C_{12}H_{17}NO_2S$	60·11	7·55	5·67	60·22	7·16	5·85
113c	52[c]	$C_{11}H_{15}NO_3S$	54·66	6·54	5·67	54·75	6·27	5·80
115a	12[d]	$C_{15}H_{27}NO_4S$	56·71	8·92	4·59	56·75	8·57	4·41
115b	42[d]	$C_{18}H_{31}NO_4S$	60·46	9·17	3·90	60·47	8·74	3·92
115c	46[e]	$C_{17}H_{29}NO_5S$	56·59	8·22	3·82	56·80	8·13	3·90
152	89[f]	$C_{11}H_{17}NO_3S$	54·18	7·25	5·52	54·30	7·04	5·76

a: column chromatography, (alumina; light petroleum–EtOAC, 2:1).
b: b.p. 115°C/18mmHg.
c: also isolated was the bis morpholino Mannich base **114**, (13%).
d: column chromatography, (alumina; light petroleum–EtOAC, 10:1).
e: also isolated was the bis morpholino Mannich base **116**, (24%).
f: column chromatography, (alumina; light petroleum–EtOAC, 4:1).

Table 5 Melting Points and Microanalytical Data for the Methiodides of the Mono-Mannich Bases

MeI salt of compound	M.p., °C	Molecular Formula	Found, %			Required, %		
			C	H	N	C	H	N
111a	152–4	$C_{10}H_{18}INO_2S$	34·85	5·24	3·60	34·99	5·29	4·08
111b	148–50	$C_{13}H_{22}INO_2S$	40·46	5·63	3·73	40·74	5·79	3·65
111c	143–5	$C_{12}H_{20}INO_3S$	37·39	5·33	3·45	37·41	5·23	3·64
113a	310 (decomp.)	$C_{10}H_{16}INO_2S$	35·15	4·84	3·91	35·20	4·73	4·11
113b	161–3	$C_{13}H_{20}INO_2S$	40·11	5·36	3·38	40·95	5·29	3·67
113c	116–8	$C_{12}H_{18}INO_3S$	38·27	5·19	3·41	37·61	4·73	3·65
152	178–80	$C_{12}H_{20}INO_3S$	37·18	5·33	3·99	37·41	5·23	3·64

Table 6 ^{1}H n.m.r. ($CDCl_3$) Data for the Mono-Mannich Bases

Compound	Ar–H	$ArOCH_n$	$ArCH_2N$	NCH_n	Other
111a	6·10 (1H, s)	3·81 (6H, s)	3·53 (2H, s)	2·27 (6H, s)	
111b	6·08 (1H, s)	3·81 (6H, s)	3·59 (2H, s)	2·41–2·44 (4H, m)	1·43, (2H, quintet, J 5·61Hz, $CH_2\underline{CH_2}CH_2$) 1·57, (4H, quintet, J 5·61Hz, $\underline{CH_2}CH_2\underline{CH_2}$)
111c	6·10 (1H, s)	3·81 (3H, s) 3·82 (3H, s)	3·60 (2H, s)	2·48–2·51 (4H, m)	3·68–3·72 (4H, m, CH_2OCH_2)
113a	6·24 (1H, s)	4·18 (4H, s)	3·48 (2H, s)	2·27 (6H, s)	
113b	6·22 (1H, s)	4·17 (4H, s)	3·56 (2H, s)	2·42–2·45 (4H, m)	1·47, (2H, quintet, J 5·61Hz, $CH_2\underline{CH_2}CH_2$) 1·57, (4H, quintet, J 5·61Hz, $\underline{CH_2}CH_2\underline{CH_2}$)
113c	6·23 (1H, s)	4·14 (3H, s)	3·55 (2H, s)	2·45–2·49 (4H, m)	3·66–3·69 (4H, m, CH_2OCH_2)

Compound	Ar–H	$ArOCH_n$	$ArCH_2N$	NCH_n	Other
115a	6·12 (1H, s)	4·08–4·11 (2H, m) 4·14–4·18 (2H, m)	3·57 (2H, s)	2·27 (6H, s)	1·22, (3H, t, J 6·93Hz, $OCH_2\underline{C}H_3$) 1·24, (3H, t, J 5·61Hz, $OCH_2\underline{C}H_3$) 3·57, (2H, q, J 6·93Hz, OCH_2CH_3) 3·58, (2H, q, J 5·61Hz, OCH_2CH_3) 3·65–3·69, (2H, m, CH_2OEt) 3·76–3·79, (2H, q, CH_2OEt)
115b	6·09 (1H, s)	4·07–4·11 (2H, m) 4·14–4·17 (2H, m)	3·62 (2H, s)	2·41–2·43 (4H, m)	1·22, (3H, t, J 6·93Hz, $OCH_2\underline{C}H_3$) 1·24, (3H, t, J 6·93Hz, $OCH_2\underline{C}H_3$) 1·42, (2H, quintet, J 5·61Hz, $CH_2\underline{C}H_2CH_2$) 1·56, (4H, quintet, J 5·61Hz, $\underline{C}H_2CH_2\underline{C}H_2$) 3·56, (2H, q, J 6·93Hz, OCH_2CH_3) 3·58, (2H, q, J 6·93Hz, OCH_2CH_3) 3·64–3·69, (2H, m, CH_2OEt) 3·76–3·79, (2H, m, CH_2OEt)

Compound	Ar–H	$ArOCH_n$	$ArCH_2N$	NCH_n	Other
115c	6·12 (1H, s)	4·07–4·11 (2H, m) 4·15–4·19 (2H, m)	3·64 (2H, s)	2·48–2·52 (4H, m)	1·22, (3H, t, J 6·93Hz, $OCH_2\underline{C}H_3$) 1·24, (3H, t, J 6·93Hz, $OCH_2\underline{C}H_3$) 3·57, (2H, q, J 6·93Hz, $OC\underline{H}_2CH_3$) 3·58, (2H, q, J 6·93Hz, $OC\underline{H}_2CH_3$) 3·65–3·79, (2H, m, CH_2OEt and morpholino OCH_2)
152	6·49 (1H, s)	4·24–4·29 (4H, m)	3·51 (2H, s)	2·27 (6H, s)	3·87–3·92, (4H, m, CH_2OCH_2)

Table 7 Carbon-13 n.m.r. Data for the Mono-Mannich Bases

Compound	C_2	C_3	C_4	C_5	$ArCH_2N$	NCH_2	Other
111a	123·9	144·7	150·3	94·4	54·5	45·1	57·1, (OCH_3 on C_4) 60·8, (OCH_3 on C_3)
111b	124·0	144·6	150·3	94·1	54·0	54·1	24·3, ($CH_2\underline{C}H_2CH_2$) 26·0, ($\underline{C}H_2CH_2\underline{C}H_2$) 57·0, ($OCH_3$ on C_4) 60·8, (OCH_3 on C_3)
111c	122·8	144·9	150·3	94·5	53·7	53·2	57·1, (OCH_3 on C_4) 60·8, (OCH_3 on C_3) 67·0, (morpholino OCH_2)
113a	114·1	139·2	141·2	97·6	53·8	44·9	64·6, ($ArOCH_2$)
113b	114·2	139·2	141·2	97·5	53·3	53·8	24·2, ($CH_2\underline{C}H_2CH_2$) 25·9, ($\underline{C}H_2CH_2\underline{C}H_2$) 64·6, ($ArOCH_2$)

Compound	C_2	C_3	C_4	C_5	$ArCH_2N$	NCH_2	Other
113c	113·2	139·4	141·1	97·8	52·9	53·0	64·4 and 64·5, ($ArOCH_2$) 66·8, (morpholino OCH_2)
115a	124·4	143·5	149·1	95·4	54·4	45·1	15·2 and 15·3, ($OCH_2\underline{C}H_3$) 66·5, 66·8, 68·8, 69·4, 69·5 and 72·0, (OCH_2)
115b	124·3	143·5	149·2	95·2	53·9	54·1	15·2 and 15·3, ($OCH_2\underline{C}H_3$) 24·3, ($CH_2\underline{C}H_2CH_2$) 26·0, ($\underline{C}H_2CH_2\underline{C}H_2$) 66·5, 66·8, 68·9, 69·4, 69·5 and 72·0, (OCH_2)
115c	123·2	143·9	149·2	95·6	53·5	53·2	15·2 and 15·3, ($OCH_2\underline{C}H_3$) 66·5, 66·8, 68·8, 69·4, 69·5 and 72·0, (OCH_2) 67·0, (morpholino OCH_2)
152	123·0	146·6	149·4	105·7	54·7	45·2	71·9, 72·3, 73·6, 74·3, and 74·3, (OCH_2)

Table 8 Mass Spectoscopic Data for the Mono-Mannich Bases

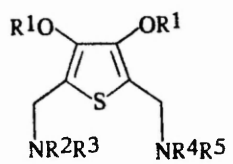
Compound	M/e	Percentage	Assignment
111a	201	32	M^+
	157	100	$M-N(Me)_2$
	99	13	$[C_5H_7S]^+$
111b	241	27	M^+
	157	100	$M-N(CH_2)_5$
	97	34	$[C_5H_5S]^+$
111c	243	31	M^+
	157	100	$M-N(CH_2CH_2)_2O$
	99	23	$[C_5H_7S]^+$
113a	199	38	M^+
	155	100	$M-N(Me)_2$
	99	13	$[C_5H_7S]^+$
113b	239	20	M^+
	155	100	$M-N(CH_2)_5$
	97	34	$[C_5H_5S]^+$
113c	241	33	M^+
	155	100	$M-N(CH_2CH_2)_2O$
	99	20	$[C_5H_7S]^+$
115a	273	20	$M-N(Me)_2$
	229	49	$M-N(Me)_2-OEt$
	155	100	$M-N(Me)_2-2(CH_2OEt)$
	98	8	$[C_5H_6S]^+$
	45	80	OEt
115b	155	2	$M-N(CH_2)_5-2(CH_2OEt)$
	73	34	CH_2CH_2OEt
	45	100	OEt
115c	314	20	M-OEt
	229	60	$M-N(CH_2CH_2)_2O-OEt$
	155	100	$M-N(CH_2CH_2)_2O-2(CH_2OEt)$
	97	42	$[C_5H_5S]^+$
152	182	39	
	149	94	
	116	100	
	97	22	$[C_5H_5S]^+$
	44	67	$[N(Me)_2]^+$

6.17.2.Synthesis of the bis-Mannich Bases

The bis Mannich bases were prepared by the reaction of a mono-Mannich base (1·0 eq.) with the amine (1·1 eq.) and aqueous formaldehyde (37%, 1·1 eq.) in glacial acetic acid (1 cm^3mmol^{-1}). Heat was applied for 4 hours by means of an oil bath, (100°C). The cooled reaction mixture was basified with aqueous sodium hydroxide (4M) and extracted with diethyl ether (3 × 30 cm^3). The ethereal portions were treated in the usual fashion. The bis-Mannich bases were purified by centrifugal chromatography, (alumina; light petroleum-EtOAc, 6:1) unless stated otherwise.

The infrared spectra of the bis-Mannich bases are typified by peaks between 2980 and 2750 cm^{-1}, (saturated C-H sretch, very intense) and a peak of medium intensity between 1505 and 1540 cm^{-1}, (C=C stretch, Ar ring). The microanalyses are given in Table 9, the proton n.m.r., carbon-13 n.m.r. and mass spectroscopic data are given in Tables 10, 11 and 12, respectively. The compounds synthesised are summarised in Figure 38.

Figure 38



123 , R^1 = Me , R^2,R^3 = R^4,R^5 = -$(CH_2)_5$-;

124 , R^1 = Me , R^2,R^3 = R^4,R^5 = -$(CH_2CH_2)_2O$;

131 , R^1,R^1 = CH_2CH_2 , R^2,R^3 = R^4,R^5 = -$(CH_2)_5$-;

136 , R^1,R^1 = CH_2CH_2 , R^2,R^3 = -$(CH_2)_5$- , R^4,R^5 = -$(CH_2CH_2)_2O$;

114 , R^1,R^1 = CH_2CH_2, R^2,R^3 = R^4,R^5 = -$(CH_2CH_2)_2O$;

125 , R^1 = CH_2CH_2OEt , R^2,R^3 = R^4,R^5 = -$(CH_2)_5$-;

116, R^1 = CH_2CH_2OEt , R^2,R^3 = R^4,R^5= -$(CH_2CH_2)_2O$;

Table 9 Melting Points and Microanalyses for the Bis-Mannich Bases

Base	Yield, %	m.p.,°C	Molecular Formula	Found, %			Required, %		
				C	H	N	C	H	N
123	27[a]	oil	$C_{18}H_{30}N_2O_2S$	63·89	9·17	8·19	63·87	8·93	8·28
124	78	85·5–87·5	$C_{16}H_{26}N_2O_4S$	56·29	7·93	8·35	56·12	7·65	8·18
131	86[b]	98–100	$C_{18}H_{28}N_2O_2S$	64·26	8·61	8·30	64·25	8·39	8·33
136	91[b]	64–66	$C_{17}H_{26}N_2O_3S$	60·12	7·91	8·04	60·33	7·74	8·28
114	91[b]	83–85	$C_{16}H_{24}N_2O_4S$	56·43	7·18	8·42	56·45	7·11	8·23
125	35	oil	$C_{24}H_{42}N_2O_4S$	63·51	9·50	6·05	63·40	9·31	6·16
116	52	oil	$C_{22}H_{38}N_2O_6S$	57·80	8·35	5·99	57·62	8·35	6·11

a: purified by centrifugal chromatography, (alumina; light petroleum–EtOAc, 30:1)
b: purified by centrifugal chromatography, (alumina; light petroleum–EtOAc, 6:1)

Table 10 ^{1}H n.m.r. ($CDCl_3$) Data for the Bis-Mannich Bases

Compound	$ArOCH_n$	$ArCH_2N$	Other
123	3·81 (6H, s)	3·55 (4H, s)	1·41, (4H, quintet, J 5·61Hz, $CH_2C\underline{H}_2CH_2$) 1·57, (8H, quintet, J 5·61Hz, $C\underline{H}_2CH_2C\underline{H}_2$) 2·41–2·45, (8H, m, CH_2NCH_2)
124	3·82 (6H, s)	3·57 (4H, s)	2·48–2·51, (8H, m, CH_2NCH_2) 3·69–3·72, (8H, m, CH_2OCH_2)
131	4·16 (4H, s)	3·56 (4H, s)	1·39, (4H, quintet, J 5·61Hz, $CH_2C\underline{H}_2CH_2$) 1·58, (8H, quintet, J 5·61Hz, $C\underline{H}_2CH_2C\underline{H}_2$) 2·43–2·46, (8H, m, CH_2NCH_2)
136	4·17 (4H, s)	3·55 (2H, s) 3·56 (2H, s)	1·40, (2H, quintet, J 5·61Hz, $CH_2C\underline{H}_2CH_2$) 1·58, (4H, quintet, J 5·61Hz, $C\underline{H}_2CH_2C\underline{H}_2$) 2·42–2·45, (4H, m, piperidino CH_2NCH_2) 2·49–2·52, (4H, m, morpholino CH_2NCH_2) 3·69–3·735, (4H, m, CH_2OCH_2)
114	4·17 (4H, s)	3·56 (4H, s)	2·49–2·52, (8H, m, CH_2NCH_2) 3·69–3·73, (8H, m, CH_2OCH_2)

Compound	$ArOCH_2$	$ArCH_2N$	Other
125	4·11–4·15 (4H, m),	3·62 (4H, m)	1·23, (6H, t, J 6·93Hz, $OCH_2C\underline{H}_3$) 1·39, (4H, quintet, J 5·61Hz, $CH_2C\underline{H}_2CH_2$) 1·57, (8H, quintet, J 5·61Hz, $C\underline{H}_2CH_2C\underline{H}_2$) 2·43–2·46, (8H, m, CH_2NCH_2) 3·56, (4H, q, J 6·93Hz, $OC\underline{H}_2CH_3$) 3·64–3·69, (4H, m, $EtOCH_2$)
116	4·12–4·16 (4H, m)	3·61 (4H, m)	1·23, (6H, t, J 6·93Hz, $OCH_2C\underline{H}_3$) 2·49–2·52, (8H, m, CH_2NCH_2) 3·56, (4H, q, J 6·93Hz, $OC\underline{H}_2CH_3$) 3·64–3·68, (4H, m, $EtOCH_2$) 3·69–3·73, (8H, m, morpholino CH_2OCH_2)

Table 11 Carbon-13 n.m.r. for the Bis-Mannich Bases

Compound	C_2/C_5	C_3/C_4	$ArCH_2N$	NCH_2	Other
123	121·4	146·8	54·1	54·1	24·3 ($CH_2\underline{C}H_2CH_2$), 26·0 ($\underline{C}H_2CH_2\underline{C}H_2$), 60·7 ($ArOCH_3$)
124	120·8	147·2	53·7	53·2	60·8 ($ArOCH_3$), 67·0 (CH_2OCH_2)
131	111·8	138·6	53·7 54·0	53·2 53·8	24·2 ($CH_2\underline{C}H_2CH_2$), 26·0 ($\underline{C}H_2CH_2\underline{C}H_2$), 64·6 ($ArOCH_2$)
136	110·8 112·3	138·6 138·9	52·9 53·2	53·0 53·9	24·2 ($CH_2\underline{C}H_2CH_2$), 26·0 ($\underline{C}H_2CH_2\underline{C}H_2$), 64·6 and 64·7 ($ArOCH_2$), 67·0 ($CH_2OCH_2$)
114	111·4	138·9	52·9	53·0	64·7 ($ArOCH_2$), 66·9 (morpholino CH_2OCH_2)
125	121·8	145·7	53·5	54·1	15·3 ($OCH_2\underline{C}H_3$), 24·3 ($CH_2\underline{C}H_2CH_2$), 26·0 ($\underline{C}H_2CH_2\underline{C}H_2$), 66·6, 69·4, 72·4, ($OCH_2$)
116	121·5	146·1	53·6	53·2	15·3 ($OCH_2\underline{C}H_3$), 66·6, 69·4, 72·4, (OCH_2 of ether side chain), 67·0 (morpholino CH_2OCH_2)

Table 12 Mass Spectroscopic Data for the Bis-Mannich Bases

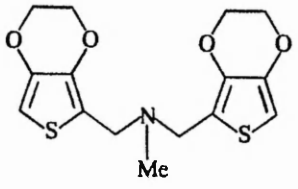
Compound	M/e	%	Assignment
123	241	21	M-[$CH_2N(CH_2)_5$]
	157	67	M-2[$CH_2N(CH_2)_5$]-CH
	97	28	$(C_5H_5S)^+$
124	240	34	M-$CH_2N(CH_2CH_2)_2O$-2H
	98	100	$(C_5H_6S)^+$
131	336	25	M^+
	252	100	M-$N(CH_2)_5$
	169	18	M-2[$N(CH_2)_5$]
	97	27	$(C_5H_5S)^+$
136	252	100	M-$N(CH_2CH_2)_2O$
	169	36	M-$N(CH_2CH_2)_2O$-$N(CH_2)_5$
	97	28	$(C_5H_6S)^+$
114	254	100	M-$N(CH_2CH_2)_2O$
	169	26	M-2[$N(CH_2CH_2)_2O$]
	98	51	$(C_5H_6S)^+$

6.18 Synthesis of the Bis-Thienylmethyl Mannich Bases

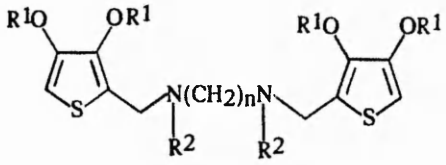
6.18.1 General Synthetic Procedure

The thiophene moiety (2·0 eq.) was dissolved in glacial acetic acid (1·25 cm^3mmol^{-1}). To an equal volume of glacial acetic acid was added the secondary diamine or primary amine (40% aqueous solution for methylamine), (1·0 eq.) and aqueous formaldehyde (37%, 2·0 eq.) with ice cooling. The solutions were fed separately and simultaneously into glacial acetic acid (0·3 cm^3mmol^{-1}) by means of a syringe pump with stirring, after the addition was complete, the solution was stirred for a further 12 hours. The solvent was removed *in vacuo* to give a dark oily residue. The work-up was similar to that described in Section 6.17.1, page 187). Purification by column chromatography, (alumina; light petroleum-EtOAc, 5:1), gave the required Mannich base. The melting points and microanalyses are presented in Table 13. The infrared spectra of these compounds are typified by a peak of medium intensity between 3093 and 3115 cm^{-1} (Ar-H stretch), peaks of strong intensity between 2930 and 2775 cm^{-1} (saturated C-H stretch) and an intense peak between 1500-1505 cm^{-1} (Ar C=C stretch). The proton n.m.r., carbon-13 n.m.r. and mass spectroscopic data are given in Tables 14, 15 and 16. Also isolated in these experiments were a series of oligomeric Mannich base, the data for which are given in the following section. The compounds sythesised in this work are identified in Figure 39.

Figure 39



(156a)



157a , $R^1,R^1 = CH_2CH_2$, R^2 = Me , n = 2;

157b , $R^1,R^1 = CH_2CH_2$, R^2 = Me , n = 3;

157c , $R^1,R^1 = CH_2CH_2$, $R^2,R^2 = CH_2CH_2$, n = 2;

163a , $R^1,R^1 = O(CH_2CH_2)_2$, R^2 = Me , n = 2;

157b , $R^1,R^1 = CH_2CH_2$, R^2 = Me , n = 3;

163a , $R^1,R^1 = O(CH_2CH_2)_2$ R^2 = Me , n = 2;

Table 13 Melting Points and Microanalyses for the Bis-2-Thienylmethyl Mannich Bases

Base	Yield, %	m.p.,°C	Molecular Formula	Found, %			Required, %		
				C	H	N	C	H	N
156a	53	78–80	$C_{15}H_{17}NO_4S_2$	53·20	5·05	4·06	53·08	5·05	4·13
157a	45	75·5–77·5	$C_{18}H_{24}N_2O_4S_2$	54·62	6·18	6·77	54·52	6·10	7·07
157b	12	oil	$C_{19}H_{26}N_2O_4S_2$	55·52	6·58	6·99	55·59	6·38	6·82
157c	22	158 (decomp.)	$C_{18}H_{22}N_2O_4S_2$	54·65	5·67	6·97	54·80	5·62	7·10
163a	46	oil	$C_{22}H_{32}N_2O_6S_2$	54·68	6·81	5·98	56·40	6·66	5·78

Table 14 ^1H n.m.r. ($CDCl_3$) Data of the Bis-2-Thienylmethyl Mannich Bases

Compound	ArH	$ArOCH_n$	$ArCH_2N$	R_2NCH_2	NCH_3	Other
156a	6·25 (2H, s)	4·18 (8H, s)	3·65 (4H, s)	N/A	2·29 (3H, s)	
157a	6·25 (2H, s)	4·17 (8H, s)	3·63 (4H, s)	2·58 (4H, s)	2·29 (6H, s)	
157b	6·22 (2H, s)	4·16 (8H, s)	3·58 (4H, s)	2·39–2·44 (4H, m)	2·26 (6H, s)	1·73 (2H, quintet, J 7·59Hz, $CH_2\underline{CH_2}CH_2$)
157c	6·22 (2H, s)	4·17 (8H, s)	3·59 (4H, s)	2·55 (4H, s)	2·55 (8H, s)	
163a	6·46 (2H, s)	4·21–4·27 (8H, m)	3·62 (4H, s)	2·57 (4H, s)	2·28 (6H, s)	3·84–3·89 (8H, m, CH_2OCH_2)

Table 15 ^{13}C n.m.r. ($CDCl_3$) Data for the Bis-2-Thienylmethyl Mannich Bases

Compound	C_2	C_3	C_4	C_5	$ArCH_2N$	NCH_2	NCH_3	Other
156a	114·6	139·2	141·2	97·8	51·0	N/A	41·7	64·7 ($ArOCH_2$)
157a	114·0	139·3	141·2	97·7	54·2	52·0	42·4	64·6 and 64·7 ($ArOCH_2$)
157b	114·5	139·1	141·2	97·5	54·2	52·0	42·2	25·2 ($CH_2\underline{C}H_2CH_2$) 64·3 and 64·6 ($ArOCH_2$)
157c	113·6	139·3	141·2	97·7	52·5	52·4	N/A	64·6 ($ArOCH_2$)
163a	122·7	146·6	149·4	105·6	54·5	53·0	42·5	71·8, 72·2, 73·5 and 74·2 ($ArOCH_2$ and OCH_2)

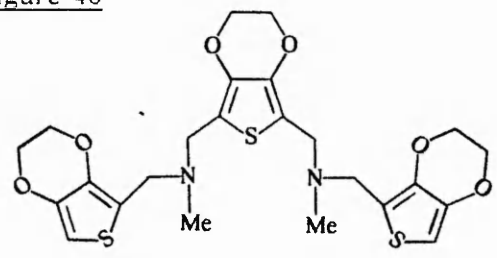
Table 16 Mass Spectroscopic Data for the Bis-2-Thienylmethyl Products

Compound	M/e	%	Assignment
156a	339	6	M^+
	197	78	
	155	100	$[C_7H_7O_2S]^+$
	97	11	$[C_5H_5S]^+$
157a	396	2	M^+
	241	100	
	155	86	$[C_7H_7O_2S]^+$
	97	7	$[C_5H_5S]^+$
157b	410	2	M^+
	255	100	
	155	83	$[C_7H_7O_2S]^+$
	97	3	$[C_5H_5S]^+$
157c	394	3	M^+
	239	100	
	155	89	$[C_7H_7O_2S]^+$
	97	4	$[C_5H_5S]^+$

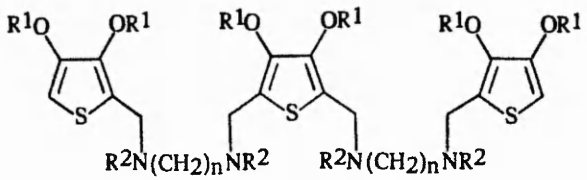
6.18.2 Oligomeric Thienylmethyl Mannich Bases

Also by continued elution of the column, the foregoing experiments gave further fractions of oligomeric material; these are summarised in Figure 40.

Figure 40



(160)



161a , $R^1,R^1 = CH_2CH_2$,
R^2 = Me , n = 2;

161b , $R^1,R^1 = CH_2CH_2$,
R^2 = Me , n = 3;

161c , $R^1,R^1 = CH_2CH_2$,
$R^2,R^2 = CH_2CH_2$, n = 2;

163b , $R^1,R^1 = O(CH_2CH_2)_2$,
R^2 = Me , n = 2;

The infrared spectra of these compounds showed a signal between 3120-3115 cm^{-1} of weak intensity, relating to the aromatic C-H stretch. A very intense set of signals were observed between 2980 and 2790 cm^{-1}, arising from the saturated C-H stretching vibrations. A peak of strong intensity, owing to the presence of C=C, was observed between 1500 and 1505 cm^{-1}. With the exception of (**161c**), the oligomeric compounds were isolated as oils, which though stable enough to obtain n.m.r. spectra, degraded over a period of time, preventing satisfactory microanalysis. The oligomer (**161c**) was isolated as a white solid, m.p. 285°C, (decomp.); (Found: C, 55·48; H, 5·85; N, 8.46. $C_{30}H_{38}N_4O_6S_3$ requires C, 55·71; H, 5·92; N, 8.66%); mass spectrum, *m/e* (relative intensity) 364 (3%), 221 (100%) and 143 (95%). The proton and carbon-13 n.m.r. data are supplied in Tables 17 and 18, respectively.

Table 17 ^1H n.m.r. ($CDCl_3$) Data for the Oligomeric Mannich Bases

Compound	ArH	$ArOCH_2$	$ArCH_2N$	NCH_2	NCH_3	Other
160	6·23 (2H, s)	4·16 (4H, s) 4·17 (8H, s)	3·63 (4H, s) 3·64 (4H, s)	N/A	2·28 (6H, s)	
161a	6·24 (2H, s)	4·16 (8H, s) 4·18 (8H, s)	3·61 (4H, s) 3·62 (4H, s)	2·62 (8H, s)	2·30 (6H, s) 2·31 (6H, s)	
161b	6·23 (2H, s)	4·17 (12H, s)	3·61 (8H, s)	2·41 (8H, m)	2·27 (12H, s)	1·70–1·78 (4H, m, $CH_2C\underline{H}_2CH_2$)
161c	6·22 (2H, s)	4·14 (4H, s) 4·17 (8H, s)	3·56 (4H, s) 3·60 (4H, s)	2·55 (16H, s)		
163b	6·52 (2H, s)	4·23–4·31 (12H, m)	3·71 (4H, s) 3·72 (4H, s)	2·69 (8H, s)	2·32 (6H, s) 2·33 (6H, s)	3·87–3·88 (12H, m, CH_2OCH_2)

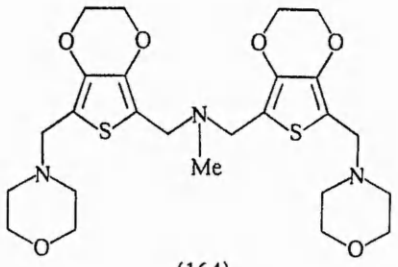
Table 18 ^{13}C n.m.r. ($CDCl_3$) Data for the Oligomeric Mannich Bases

Compound	C_2/C_5	C_3/C_4	$C_{2'}$	$C_{3'}$	$C_{4'}$	$C_{5'}$	$ArCH_2N$	NCH_2	NCH_3	Other
160	112·1	138·7	114·2	139·3	141·2	97·9	50·8 50·9	N/A	41·5	64·6, ($ArOCH_2$)
161a	111·7	138·8	114·0	139·3	141·2	97·7	54·1 54·2	51·8 52·0	42·3 42·4	64·6, ($ArOCH_2$)
161b	112·3	138·1	113·7	139·3	141·2	97·8	54·4	52·9 53·0	41·9 42·0	24·7, $(CH_2)_2\underline{CH_2}$ 64·6, ($ArOCH_2$)
161c	111·5	138·8	113·6	139·3	141·3	97·7	52·5	52·4	N/A	64·6, ($ArOCH_2$)
163a	118·9	147·0	119·9	146·7	149·5	106·8	53·1	52·1 52·3	41·7	71·6, 71·7, 72·4, 72·9 and 73·3, (OCH_2)

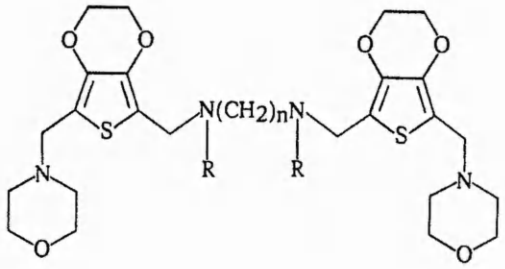
6.18.3 Bis Morpholino Derivatives of the Bis-2-Thienylmethyl Mannich Bases

To the bis-2-thienylmethyl Mannich base (0·50g) in glacial acetic acid (3 cm^3) was added aqueous formaldehyde (37%, 2·2 eq.) and morpholine (2·2 eq.) with ice cooling. The mixture was stirred for 12 hours. Basification with aqueous sodium hydroxide (4M) was followed by extraction with dichloromethane, (3 × 10 cm^3). The organic phase was worked up in the usual manner, and the crude product was then purified by column chromatography, (alumina; light petroleum-EtOAc, 4:1). The melting points and microanalyses are reported in Table 19. The infrared spectra were typified by peaks of strong intensity between 2930 and 2806 cm^{-1} (saturated C-H stretch), and an intense peak at 1540 cm^{-1} (Aromatic C=C stretch). The proton and carbon-13 n.m.r.data are reported in Tables 20 and 21, respectively. The compounds synthesised are summarised below in Figure 41.

Figure 41



(164)



165a , R = Me , n = 2;
165b , R = Me , n = 3;
165c , R,R = CH_2CH_2 , n = 2;

Table 19 Melting Points and Microanalyses for the Bis-Morpholino-Bis-2-Thienylmethyl Mannich Bases

Base	Yield, %	m.p.,°C	Molecular Formula	Found, %			Required, %		
				C	H	N	C	H	N
164	97	90–92	$C_{25}H_{35}N_3O_6S_2$	55·91	6·43	7·66	88·85	6·56	7·82
165a	97	111–113	$C_{28}H_{42}N_4O_6S_2$	56·39	7·23	9·28	56·54	7·12	9·42
165b	92	oil	$C_{29}H_{44}N_4O_6S_2$	56·93	7·46	9·60	57·21	7·29	9·20
165c	83	220 (decomp.)	$C_{28}H_{40}N_4O_6S_2$	56·59	6·79	9·65	56·73	6·80	9·45

Table 20 ^1H n.m.r. ($CDCl_3$) Data for the Bis-Morpholino-Bis-2-Thienylmethyl Mannich Bases

Base	NCH_3	Morpholino NCH_2	Bridging NCH_2	$ArCH_2N$	Morpholino OCH_2	$ArOCH_2$	Other
164	2·28 (3H, s)	2·49–2·53 (8H, m)	N/A	3·57 (4H, s, morpholino) 3·61 (4H, s, bridging)	3·70–3·73 (8H, m)	4·17 (8H, s)	
165a	2·27 (6H, s)	2·48–2·51 (8H, m)	2·56 (4H, s)	3·55 (4H, s, morpholino) 3·60 (4H, s, bridging)	3·68–3·72 (8H, m)	4·17 (8H, s)	
165b	2·25 (6H, s)	2·48–2·51 (8H, m)	2·39–2·45 (4H, m)	3·55 (8H, s,)	3·68–3·72 (8H, m)	4·16 (8H, s)	1·73, (2H, quintet, J 7·59Hz, $CH_2\underline{CH_2}CH_2$)
165c	N/A	2·48–2·51 (8H, m)	2·55 (8H, m)	3·54 (4H, s, morpholino) 3·59 (4H, s, bridging)	3·68–3·73 (8H, m)	4·16 (8H, s)	

Table 21 ^{13}C n.m.r. ($CDCl_3$) Data for the Bis-Morpholino-Bis-2-Thienylmethyl Mannich Bases

Base	C_2	C_5	C_3	C_4	Morpholino $ArCH_2N$	Bridging $ArCH_2N$	NCH_3	Other
164	112·8	111·1	138·7	138·9	52·9	51·0	41·7	53·0, (morpholino CH_2N) 64·6, ($ArOCH_2$) 64·7, ($ArOCH_2$) 67·0, (morpholino CH_2O)
165a	112·3	111·0	138·7	138·9	52·9	54·3	42·4	52·0, (bridging CH_2N) 53·0, (morpholino CH_2N) 64·6, ($ArOCH_2$) 64·7, ($ArOCH_2$) 67·0, (morpholino CH_2O)

Base	C_2	C_5	C_3	C_4	Morpholino $ArCH_2N$	Bridging $ArCH_2N$	NCH_3	Other
165b	112·6	110·9	138·6	138·9	52·9	54·8	42·2	25·2, ($CH_2\underline{CH_2}CH_2$) 51·5, (bridging CH_2N) 53·0, (morpholino CH_2N) 64·6, ($ArOCH_2$) 64·7, ($ArOCH_2$) 66·9, (morpholino CH_2O)
165c	111·6	111·2	138·8	138·9	52·9	52·4	N/A	52·4, (bridging CH_2N) 53·1, (morpholino CH_2N) 64·6, ($ArOCH_2$) 67·0, (morpholino CH_2O)

6.19 Attempts to Macrocyclise the Bis-2-Thienylmethyl Mannich Base, (**157a**)

N,N'-Bis[(3,4-ethylenedioxy-2-thieny)methyl]-*N,N'*-dimethylethylenediamine, (**157a**), (1·00 g, 2·53 mmols) was dissolved in glacial acetic acid (10 cm^3). To an equal volume of glacial acetic acid was added *N,N'*-dimethylethylenediamine (0·26 cm^3, 2·53 mmols) and aqueous formaldehyde (37%, 0·41 cm^3, 5·05 mmols) with ice cooling. These solutions were fed, by means of a syringe pump into a stirred solution of glacial acetic acid, (5 cm^3) and nickel(Ⅱ) acetate (0·45 g, 2·56 mmols), maintained in an oil bath at 60°C. The addition took 15 hours. The mixture was stirred for a further 12 hours, then the solvent was removed *in vacuo*. The resultant oily residue was basified and filtered through 'Hyflow', which was then washed by portions of dichloromethane, (2 × 20 cm^3). The combined filtrates were treated in the usual way to afford a brown oil which was purified by column chromatography, (alumina; light petroleum-EtOAc, 5;1). Thus was obtained *5-methyl-3,4-ethylenedioxythiophene-2-carboxaldehyde*, (0·21 g, 23%), as a white solid which darkened slowly on exposure to light, m.p. 134°C, (decomp.); ν_{max} (KBr) 2950, 2830, 1650 and 1505 cm^{-1}; δ_H ($CDCl_3$) 2·31 (3H, s, $ArCH_3$), 4·25-4·36 (4H, m, $ArOCH_2$), 9·82 (1H, s, ArCHO), δ_C ($CDCl_3$) 12·0 ($ArCH_3$), 64·4 and 65·3 ($ArOCH_2$), 114·2 (C_2), 126·3 (C_5), 138·3 (C_4), 148·8 (C_3), 179·3 (ArCHO); (Found: C, 52·26; H, 4·28. $C_8H_8O_3S$ requires C, 52·16; H, 4·38%); *m/e* 184 (M^+, 100%).

Also isolated by further elution of the column was a pale brown solid (80 mg, 6%); δ_H ($CDCl_3$) 2·32 (12H, s, NCH_3), 2·50 (8H, s, NCH_2), 3·58 (8H, s, $ArCH_2N$), 4·15 (8H, s, $ArOCH_2$); δ_C ($CDCl_3$) 43·6 (NCH_3), 51·9 (NCH_2), 53·8 ($ArCH_2N$), 64·7 ($ArOCH_2$), 112·7 (C_2/C_5), 138·3 (C_3/C_4). Upon removal of the $CDCl_3$, this compound degraded.

6.20 Synthesis of a Large Ring Macrocycle

6.20.1 Synthesis of 2,5,8,14,17,20-Hexaoxa-27,30-diaza-11,24,33-trithia-27,30-ethylenpentacyclo[30.3.$1,32_2.27,30_0.21,25_0.9,13$]-pentatriaconta-1(32),9,12,21,(25),22,34-hexene, (**153a**)

To glacial acetic acid (50 cm^3) was added piperazine (0·13 g, 1·51 mmols) and aqueous formaldehyde (37%, 0·24 cm^3, 2·96 mmols). To this solution was added 3,4-bis[5'-(3''-thienyloxy)-3'-oxapentyloxy]thiophene, (**96**), (0·67 g, 1·47 mmols) and the whole was stirred overnight. The solvent was removed *in vacuo* and the residue was basified, (4M NaOH) and extracted with dichloromethane, (3 × 20 cm^3). The combined organic layers were treated in the usual, and was purified by column chromatography, (alumina; light petroleum-EtOAc, 5;1), to give unreacted (**96**), (0·24 g) and the title Thus was obtained *macrocycle*, as a white crystalline solid (0·41 g, 49%), m.p. 94-96°C; ν_{max} (KBr) 3110, 2930, 2890, 1570 and 1555 cm^{-1}; δ_H ($CDCl_3$-DMSO-d_6) 2·49 (8H, s, NCH_2), 3·61 (4H, s, $ArCH_2N$), 3·81-3·90 (8H, m, CH_2OCH_2), 4·09-4·15 (8H, m, $ArOCH_2$), 6·25 (2H, s, ArH), 6·79 (2H, d, J 5·28Hz, ArH on $C_{4'}$), 7·08 (2H, d, J 5·60Hz, ArH on $C_{5'}$); δ_C ($CDCl_3$-DMSO-d_6) 51·8 ($ArCH_2N$), 52·0 (NCH_2), 69·6 70·0 70·1 and 71·6 (OCH_2), 98·2 (C_2/C_5), 117·7 ($C_{4'}$), 118·0 ($C_{2'}$), 122·4 ($C_{5'}$), 147·0 (C_3/C_4), 154·1 ($C_{3'}$); (Found: C, 55·27; H, 6·16; N, 4·74. $C_{26}H_{34}N_2O_6S_3$ requires C, 55·10; H, 6·05; N, 4·94%); *m/e* 566 (M^+, 100%).

6.21 Attempts to Synthesise Bis(Dialkylmethyleneammonium) Salts

6.21.1 Synthesis of the Diamine Dioxides

N,N,N',N'-Tetramethylethylenediamine-*N,N'*-dioxide Dihydrate[176]

To *N,N,N',N'*-tetramethylethylenediamine (15·60 g, 0·13 mols) at 0°C (ice/salt bath) was added aqueous hydrogen peroxide solution (30%, 50 cm^3, 0·79 mols), dropwise over 30 minutes with constant rapid stirring. The mixture was stirred at room temperature overnight, after which, any excess of hydrogen peroxide

was decomposed with manganese dioxide. The solution was concentrated *in vacuo* (temp.<80°C). Upon formation of a viscous clear syrup, water (25 cm^3) was added and the volume was again reduced. The crystalline white solid was repeatedly washed with acetone and dried *in vacuo* at 50°C over phosphorus pentoxide, giving the title diamine dioxide as a dihydrate, (14·85 g, 62%), m.p. 135–138°C, (Lit.[176] 139–140°C). The spectoscopic data was in accordance with that given.

1,4-Dimethylpiperazine-*N,N'*-dioxide[184]

To a stirred solution of 1,4-dimethylpiperazine (11·21 g, 0·098 mols) in methanol (30 cm^3) at 5°C was added aqueous hydrogen peroxide solution (30%, 27 cm^3, 0·24 mols), during 30 minutes. Stirring continued for 6 hours, after which, any excess of hydrogen peroxide was decomposed with manganese dioxide. The solvent was removed *in vacuo* to leave a solid, which, upon recrystallisation from acetone and drying *in vacuo* over phosphorus pentoxide, gave the title diamine dioxide as a white crystalline solid, (14·31 g, 80%), m.p. 278°C, (decomp.), [Lit.[175] 283–284°C, (decomp.)]. The spectoscopic data was in accordance with that given.

6.21.2 Attempted Synthesis of *N,N'*-Bis[(3-methoxy-2-thienyl)methyl]-*N,N'*-dimethylethylenediamine

Trifluoroacetic anhydride (1·53 cm^3, 10·84 mmols) was added dropwise to a slurry of *N,N,N',N'*-tetramethylethylenediamine-*N,N'*-dioxide (0·50 g, 2·71 mmols) in dry dichloromethane (10 cm^3) maintained at 0°C. This was then stirred at room temperature for a further 2 hours, when the solvent was removed. To the residual dark oil was added a solution of 3-methoxythiophene (0·62 g, 5·42 mmols) in dry acetonitrile (10 cm^3). The reaction mixture was heated to boiling under reflux, under nitrogen for 8 hours, after which, the

solvent was removed *in vacuo*. The residue was taken up in diethyl ether (30 cm^3) and washed with saturated sodium bicarbonate solution (2 × 10 cm^3), followed by aqueous hydrochloric acid (4M, 3 × 10 cm^3). The ethereal layer was worked up in the normal way to give some unreacted 3-methoxythiophene, (0·21 g, 42%). Basification and extraction of the aqueous acidic layer failed to give any tertiary diamine.

6.21.3 Attempted Synthesis of 1,4-Bis[(3-methoxy-2-thienyl)methyl]-piperazine, (170)

To a solution of 1,4-dimethylpiperazine (0·24 g, 2·11 mmols) in dry dichloromethane (10 cm^3) was added triphenylcarbenium tetrafluoroborate (1·39 g, 4·20 mmols). The reaction mixture was then stirred at room temperature for 3 hours, under an inert atmosphere of nitrogen, after which, the solvent was removed. To residue, was added a solution of 3-methoxythiophene (0·48 g, 4·20 mmols) in dry acetonitrile (10 cm^3), then this mixture was heated to boiling under reflux, under nitrogen for 8 hours, after which, the solvent was removed *in vacuo*. The residue was taken up in diethyl ether (30 cm^3) and washed with aqueous hydrochloric acid (4M, 3 × 10 cm^3). The aqueous portions were combined, basified with aqueous sodium hydroxide (4M). This was then extracted with dichloromethane (3 × 20 cm^3), and the organic phase worked up in the normal way. The white solid obtained, was purified by centrifugal chromatography, (alumina; light petroleum-EtOAc, 5:1), to give the previously described Mannich base, (64 mg, 9%).

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