TRENT POLYTECHNIC

# THIENOPYRIDINE ANALOGUES OF PAPAVERINE

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The Council for National Academic Awards

for the degree of

DOCTOR OF PHILOSOPHY

by

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March 1978

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## PREFACE

The work described in this thesis was carried out by the author in the laboratories of the Department of Physical Sciences, Trent Polytechnic, Nottingham, between September 1974 and September 1977.

The author wishes to thank Dr. P. R. Huddleston for his excellent supervision and constant encouragement throughout the course of the work. Thanks are also due to Dr. J. M. Barker for his helpful advice, to Mr. M. L. Wood for spectral determinations and to Mrs. S. A. McIntyre for typing this thesis.

The author is also indebted to the Science Research Council for the provision of a research studentship between the above dates.

B. Lawson.

Barbara Lawson
Trent Polytechnic

March 1978

## SUMMARY

This thesis reports attempts to prepare the thiophene analogue of papaverine in which the dimethoxy isoquinoline system is replaced by a dimethoxy thienopyridine.

In the first approach the intention was the preparation of a 4-substituted 3-methoxy thieno[3,2-c]pyridine, starting from ethyl 4-hydroxy-2-thienylacetate, for which a synthesis had been published. However, on repeating this preparation it was found that the product was actually ethyl 3-hydroxy-5-methyl thiophene-2-carboxylate.

Alternative routes to the desired methoxy thienopyridine system involving the reactions of 5-methoxythiophene-2-carboxaldehyde, substituted 2-iodo thiophene and substituted pyridine systems were then followed. Unfortunately all proved unsuccessful.

In another approach the intention was to introduce the methoxy group into a thienopyridine system by adaptation of published procedures. Thus, in one instance, 3-iodo-7-methyl thieno[2,3-c] pyridine was reacted with sodium methoxide in the presence of copper oxide, giving a product which appeared to contain some of the desired methoxylated thienopyridine. However, the reaction could not be brought to completion.

In a final approach, cyclisation of the amides formed by condensation of β-(4-methoxy-2-thienyl)ethylamine with phenylacetic acid, 4-methoxyphenyl- and 3,4-dimethoxyphenylacetic acids was attempted, giving in each case the appropriate dihydrothieno[3,2-c]pyridine.

Further reaction of one of these, 3-methoxy-4-(3'4'-dimethoxybenzyl)-6,7-dihydrothieno[3,2-c]pyridine, with activated manganese dioxide gave a product which was identified as 3-methoxy-4-(3'4'-dimethoxybenzoyl)-6,7-dihydrothieno[3,2-c]pyridine. Reduction of this compound gave a material imperfectly characterised as the corresponding carbinol.

As an extension of the project, several attempts were made to prepare a methoxy thienylacetic acid in the hope that such an acid could be condensed with β-(4-methoxy-2-thienyl)ethylamine to give, at the end of the synthesis, a true thiophene analogue of papaverine. Unfortunately, insufficient time was available to carry this through to completion.

# CHAPTER ONE

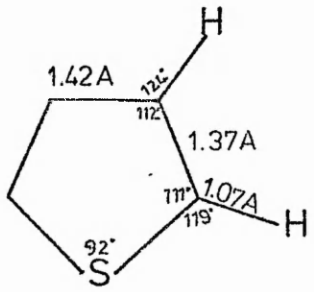
# INTRODUCTION

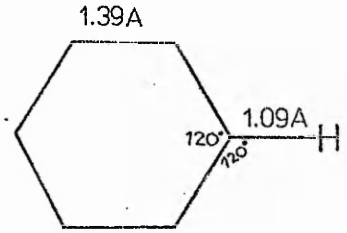
A comparison of the structural, physical and chemical properties of thiophene and benzene

The similarities in physical and chemical properties of thiophene and benzene, each having a delocalised six π-electron system, have long been recognised. It therefore follows that the thiophene analogues of biologically active compounds containing benzene rings should have been prepared and examined for their pharmacological activity.

At this point it is appropriate to tabulate the properties of thiophene and benzene, showing they do have much in common and also demonstrating the differences between them.

1. Molecular dimensions[1-3]



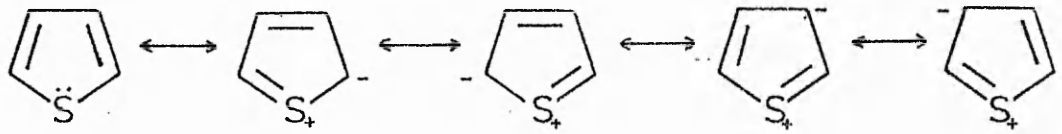

The scale drawings show that, although the thiophene molecule has lower symmetry, the dimensions are very similar.

2. Physical constants

| Property | Benzene | Thiophene |
|---|---|---|
| Boiling point, (760 mm), $^{o}C$ | 80.10 | 84.12 |
| Freezing point, $^{o}C$ | 5.5 | -38.3 |
| $d_4^{20}$, g $cm^{-3}$ | 0.8790 | 1.0644 |
| $n_b^D$ | 1.5011 | 1.5287 |
| $n_{20}^D$ | 0.650 | 0.662 |
| Molecular refraction ($20^{o}$) | 26.185 | 24.365 |

3. Electronic structure

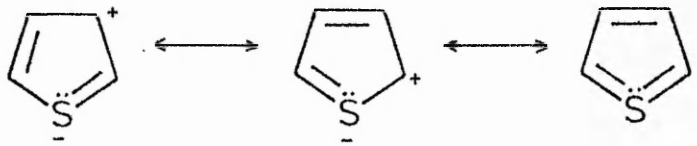
In terms of resonance theory, thiophene is best represented as a resonance hybrid of the five principal canonical structures (I a-e) in which the sulphur atom contributes a lone pair of electrons to the aromatic sextet.



[a] [b] [c] [d] [e]

I

It is also possible that the sulphur d-orbitals participate in the bonding, so that canonical structures such as (I f-h) should also be considered, but at present the question of d-orbital participation is unresolved.



[f] [g] [h]

I

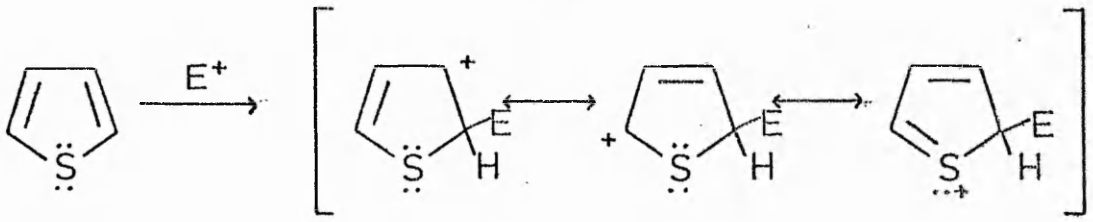
The resonance energy of thiophene (116-129.5 KJ $mole^{-1}$) is somewhat less than that of benzene (150.5 KJ $mole^{-1}$).

The simple molecular orbital pictures of thiophene and benzene again reveal similarities and differences. In both systems there is a planar, σ-bond framework of $sp^2$ hybridised atoms. It must be remembered, however, that in thiophene the sulphur 3p orbital is involved in the construction of the π-bonding molecular orbitals, whereas in benzene only 2p orbitals contribute.

4. Chemical Behaviour

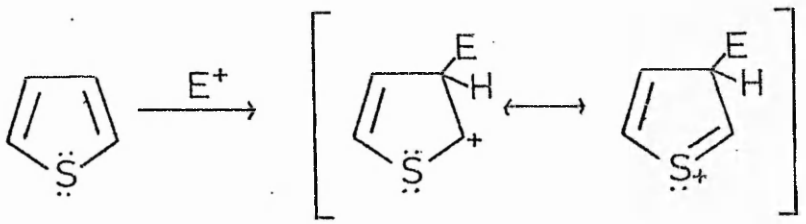
The usual reactions of thiophene are, as with benzene, with electrophiles in substitution reactions. In the heterocyclic systems consideration of the localisation energies of the Wheland intermediates for the two possible positions of substitution show that the reaction takes place predominantly, if not exclusively, at the 2-position.[4,5]

2-substitution:-




3 canonical structures

3-substitution:-




2 canonical structures

As would be expected from its π-excessive nature, thiophene is considerably more reactive towards electrophiles than benzene; it can be brominated, acylated, formylated, chloromethylated and mercurated under conditions which fail to give a reaction with benzene. This is illustrated by the fact that typical Friedel-Crafts acylation of thiophene can be carried out in benzene as solvent.

In general, substituents attached to the thiophene ring show unexceptional behaviour; however, hydroxy and amino groups prove to be exceptions. Hydroxythiophenes are inaccessible and rather unstable, preferring to exist in the keto form; the nmr spectrum of 2-hydroxy-thiophene indicated the dominance of 5[H]-thiophene-2-one.[6] Both 2- and 3-amino thiophenes are very unstable as free bases although acyl derivatives and salts are stable.

Thus, although in most cases it may be assumed that a given thiophene derivative will behave in a manner close to that of its benzene counterpart, it is quite possible that the differences in reactivity, electron distribution and shape may be significant in its pharmacological behaviour.

Biological activity of Thiophenes

Thiophene exerts its toxic action predominantly on the nervous system[7] and causes the greatest histological injury in the cerebellum, especially in the granulosa elements.[8] It produces convulsions, muscular weakness, fall in blood pressure and death[9] and has a feeble action on bone marrow, similar to that of benzene. Like benzene, thiophene is claimed to have slight solvent action on cancer cells[10] and to act as a cure for gonorrhoea.[11]

Aurousseau[12] mentiones the use of thiophene therapeutically as a bacteriostat, insecticide and anthelmintic and it has been used as an ingredient of an ointment used for treating skin infections.[13]

The simpler thiophene derivatives such as thiophene-2-carboxylic acid, thiophene-2-aldehyde, 2-nitrothiophene and 2-chloromercuri-thiophene have also been investigated.[14]

The general conclusion to be drawn from the work on the simpler thiophenes is that the compounds usually possess similar, but less pronounced, activity to their benzene analogues. In some cases,

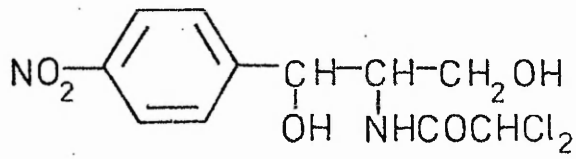
however, related compounds have different effects, eg. thienylketones are convulsants, whereas their benzene counterparts are hypnotics.[15]

Many thiophene compounds have been tested for biological activity. As this number is particularly large what follows is a consideration of those thiophene compounds that are analogues of a benzene counterpart, with a comparison of their relative activities.

The thiophene isosteres of cocaine, atropine, eucaine A, benzoylquinoline and phenacetin were prepared by Steinkopf and co-workers[16] and were found to possess similar activity to the benzene derivatives, although, in general, they appeared to be less toxic.

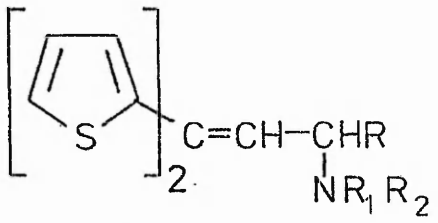
Schulte et al.[17] found that β-2-thienylethylamine[18,19] showed pronounced central nervous stimulating properties, being about as active as the benzene counterpart, but possessing a considerably lower threshold dose.

Thiophene compounds structurally related to chloramphenicol [II] have also been synthesised.[20] However, the antibacterial activity proved to be much lower than that of the natural antibiotic.[21]



II

The thiophene analogues [III] of 3,3-diphenylallylamine were found, like the benzenoid compounds, to have antihistaminic and local anaesthetic properties[22] as well as pronounced analgesic activity.[23] Unfortunately, they also possess the same disadvantage as the benzenoid derivative in that they are addictive.[24]

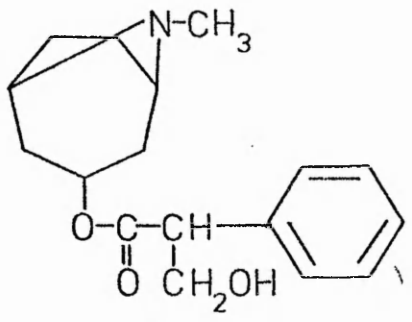


III

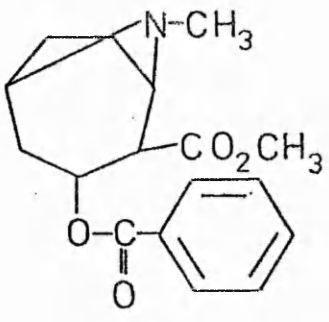
The thiophene analogues of methadone and isomethadone have also been prepared and shown to be active analgesics.[25]

The first synthesis of the thiophene analogues of D.D.T. [2,2-bis-(p-chlorophenyl)-1,1,1-trichloroethane] was reported by Prill et al.[26] who discovered that 2,2-bis-(2-thienyl)-1,1,1-trichloroethane was inactive against the house fly; however, the nuclear chlorinated compound 2,2-bis-(2-chloro-5-thienyl)-1,1,1-trichloroethane has been reported to be effective against cockroaches.[27]

The synthesis of 2-thienyl analogues of atropine (IV) and cocaine (V) were reported by Steinkopf and co-workers[16] as long ago as 1924. These analogues were shown to possess approximately the same pharmacological activity as the natural substance.

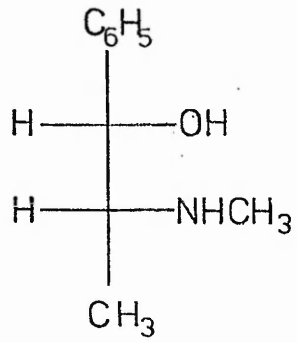


[IV]

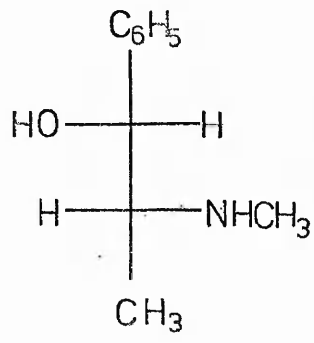


[V]

Barker, Byron and Huddleston[28] have prepared the 2-thienyl analogues of ephedrine (VI) and ψ-ephedrine (VII). It was found that the ephedrine analogues had about one third of the activity of ephedrine in its effect on the blood pressure of the spinal cat, but the ψ-ephedrine analogue was inactive. The synthesis of the 3-thienyl analogues of ephedrine and a number of related halogenated substances was achieved by Barker and Huddleston.[29]



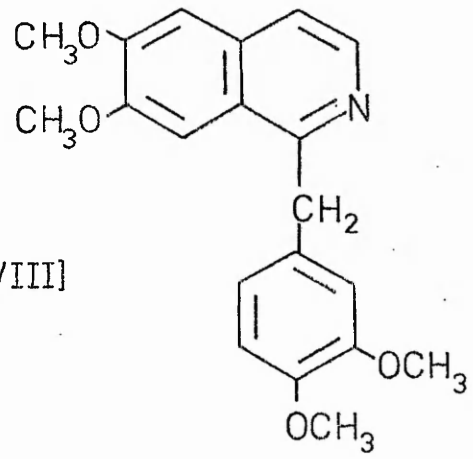

[VI]




[VII]

## PAPAVERINE

Papaverine is one of the many alkaloids occurring in opium - the dried juice of the oriental poppy, Papaver somniferum - and was isolated from this source in 1848 by Merck.[30] The structure of papaverine was elucidated during the period 1880-1890 by Goldschmiedt and co-workers[31] who showed it to be 1-(3,4-dimethoxybenzyl)-3,4-dimethoxyisoquinoline (VIII).




[VIII]

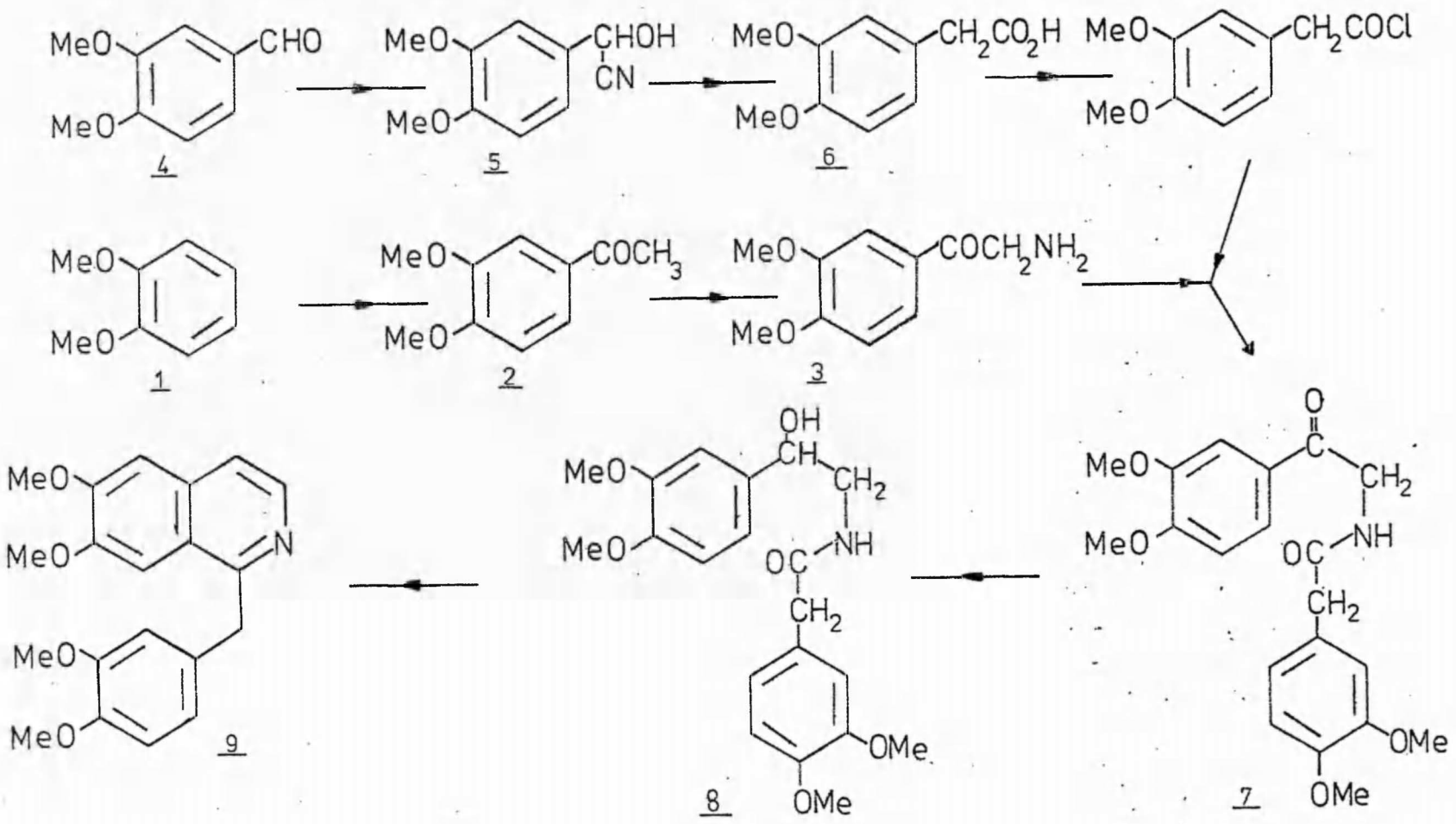
1. Synthesis

Synthesis of Pictet and Gams[32] (Scheme I)

Veratrole (1) was acylated with acetyl chloride to give 3,4-dimethoxy acetophenone (2) which by nitrosation and reduction of the resulting oximino-ketone yielded ω-amino-3,4-dimethoxy acetophenone (3). Veratraldehyde (4) was converted into the cyanohydrin (5), which, on treatment with hydriodic acid, followed by remethylation, gave homoveratric acid (6).

Condensation of ω-amino-3,4-dimethoxy acetophenone with homoveratroyl chloride gave the β-keto amide (7), which was reduced by sodium amalgam to the β-hydroxy amide (8). Cyclisation of the latter with phosphoryl chloride yielded papaverine (9).

Scheme I


MeO
MeO
CHO
4
CHOH
CN
5
CH2CO2H
6
CH2COCl
COCH3
2
COCH2NH2
3
1
9
OH
CH
CH2
NH
OC
OMe
8
O
7

The Pictet-Finkelstein[33] and Späth-Berger[34] synthesis (Scheme II)

Pictet and Finkelstein improved the above synthesis by condensing β-(3,4-dimethoxyphenyl) ethylamine (10) with homoveratroyl chloride (11) to obtain homoveratryl homoveratramide (12), which on cyclisation with phosphoryl chloride by the Bischler-Napieralski procedure yielded dihydropapaverine (13). Späth and Berger showed that dehydrogenation of the latter could be effected by heating with palladised asbestos at 200° to give papaverine in good yield. They also showed that 1,2,3,4-tetrahydropapaverine could be dehydrogenated by means of the same catalyst.

Syntheses of Rosenmund[35] and Mannich[36] (Scheme III)

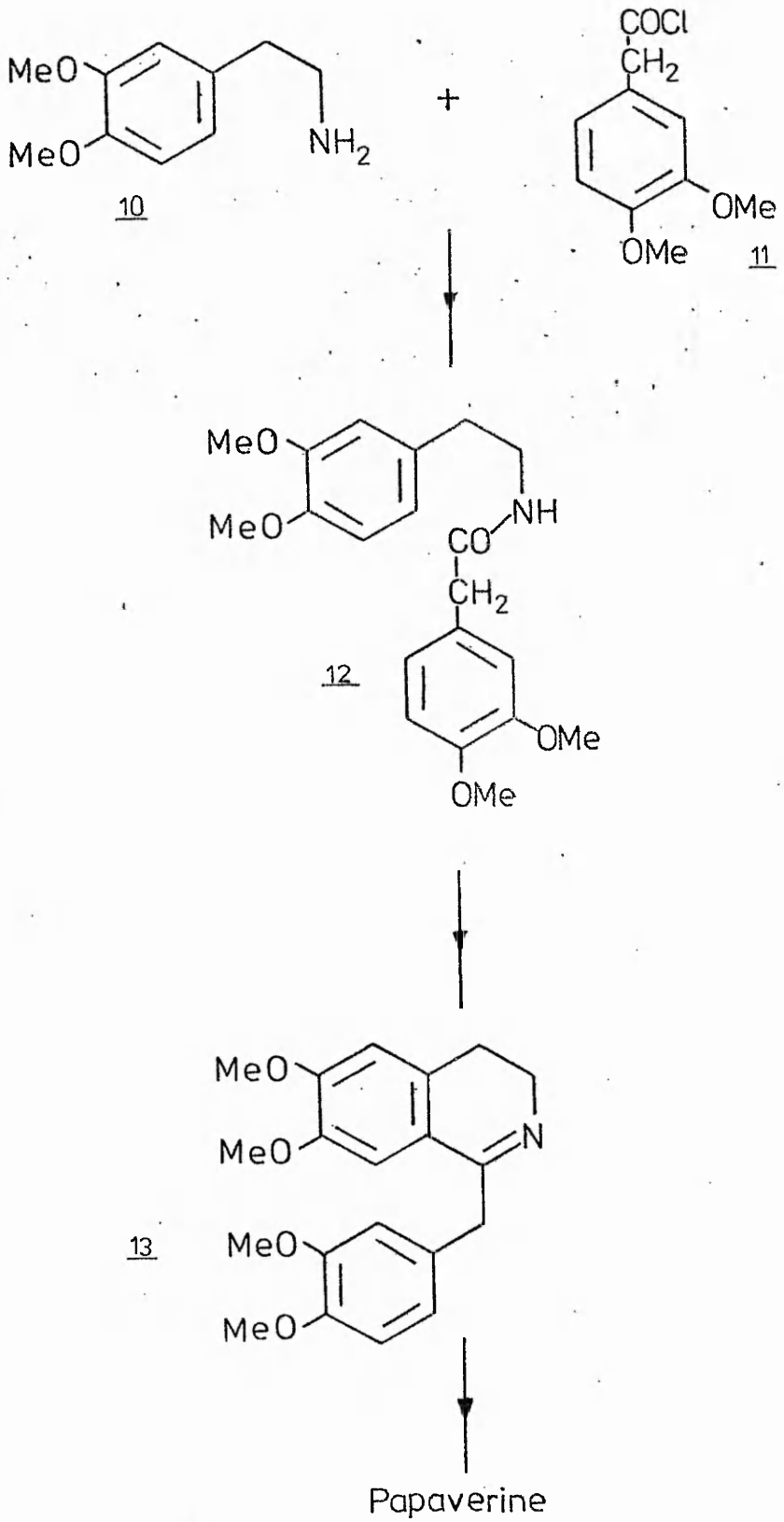
Veratraldehyde (14) was condensed with nitromethane to give ω-nitro-3,4-dimethoxystyrene (15), which on treatment with methanol yielded 2-methoxy-2-(3,4-dimethoxy phenyl) nitroethane (16). Reduction of the latter with sodium amalgam gave the methoxy amine (17) which on condensation with homoveratroyl chloride yielded the β-methoxyamide (18); treatment of this with either phosphoryl chloride or phosphorous pentoxide gave papaverine.

The azlactone synthesis (Scheme IV)

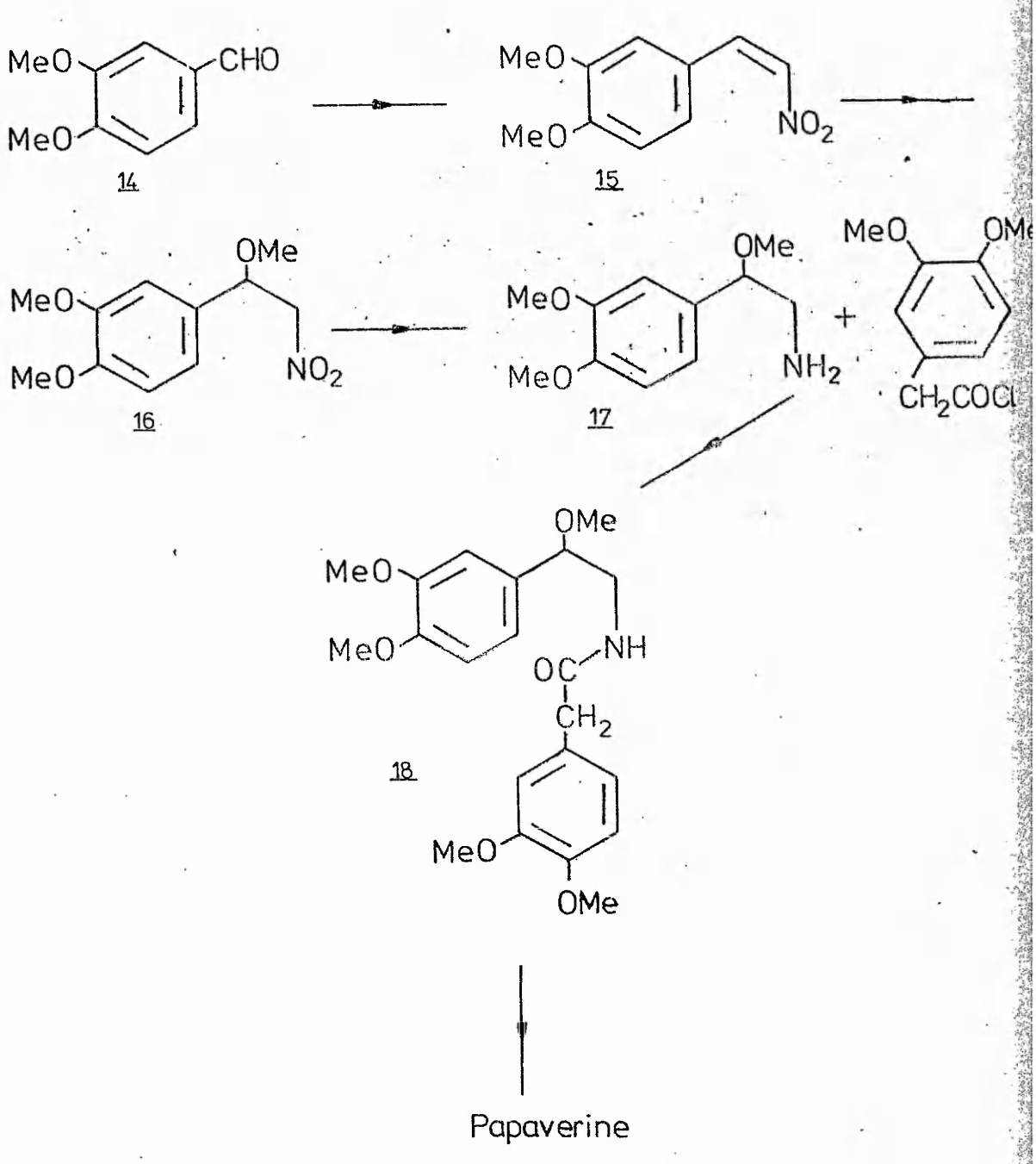
A further important synthesis, described independently by Wahl[37] and by Galat[38] was derived from the work of Erlenmeyer on the reactions of azlactones.

Veratraldehyde was condensed with hippuric acid in the presence of acetic anhydride and sodium acetate and the azlactone (19) thus produced was hydrolysed with sodium carbonate to yield veratrylidene hippuric acid (20). This, on heating with aqueous ammonia underwent autocondensation to give N-homoveratroyl-3,4-dimethoxy phenylalanine (21). Esterification and cyclisation with phosphoryl chloride yielded 3-carbethoxy-3,4-dihydropapaverine (22) which on hydrolysis, decarboxylation and dehydrogenation gave papaverine.

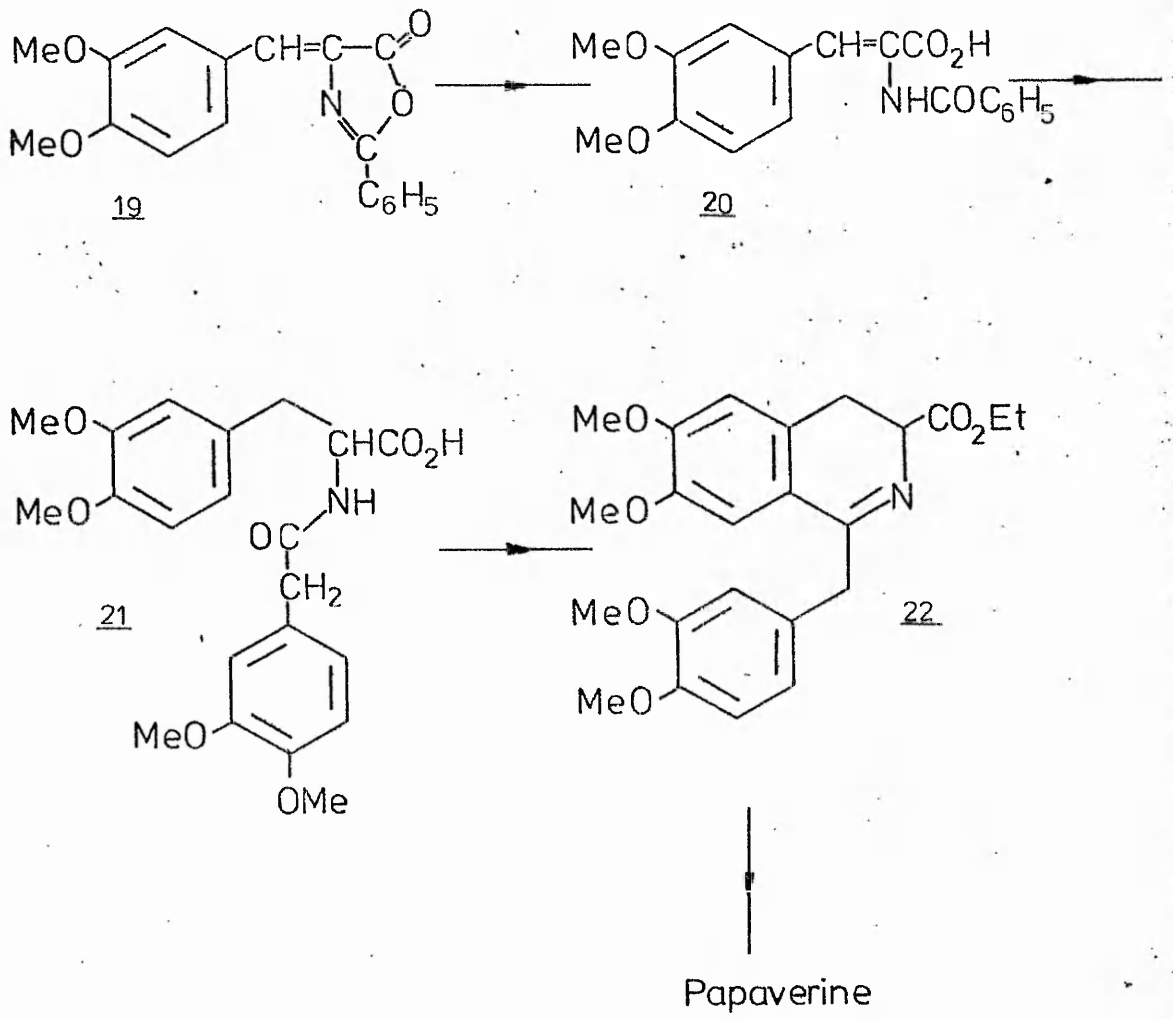
## Scheme II


MeO
MeO
NH2
10
+
COCl
CH2
OMe
OMe
11
MeO
MeO
NH
CO
CH2
12
OMe
OMe
MeO
MeO
N
13
MeO
MeO
Papaverine

## Scheme III


MeO
MeO
CHO
14
MeO
MeO
NO2
15
OMe
MeO
MeO
NO2
16
OMe
MeO
MeO
NH2
17
+
MeO
CH2COCl
OMe
MeO
MeO
NH
OC
CH2
18
MeO
OMe
Papaverine

## Scheme IV


MeO
MeO
CH=C—C=O
N
O
C
C6H5
19
MeO
MeO
CH=CCO2H
NHCOC6H5
20
MeO
MeO
CHCO2H
NH
OC
CH2
MeO
OMe
21
MeO
MeO
CO2Et
N
MeO
MeO
22
Papaverine

Other syntheses

Several other syntheses of papaverine have been accomplished, the most interesting being those of Buck[39] (see also Young and Robinson[40]) and Späth and Berger.[41] The last-named method is important because, although it has no practical value, it may be indicative of the biogenesis of papaverine since it makes use of natural precursors and of biogenetically possible reaction mechanisms. Methyl eugenol (23) was oxidised to 3,4-dimethoxyphenyl acetaldehyde (24) and this was condensed with homoveratrylamine; the azomethine (25) thus obtained was cyclised by treatment with dilute hydrochloric acid to 1,2,3,4-tetrahydropapaverine (26), which as previously mentioned can be dehydrogenated to papaverine. (Scheme V)

Kindler and Peschke[42] introduced several important modifications to the Pictet-Gams synthesis and improved the overall yield of papaverine. They found that:

i) homoveratric acid was obtained by submitting 3,4-dimethoxy acetophenone to a Willgerodt reaction, (treatment with sulphur and dimethylamine) followed by hydrolysis of the thioamide with potassium hydroxide;

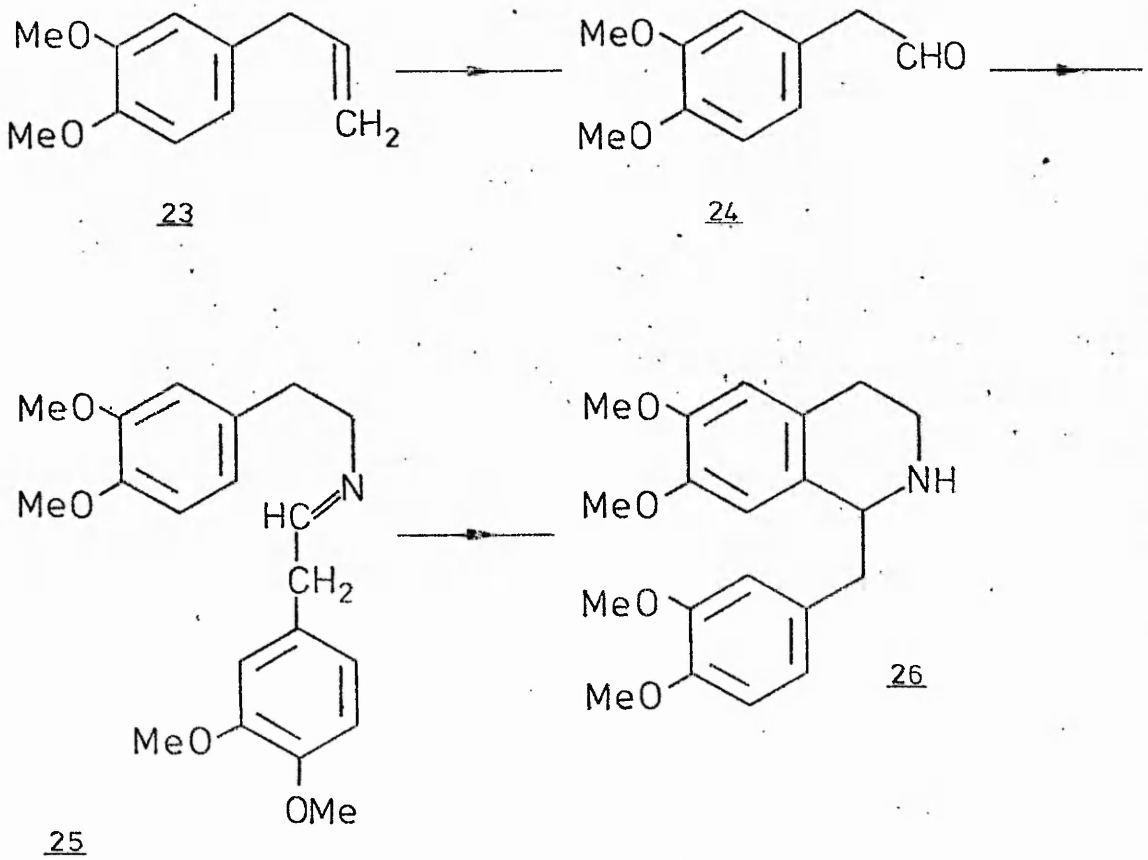
ii) homoveratrylamine and homoveratric acid can be directly condensed by heating the two compounds together in tetralin;

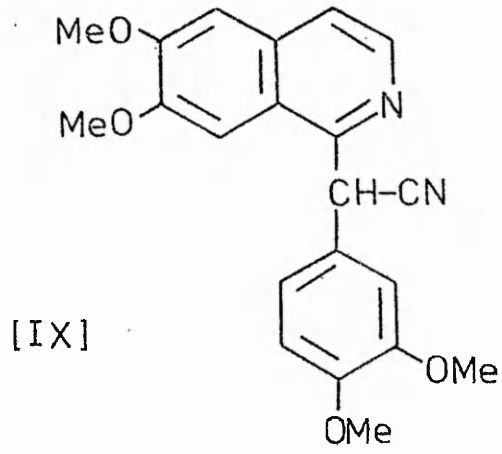
iii) 3,4-dihydropapaverine can be dehydrogenated by heating in dihydrophellandrene solution with palladium.

Gibson, Popp and Cantala[43] obtained papaverine in low yield by applying the Reissert reaction to 6,7-dimethoxyisoquinoline.

Eloy and Deryckere[44] reacted 1-chloro-6,7-dimethoxyisoquinoline with 3,4-dimethoxyphenylacetonitrile to give the nitrile (IX), which on hydrolysis followed by decarboxylation gave papaverine.

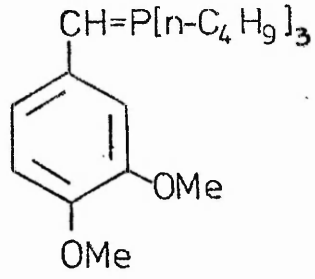
## Scheme V


MeO
MeO
CH2
23
MeO
MeO
CHO
24
MeO
MeO
HC=N
CH2
MeO
OMe
25
MeO
MeO
NH
MeO
MeO
26




[IX]

Finally, Taylor and Martin[45] report a direct synthesis of papaverine in 74% yield in one step by the reaction of 1-chloro-6,7-dimethoxyisoquinoline with the Wittig reagent (X) prepared from veratryl chloride and tri-n-butylphosphine.



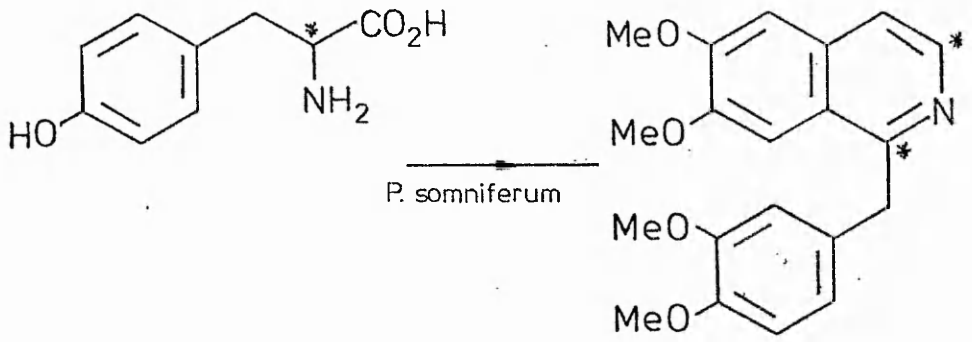

[X]

This survey of methods of preparation of papaverine is by no means complete. A review[46] of all the methods of synthesis with modifications can be found in the literature.

## 2. Biosynthesis

The formation of papaverine from 2 moles of tyrosine was demonstrated by Battersby and Harper[47] who fed Papaver somniferum with (+)-[2-$^{14}$C]tyrosine. The papaverine isolated had radioactivity at C-1 and C-3 only. Degradation to formaldehyde (C-3) and carbon

dioxide (C-1) showed each had activities equal to half the activity of the isolated papaverine.




Subsequently, it has been shown that norlaudanosoline,[47,48] norreticuline[48,49] and tetrahydropapaverine[50] are successive biosynthetic intermediates (Scheme VI).

In a very recent paper Battersby and co-workers[51] have determined the stereochemistry of hydrogen removal from C-3 and C-4 in the aromatisation of the heterocyclic ring of papaverine.

## 3. Reactions

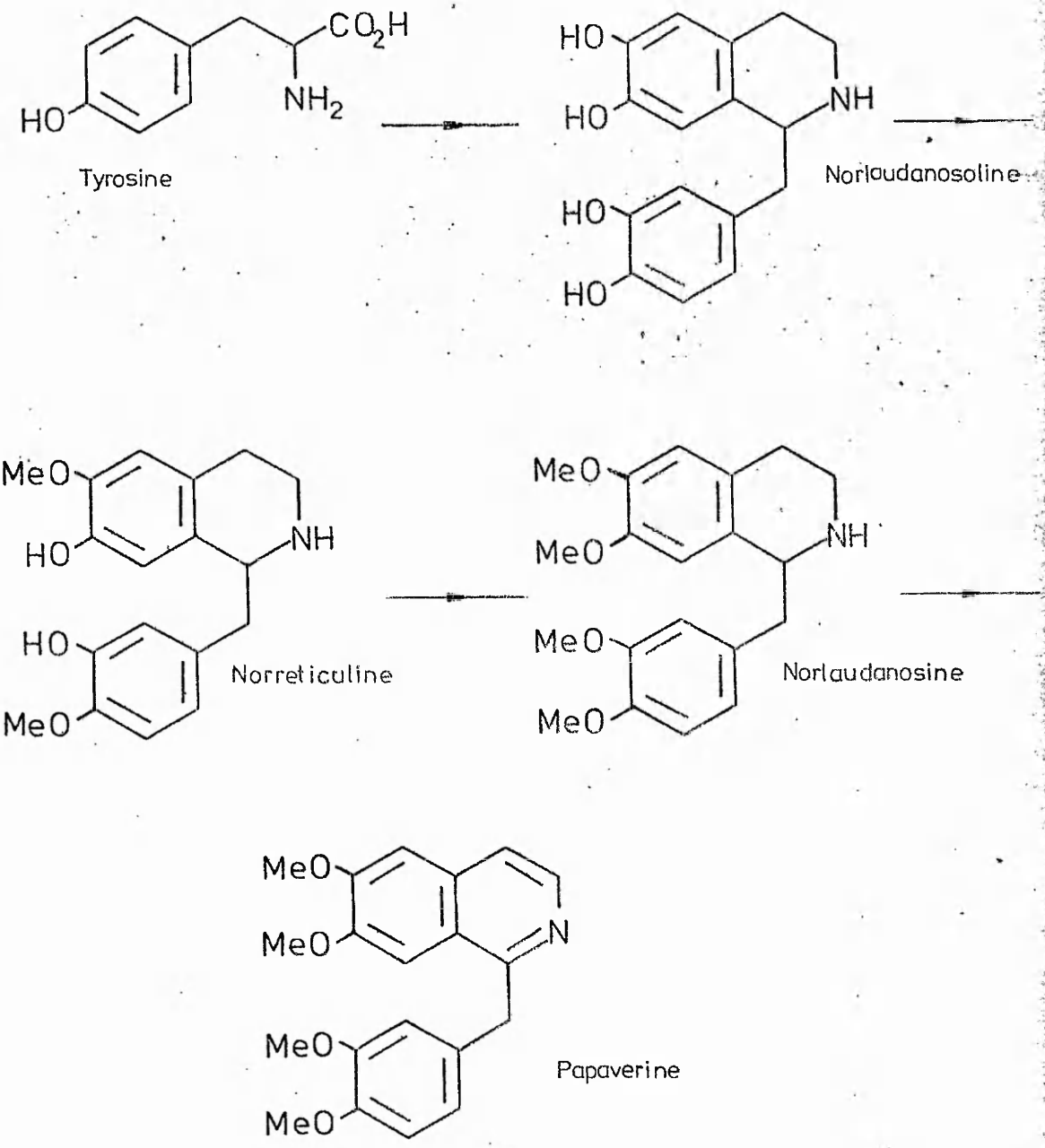
### a) Oxidation

The oxidation products of papaverine are dependent on the conditions used; mild oxidation, using mercuric acetate gives papaverinol; stronger oxidants, dichromate, permanganate or selenium dioxide, produce papaveraldine;[52,53] vigorous conditions result in a mixture of products including m-hemipinic acid, veratric acid, pyridine-2,3,4-tricarboxylic acid and papaveric acid.[54]

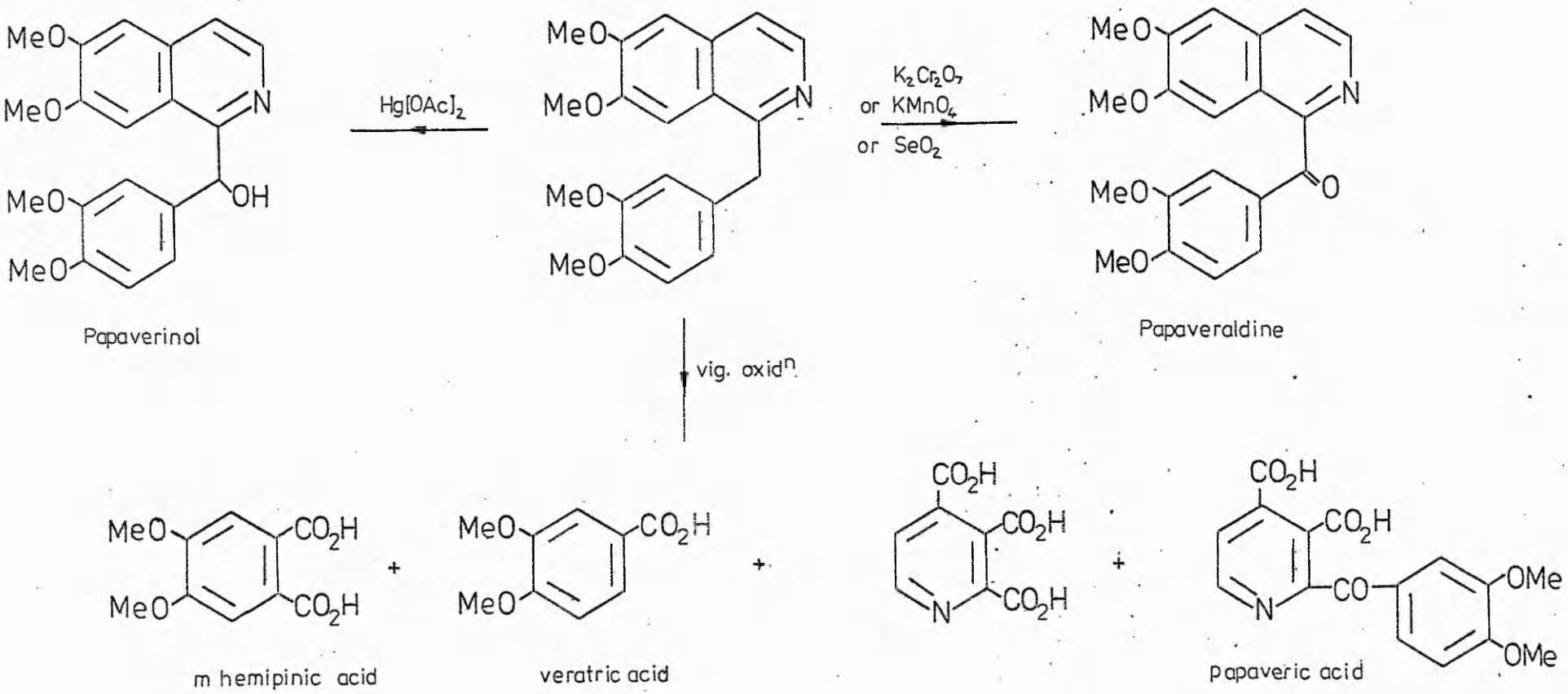
### b) Reduction

Papaverine can be easily reduced catalytically to tetrahydropapaverine, but reduction with tin and hydrochloric acid gives two

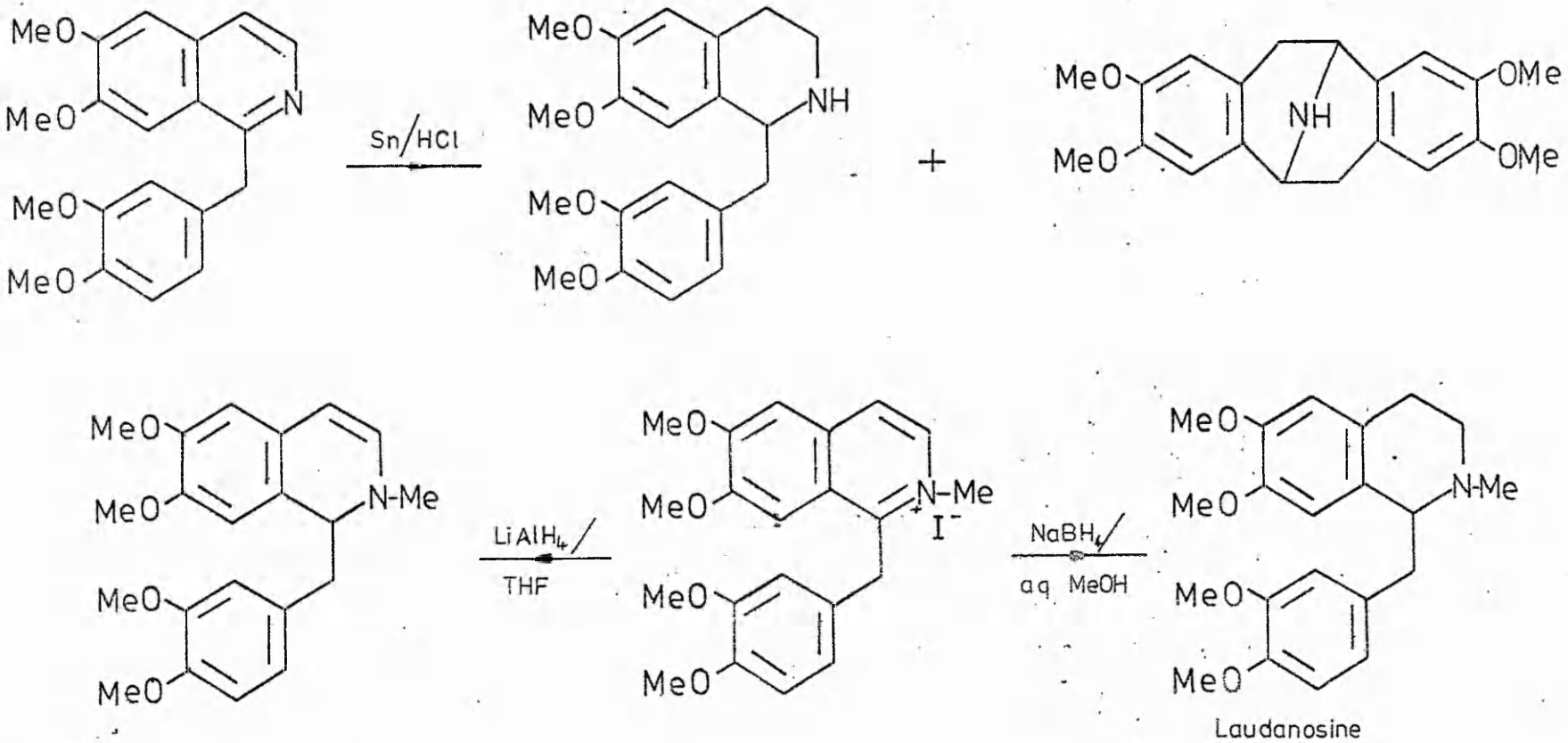
## Scheme VI


HO
CO2H
NH2
Tyrosine
HO
HO
NH
HO
HO
Norlaudanosoline
MeO
HO
NH
HO
MeO
Norreticuline
MeO
MeO
NH
MeO
MeO
Norlaudanosine
MeO
MeO
N
MeO
MeO
Papaverine

a) Oxidation


MeO
MeO
MeO
MeO
N
OH
Papaverinol
Hg[OAc]2
MeO
MeO
MeO
MeO
N
K2Cr2O7
or KMnO4
or SeO2
MeO
MeO
MeO
MeO
N
O
Papaveraldine
vig. oxidn.
MeO
MeO
CO2H
CO2H
m hemipinic acid
+
MeO
MeO
CO2H
veratric acid
+
CO2H
CO2H
CO2H
N
+
CO2H
CO2H
N
CO
OMe
OMe
papaveric acid

b) Reduction


MeO
MeO
MeO
MeO
N
Sn/HCl
NH
+
OMe
OMe
N-Me
LiAlH4/
THF
I⁻
NaBH4/
aq MeOH
Laudanosine

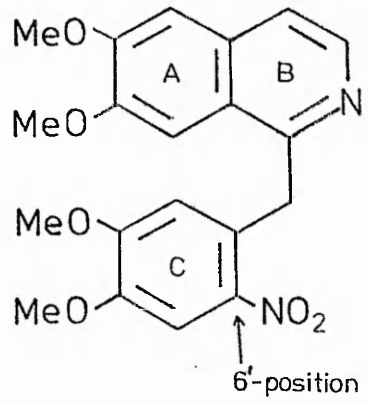
products, tetrahydropapaverine (N-norlaudanosine) and pavine.[55] The primary product is probably the unknown 1,2-dihydropapaverine which, under acidic conditions, is stabilised by conversion to pavine.

If the methiodide of papaverine is reduced with lithium aluminium hydride in a non protic solvent, eg. THF, the product is the 1,2-dihydroisoquinoline[56]; if sodium borohydride in aqueous methanol is used, the product is racemic laudanosine.[57]

c) Nitration, Sulphonation, Acylation and Bromination

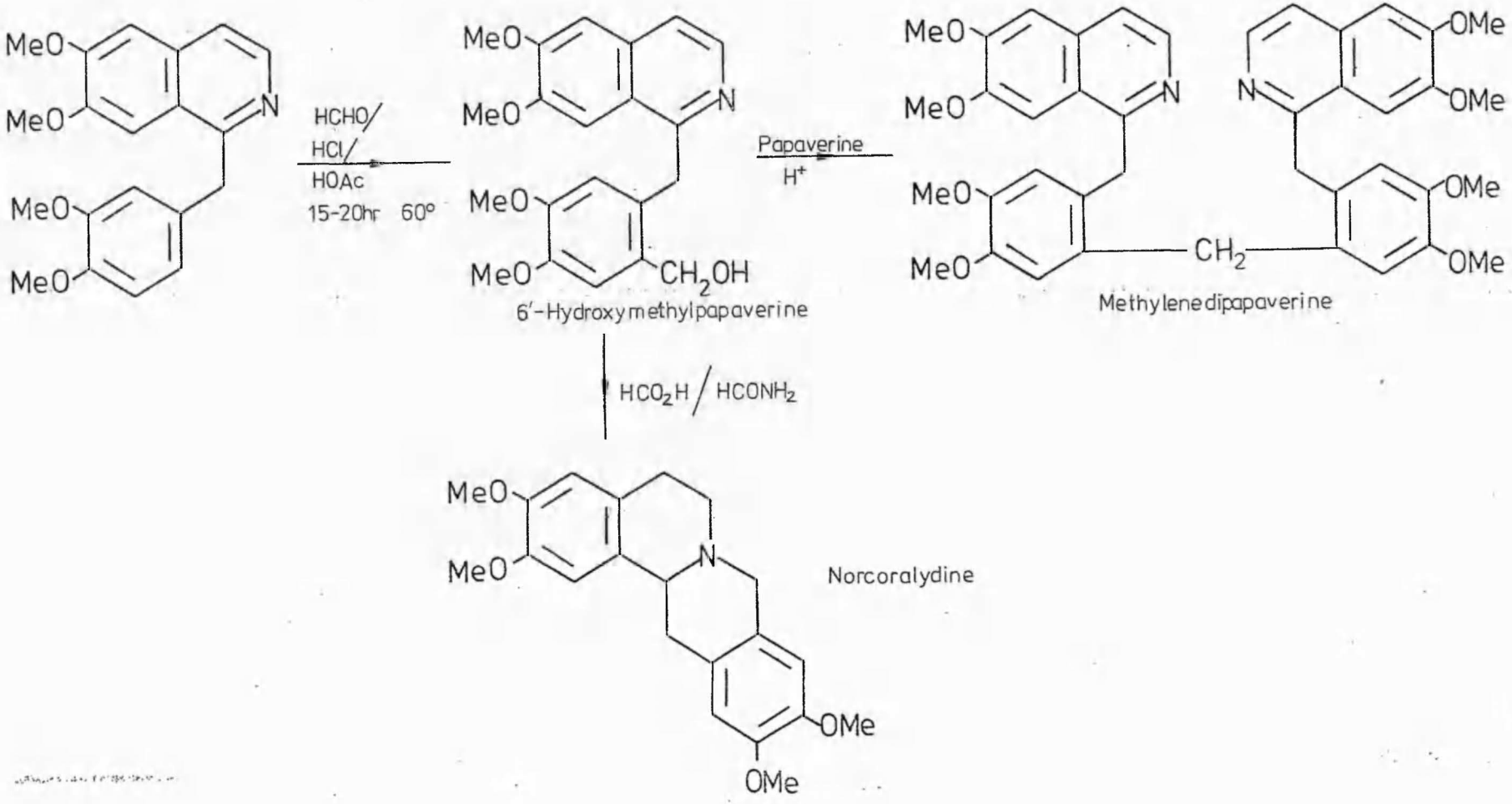
Ring A in papaverine is deactivated and less sensitive to electrophilic attack than ring C, so that the alkaloid can be cleanly nitrated with nitric acid in acetic acid to 6'-nitropapaverine[58]. Papaverine can also be sulphonated with cold sulphuric acid, acylated with acetic anhydride and sulphuric acid, and brominated, all substituents attacking the C-6' position.

eg.

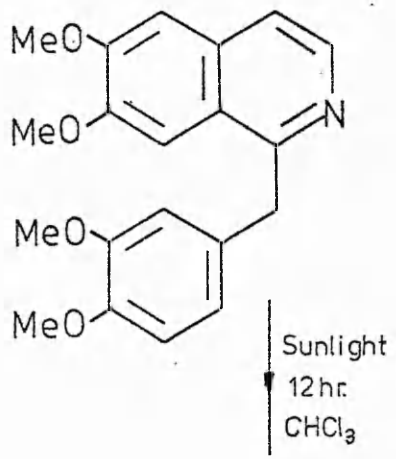


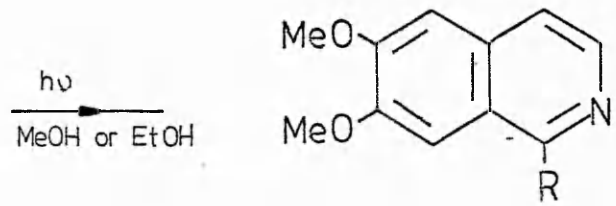

d) Formation of 6'-Hydroxymethylpapaverine and methylene dipapaverine[59]

When formaldehyde is added to papaverine in acetic acid with a little hydrochloric acid, condensation occurs at C-6' rather than at the $\alpha$-methylene. The product is the crystalline 6'hydroxymethylpapaverine

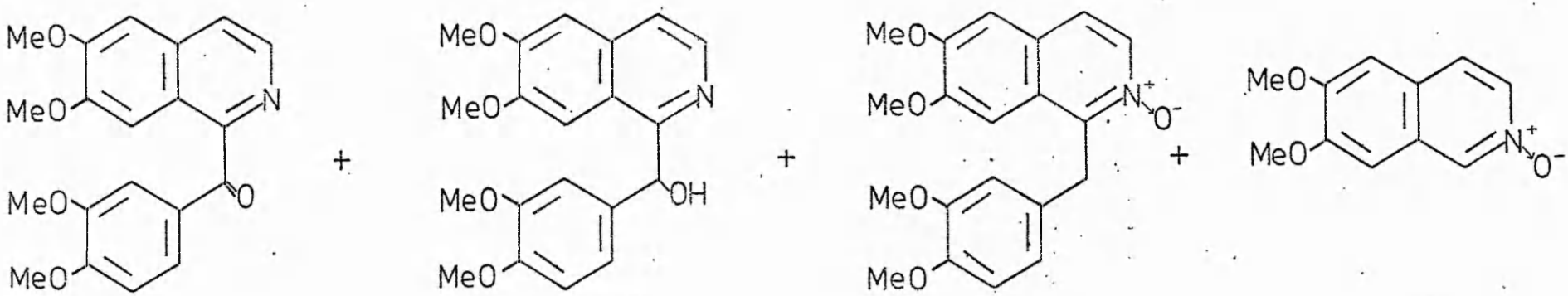

MeO
MeO
MeO
MeO
N
HCHO/
HCl/
HOAc
15-20hr 60°
CH2OH
6'-Hydroxymethylpapaverine
Papaverine
H+
CH2
OMe
Methylenedipapaverine
HCO2H / HCONH2
Norcoralydine

e) Photolysis




$R = CH_3$ or $C_2H_5$



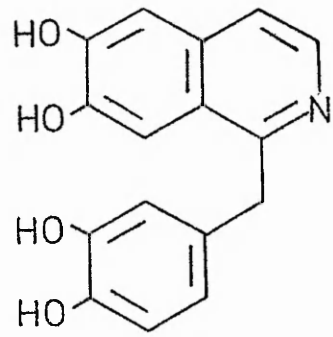
which can undergo acid-catalysed condensation with a molecule of papaverine to yield methylene dipapaverine. Otherwise, heating 6'-hydroxymethylpapaverine in formic acid-formamide solution leads to norcoralydine.

e) Photolysis

When papaverine is photolysed in methanol or ethanol, cleavage of the benzyl group occurs with concomitant introduction of the alcohol alkyl residue at C-1[60]. However, in chloroform, after 12 hrs exposure to direct sunlight the products were identified as papaveraldine, papaverinol, papaverine-N-oxide and 6,7-dimethoxyisoquinoline-N-oxide[61].

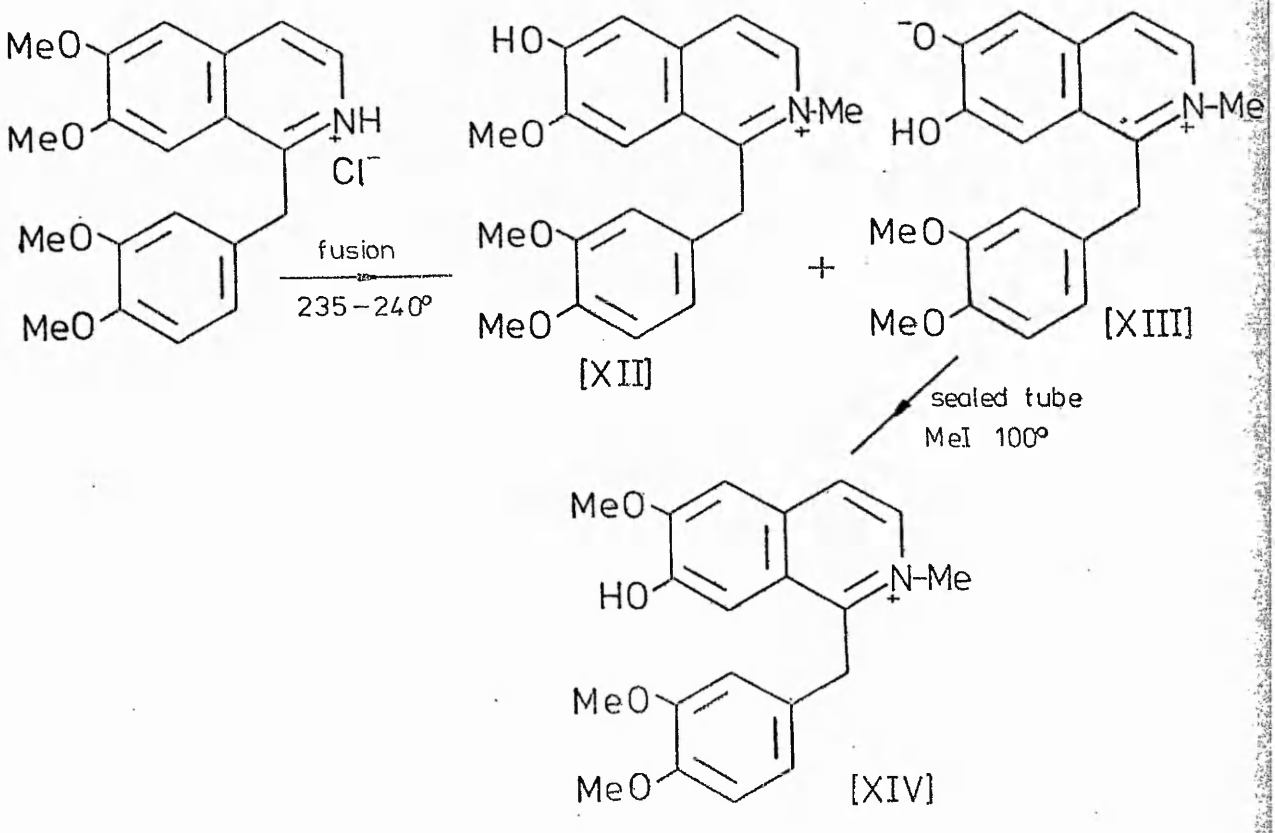
f) Selective O-demethylation

The course of O-demethylation of papaverine with mineral acid involves first the two methoxy groups on ring C to provide a mixture of the two monophenols and the diphenol. The next group to be hydrolysed is at C-7 to form the triphenol and finally the 6-methoxyl to give papaveroline.[62]




The relative resistance of the 6- and 7-methoxyls in papaverine to cleavage with mineral acid is in marked contrast to their lability

on thermal fusion. Fusion of papaverine hydrochloride furnished the monophenol (XII) and the betaine (XIII). When the latter was heated with methyl iodide in a sealed tube the monophenol (XIV) was produced.[63]




4. Pharmacology

The main effect of papaverine, used in the form of its hydrochloride, is relaxation of the smooth muscle by direct action on the muscle fibre.[53] Intestine, bladder, uterus, all sphincters, the biliary tract, the bronchii, heart muscle and the blood vessel walls are all susceptible to the spasmolytic action of papaverine.

Papaverine dilates the peripheral and splanchnic blood vessels causing a fall in blood pressure; this is followed by a transient

rise due to induced release of adrenalin and then by a prolonged fall below the normal level. The alkaloid counteracts the pressor effect of adrenalin. Papaverine acts directly upon heart muscle, slowing its rate but increasing the tonicity, thereby causing an increase in volume output and strength of contraction. The coronary arteries are dilated and the coronary flow is increased.

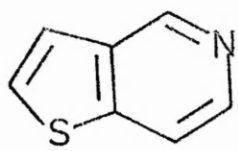
Papaverine has a comparatively low toxicity for a plant alkaloid; the $LD_{50}$ in mice is 120 mg per kg and a dosage of 40-80 mg repeated daily for long periods in human subjects has been found to be safe. It is a valuable drug for all conditions in which relaxation of spasms is desired, eg. for relief of post-operative discomfort after gastro-intestinal operation, hypersensitive states, bronchial asthma etc.

The drug does produce side-effects, drowsiness, constipation, increased reflex excitability and gastric distress, together with a distinct local anaesthetic activity. However, unlike other alkaloids it is not a narcotic and is not addictive.

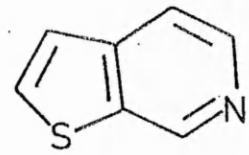
## THIENOPYRIDINES

Thienopyridines have received considerable attention over the last few years for two reasons; firstly their isosteric resemblance to quinoline and isoquinoline makes them important from a pharmacological standpoint and, secondly, from a chemical point of view, the presence of a ring susceptible to electrophilic attack (thiophene) and a ring vulnerable to nucleophilic attack (pyridine) make selective chemical functionalisation on the individual rings a theoretical possibility.

There are six isomeric thienopyridines all of which have been prepared. However, in the following discussion only two will be considered, thieno[3,2-c] pyridine (XV) and thieno[2,3-c] pyridine (XVI).




[XV]



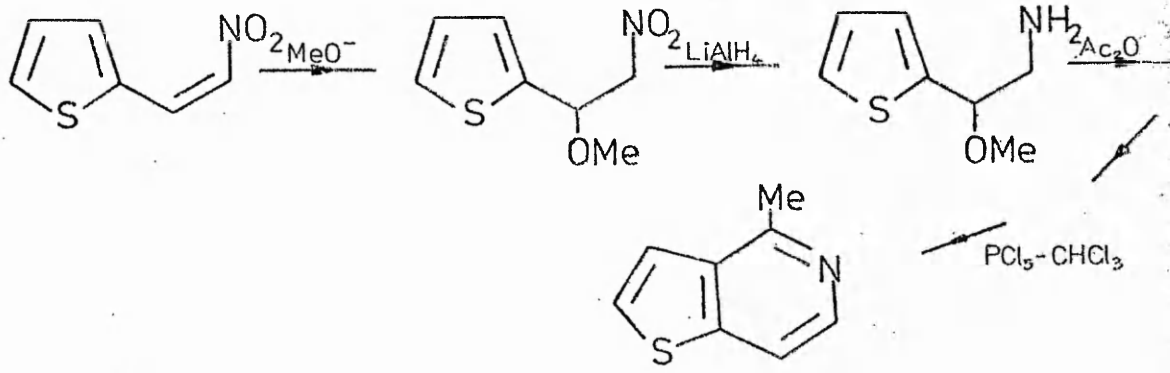

[XVI]

At this point it is worthwhile noting that recently two separate reviews of thienopyridines have appeared in the literature. The one by Schneller[64] discusses both the synthesis and chemical reactivity of all the isomeric thienopyridines; the one by Barker[65] is much more comprehensive covering synthesis and chemical properties together with electron distribution, physical properties, spectroscopy and biological activity.

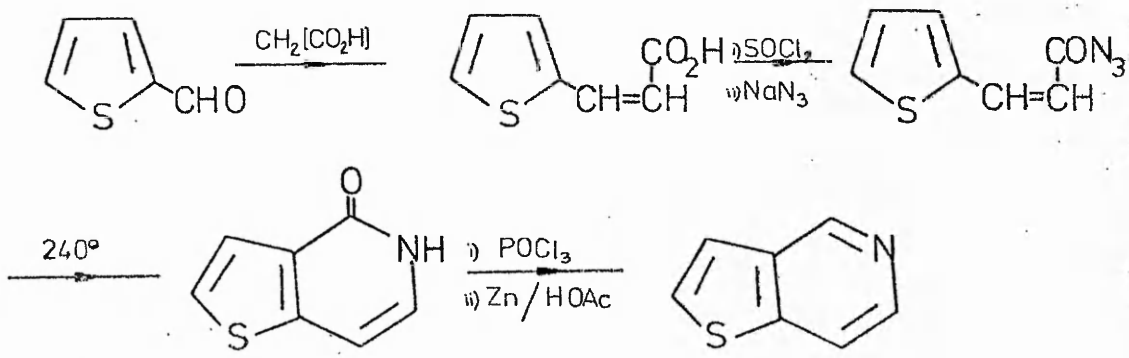
1. Synthesis

By analogy to isoquinoline syntheses, the Pomeranz-Fritsch reaction[66], the Bischler-Napieralski reaction[67-70] and the Pictet-Spengler method[71] have all been employed as routes to thieno[3,2-c] and [2,3-c] pyridines. (Scheme VII)

The only report of the use of the Pictet-Gams method for the preparation of thienopyridines is by Herz and Tsai[68] who obtained 4-methyl thieno[3,2-c] pyridine in very low yield.

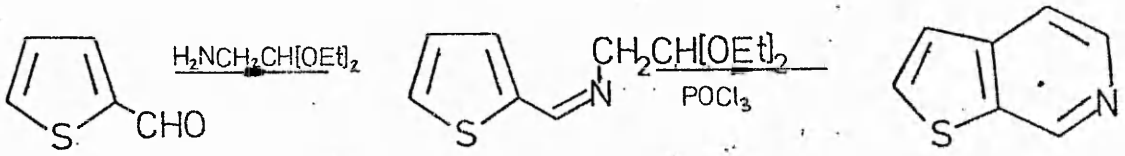



Compounds XV and XVI and various substituted derivatives have also been prepared in a process which involves the cyclisation of β-thienylvinylisocyanates to thienopyridines, followed by chlorination and reduction[72] as shown below:-

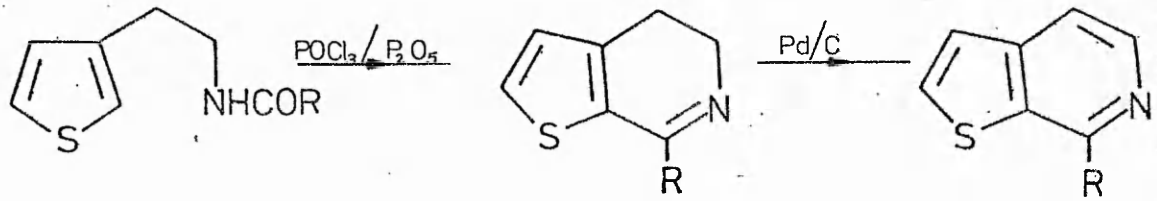


## Scheme VII

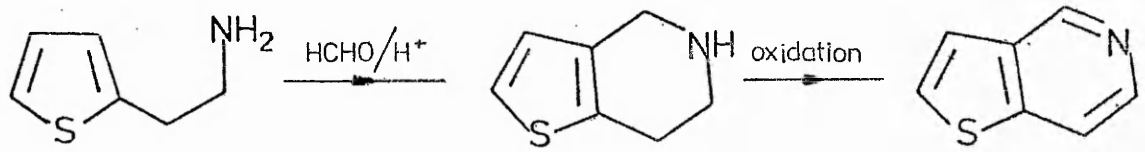
1) Pomeranz - Fritsch reaction



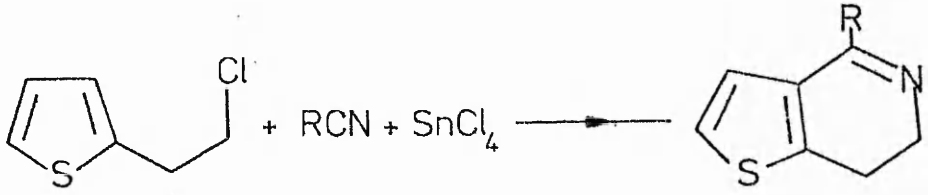

2) Bischler - Napieralski reaction



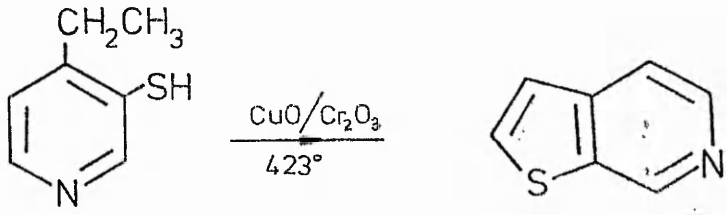

3) Pictet - Spengler reaction



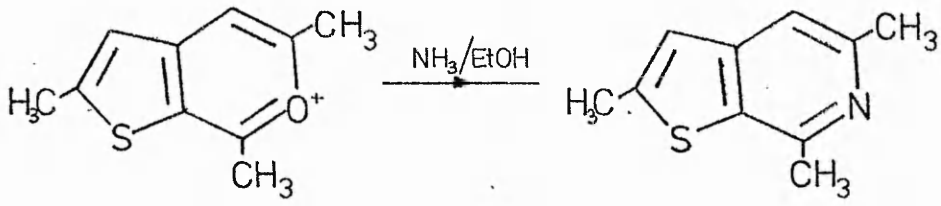
Several less useful preparations have also appeared in the literature. These include a stannic chloride cyclisation;[73]



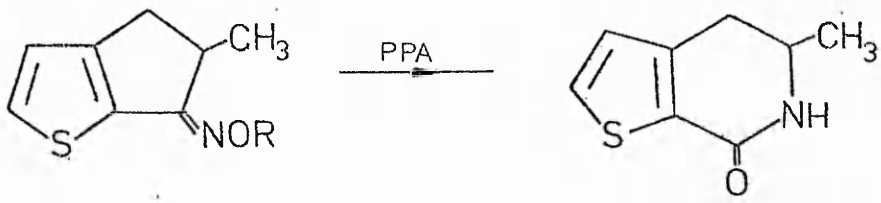

the high temperature oxidative cyclisation of 4-ethyl pyridine-3-thiol;[74]




the treatment of a thienopyrilium salt with ammonia[75]; and



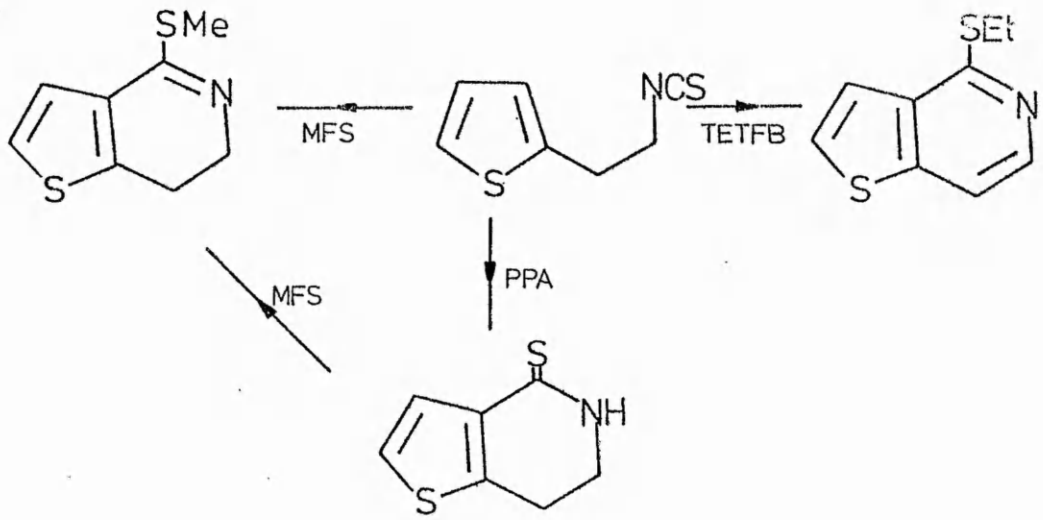

the Beckmann rearrangement to produce precursors to XI and XVI.[76]



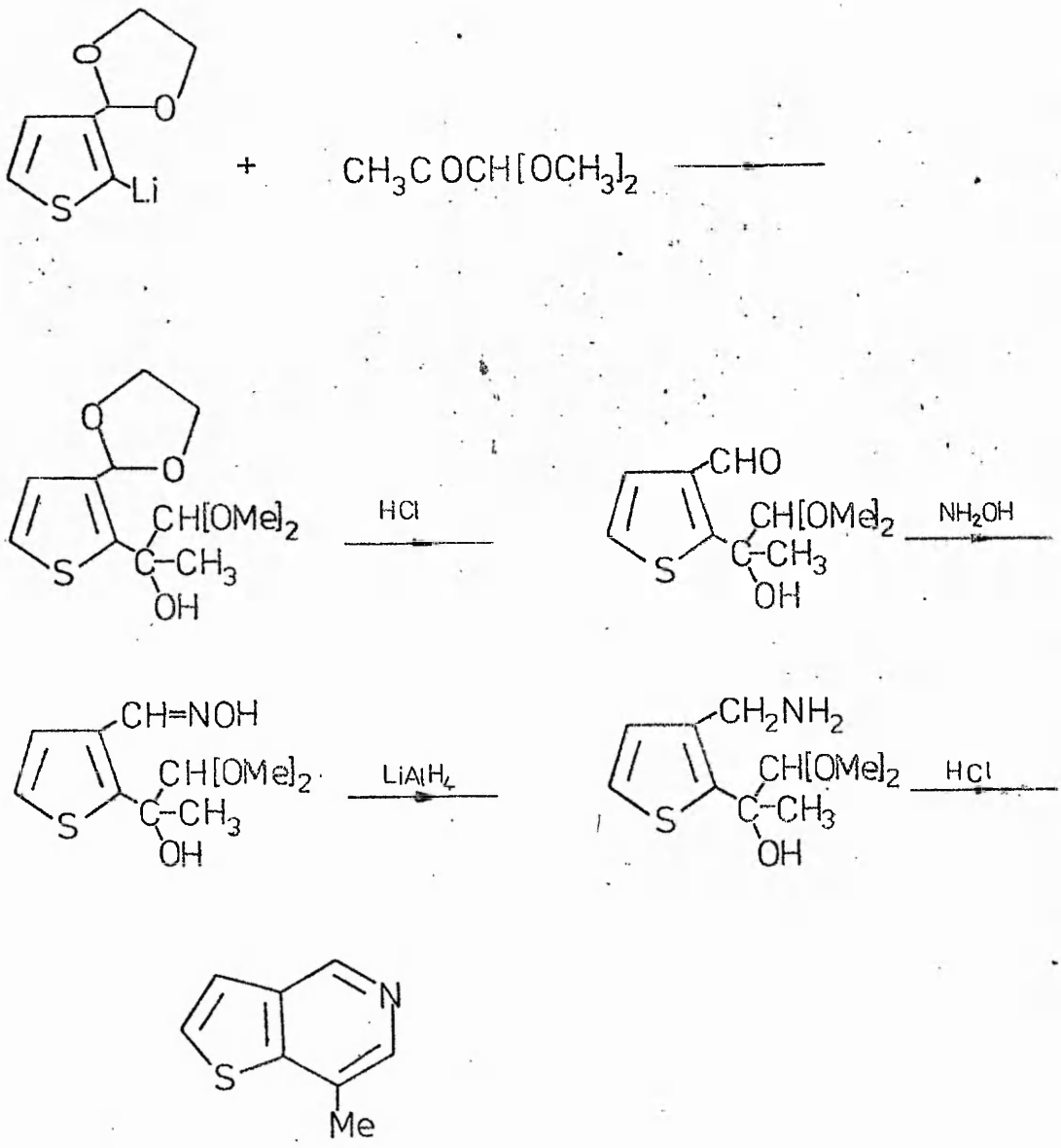
Sandberg[77] has published an account of a new approach to thieno [2,3-c] and [3,2-c] pyridines. The preparation of 7-methyl thieno [3,2-c] pyridine illustrates the route (Scheme VIII).

More recently several new papers on the synthesis of thienopyridines have been published. Farnier[78] reacted ethyl azidoacetate with thiophene-2,3-dialdehyde in which the two formyl groups are free, or in which one of them is blocked, to yield after cyclisation, thieno [3,2-c] and [2,3-c] pyridines and pyridines respectively. The reaction series is depicted in Scheme IX.

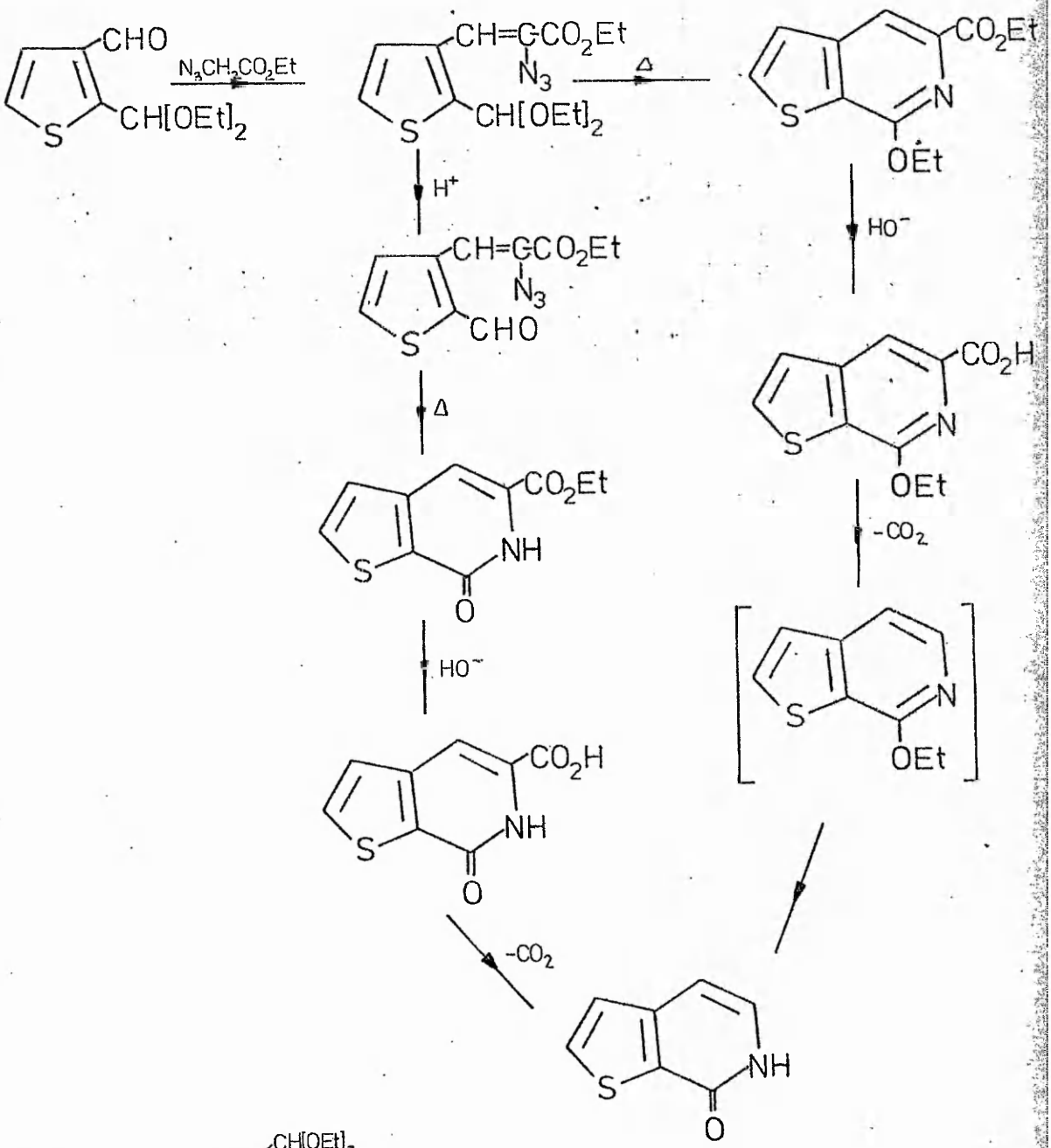
Following their success with a novel synthesis of 3,4-dihydroisoquinolines from 2-arylethylisothiocyanates[79], Davies and co-workers investigated an analogous synthesis of dihydrothienopyridines[80]. The isothiocyanate was cyclised with methyl fluorosulphate (M.F.S.), triethyloxonium tetrafluoroborate (TETFB) or polyphosphoric acid (PPA). The alkylthiodihydrothieno[3,2-c] pyridines produced were reacted further to produce a variety of substituted dihydrothienopyridines.

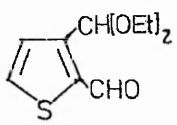


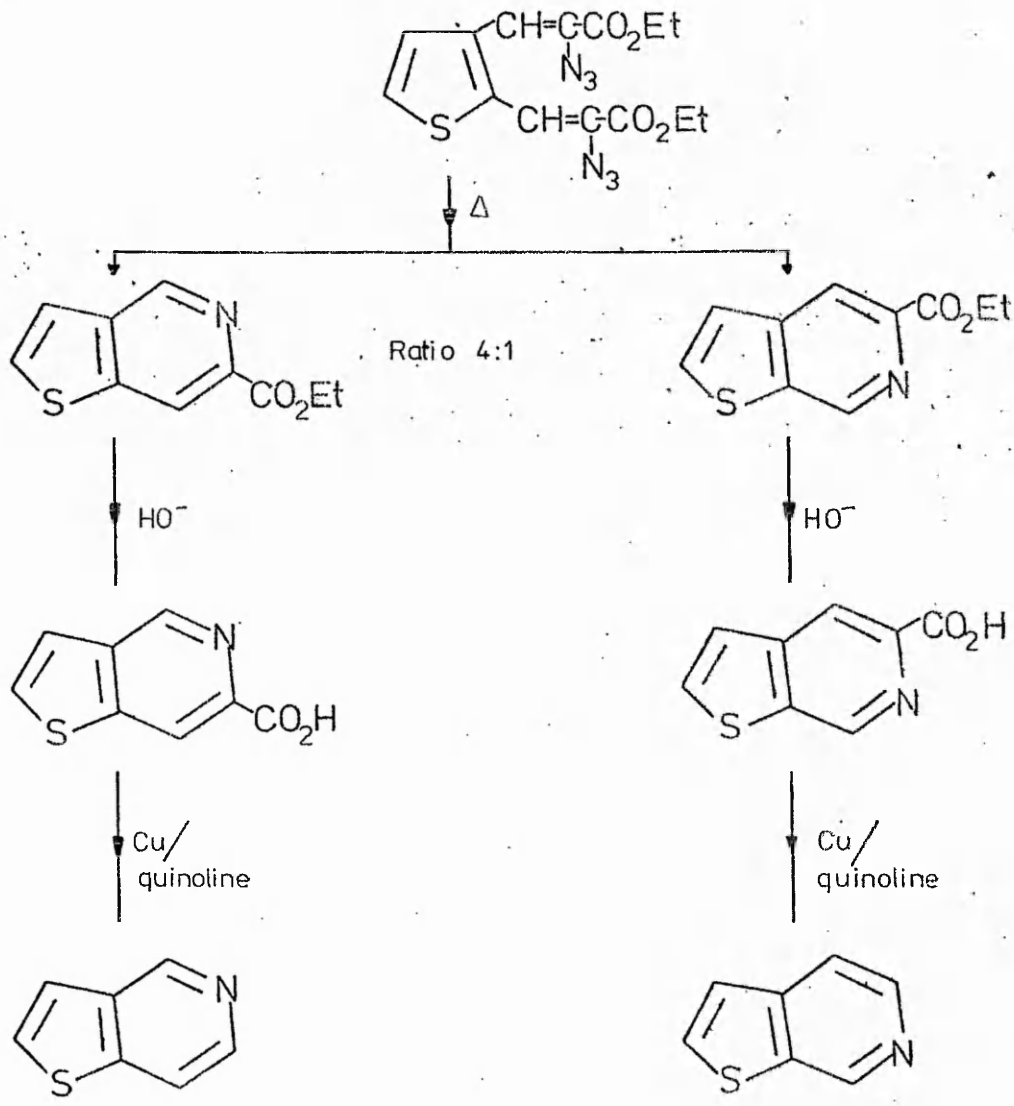
## Scheme VIII


Li
+
$CH_3C\,OCH[OCH_3]_2$
$CH[OMe]_2$
$C-CH_3$
OH
HCl
CHO
$NH_2OH$
CH=NOH
$LiAlH_4$
$CH_2NH_2$
S
N
Me

## Scheme IX




Similarly with 

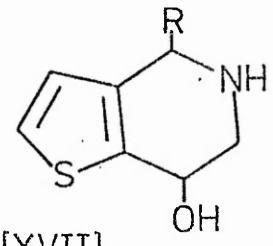



Yield 57%

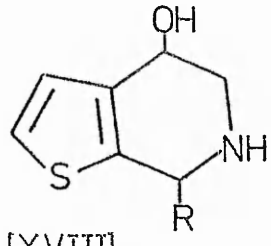
Yield 41%

A new method for the synthesis of thieno[2,3-c] and [3,2-c] pyridines and their tetrahydroderivatives[81] based on a modified Pomeranz-Fritsch reaction[82,83] has been published. The Schiff's base, obtained by reaction of aminoacetaldehydedimethylacetal with the thiophene aldehyde, was reduced with sodium borohydride to the amine. The amine was cyclised by shaking with 6N hydrochloric acid giving a hydroxy-4,5,6,7-tetrahydrothienopyridine, which was reduced with stannous chloride to the tetrahydrothienopyridine. The N-tosyl derivative of the amine was converted into the thienopyridine by refluxing in a mixture of 12N hydrochloric acid and dioxan (Scheme X).

The reaction scheme has also been carried out with 3-acyl- and 2-acyl thiophenes[81b], the products being 4-alkyl-7-hydroxy tetrahydrothieno[3,2-c] pyridine (XVII) and 7-alkyl-4-hydroxytetrahydrothieno [2,3-c] pyridine (XVIII).




[XVII]




[XVIII]

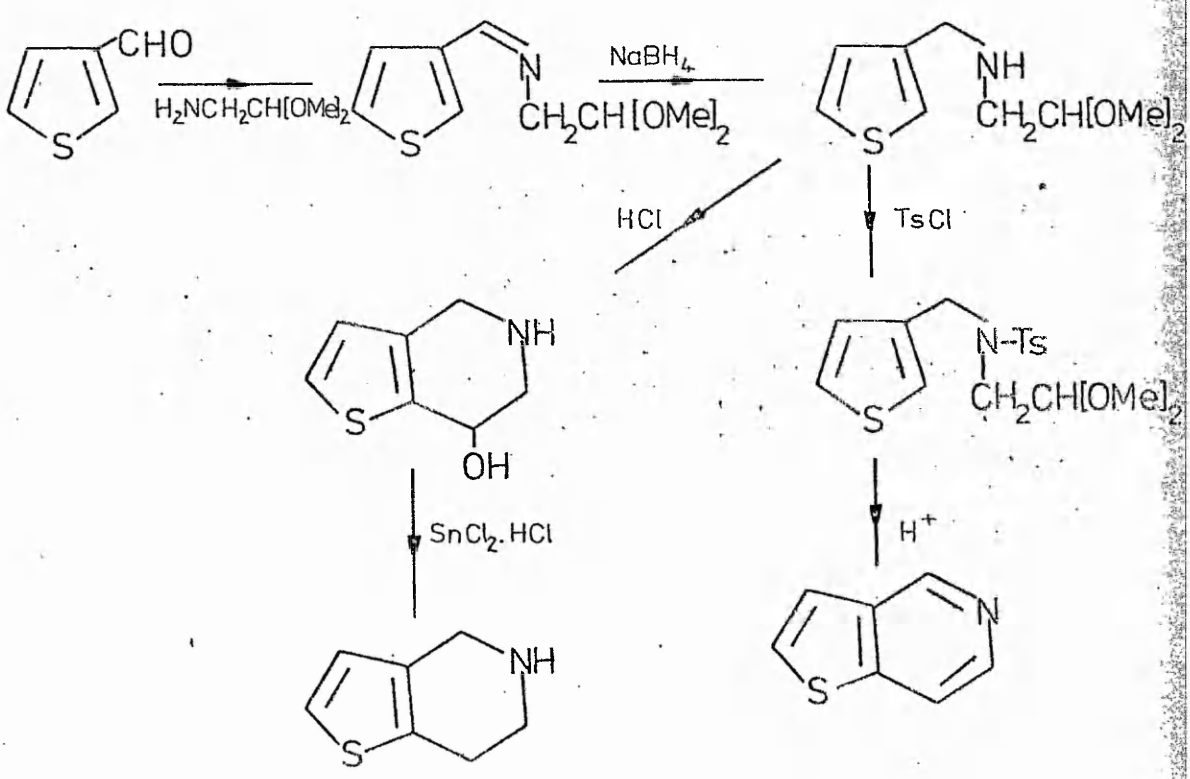
R = Et, Me, H.

2. Reactions

a) Electrophilic substitution

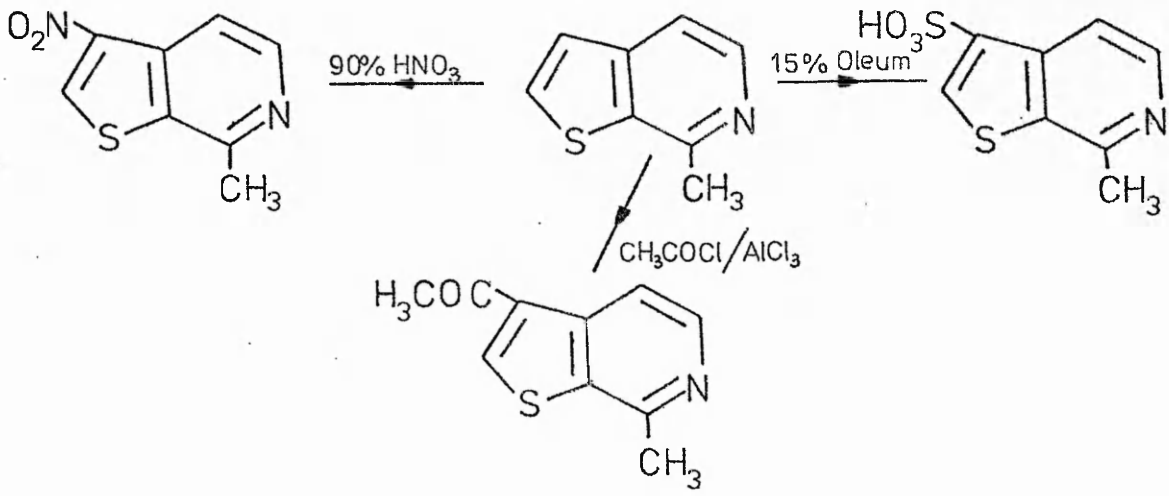
A detailed study of electrophilic substitution in thieno[2,3-c] and [3,2-c] pyridine has been carried out by Gronowitz and Sandberg[84]. They found that nitration with fuming nitric-sulphuric acid gave excellent yields of the 3-nitro derivative, but no nitration occurred at all if the sulphuric acid was replaced by acetic acid or acetic anhydride. The general resistance to electrophilic attack was shown

## Scheme X


CHO
S
$H_2NCH_2CH[OMe]_2$
N
$CH_2CH[OMe]_2$
$NaBH_4$
NH
$CH_2CH[OMe]_2$
HCl
TsCl
NH
OH
N-Ts
$CH_2CH[OMe]_2$
$SnCl_2.HCl$
$H^+$
NH
N

by the conditions necessary to effect bromination; treatment with bromine in carbon tetrachloride and acetic acid caused no reaction; bromine in 48% hydrobromic acid or in thionyl chloride gave the mono-bromo compound; whilst bromine in sulphuric acid with silver sulphate yielded appreciable amounts of the dibromothienopyridine.

Reactions carried out by Dressler and Joullié[70] showed that 7-methyl thieno[2,3-c] pyridine could be nitrated, sulphonated and acetylated at the 3-position, though it failed to react under Vilsmeier formylation conditions.




Under the same conditions 4-methylthieno[3,2-c] pyridine can be nitrated and sulphonated, though it resists acetylation and formylation.

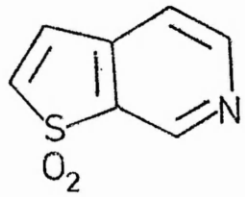
b) Nucleophilic substitution

Nucleophilic displacement of halogen at C-1 of isoquinoline takes place readily; halogens at other positions in the molecule are much more resistant to nucleophilic attack. Similar behaviour is observed in halogenated thienopyridines.

Derivatives in which a chlorine atom is $\alpha$ to the nitrogen are readily available from the pyridines produced by the synthesis of Eloy and Deryckere.[85] Such chlorine atoms are readily replaced by a variety of nucleophiles, opening up a pathway to a number of substituted thienopyridines.

c) Oxidation

Oxidation in thienopyridines is possible at two sites, the nitrogen, producing N-oxides and the sulphur, producing sulphones or sulphoxides. Treatment of various methyl-substituted thieno[3,2-c] and [2,3-c] pyridines with monoperphthalic acid produces in each case the N-oxide. The preparation of sulphones and sulphoxides is more difficult. However, the sulphone of thieno[2,3-c] pyridine (XIX) was prepared by Klemm and Merrill[86] by reaction of the heterocycle with sodium hypochlorite and dilute hydrochloric acid.

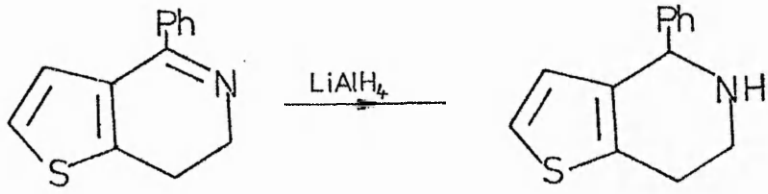



[XIX]

d) Reduction

Thienopyridines are resistant to reduction by tin-hydrochloric acid, since the parent systems can be obtained by reductive dehalogenation of chloroderivatives[72]. Quaternary salts are reduced to the N-alkyl-4,5,6,7-tetrahydrothienopyridines by sodium borohydride[68,70] and the azomethine bond in dihydro derivatives is reduced by lithium aluminium hydride[69].

eg.




3. Biological Activity

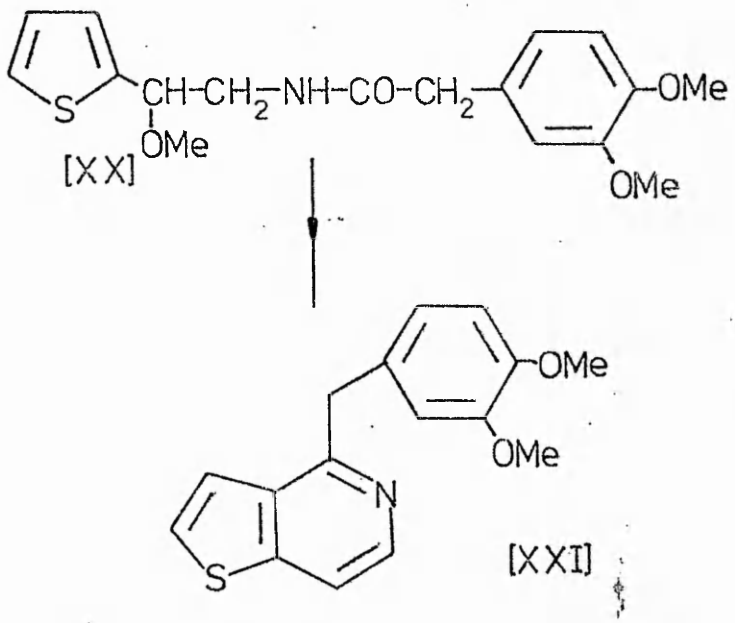
Most interest in biological activity has been centred on 4,5,6,7-tetrahydro thieno[2,3-c] and [3,2-c] pyridines. A considerable number of derivatives of these systems have been prepared and evaluated pharmacologically[87] and have been found to show activity, for example against diabetes mellitus, as analgesics and antiinflammants, as sedatives and as anticoagulants.

Shen and Clark[88] have prepared and tested pharmacologically a large number of substituted thieno[3,2-c] pyridines. The compounds have been found to be potent anti-inflammatory, anti-pyretic, tranquillizing and analgesic agents which are effective in counteracting inflammation, emotional disorders, pain and fever. Also covered by the patent are 4-oxo-4,5-dihydrothieno[3,2-c] pyridine and 4-chloro-4,5-dihydrothieno[3,2-c] pyridine, which also possess potent anti-inflammatory, anti-pyretic, tranquillizing and analgesic activities.

Thiophene analogues of Papaverine

Recorded in the literature are three attempts to prepare thiophene analogues of papaverine. However, none can be regarded as a true analogue as in all cases they lack the two methoxy groups which should be sited on the vacant positions of the thiophene ring.

The first attempt was by Herz and Tsai[68] who applied the Pictet-Gams isoquinoline synthesis to the preparation of a papaverine analogue XXI; the final step, cyclisation of N-homoveratroyl-2-methoxy-2-(2-thienyl) ethylamine (XX) took place in only very low yield.

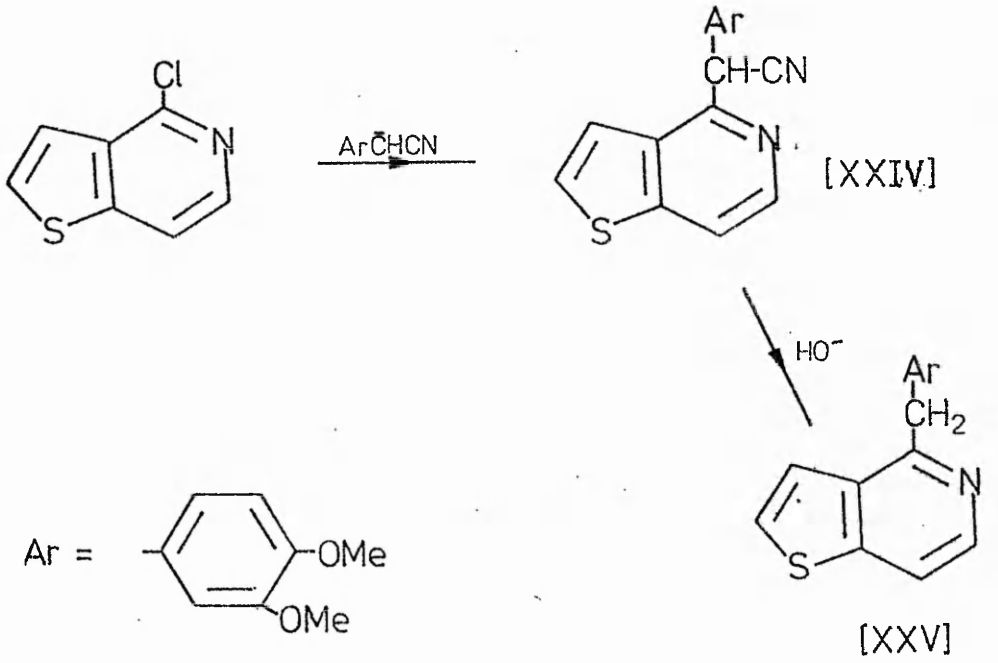



[XX] [XXI]

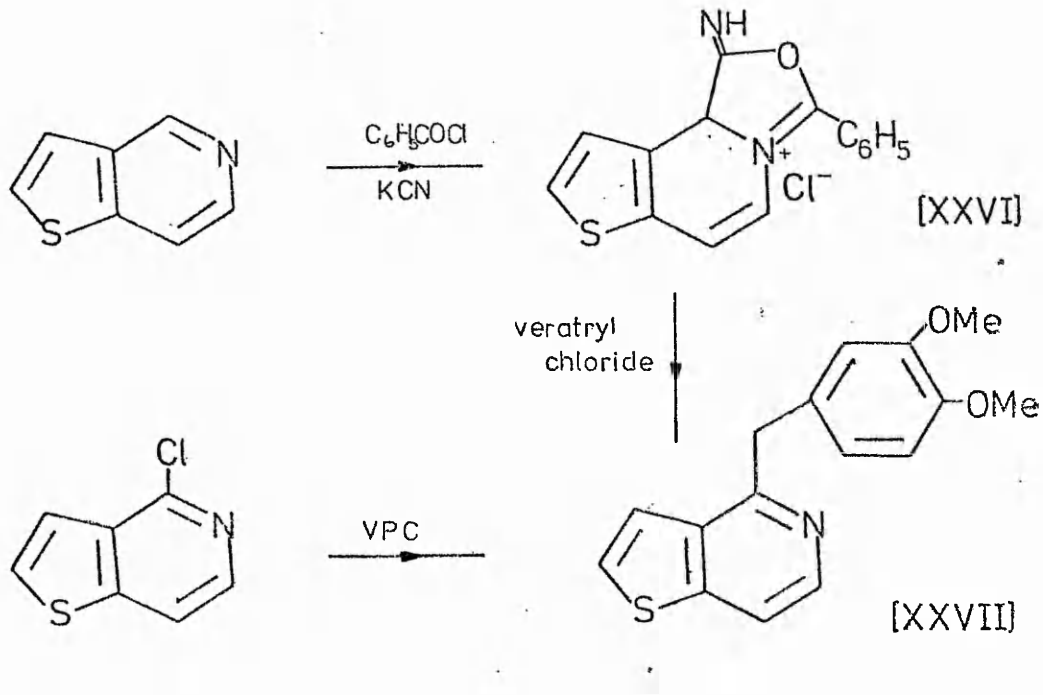
In an attempt to improve the yield in the ring closure step by activating the thiophene ring with a methoxy group, Herz attempted the cylisation of compound XXII. However, reaction conditions were too severe for the methoxy group to survive and the isolated product was XXIII.


[XXII] [XXIII]

More recently Eloy and Deryckere[89] have prepared compound XXIV by reaction of 4-chlorothieno[3,2-c] pyridine with 3,4-dimethoxyphenyl-acetonitrile in the presence of sodium hydride. Basic hydrolysis of XXIV gave the analogue XXV.




Following the procedure of Popp and Blount[90] for the synthesis of isoquinoline Reissert compounds, Clough[91] allowed thieno[3,2-c] pyridine to react with benzoyl chloride and potassium cyanide to give a product identified as XXVI. Treatment of this first with sodium hydride, then with veratryl chloride followed by basic hydrolysis gave 4-(3,4-dimethoxy-benzyl) thieno[3,2-c] pyridine XXVII.




V.P.C. = 3,4-dimethoxybenzyl(tri-n-butyl)phosphonium chloride.

Compound XXVII was also prepared from an adaptation of Taylor's[45] work with isoquinolines by the reaction of 4-chlorothieno[3,2-c] pyridine with the ylid derived from 3,4-dimethoxybenzyl(tri-n-butyl) phosphonium chloride with n-butyllithium.

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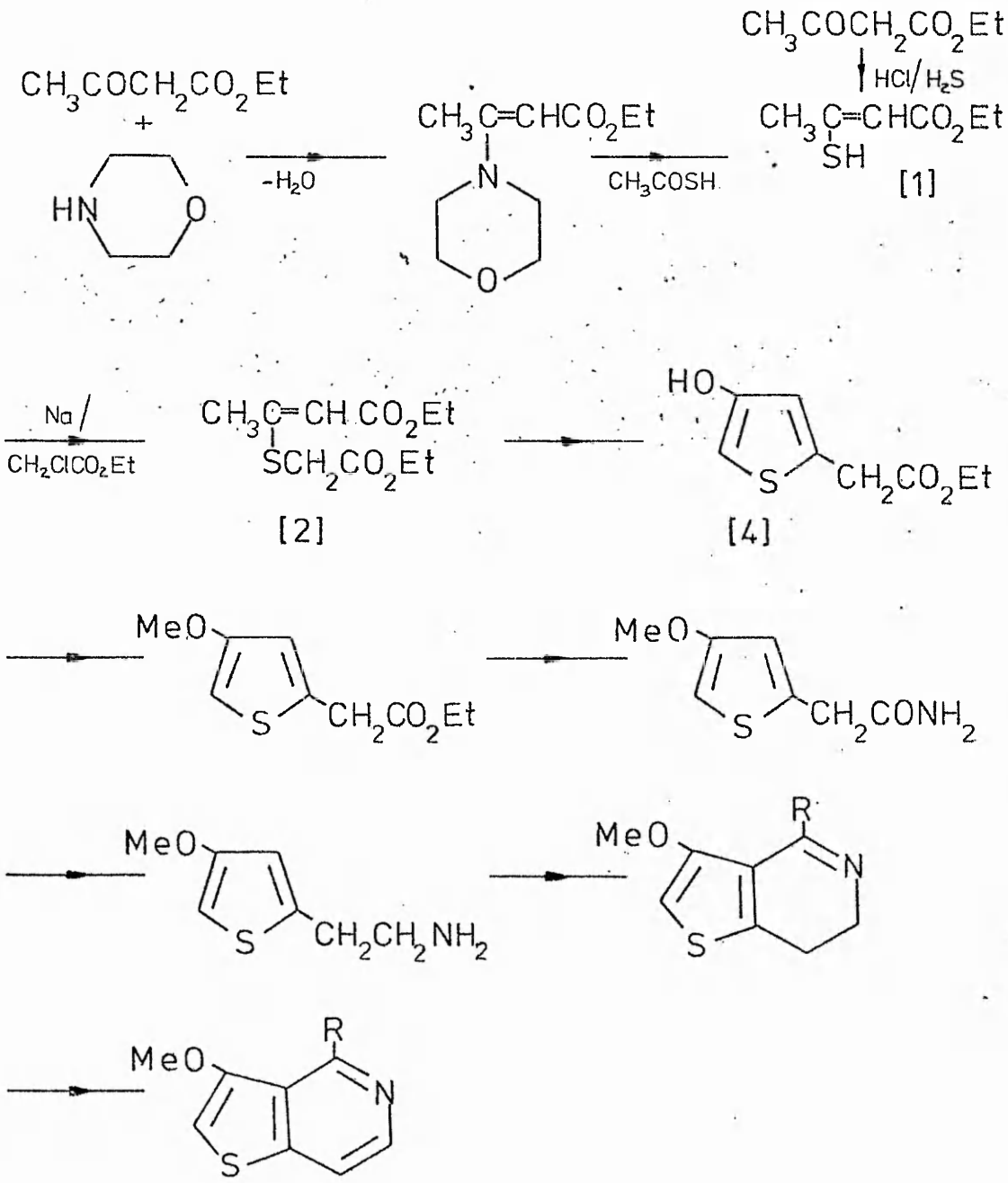
# CHAPTER TWO

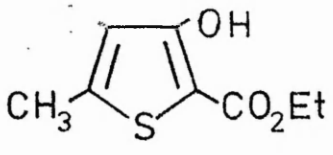
# D I S C U S S I O N

The original plan was the preparation of a thiophene analogue of papaverine, namely 2,3-dimethoxy-7-(4,5-dimethoxy-2-thienyl) thieno[2,3-c]pyridine and its isomer 2,3-dimethoxy-4-(4,5-dimethoxy-2-thienyl)thieno[3,2-c]pyridine. However, the preparation of a methoxylated thienopyridine proved to be more difficult than was anticipated. The discussion that follows shows the various schemes followed in attempting to achieve this end and also the preparation of some methoxylated thienyl acetic acids.

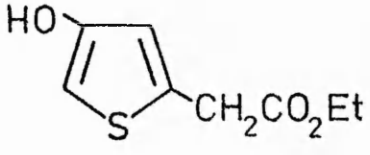
## Scheme 1


CH3COCH2CO2Et
+
HN
O
-H2O
CH3C=CHCO2Et
N
O
CH3COSH
CH3COCH2CO2Et
HCl/H2S
CH3C=CHCO2Et
SH
[1]
Na/
CH2ClCO2Et
CH3C=CHCO2Et
SCH2CO2Et
[2]
HO
S
CH2CO2Et
[4]
MeO
S
CH2CO2Et
MeO
S
CH2CONH2
MeO
S
CH2CH2NH2
MeO
R
N
S
MeO
R
N
S

Scheme 1 shows the proposed reaction plan for the preparation of a 4-substituted-3-methoxy thieno[3,2-c]pyridine. Ethyl β-morpholinocrotonate[1] (prepared in excellent yield by condensation of ethylacetoacetate and morpholine) was converted to the thiol[2] (1) by reaction with thioacetic acid; ethylthioacetoacetate could also be prepared by treatment of ethyl acetoacetate with a mixture of hydrogen sulphide and hydrogen chloride gases.[3] Reaction of the thiol with sodium and ethyl chloroacetate gave the thioether[4] (2); attempts to prepare this compound under milder conditions (viz. using sodium hydride and ethyl chloroacetate) failed. Cyclisation of the thioether following the method of Chakrabarty and Mitra[4], however, gave a substituted thiophene whose spectroscopic data was not in agreement with that of the product claimed. The nmr spectrum suggested that the substance obtained was ethyl 3-hydroxy-5-methyl thiophene-2-carboxylate[5] (3) and not the claimed ethyl 4-hydroxy-2-thienylacetate (4). An authentic sample of compound (3) was prepared according to the method of Fiesselmann[5] as proof of identification.




[3]

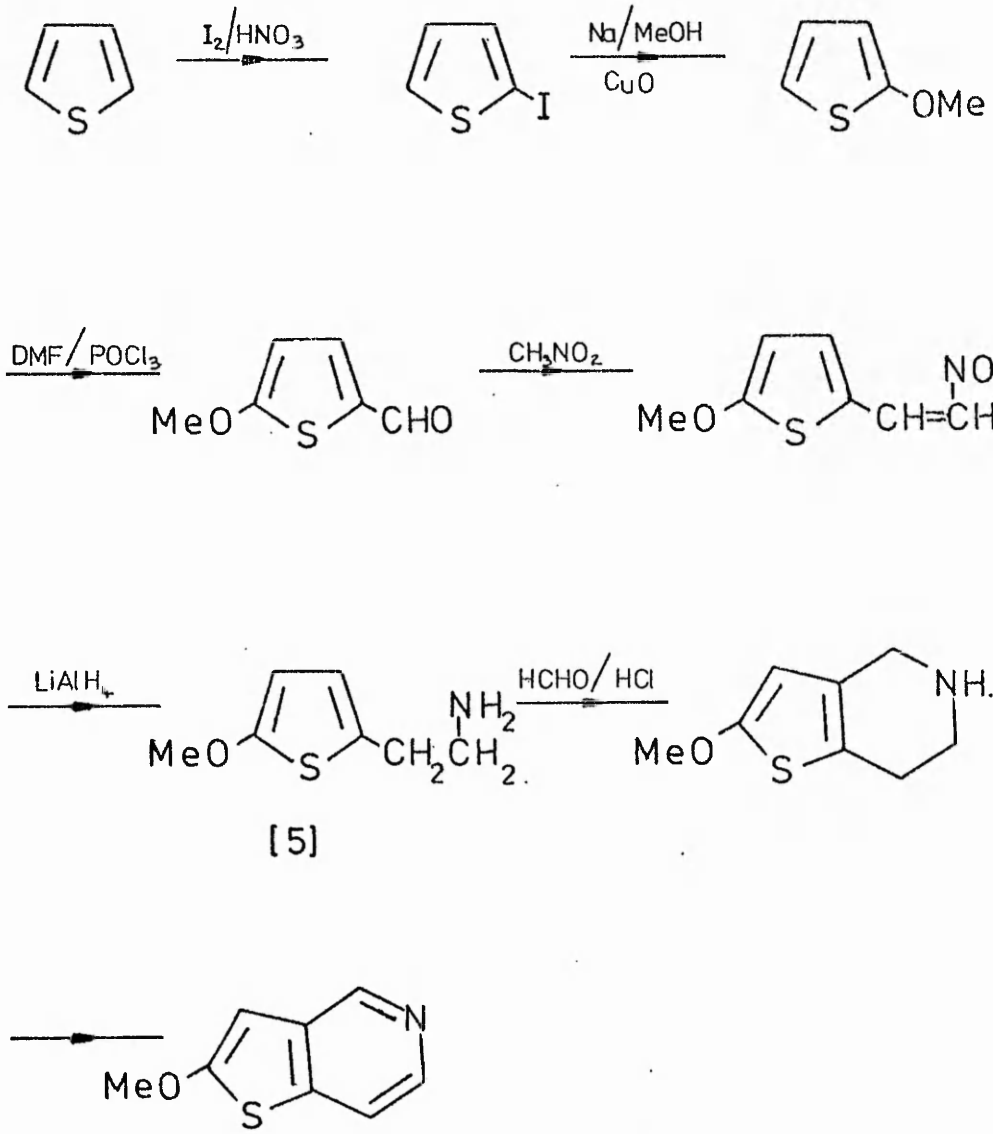



[4]

In view of this result it was decided to follow a route using the readily accessible 2-methoxythiophene (scheme 2).

2-Iodo-[6] and 2-methoxythiophene[7] were prepared by published procedures; 5-methoxythiophene-2-aldehyde was prepared by a Vilsmeier formylation reaction using methylene chloride as solvent. Several methods were attempted for the preparation of 5-methoxy-2-(β-nitrovinyl) thiophene[8], the best yield (44%) being obtained by

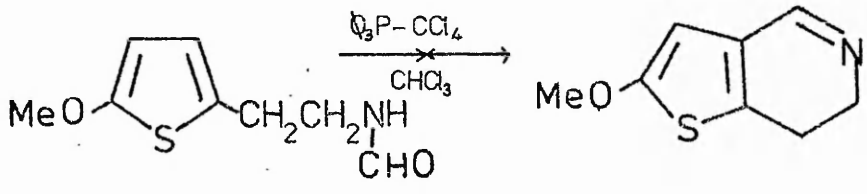
## Scheme 2


I2/HNO3
Na/MeOH
CuO
OMe
DMF/POCl3
MeO
CHO
CH3NO2
NO2
CH=CH
LiAlH4
NH2
CH2CH2
HCHO/HCl
NH.HCl
[5]
N

mixing the aldehyde with nitromethane and a catalytic amount of benzylamine, the mixture then being left in the dark for 8 days.[8] The crystals formed were filtered off and were ready for use in the next stage, a lithium aluminium hydride reduction, which gave the amine[8] (5) in reasonable yield. Unfortunately, ring closure of the amine following the method of Gronowitz[9] resulted in tar formation or complex mixtures from which no product could be obtained.

In order to gain expertise in this procedure, the work of Gronowitz[9] was repeated using thiophene-2-aldehyde. However, in the present author's hands an unresolvable mixture was obtained, from which none of the desired product, 4,5,6,7-tetrahydrothieno [3,2-c]pyridine hydrochloride, could be isolated.

It was known from the work of Herz and Tsai[8] that the Bischler-Napieralski ring closure under normal conditions of acyl derivatives of β-( 5-methoxy-2-thienyl)ethylamine leads to loss of the methoxy group. Accordingly, the cyclisation of N-formyl-β-(5-methoxy-2-thienyl)ethylamine[8] (prepared by the treatment of β-( 5-methoxy-2-thienyl)ethylamine with chloral hydrate in methanol) by a mild method using triphenylphosphine and carbon tetrachloride in chloroform[10] was attempted. When the reactants were heated under reflux for 3 hr a complex mixture was obtained, from which no product could be isolated; when the mixture was left at room temperature for 1½ hr followed by heating under reflux for ½ hr only tar formation was observed.



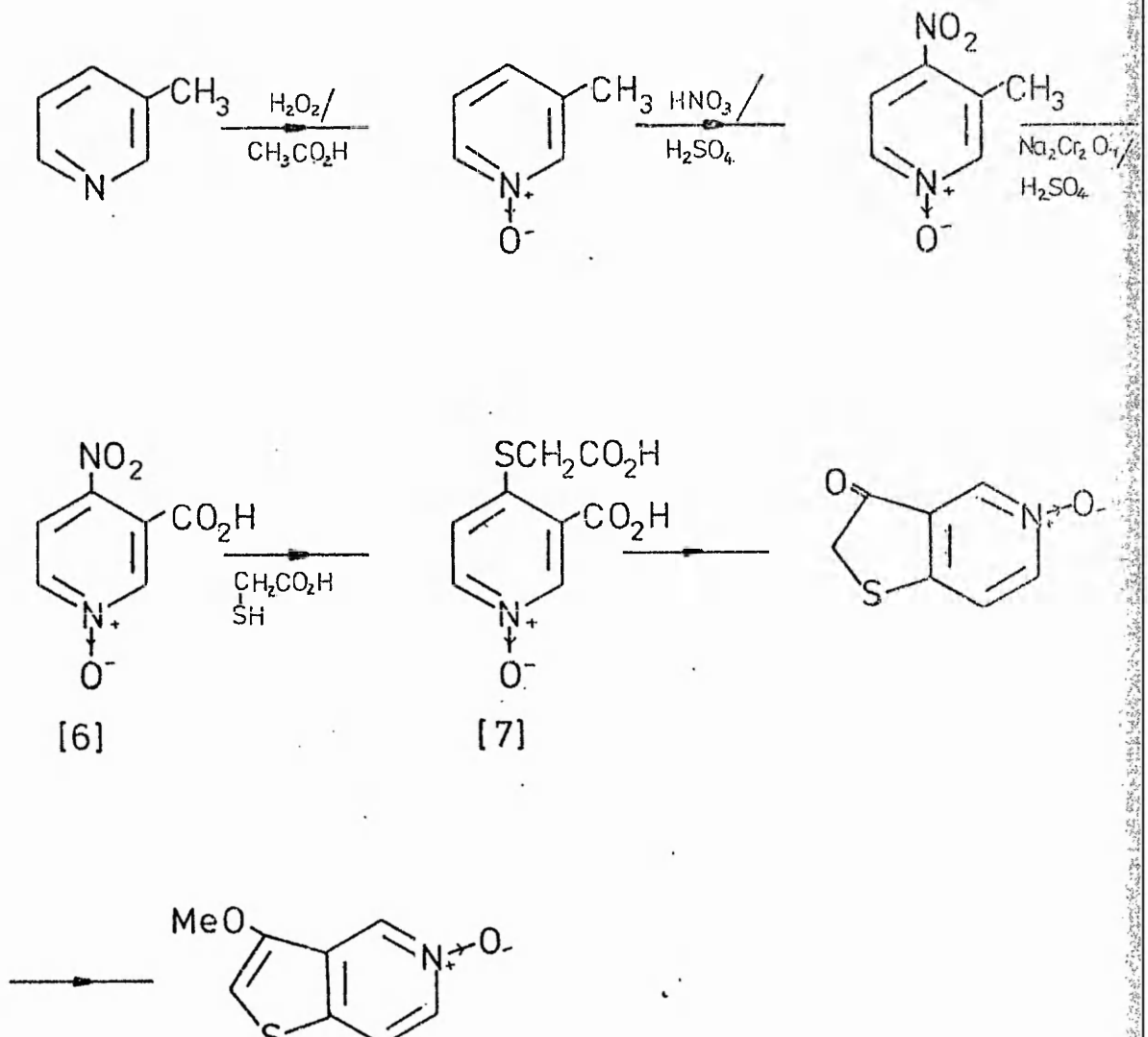
Several attempts were made to cyclise N-acetyl-β-(5-methoxy-2-thienyl)ethylamine[8] (prepared by condensation of β-(5-methoxy-2-thienyl)ethylamine and acetic acid under the influence of dicyclohexylcarbodiimide). With triphenylphosphine and carbon tetrachloride in chloroform[10], after refluxing for 2 hr only tar was observed; with triphenylphosphine and carbon tetrachloride in methylene chloride under reflux for 3½ hr a complex mixture (containing some starting material) was obtained. With tri-n-butylphosphine and carbon tetrachloride in methylene chloride (room temperature, overnight) no reaction took place at all.

At this point it was decided to explore the preparation of a thienopyridine starting with an appropriately substituted pyridine ring, as depicted in scheme 3.

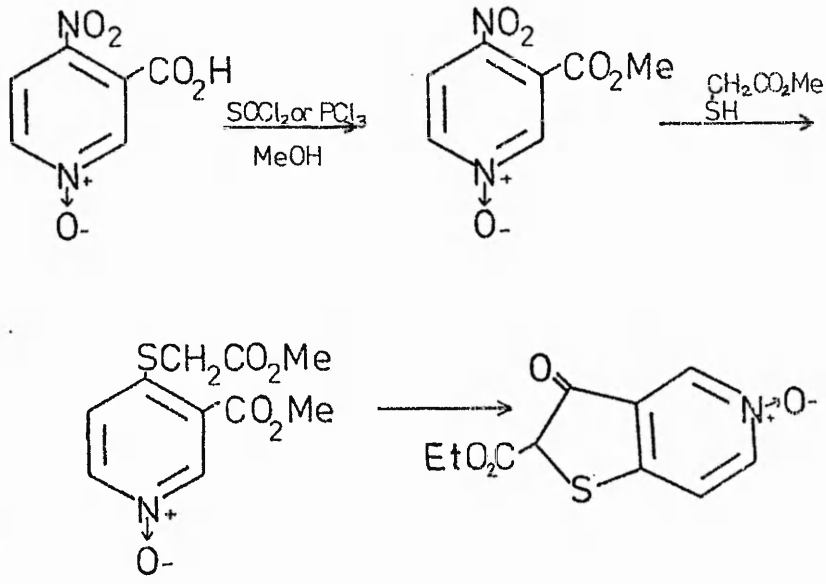
4-Nitro-3-picoline-1-oxide[11] was prepared by oxidation of 3-picoline to the N-oxide using hydrogen peroxide in glacial acetic acid[12], followed by nitration with fuming nitric acid and concentrated sulphuric acid[11], both reactions giving excellent yields. Oxidation to the acid[13] (6) was brought about using sodium dichromate in concentrated sulphuric acid. Unfortunately, the next stage, replacement of the nitro group by thioglycollic acid, following the method of Okamoto and Itoh[14], proved unsuccessful.

As the preparation of the diacid (7) had proved to be so difficult, it was decided to attempt the preparation of the diester (8), the proposed reaction scheme being shown below.

## Scheme 3


CH3
H2O2/
CH3CO2H
HNO3/
H2SO4
NO2
Na2Cr2O7/
H2SO4
CO2H
CH2CO2H
SH
SCH2CO2H
MeO
N+
O-
S
O

[6] [7]



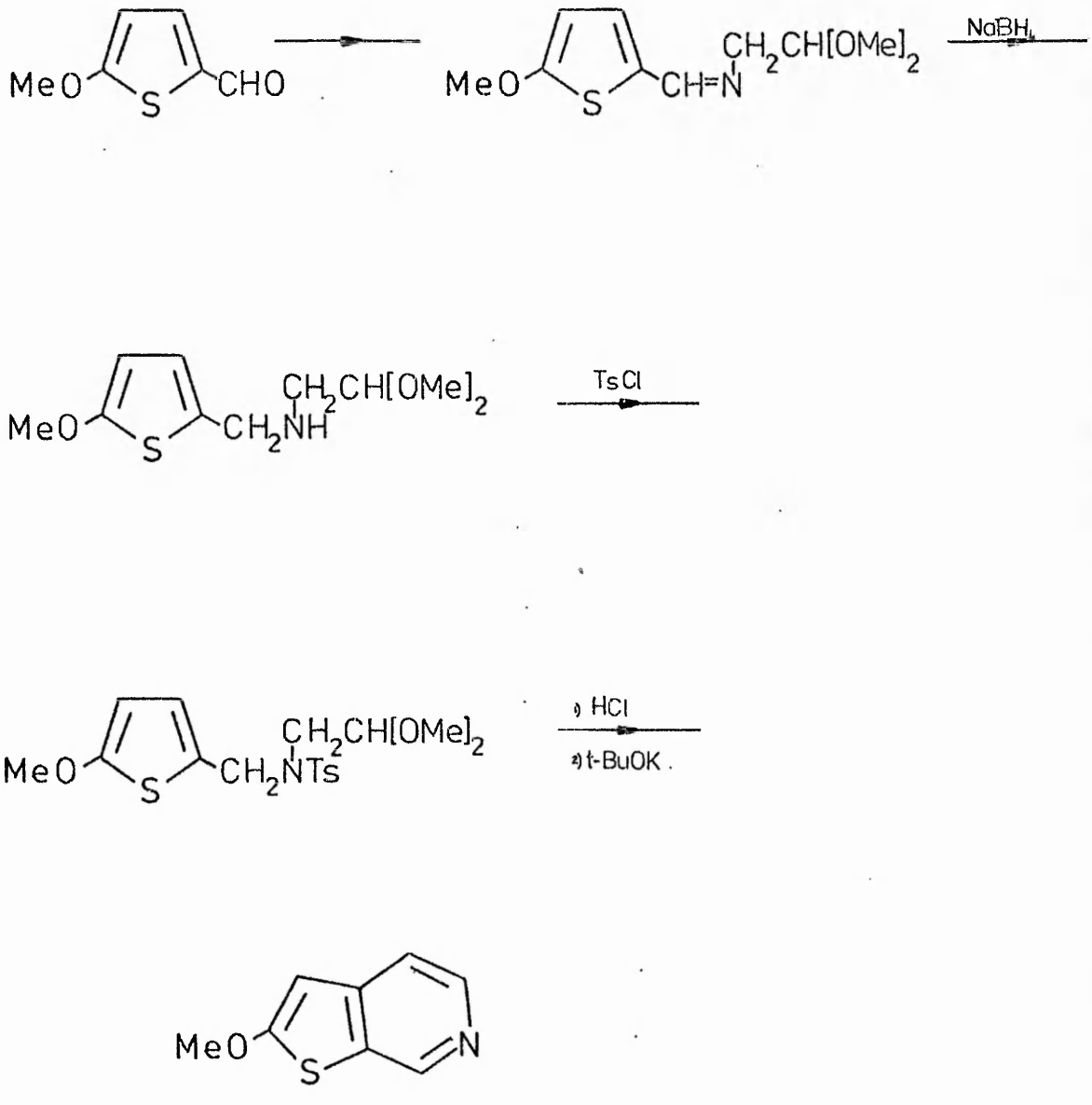
[8]

The preparation of the nitroester, however, also proved to be difficult. Treatment of the nitroacid with phosphorous trichloride or thionyl chloride followed by methanol gave a white crystalline solid which proved to be methyl 4-methoxynicotinate[15] and not the desired methyl 4-nitronicotinate-1-oxide or its deoxygenated derivative.

Another approach using 2-methoxythiophene was based on the Jackson modification of the Pomeranz-Fritsch reaction.[16] The proposed sequence is shown in scheme 4.

Condensation of 5-methoxythiophene-2-aldehyde with aminoacetaldehyde dimethylacetal proceeded in reasonable yield. This new Schiff's base gave satisfactory analytical results and the infrared spectrum showed a stretching frequency for the imine at 1615 $cm^{-1}$. Reduction of this Schiff's base to 5-methoxythenylaminoacetaldehyde dimethyl acetal with sodium borohydride in ethanol also proceeded well, but gave a product which was too unstable to give a satisfactory analysis although spectroscopic data were sufficient to establish its identity. The next stage, tosylation of the amine with p-toluene-

## Scheme 4


MeO
S
CHO
CH2CH[OMe]2
CH=N
NaBH4
CH2NH
TsCl
CH2NTs
1) HCl
2) t-BuOK .
N

sulphonyl chloride in pyridine, gave a good yield of the sulphonamide. This new tosyl compound also gave satisfactory analytical results and had stretching frequencies in the infrared spectrum at 1320 $cm^{-1}$ and 820 $cm^{-1}$ indicating the presence of $>SO_2$ and a p-disubstituted benzene ring respectively.

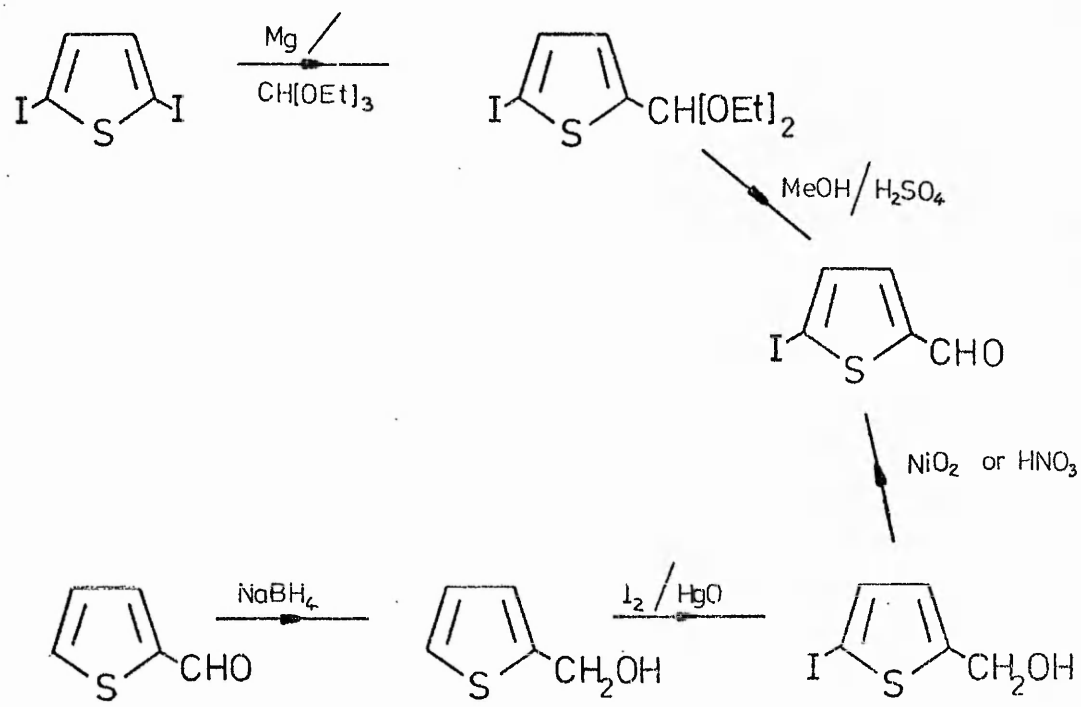
Attempts to cyclise 2-(5-methoxythenyl)-N-tosyl-aminoacetaldehyde dimethyl acetalby treatment with hydrochloric acid, however, were unsuccessful. A product was obtained from the reaction which spectroscopy suggested may have been N-tosyl-6,7-dihydrothieno[2,3-c] pyridine-2-[3H]-one; unfortunately, attempts to purify this to analytical standard failed.

Several methods were tried in attempts to bring about ring closure of the Schiff's base; these included the use of polyphosphoric acid at 60°, boron trifluoride-ether complex in ether at 0° and the same reagent in toluene at 100°. In all cases hydrolysis of the Schiff's base appeared to take precedence over cyclisation, as the only product obtained was 5-methoxythiophene-2-aldehyde. Using triphenylphosphine and carbon tetrachloride in chloroform as the reagent a mixture was obtained from which only triphenylphosphine oxide[17] was obtained.

It should be noted at this point that the work described in scheme 4 was carried out at the same time, but independently, from that of Maffrand and Eloy[18] and also work published in a German Patent[19].

Attempts were next made to prepare 2-iodo-5-thiophenecarboxaldehyde for conversion into the nitrostyrene, or into the Schiff's base with aminoacetaldehyde dimethyl acetal, and thence into an iodothienopyridine by the routes outlined in Schemes 2 and 4. Two approaches were followed for the preparation of 2-iodo-5-thiophenecarboxaldehyde (scheme 4a).

## Scheme 4a


Mg
CH[OEt]3
I
S
I
CH[OEt]2
MeOH / H2SO4
CHO
NiO2 or HNO3
CH2OH
I2 / HgO
NaBH4
CHO
CH2OH

[9]

In the first an attempt was made to prepare the mono-Grignard reagent from 2,5-diiodothiophene, and to react it with triethyl orthoformate. Only starting material was recovered, however, which suggests that the Grignard reagent had failed to form.

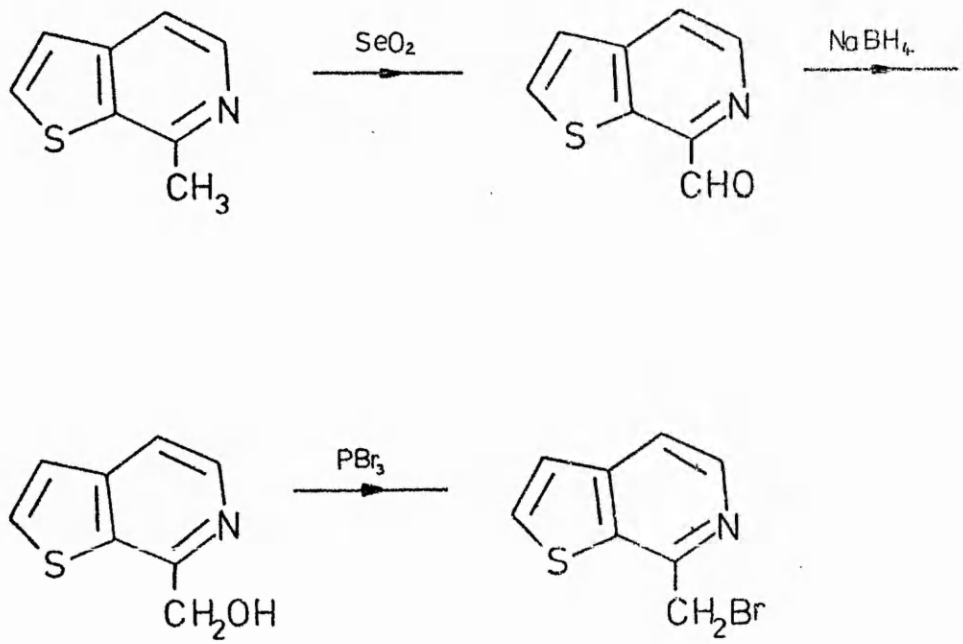
In the second, thiophene-2-aldehyde (prepared by a Vilsmeier formylation reaction)[20] was reduced to the alcohol[21] (9) with sodium borohydride. Iodination of this alcohol with iodine and mercuric oxide gave the desired 2-iodo-5-thenyl alcohol[22] as an oil. Attempts to purify this oil by distillation resulted in polymer formation so the next stage was performed on the crude compound.

Two methods were attempted for the oxidation; by using nickel peroxide,[23] some 2-iodo-5-thiophene carboxaldehyde[23] was obtained but the yield (26%) was far short of that reported in the literature (70%). Using aqueous nitric acid[53] for the oxidation, some product was obtained; however, the yield (12%) was much lower than in the previous case (26%). In view of these poor yields the scheme had to be abandoned.

An entirely different approach to a papaverine analogue, summarised in scheme 5 was then examined.

7-Methyl thieno[2,3-c] pyridine was prepared according to the method of Dressler and Joullié.[24] An improvement in the yield in the preparation of the aldehyde was obtained by direct oxidation of the methyl group using selenium dioxide[25] (50%), rather than by the two stage process of Dressler and Joullié[24] who first condensed the methyl group with benzaldehyde then oxidised the 7-styrylthieno[2,3-c] pyridine formed with osmium tetroxide (30%). Reduction of the aldehyde with sodium borohydride in ethanol gave the new 7-hydroxymethyl thieno[2,3-c] pyridine, for which satisfactory analytical results were obtained. Treatment of a chloroform solution of the alcohol with phosphorous tribromide gave 7-bromomethylthieno[2,3-c] pyridine.

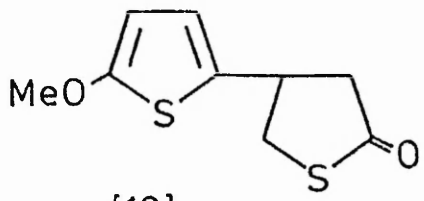
## Scheme 5



This new bromomethyl compound was characterised as the hydrobromide since the free base was too unstable for a successful analysis. A picrate was also obtained for this compound.

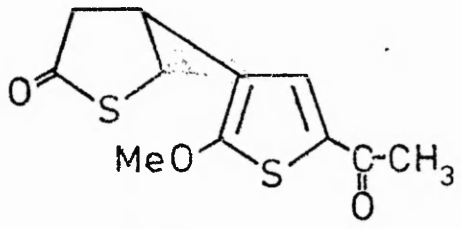
With the success of this method for the preparation of a thienopyridine it was decided to attempt the preparation of 2-methoxy-7-methyl thieno[2,3-c]pyridine from 5-methoxy-2-acetylthiophene[7] following the same reaction scheme.

A solution of 2-methoxythiophene in acetic anhydride was treated with phosphoric acid, the product being a white crystalline solid. However, the nmr spectrum of this indicated that it was not the desired product. Experimentation established that this product was formed by the action of the phosphoric acid alone on the 2-methoxythiophene. The same product was also obtained from the reaction of dimethylacetamide and phosphoryl chloride with 2-methoxythiophene. Spectral data suggested that this material was the thiolactone (10) m.p. 51-52°, and this view was supported by elemental analysis.




[10]

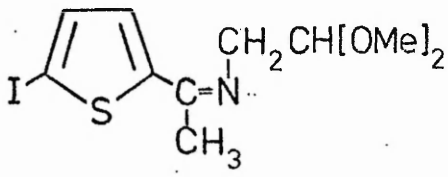
A recent paper[26] describes the acetylation of 2-methoxythiophene using acetyl chloride and stannic chloride in benzene in 0°. The reaction produced a by-product which was identified as the thiolactone (11)m.p. 117-118°.



[11]

As 5-methoxy-2-acetyl thiophene could not easily be prepared in good yield it was decided to abandon this scheme for the time being.

Along the same lines an attempt was made to prepare 2-iodo-7-methylthieno[2,3-c] pyridine from 5-iodo-2-acetyl thiophene.[27] The latter compound (prepared in reasonable yield by acetylation of 2-iodothiophene with acetyl chloride and stannic chloride)[28] was condensed with aminoacetaldehyde dimethyl acetal to give the azomethine (12).



[12]

However, after 16 hrs reflux the percentage conversion (< 5 %) was so small that the reaction was clearly not worthwhile from a practical point of view.

An alternative method for the preparation of this iodo Schiff's base(12) was then attempted, ie. iodination of [(α-methyl-2-thenylidene) amino] acetaldehyde dimethyl acetal, using iodine and yellow mercuric oxide. This too was unsatisfactory, an unresolvable mixture being obtained.

The next reaction sequence considered involved the attempted coupling of 2-lithio-5-methoxythiophene with either 7-bromomethyl-thieno[2,3-c]pyridine or thieno[2,3-c]pyridine-7-carboxaldehyde (scheme 6).

Sice[7] had already shown that 2-methoxythiophene formed a lithio derivative when treated with phenyl lithium in ether and he converted the lithio compound into the corresponding carboxylic acid by reaction with carbon dioxide. In the present work it was decided to test the efficiency of lithiation of 2-methoxythiophene with n-butyl lithium by conversion of the lithio derivative into 5-methoxy-2-thenoic acid. The percentage conversion (50%) was sufficient to make the process viable.

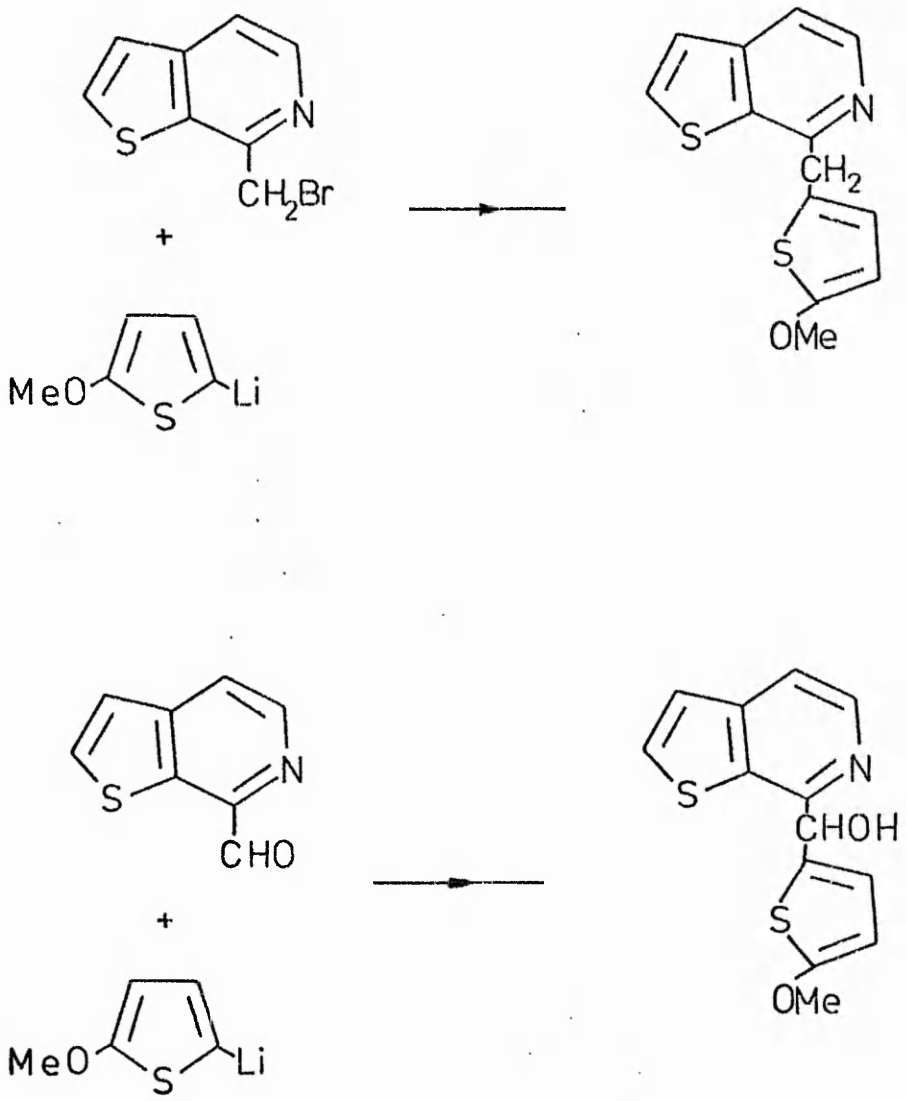
2-Bromo-5-methoxythiophene[7] (prepared by bromination of 2-methoxy-thiophene with 1,3-dibromo-5,5-dimethylhydantoin) was also shown to form a lithio derivative.

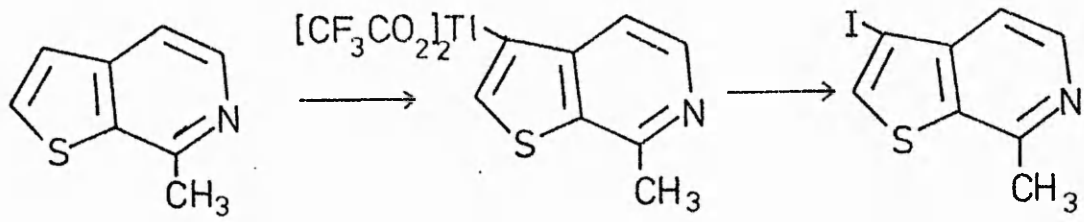
However, attempts to couple the bromomethyl thienopyridine and the corresponding aldehyde with 2-lithio-5-methoxythiophene resulted only in the recovery of the respective starting materials together with some 2-methoxythiophene.

As 2-iodothiophene gives excellent yields of 2-methoxythiophene on treatment with sodium methoxide in methanol in the presence of copper oxide,[6] it was decided to try to introduce the methoxy group into the thienopyridine by a similar method.

The preparation of iodo compounds by reaction of the product of thallation with thallium trifluoroacetate with potassium iodide has been described in the literature.[29] This method was applied to 7-methylthieno[2,3-c]pyridine. However, no reaction occurred, a small percentage of the thienopyridine being recovered.

Scheme 6






Arotsky[30] describes a method of iodination using iodine in 20% oleum. Using this reagent with the 7-methylthieno[2,3-c]pyridine a mixture of the 3-iodo- and the 3-sulphonyl-thienopyridines[24] was obtained. As it proved impossible to separate the two products, this method was of no practical use in the present case.

Recorded in the literature[31] is a method for the preparation of 3-iodothieno[2,3-b]pyridine using silver sulphate and iodine in concentrated sulphuric acid. Application of this method to 7-methylthieno[2,3-c]pyridine produced 3-iodo-7-methylthieno[2,3-c]pyridine although the yield was rather low (15%). This new compound gave satisfactory analytical results.

The iodine in 3-iodo-7-methylthieno[2,3-c]pyridine was replaced using the same conditions as in the preparation of 2-methoxythiophene. Unfortunately, the reaction failed to go to completion and a pure sample of the methoxy thienopyridine was not obtained. However, nmr spectroscopy showed the presence of the methoxy group in the molecule (peak at $\tau(CDCl_3)$ 6.1, $-OCH_3$).

Another more recent paper[32] describes the preparation of methoxy compounds by replacement of a nitro group. As 3-nitro-7-methylthieno-[2,3-c]pyridine[24] is a known compound it was decided to attempt to prepare a methoxythienopyridine using this method. In the present author's hands, however, the method described by Dressler and Joullié[24] failed to yield the 3-nitro derivative, so this approach had to be abandoned.

A further reaction scheme leading to a methoxylated thieno-pyridine, outlined in Scheme 7, was now attempted.

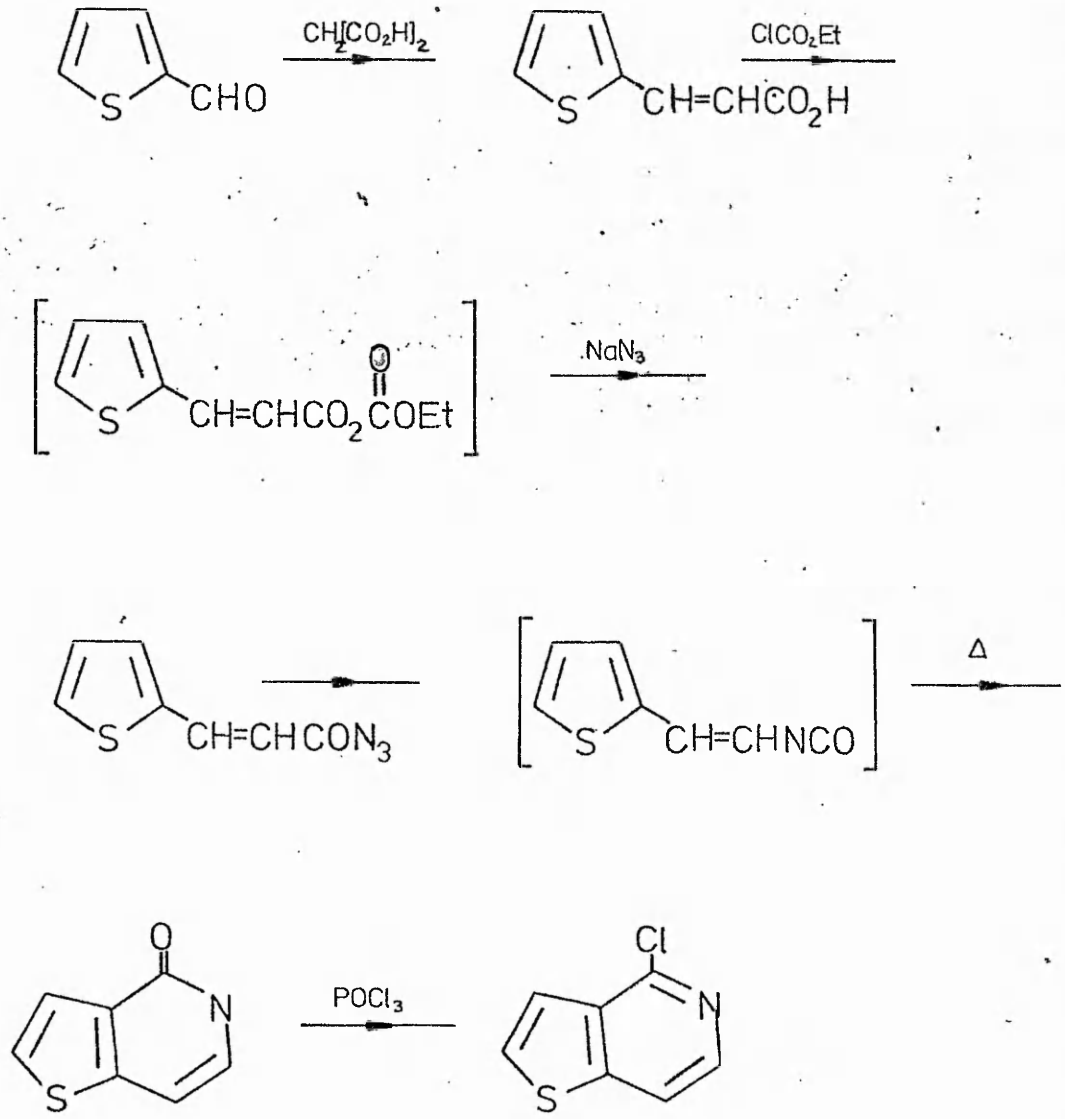
4-(3,4-Dimethoxybenzyl)thieno[3,2-c]pyridine[33] has been prepared by treatment of 4-chlorothieno[3,2-c]pyridine with veratrylnitrile and sodium hydride followed by basic hydrolysis of the intermediate nitrile and decarboxylation.[33] If two methoxy groups could be substituted in the thiophene ring of the thienopyridine a papaverine analogue could be obtained.

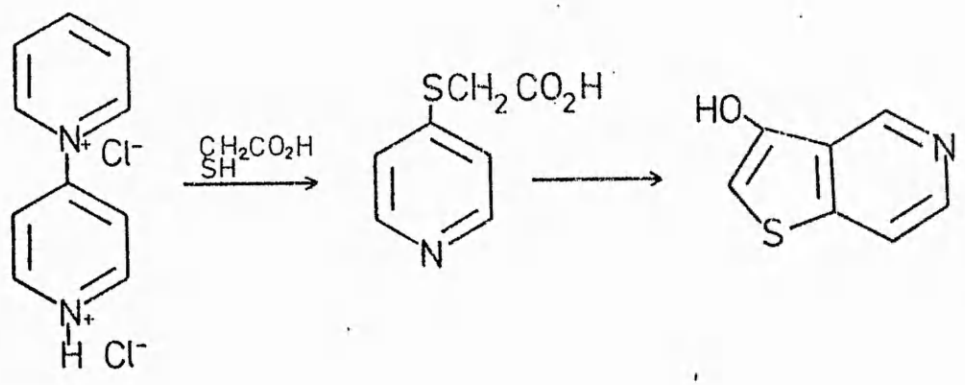
β-(2-Thienyl)acrylic acid was prepared in good yield by a Doebner modification of the Knoevenagel reaction.[34] Treatment of the acid with ethyl chloroformate in acetone followed by sodium azide gave β-(2-thienyl)acryloylazide.[35] Ring closure of the azide was achieved by heating in diphenylether at 220°;[35] however, the literature yield (70%)[35] could not be achieved. The yield obtained (23%) was so small that it made the proposed scheme impractical.

Following a report in the literature for the preparation of polychloroheterocyclic systems from 2,3,6-trichloro-4-mercaptopyridine[36] it was decided to attempt a similar reaction with a non-chlorinated mercaptopyridine.

Several attempts were made to cyclise (4-pyridylthio)acetic acid[37] (prepared from pyridyl pyridinium chloride hydrochloride by treatment with thioglycollic acid).[37]

## Scheme 7

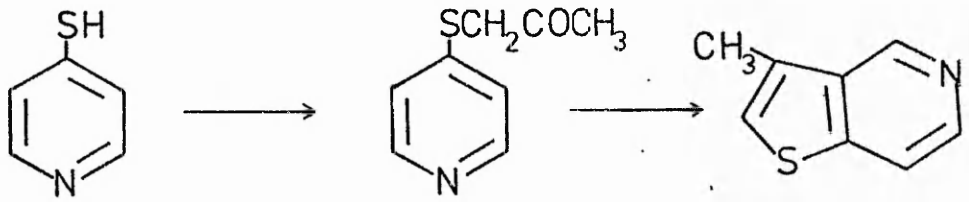

CHO
$CH_2(CO_2H)_2$
$ClCO_2Et$
$CH=CHCO_2H$
$CH=CHCO_2COEt$
$NaN_3$
$CH=CHCON_3$
$CH=CHNCO$
Δ
O
N
S
$POCl_3$
Cl



The agent employed was polyphosphoric acid; at 120° no reaction took place, most of the starting material being recovered. However, at higher temperatures (170°, 200°), although no thienopyridine was obtained, the recovery of acid was progressively poorer.

Treatment of the pyridyl acid with phosphoryl chloride in dry pyridine at room temperature resulted in polymer formation, yet the same reagent at -20° effected no appreciable change.

In an alternative approach attempts were made to cyclise 1-(4-pyridylthio)propan-2-one (13). This new compound, prepared from 4-mercaptopyridine[38] and chloroacetone, was characterised by elemental analysis and by infra red and nmr spectroscopy.



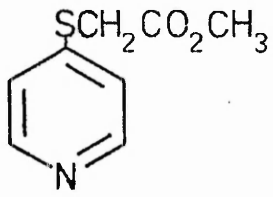
[13]

The ketone could not be cyclised under a variety of conditions, however, no reaction occurred using phosphorous pentoxide in chloroform at room temperature, or in toluene at 100°; triphenylphosphine and carbon tetrachloride in chloroform also effected no reaction; phosphoryl chloride in pyridine under reflux gave only polymer, similar results were obtained at 100° and 70° yet at room temperature

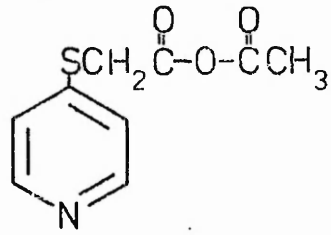
the reagent appeared to have no effect, suggesting the optimum reaction temperature must be somewhere between say 15° and 70°.

An attempt was made to prepare the above ketone from (4-pyridylthio)acetic acid and acetic anhydride. The product, however, was not the desired one. A positive hydroxamic acid test was obtained, indicating that the product was either an ester (perhaps A) or an anhydride (eg. B). Basic hydrolysis gave the starting material, which is consistent with both structures.

[A]

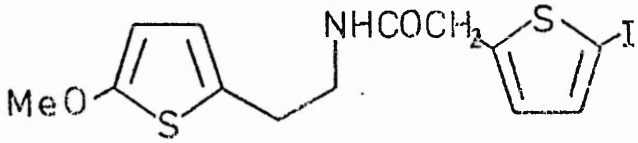


[B]

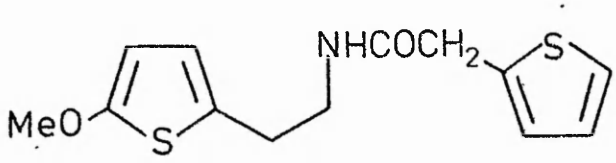


Nmr spectroscopy does not distinguish between the two alternatives, but the infra red spectrum indicated that the product could be the ester as only one band at 1700 $cm^{-1}$ was observed and not the two bands normally associated with anhydrides. The elemental analytical data, although not a perfect fit for either structure, were closest to those expected for the ester.

At this point it was decided to explore the preparation of a 1-(4-thenyl)-3,4-dihydrothienopyridine by cyclisation of the amides (14) and (15).



[14]




[15]

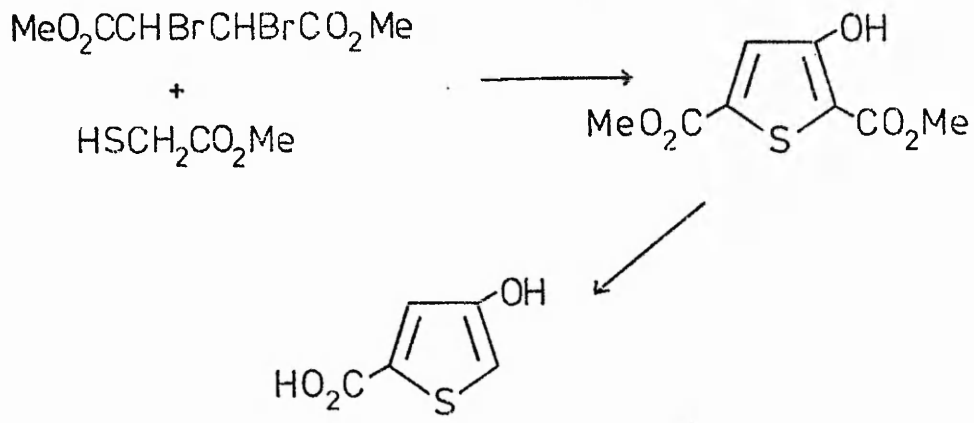
Iodination of 2-thienylacetic acid (using iodine and nitric acid) gave the new 5-iodo-2-thienyl acetic acid. Attempts to form 5-methoxy-2-thienyl acetic acid from this iodo compound(by treatment with sodium methoxide in the presence of copper oxide) however, failed, impure starting material being recovered.

Condensation of 5-iodo-2-thienyl acetic acid and β-(5-methoxy-2-thienyl)ethylamine in the presence of dicyclohexylcarbodiimide gave a product which was confirmed by spectroscopic data as being the desired N-(5-iodothienyl-2-acetyl)-2-(5-methoxy-2-thienyl)ethylamine (14); however, the product failed to give the expected elemental analysis results.

A similar condensation was carried out between 2-thienylacetic acid and β-(5-methoxy-2-thienyl)ethylamine giving the amide (15). This new amide had the expected infra red and nmr spectral features. Several attempts were made to bring about ring closure of the amide. The reagents used, phosphorus pentoxide in pyridine or triphenyl-phosphine and carbon tetrachloride in chloroform, however, failed to give any product whatsoever.

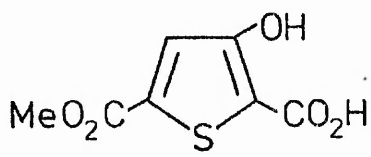
Having had very little success with the schemes just discussed it was decided to try yet another approach, this time based on 3-methoxythiophene.

The starting compound for the series of reactions envisaged was 4-methoxythiophene-2-carboxylic acid. This was obtained by the route shown in scheme 8.

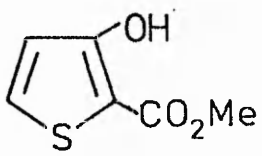



SCHEME 8

Treatment of meso dimethyl 1,2-dibromosuccinate[39] with methanolic potassium hydroxide solution and methyl thioglycollate brought about cyclisation, to give dimethyl 3-hydroxythiophene-2,5-dicarboxylate[39] together with the by-products, the half ester[39] (16) and methyl 3-hydroxythiophene-2-carboxylate[39] (17).




[16]

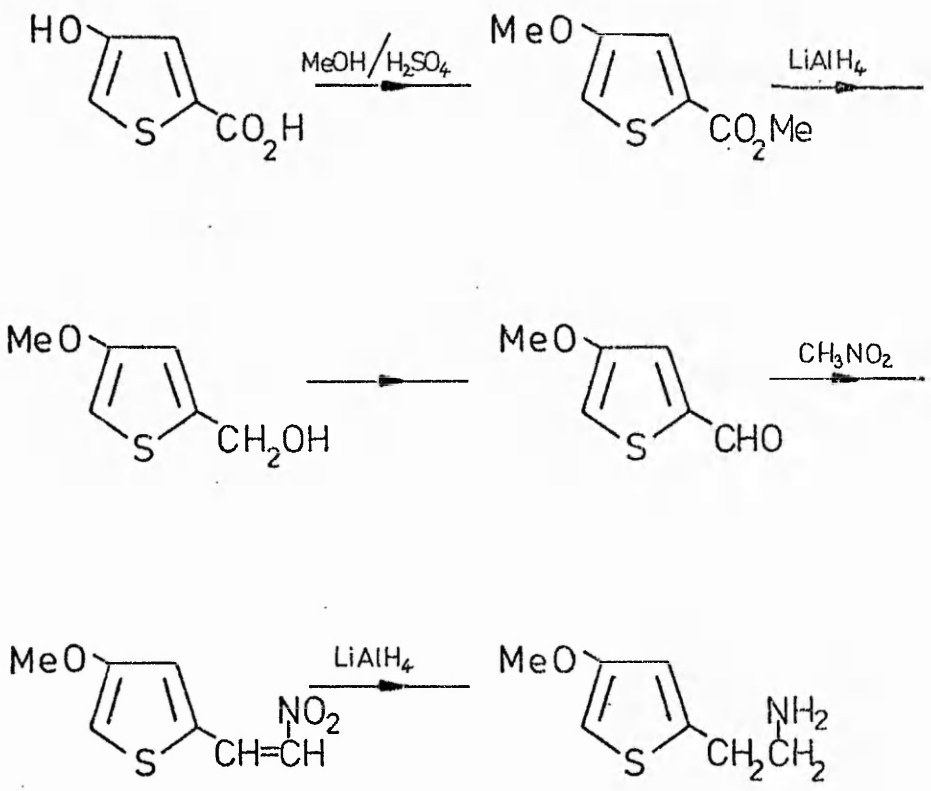



[17]

Basic hydrolysis of the diester followed by decarboxylation gave the required starting material, 4-hydroxythiophene-2-carboxylic acid, in quantitative yield.

The next series of reactions is shown in scheme 9. Following the method of Clinton and Laskowski,[40] the hydroxy acid was esterified giving methyl 4-methoxythiophene-2-carboxylate.[40,41] Generally, yields of this ester were ca 70%, the balance being accounted for by the by-products, 4-methoxythiophene-2-carboxylic acid[41] (18) and methyl 4-hydroxythiophene-2-carboxylate (19).[42]

## Scheme 9


HO
S
$CO_2H$
$MeOH/H_2SO_4$
MeO
S
$CO_2Me$
$LiAlH_4$
MeO
S
$CH_2OH$
MeO
S
CHO
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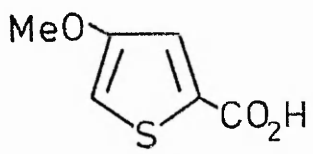
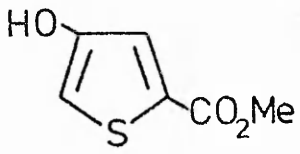
S
$NH_2$
$CH_2CH_2$




[18]




[19]

Lithium aluminium hydride reduction of the methoxy ester gave the new alcohol, 2-hydroxymethyl-4-methoxythiophene, in excellent yield. The product, however, proved to be too unstable to give a satisfactory elemental analysis, although its nmr and infra red spectra were in agreement with the postulated structure. The phenyl urethane derivative was prepared to characterise the alcohol and a satisfactory elemental analysis was obtained for this compound.

Oxidation of the alcohol proved to be a little more difficult than was anticipated. Several methods were investigated before a suitable reagent was found. Using a 1N solution of ceric ammonium nitrate[43] none of the desired aldehyde was obtained and only a small percentage of impure alcohol was recovered. Nickel peroxide[23] in benzene gave a clean reaction, but spectroscopy indicated that the product was a mixture of aldehyde and alcohol. However, even with a large excess of nickel peroxide present the reaction failed to go to completion. A similar result was obtained with Seloxcette[44] in boiling toluene. An extension of the reaction time also failed to take the reaction to completion. With silver carbonate on Celite[45] in benzene under reflux for 1 hr no reaction occurred, starting alcohol being recovered. An increase in reflux time (7 hrs) did produce some aldehyde, but starting material was still present and a further increase in time had no effect on the proportion of aldehyde produced. Pyridinium chlorochromate, prepared according to the

method of Corey and Sugges,[46] appeared to be the most suitable reagent for the oxidation. A mixture of pyridinium chlorochromate and the alcohol in dry methylene chloride when stirred at room temperature gave the aldehyde in approximately 60% yield. The crude aldehyde was contaminated with some alcohol but distillation gave pure 4-methoxythiophene-2-aldehyde as a crystalline solid. This new compound gave satisfactory analytical results and the infra red spectrum showed a stretching frequency at 1670 $cm^{-1}$ (aldehyde carbonyl). The aldehyde was characterised by the preparation of a 2,4-dinitrophenylhydrazine derivative.

5-Methoxy-2-(β-nitrovinyl) thiophene was prepared by leaving a mixture of the aldehyde, nitromethane and a catalytic amount of benzylamine in the dark for 8 days. When this method was applied to the preparation of 4-methoxy-2-(β-nitrovinyl)thiophene, the percentage conversion after 8 days was so small (10%) that the method was impractical.

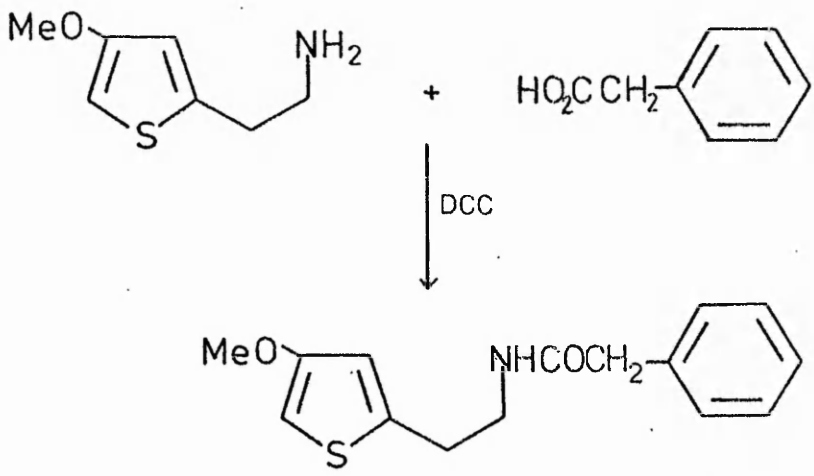
The next method[47] attempted (heating a mixture of aldehyde, nitromethane, glacial acetic acid and ammonium acetate under reflux) gave the nitrostyrene in good yield. However, the product proved to be slightly contaminated by impurities which caused problems in the next stage.

An attempt was made to prepare the nitrostyrene by warming a mixture of the aldehyde and nitromethane in aniline on a water bath;[48] no reaction occurred, however, the aldehyde being recovered unchanged.

The method finally adopted for the preparation of the nitrostyrene gave pure 4-methoxy-2-(β-nitrovinyl)thiophene in approximately 50% yield. A basic solution, made by adding a concentrated sodium hydroxide solution to the aldehyde and nitromethane in methanol, was added to dilute hydrochloric acid[49] when bright yellow crystals of the nitrostyrene were formed. This new compound gave satisfactory analytical figures and also the expected nmr and infra red spectra.

Reduction of the nitrostyrene with lithium aluminium hydride gave β-(4-methoxy-2-thienyl)ethylamine in acceptable yield (55%). The new amine was characterised as its hydrochloride since the free base was too unstable for successful elemental analysis. The infra-red and nmr spectra were consistent with the proposed structure.

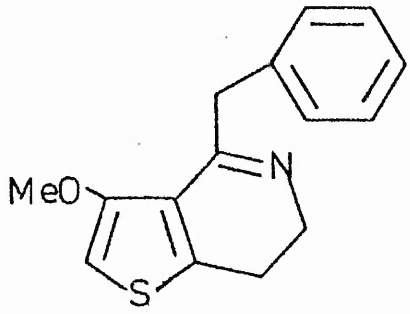
In an attempt to form a papaverine analogue β-(4-methoxy-2-thienyl)ethylamine was condensed with phenylacetic acid under the influence of dicyclohexylcarbodiimide. This new amide (20) was characterised by elemental analysis and by nmr and infra-red spectroscopy.




[20]

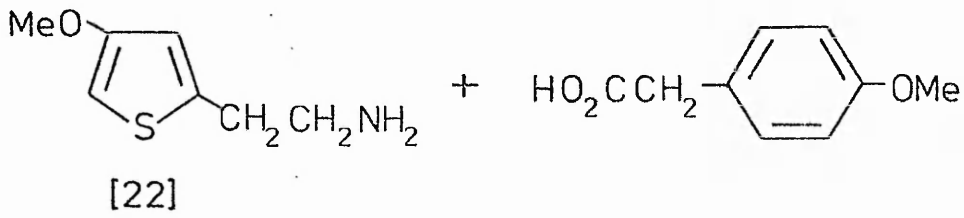
It is of interest to note that the $-CH_2CH_2-$ group in the amide appears as the expected two sets of triplets in the nmr spectrum, whereas in the amine they are not separated.

Ring closure of the amide by a Bischler-Napieralski reaction gave a substance which was indicated by spectroscopy to be the desired dihydrothienopyridine (21). Evidence for this is the disappearance from the nmr spectrum of a peak equivalent to one thiophene proton and the disappearance of the amide carbonyl from the infra-red spectrum.

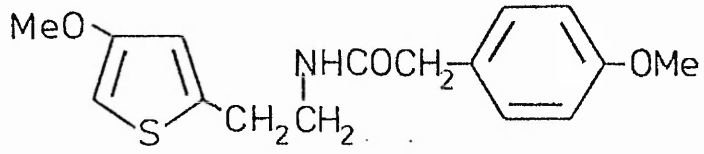



The new amine was converted into a picrate which gave a satisfactory elemental analysis.

A similar condensation was carried out between the amine (22) and 4-methoxyphenyl acetic acid. This new amide also gave satisfactory analytical figures and the nmr and infra-red spectrum were consistent with the proposed structure.

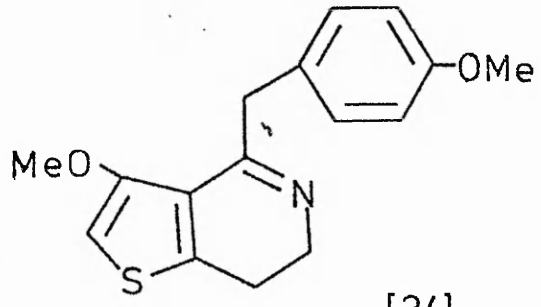



[22]




[23]

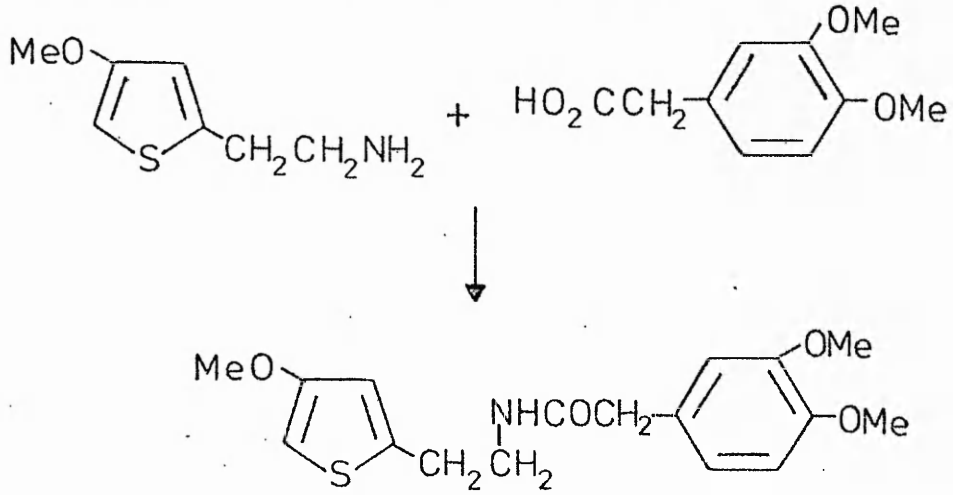
Cyclisation of this amide (23) under Bischler-Napieralski conditions gave an oil which spectroscopy indicated was the required product (24), using the same criteria as described in the previous case.




[24]

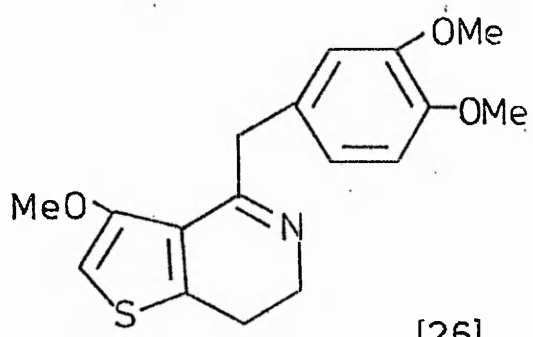
From this new base (24) a picrate and a hydrochloride were made. The analysis figures obtained for the picrate, however, indicated that the compound was impure.

In an attempt to acquire a true thiophene analogue of papaverine (lacking only one methoxy group on the thienopyridine system), β-(4-methoxy-2-thienyl)ethylamine was condensed with 3,4-dimethoxyphenylacetic acid under the influence of dicyclohexyl-carbodiimide, giving the new amide (25) for which satisfactory analytical figures and nmr and infra-red spectra were obtained.




[25]

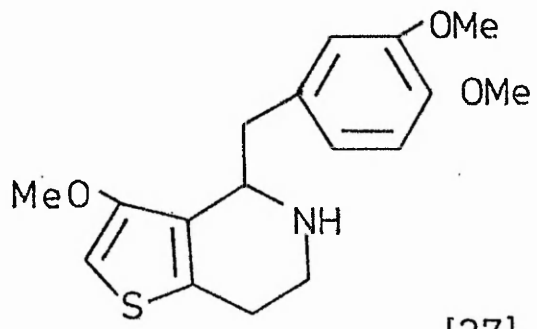
Ring closure of this amide (25), as in the two previous cases, gave a product which was identified as the new dihydrothienopyridine (26).




[26]

The base formed a picrate and a hydrochloride.

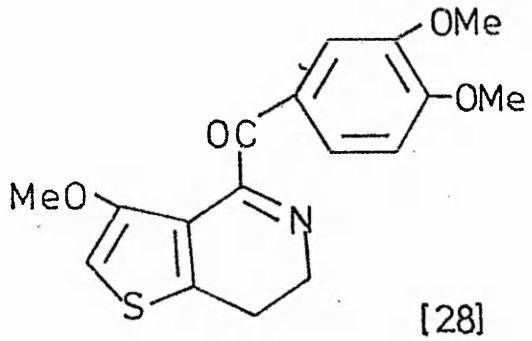
A small sample of (26) was reduced with sodium borohydride in ethanol. That the new tetrahydrothienopyridine (27) had been obtained was indicated by the disappearance of the C=N- stretching frequency at 1610 $cm^{-1}$ from the infra-red spectrum. A picrate was made to characterise this new amine.




[27]

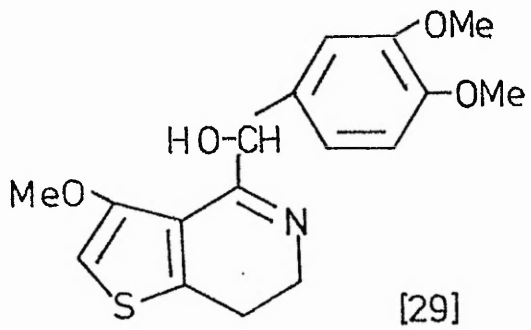
In an attempt to form the fully aromatic 3-methoxy-4-(3',4'-dimethoxybenzyl)thieno[3,2-c]pyridine, the dihydrothienopyridine

(26) was treated with activated manganese dioxide in dry benzene under reflux. The product obtained, however, was not the desired one. Although no conclusive evidence could be gathered from the nmr spectrum, it would appear that the product was 3-methoxy-4-(3',4'-dimethoxybenzoyl)-6,7-dihydrothieno[3,2-c]pyridine (28).




[28]

In order to establish this identity, a small sample of (28) was reduced with boron trifluoride-ether complex and sodium borohydride. Although pure product could not be isolated from the reaction, ir spectroscopy showed the presence of the alcohol group. The product was, therefore, suspected to be 3-methoxy-4-(3',4'-dimethoxyphenyl-carbinyl)-6,7-dihydrothieno[3,2-c]pyridine (29).

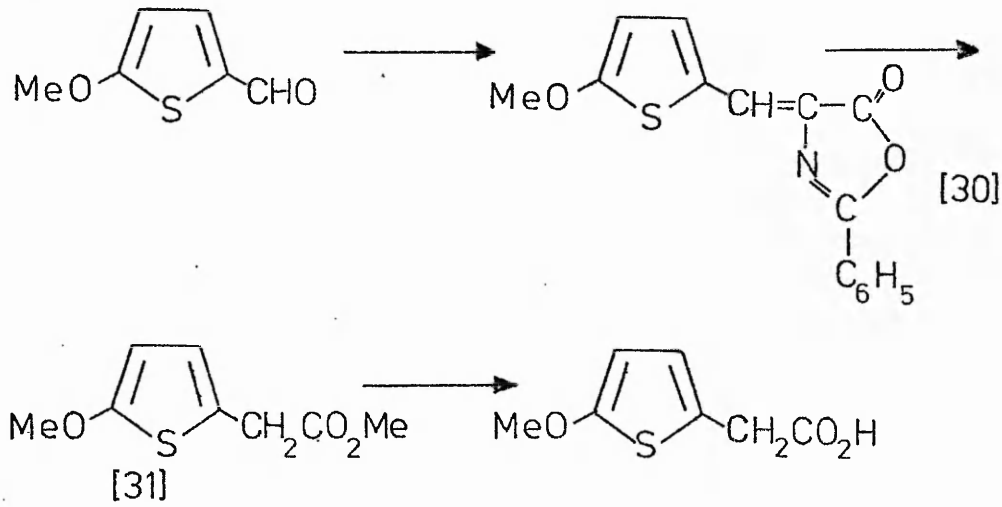



[29]

The following discussion describes attempts to prepare a methoxythienylacetic acid. Of the available methoxylated thiophenes only 2-methoxy- and 3,4-dimethoxythiophenes are considered as they were the most appropriate conveniently accessible starting materials.

The standard method for the preparation of phenylacetic acids is by hydrolysis[50] of the azlactone formed from the corresponding aldehyde and hippuric acid. This method was applied to 5-methoxythiophene-2-aldehyde in an attempt to prepare a methoxythienyl acetic acid.

2-Phenyl-4-(5-methoxy-2-thenylidene)oxazol-5-one (30) was prepared from 5-methoxythiophene-2-aldehyde according to Erlenmeyer's azlactone synthesis[50] (scheme 10). This new azlactone gave satisfactory analytical results and the nmr and infra red spectra were consistent with the proposed structure.



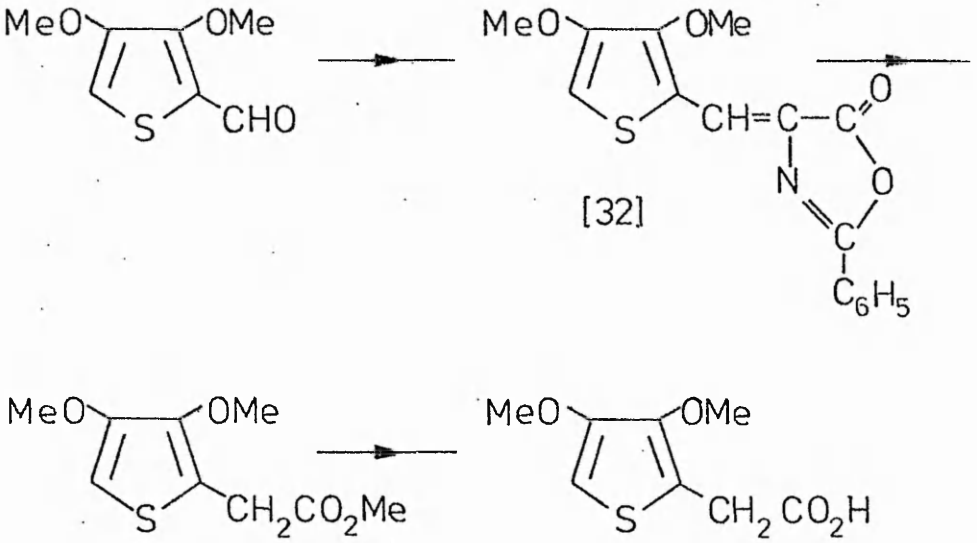

Scheme 10

Basic hydrolysis of the azlactone, followed by methylation, gave a mixture of methyl benzoate and the required methyl 5-methoxy-2-thienylacetate (31), although the yield was very poor. The expected nmr and infra red spectra were obtained for this compound.

Hydrolysis of the ester (31) gave a very small amount of solid which appeared to be the desired 5-methoxy-2-thienylacetic acid ($\nu_{max}$ (KBr) -OH 3000-2600 $cm^{-1}$; -C=O 1680 $cm^{-1}$).

The overall yield (5%) of the acid was so poor, however, that an alternative method of preparation had to be found.

The process was then repeated, using 3,4-dimethoxythiophene-2-aldehyde. 2-Phenyl-4-(3,4-dimethoxy-2-thenylidene)oxazol-5-one (32) was prepared in excellent yield by Erlenmeyer's azlactone synthesis. This new azlactone was characterised by analysis and by infra red and nmr spectroscopy (scheme 11).

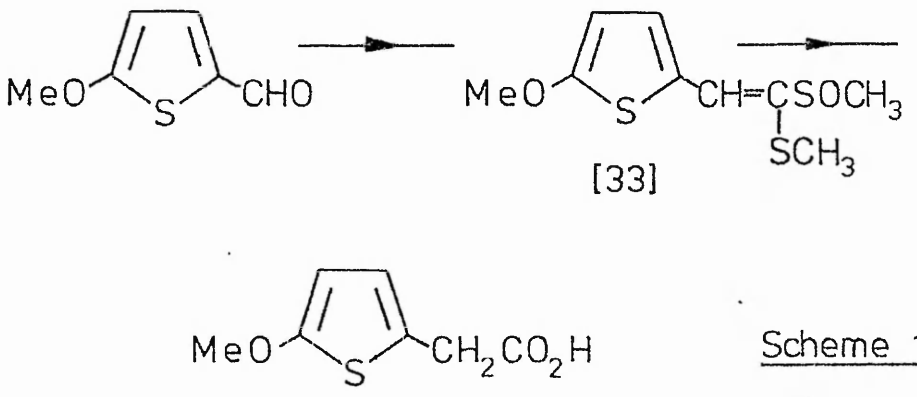



Scheme 11

Basic hydrolysis of this azlactone, followed by esterification, gave a small amount of methyl benzoate together with a black polymeric material which suggests that the conditions were too vigorous for the methyl 3,4-dimethoxy-2-thienylacetate to survive.

A recent paper[51] describes the preparation of phenylacetic acid derivatives by acid-catalysed degradation of the condensation product formed between the appropriate aldehyde and methyl methylthiomethyl sulphoxide.

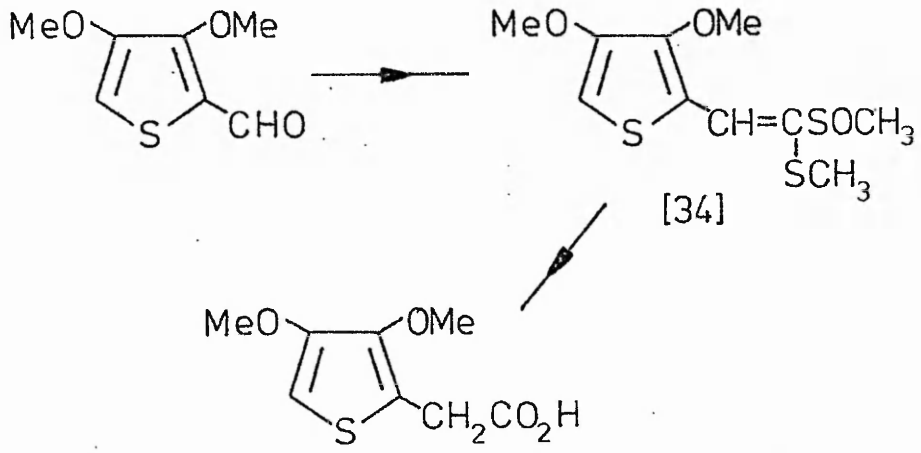
In applying this method to the methoxythiophenes, 5-methoxythiophene-2-aldehyde was condensed with methyl methylthiomethyl sulphoxide (scheme 12) to give the intermediate 1-methylsulphinyl-1-methylthio-2-(5-methoxy-2-thienyl)ethylene (33). The product was purified by column chromatography as an attempt at distillation had resulted in decomposition as evidenced by the formation of an obnoxious smell. On purification, a substantial proportion of aldehyde (50%) was recovered, indicating that the reaction had not gone to completion, and this was also found to be the case when an excess of the reagent was used. The new condensation product gave satisfactory analytical figures and nmr and infra red spectra.




Scheme 12

Because the percentage conversion was small it was decided to attempt yet another method for the preparation of this acid.

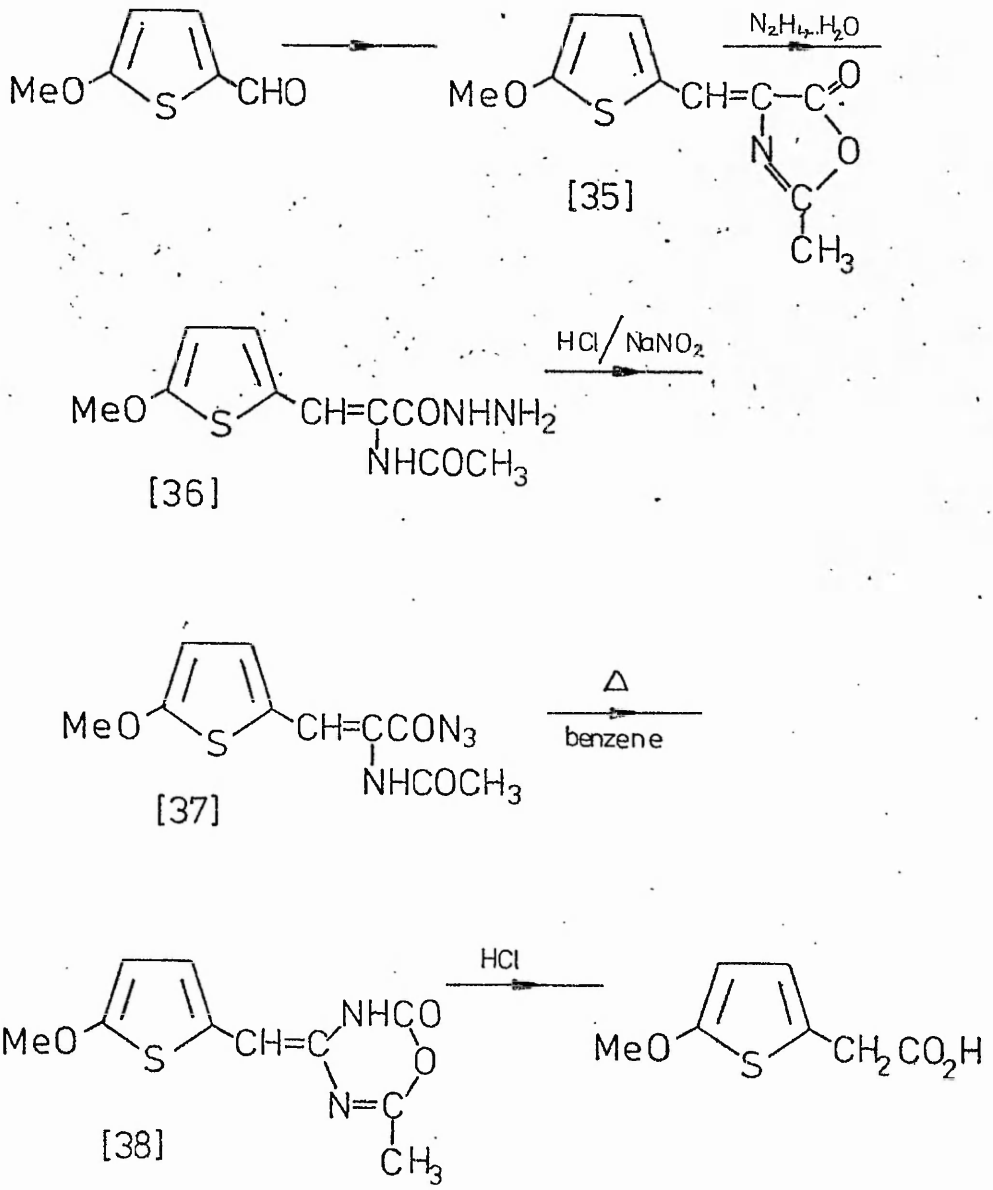
The reaction was repeated using 3,4-dimethoxythiophene-2-aldehyde. The product, 1-methylsulphinyl-1-methylthio-2-(3,4-dimethoxy-2-thienyl)ethylene (34), obtained in a better yield than in the previous example, was purified by column chromatography. Satisfactory analytical figures, together with the required nmr and infra-red spectra were obtained for this product.




In an attempt to prepare 3,4-dimethoxythienyl-2-acetic acid the condensation product (34) in 1,2-dimethoxyethane was treated with hydrochloric acid. However, the reaction conditions proved to be too severe as only polymeric material was produced.

The next method followed was that reported by Jennings[52] for the preparation of m-nitrophenylacetic acid. Scheme 13 shows the stages involved for the preparation of 5-methoxy-2-thienylacetic acid.

## Scheme 13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CHO
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CH=C
C
O
N
O
C
$CH_3$
[35]
$HCl/NaNO_2$
$CH=CCONHNH_2$
$NHCOCH_3$
[36]
$CH=CCON_3$
$NHCOCH_3$
[37]
Δ
benzene
HCl
NHCO
N=C
$CH_2CO_2H$
[38]

2-Methyl-4-(5-methoxy-2-thenylidene)oxazol-5-one (35) was prepared in reasonable yield from 5-methoxythiophene-2-aldehyde and aceturic acid in the presence of sodium acetate and acetic anhydride. Satisfactory analytical figures and nmr and infra-red spectra were obtained for this new azlactone.

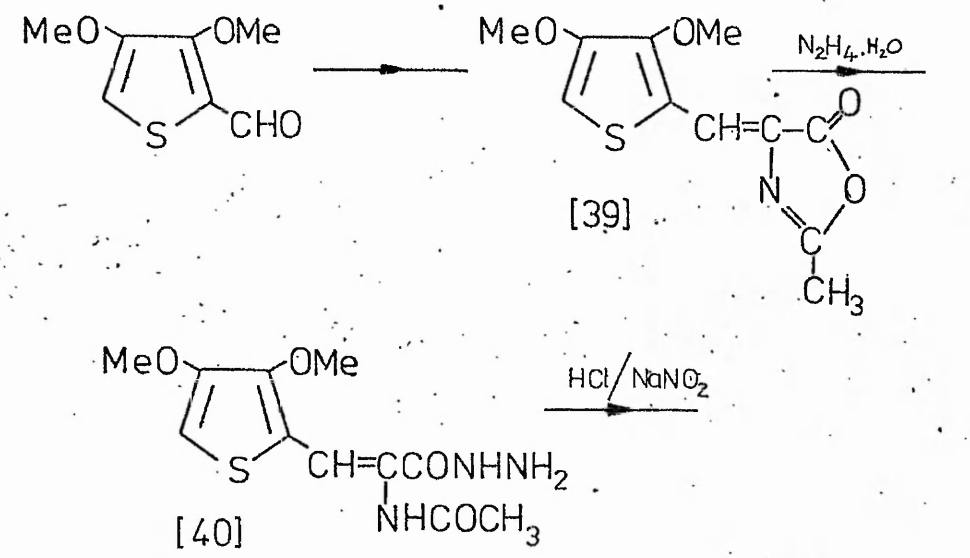
Addition of the azlactone (35) to hydrazine hydrate gave the new hydrazide (36) which was converted into the azide (37) by treatment with hydrochloric acid and sodium nitrite; decomposition and rearrangement of the azide to the oxadiazine (38) was brought about by heating in benzene; acid hydrolysis of the oxadiazine gave a solid which was spectroscopically identical with the acid obtained from the azlactone (Scheme 10). All new compounds, where possible, were characterised by analysis and by nmr and infra red spectroscopy.

The reaction sequence was then repeated using 3,4-dimethoxythiophene-2-aldehyde (scheme 14).

The azlactone (39) was formed in reasonable yield, the preparation of the hydrazide (40), the azide (41) and the oxadiazine (42) all proceeded in good yield. Satisfactory analytical figures were obtained, where possible, for the new compounds, together with the required nmr and infra-red spectra.

Acid hydrolysis of the oxadiazine gave an oil which, although possessing the characteristic features of a carboxylic acid in the infra-red spectrum, was too impure to give a satisfactory nmr spectrum.

## Scheme 14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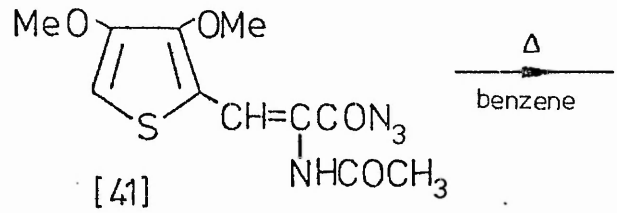
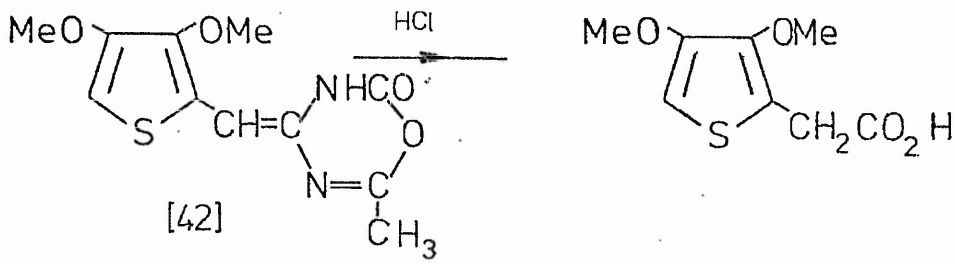
OMe
S
CHO
$N_2H_4.H_2O$
CH=C–C
O
N
O
C
$CH_3$
[39]
HCl/NaNO₂
CH=CCONHNH₂
NHCOCH₃
[40]


MeO
OMe
S
CH=CCON₃
NHCOCH₃
[41]
Δ
benzene


MeO
OMe
S
CH=C
NHCO
O
N=C
$CH_3$
[42]
HCl
$CH_2CO_2H$

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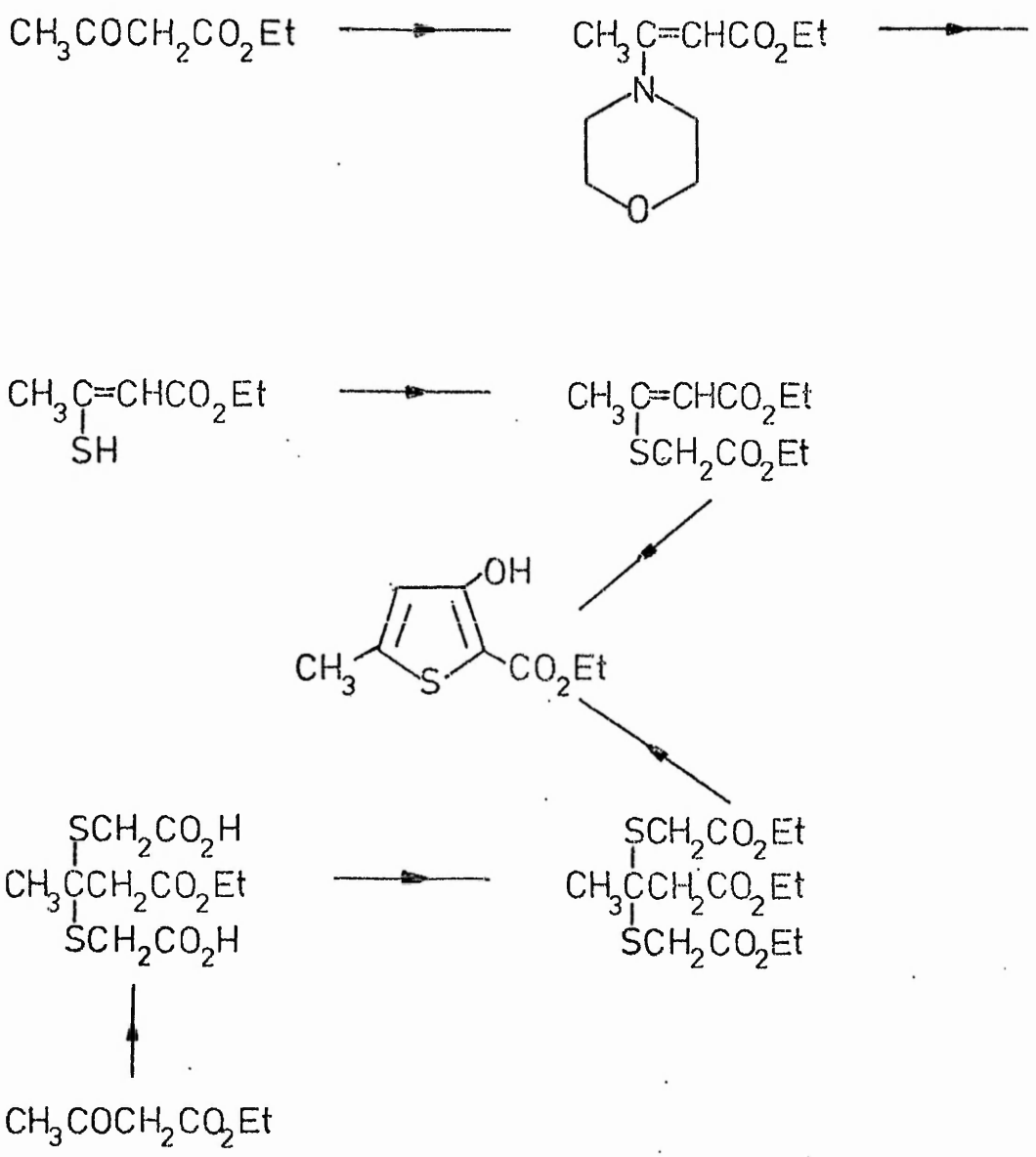
# CHAPTER THREE

# E X P E R I M E N T A L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CH3C=CHCO2Et
N
O
CH3C=CHCO2Et
SH
CH3C=CHCO2Et
SCH2CO2Et
OH
CH3
S
CO2Et
SCH2CO2H
CH3CCH2CO2Et
SCH2CO2H
SCH2CO2Et
CH3CCH2CO2Et
SCH2CO2Et
CH3COCH2CO2Et

Ethyl β-morpholinocrotonate

a)[1] A mixture of ethylacetoacetate (51.1 g), morpholine (40 ml), formic acid (1 ml) and benzene (250 ml) was heated under reflux using a Dean and Stark apparatus. The solvent was removed under reduced pressure and the residue was distilled giving the product as a pale yellow liquid (68 g, 87%), which solidified on standing, b.p. 125-130°/0.5 mm(lit[1] 120-125°/0.5 mm).

b) The desired product could also be obtained by mixing equimolar quantities of ethyl acetoacetate and morpholine and leaving to stand at room temperature overnight. The water was removed by azeotroping with benzene. Removal of the solvent and distillation of the residue gave the desired product in quantitative yield.

Ethyl thioacetoacetate

Two preparations were used for this compound:-

a)[2a] A solution of ethyl β-morpholinocrotonate (19.9 g) and thioacetic acid (9.5 g) in benzene (50 ml) was heated under reflux for 3 hr. Immediate distillation, under nitrogen, after removal of the benzene gave two fractions:-

1. pink oil b.p. 82-89°/15 mm
2. colourless oil b.p. 122°/15 mm.

The first fraction was the desired product (75% yield) (lit[2] 72.5-74.5°/12 mm), and the second was identified as N-acetyl morpholine.

b)[2b] A solution of ethyl acetoacetate (57.6 g) in ethanol (300 ml) was cooled to -20°. Hydrogen sulphide gas was passed through the solution for 30 min. followed by dry hydrogen chloride gas for 45 min. The pink reaction mixture was poured into ice-water and extracted with benzene. The extract was washed with 10% sodium carbonate solution

and water, dried ($MgSO_4$) and concentrated. The product was obtained by distillation (21 g, 33%) b.p. 76-76°/16 mm (lit[2] 72.5-74.5°/12 mm).

Ethyl β-carbethoxymethyl thiocrotonate

Several attempts were made to synthesise this compound before a reliable method was found.

a) The sodium salt of ethyl thioacetoacetate was generated using sodium hydride in benzene at 0°. This was treated with ethyl chloroacetate and the solution was refluxed for periods varying from 1-3½ hrs. The aqueous layer was acidified and extracted with ether. In all cases an intractable mixture was obtained.

b) The sodium salt of ethyl thioacetoacetate was prepared using sodium metal in absolute ethanol. Addition of ethyl chloroacetate produced a precipitate of sodium chloride. Filtration, followed by removal of the solvent gave an oil which n.m.r. confirmed as being the desired product. However, the yield was very low.

c)[3] Powdered sodium (1 g) was suspended in dry benzene (20 ml) and kept at 0° whilst a solution of ethyl thioacetoacetate (5 g) in dry benzene (10 ml) was added slowly. Effervescence was observed, the solution becoming pink and cloudy. After addition was complete the mixture was kept at room temperature for 8 hr. Ethyl chloroacetate (4.2 g) was added and the mixture was heated under reflux for 6 hr. after which it was poured into water. The benzene layer was separated, dried ($MgSO_4$) and concentrated. Distillation of the residue yielded the required compound (4.8 g, 60%) b.p. 172-178°/12 mm (lit[3] 116°/9 mm).

Ethyl 3-hydroxy-5-methyl thiophene-2-carboxylate

(Procedure of ref. 3)

Ethyl β-carbethoxymethyl thiocrotonate (6.5 g) was dissolved in dry benzene (15 ml) containing a few drops of ethanol. A small portion

was added to powdered sodium (0.63 g) suspended in dry benzene (20 ml) at room temperature. After the initial reaction had subsided the mixture was cooled to $0^{o}$ and the remainder of the solution was added. The mixture was kept at $0^{o}$ for 8 hr. and left standing overnight in ice-water, during which time a gel had formed. This was dissolved in water and the solution acidified. The oil which separated was taken up in benzene, the extracts were dried ($MgSO_4$) and the solvent was removed, leaving 2 g of a brown oil. Bulb distillation of part of this product gave a yellow oil which darkened on standing. This was identified as ethyl 3-hydroxy-5-methyl thiophene-2-carboxylate by comparison of its nmr spectrum with that of authentic material.

$\tau$ ($CDCl_3$):

3.6 (s thiophene H) 5.7 (q-$\underline{CH_2}$-$CH_3$ J = 7 Hz)

7.59 (s-$CH_3$) 8.65 (t-$CH_2$-$\underline{CH_3}$ J = 7 Hz)

0.4 (broad -OH)

$\nu$(max) (thin-film):

3250 $cm^{-1}$ (OH) 1650 $cm^{-1}$ (=C = O)

Ethyl β,β-bis(carboxymethymercapto)butyrate[4]

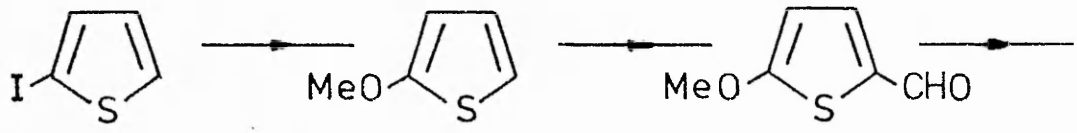
Dry hydrogen chloride gas was passed slowly through a mixture of ethyl acetoacetate (13 g) and thioglycollic acid (18.4 g). After 5 mins heat was evolved and the solution became viscous. The passage of gas was continued until the vessel had cooled (approx. 25 min). The viscous oil was poured into water, when two layers were formed, and extracted into ether; the extracts were dried and evaporated giving the desired product, 24 g (87%). This was used without further purification in the next stage of the synthesis.

Ethyl β,β-bis(ethoxycarbonylmethylmercapto)butyrate[5]

The above product (24 g) in absolute ethanol (30 ml) was treated with dry hydrogen chloride gas until a cloudiness appeared. The solution was left to stand until it had settled into two layers. After removal of the lower layer the remaining liquid was treated with water and again left to settle, any ester separating out being combined with the first. Distillation gave the pure ester as a yellow oil, b.p. 174°/0.05 mm (lit[5] 178°/0.1 mm), yield 20 g (60%).

Ethyl 3-hydroxy-5-methylthiophene-2-carboxylate[5]

The above ester (10 g) in ethanol (10 ml) was added to 2N ethanolic potassium hydroxide solution (50 ml), there being an immediate colour change to golden yellow. The mixture was left at room temperature for 1 hr, then diluted with ice-water and acidified with dilute hydrochloric acid, cooling as necessary. The yellow oil produced was isolated with benzene and was purified by distillation, b.p. 76°/0.1 mm (lit[5] 71°/0.2 mm), yield 3.3 g (69%).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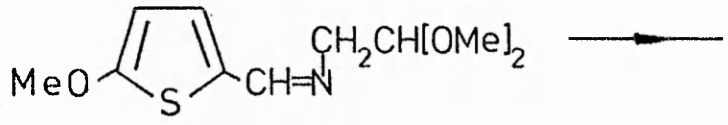
S
MeO
S
CHO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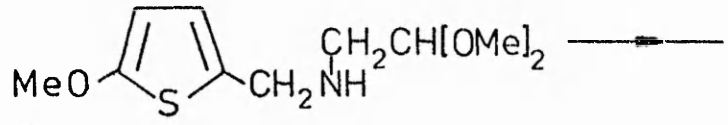
CH=N
CH2CH[OMe]2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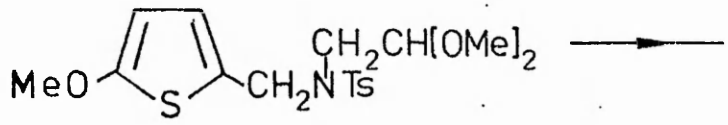
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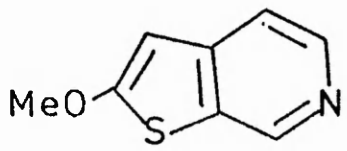

MeO
S
N

2-Iodothiophene[6]

This was prepared by the method of ref. 6, in 60% yield, as a dark red liquid, b.p. 69-71°/18 mm; 10% of 2,5-diiodothiophene m.p. 40-42° (lit[6] b.p. 67-70°/0.05 mm) was simultaneously produced.

2-Methoxythiophene[7]

This was obtained, in 66% yield, as a colourless liquid, b.p. 46-48°/15 mm (lit[7] 74-75°/50 mm) by a literature method.[7]

5-Methoxythiophene-2-carboxaldehyde[7]

Phosphorous oxychloride (40 ml) was added dropwise to ice cold DMF (34 ml) (T < 10°) with stirring. When the addition was complete the mixture was stirred for 15 min (T < 10°). Methylene chloride (50 ml) was added and the whole mixture was stirred at room temperature for 30 min, after which it was cooled again. A solution of 2-methoxythiophene (45.6 g) in methylene chloride (50 ml) was added dropwise (T < 6°). Stirring was continued for 1½ hr at T = 0-5°, then for 2 hr at room temperature, after which the mixture was left in the dark overnight. Ice-cold sodium hydroxide solution (4M, 500 ml) was added, then the aqueous layer was separated and extracted with methylene chloride. All extracts were combined, washed with water, hydrochloric acid (4M), and brine, dried ($MgSO_4$) and concentrated. Distillation yielded the aldehyde as a pale yellow liquid, 41 g (75%), b.p. 128°/14 mm (lit[7] 79-81°/0.9 mm).

5-Methoxy-2-thenylidene aminoacetaldehyde dimethyl acetal

5-Methoxythiophene-2-carboxaldehyde (41 g) was mixed with aminoacetaldehyde dimethylacetal (34 g, 15% excess) and heated on a steam bath for 3 hrs. Distillation of the resulting oil gave the desired amino acetal (38 g, 58%) as a yellow liquid, b.p. 156-158°/2 mm.

(Found: C, 51.8; H, 6.49; N, 5.65;

$C_{10}H_{15}NO_3S$ requires C, 52.40; H, 6.55; N, 6.11%)

$\tau$ ($CCl_4$):

1.8 (s -CH=N-), 3.03, 3.85 (2d 2 thiophene H J = 4 Hz)

5.45 (t $-CH_2-\underline{CH}<$ J = 5 Hz), 6.05 (s Ar-OMe) 6.4 (d $-\underline{CH_2}-CH<$ J = 5Hz),

6.65 (s $-CH(OMe)_2$ )

$\nu$(max) (thin film):

1640 $cm^{-1}$ (-C=N-)

5-Methoxy thenylaminoacetaldehyde dimethyl acetal

5-Methoxythenylideneaminoacetaldehyde dimethyl acetal (38.4 g) was dissolved in ethanol (60 ml) and finely powdered sodium borohydride (6 g) was added in one portion. The mixture was left to stand at room temperature for 2 hr, then the solvent was removed. The semi-solid residue was treated with water and extracted with methylene chloride. The extract was dried ($MgSO_4$), concentrated and distilled under reduced pressure, 5-methoxythenylaminoacetaldehyde dimethyl acetal being obtained as a yellow liquid (32 g, 84%), b.p. 124°/0.2 mm.

This compound proved to be too unstable to give a reliable analysis.

$\tau$ ($CCl_4$) :

3.5, 3.9 (2d 2 thiophene H J = 4Hz)

6.1 (m -CH-, $-CH_2$, -OMe).

2-(5-Methoxythenyl)-N-tosylaminoacetaldehyde dimethyl acetal

5-Methoxy-2-thenylaminoacetaldehyde dimethyl acetal (10 g) was dissolved in dry (KOH) pyridine (20 ml) and p-toluenesulphonyl chloride (6.67 g) in dry pyridine (20 ml) was added. This mixture was stirred at room temperature for 24 hr, after which it was poured into water (100 ml) and extracted with ether (3 x 50 ml). The combined extracts were washed with hydrochloric acid (< 1M, 2 x 50 ml),

and water (2 x 50 ml), dried ($MgSO_4$) and the solvent was removed. The residue was left to crystallise, giving pink crystals of the desired product (9.9 g 78%), m.p. 56-57°.

(Found: C, 52.71; H, 6.29; N, 3.43; $C_{17}H_{23}NO_5S$ requires C, 52.98; H, 5.97; N, 3.63%)

τ ($CDCl_3$):

2.2, 2.65 (2d 4 benzene H J = 9Hz)

3.4, 4.0 (2d 2 thiophene H J = 4Hz), 5.4 (s Ar-CH-N<),

5.5 (t $-CH_2-CH<$ J = 5Hz), 6.15 (Ar-OMe), 6.6 (s $-CH(OMe)_2$)

6.7 (d $>N-CH_2-CH<$ J = 5Hz), 7.55 (s Ar-Me).

Attempts to prepare 2-methoxythieno[2,3-c] pyridine

1. By cyclisation of 5-methoxythenylideneaminoacetaldehyde dimethyl acetal

a) 5-Methoxythenylideneaminoacetaldehyde dimethyl acetal (2 g) was added, with stirring, to polyphosphoric acid at 60° C and the mixture was kept at that temperature for 20 mins, after which it was poured onto ice. Basification, followed by extraction with ether and removal of solvent gave a dark coloured oil. Purification (distillation) gave a yellow oil which was identified by nmr as 5-methoxythiophene-2-carboxaldehyde, by comparison with an authentic sample.

b) The Schiff's base (2 g) was stirred in ether at 0° whilst boron trifluoride-ether complex (2 ml) was added in 0.2 ml portions, the reaction being followed by t.l.c. (EtOAc/silica). A red oil separated out. When no starting material was present in the ether the solvent was decanted, the oil was treated with 2M sodium hydroxide solution and extracted with chloroform. Removal of the solvent gave an oil which nmr and ir spectroscopy confirmed to be 5-methoxythiophene-2-carboxaldehyde.

c) The Schiff's base (0.5 g) in toluene (10 ml) was treated with triphenylphosphine (1.64 g) and carbon tetrachloride (0.8 g) and the mixture was heated under reflux for 2 hr. After removal of the solvent the dark oil was treated with acid and extracted with ethyl acetate, the extracts being discarded. The acid solution was basified and re-extracted with methylene chloride. The combined extracts were dried ($MgSO_4$) and concentrated to give an oil, which proved to be a mixture. This was purified by column chromatography (silica/EtOAc) giving a brown solid m.pt 153-154°, identified as triphenylphosphine oxide (lit[8] m.p. 156°). No other product could be isolated.

2. By cyclisation of 2-(5-methoxythenyl )N-tosylaminoacetaldehyde dimethyl acetal

The tosylate (2 g) in dioxan (48 ml) under dry nitrogen in the dark, was treated with hydrochloric acid (6M, 3.7 ml). The reaction was followed by t.l.c. (EtOAc/silica); after 6½ hr under reflux a new spot had appeared. The mixture was poured into water, washed with ether and the aqueous layer was basified and re-extracted with ether. Removal of solvent gave a solid which was a mixture (t.l.c.). The ir spectrum suggested that the product was an aldehyde or ketone (peak at 1680 $cm^{-1}$) and the nmr spectrum contained no peak in the aldehyde region but confirmed that the tosyl group was present.

The process was repeated, the mixture being heated under reflux for 24 hr though the reaction had still not gone to completion. Work up as above gave a solid; the same compound was obtained from both the acid and basic extracts. The ir and nmr spectra suggested that the compound may have been N-tosyl-6,7-dihydro-thieno[2,3-c] pyridine-2[3H]-one.

$\tau$ ($CDCl_3$):

2.6 (m 4 benzene H, thiophene H), 3.8 (d thiophene H J = 5Hz)

6.3 (m $-CH_2-$)

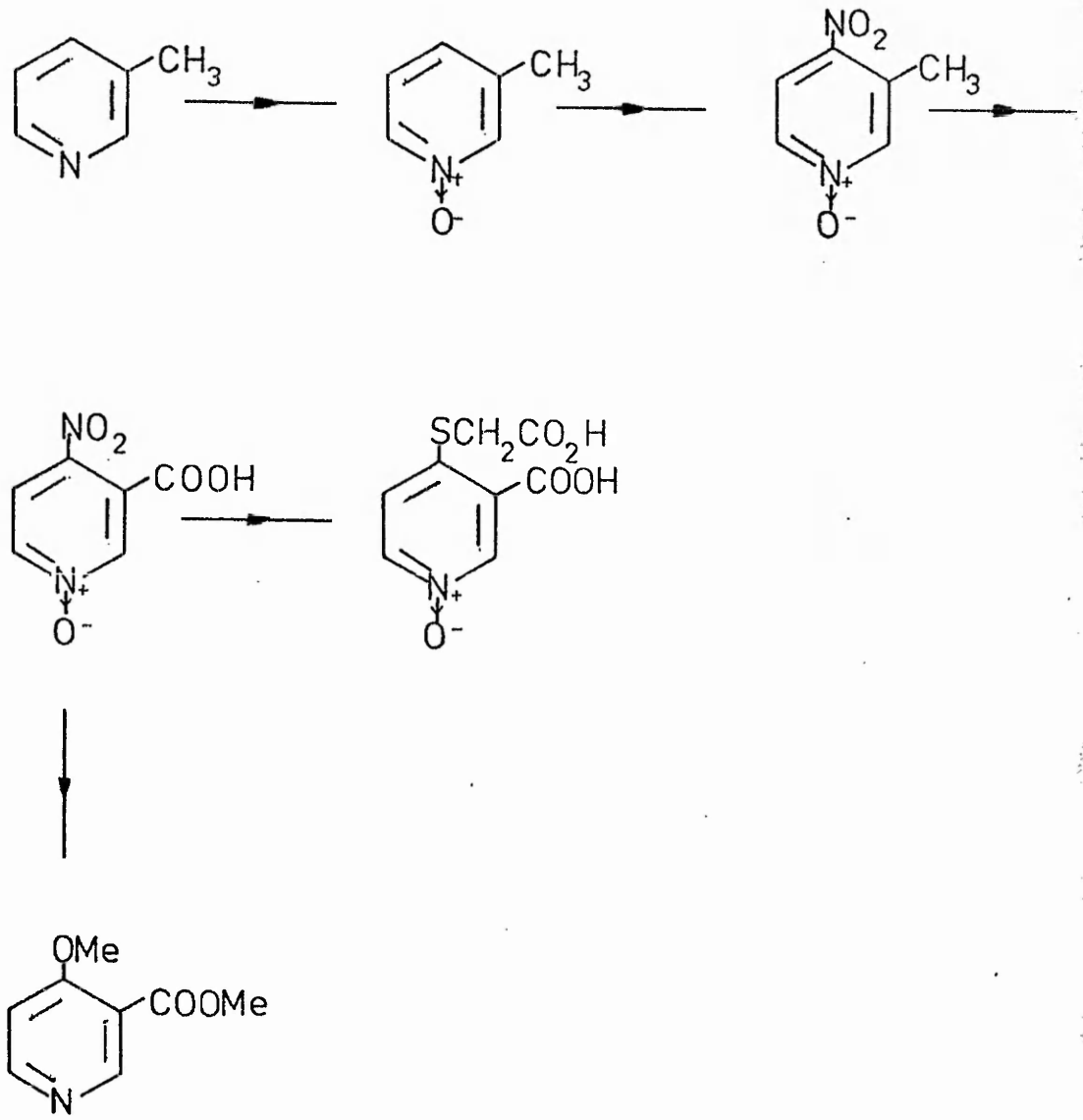
7.5 (s $Ar-CH_3$)

$\nu_{max}$ (KBr disc):

3400 $cm^{-1}$ (OH) 1640 $cm^{-1}$ (-C=O)

1600 $cm^{-1}$, 1500 $cm^{-1}$ (aromatic -CH)

In a further approach an attempt was made to purify the product via a salt. Reaction of the tosylate (2 g) with hydrochloric acid in dioxan as above (reflux time 30 min) gave 1 g of crude product which was boiled under reflux for 30 min with 10 ml of a solution of potassium t-butoxide in t-butanol (from 0.46 g of potassium). The solvent was removed under reduced pressure and the residue was stirred several times with ether. Removal of the ether left an oil which was shown by t.l.c. (MeOH + 1% $NH_4OH$/silica) to be a mixture and which gave no picrate of the desired material.


CH3
N
CH3
N+
O-
NO2
CH3
N+
O-
NO2
COOH
N+
O-
SCH2CO2H
COOH
N+
O-
OMe
COOMe
N

3-Picoline-1-oxide[9]

This was prepared by the method of ref. 9 in 70% yield as a colourless oil b.p. 111-115°/0.5 mm which solidified on standing m.p. 33-36° (lit[9] m.p. 33-36°).

4-Nitro-3-picoline-1-oxide[10]

This was prepared by a literature method[10] in 70% yield, as yellow crystals m.p. 138-139° (lit[10] 136-138°).

4-Nitronicotinic acid-1-oxide

Method 1[11]

4-Nitro-3-picoline-1-oxide (50 g) was added to concentrated sulphuric acid (385 ml) (T = 20-25°), then sodium dichromate (96.5 g) was added over a period of 1½ hr (T = 30°). The reaction was left at room temperature for 2½ hr and then the dark green viscous mixture was poured onto crushed ice and the volume made up to 1 litre with ice-water. The mixture was kept at 5° for 6 hr, the solid was filtered off, washed with ice-water and dried in vacuo over calcium chloride.

Although this reaction proceeded well on a small scale (5 g of starting material), on scaling up it proved very difficult to control the temperature and low yields of product resulted.

Method 2[12]

A solution of 4-nitro-3-picoline-1-oxide (7.5 g) in concentrated sulphuric acid (60 ml) was oxidised by sodium dichromate (27 g) at 45-55°. After 4 hrs the viscous mixture was poured onto ice, the product was filtered off and washed with ice-cold water.

This method gave a product contaminated with inorganic salts. Attempts to recrystallise failed to give a pure product. Yields were low.

Method 3[13]

4-Nitro-3-picoline-1-oxide (10 g) was added slowly to concentrated sulphuric acid (35 ml) with stirring and ice cooling. The resulting solution was added dropwise to a solution of sodium dichromate (24 g) in concentrated sulphuric acid (35 ml) which had been cooled to $0^{\circ}$. During the addition the temperature was maintained at $20-30^{\circ}$. When addition was complete (ca. 1.5 hr) the mixture was kept at room temperature for $\frac{1}{2}$ hr then at $45-55^{\circ}$ for 5 hr; alternate warming and cooling were necessary. After re-cooling to room temperature the reaction mixture was poured onto ice and left in a cold room overnight. The precipitate was filtered off, washed with ice-water and dried in vacuo over concentrated sulphuric acid. The crude product was purified by reprecipitation by dilute hydrochloric acid from a solution in dilute ammonium hydroxide. The purified material (9 g 75%) had m.p. $172^{\circ}$ (dec.) (lit[13] $172^{\circ}$(dec.)).

Attempts to prepare S-(1-oxy-3-carboxy-4-pyridyl) thioglycollic acid

a) To 4-nitronicotinic acid-1-oxide (1.47 g) in 50% ethanol (250 ml) was added thioglycollic acid (1.5 g). The pH of the solution was adjusted to 7 by the addition of 10% sodium hydroxide solution and the mixture was then kept at $35^{\circ}$ for 2 hr. The solution was brought to pH 2.5-3.0 by the addition of 1M hydrochloric acid, no precipitate being formed. The solvent was removed under reduced pressure, the residue was dissolved in water and extracted with ether. An orange oil which solidified on standing (m.p. $115-117^{\circ}$) was obtained from the ether extract. This material was thought to be dithiodiacetic acid (m.p.[14] $107-108^{\circ}$).

The aqueous phase was evaporated to dryness to give a dark brown solid which had no definite melting point. Attempts to purify it by crystallisation failed. The solid was too impure to give any meaningful ir or nmr data.

b) Thioglycollic acid (1 g) was added to a solution of 4-nitronicotinic acid 1-oxide (0.99 g) in 50% ethanol (200 ml) and the pH of the solution was adjusted to 7. This mixture was kept at 50° overnight. On acidification, no precipitate was formed. The mixture was concentrated to approximately 100 ml and left to cool, whereupon a solid formed. This was filtered off and the filtrate was concentrated further to produce a second crop of solid. The product was recrystallised from glacial acetic acid to give a solid (0.4 g) m.p. 220° (dec.). The coupling constant from the nmr spectrum was consistent with that of a 3,4-disubstituted pyridine-1-oxide (J = 2 Hz). The analytical results, however, were not a good fit for S-(1-oxido-3-carboxy-4-pyridyl) thioglycollic acid.

(Found: C, 38.49; H, 3.25; N, 5.28; $C_8H_7NO_5S$ requires C, 41.92; H, 3.06; N, 6.11%)

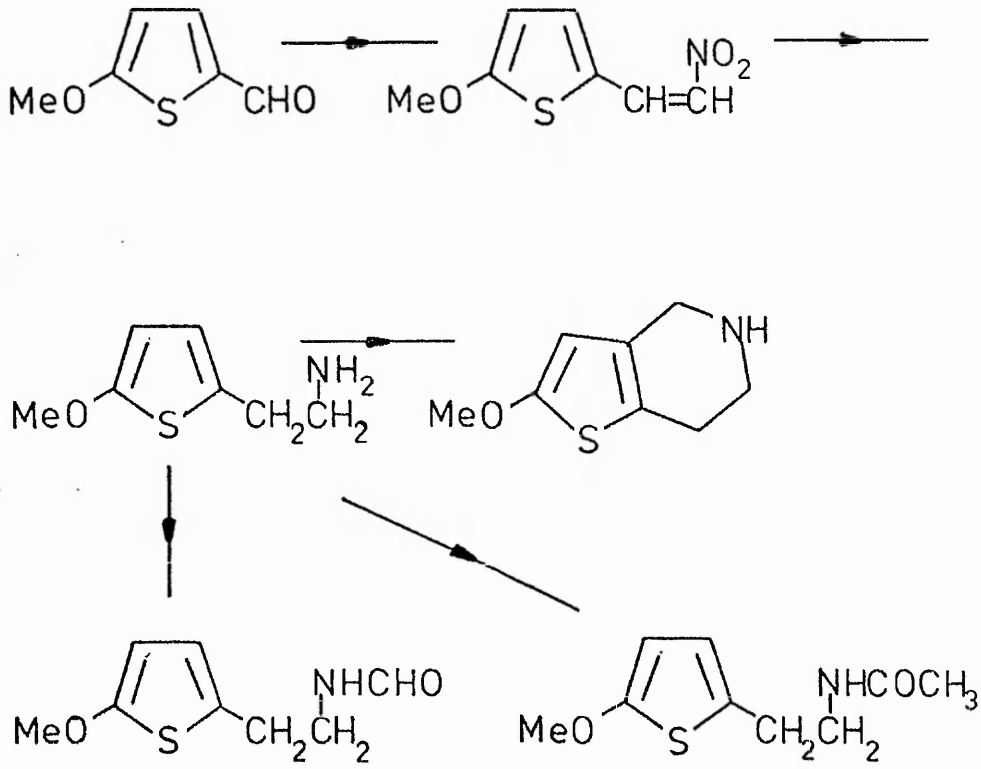
Attempts to prepare methyl 4-nitronicotinate-1-oxide

a) 4-Nitronicotinic acid-1-oxide (1 g) and phosphorous trichloride (10 ml) were heated under reflux for 5 hr. The excess of phosphorous trichloride was removed and the residue was treated with methanol (10 ml) whereupon an exothermic reaction occurred. After 1 hr the excess methanol was removed and the residual solid treated with 10% sodium carbonate solution and the mixture was extracted with methylene chloride. The extract was dried ($MgSO_4$) and concentrated to give a white solid, identified as methyl 4-methoxynicotinate.[16]

b) 4-Nitronicotinic acid-1-oxide (1 g) was heated under reflux for 1½ hr with thionyl chloride (10 ml). After approximately 30 mins a clear solution was formed which then deposited a solid. The excess of thionyl chloride was removed by distillation and the residue treated

with methanol (10 ml), whereupon a vigorous reaction occurred. The residue, after removal of methanol, was treated with 10% sodium carbonate solution and extracted with chloroform. Removal of the dried solvent gave a solid which, after recrystallisation (benzene-light petroleum (b.p. 60-80$^{o}$)), was identified as methyl 4-methoxy nicotinate.

c) 4-Nitronicotinic acid-1-oxide (0.5 g) suspended in methanol (5 ml), was treated with an ethereal solution of diazomethane in small portions; effervescence was noted. The reaction was left overnight. Unfortunately, insufficient diazomethane had been prepared for the reaction to go to completion, insoluble starting acid being present in the solution. The liquor was decanted off, evaporated to dryness and the residue treated with dilute base and re-extracted with chloroform. Removal of the solvent gave a very small amount of solid which was insufficient for identification.


MeO
S
CHO
MeO
S
NO2
CH=CH
NH2
MeO
S
CH2CH2
MeO
S
NH
NHCHO
MeO
S
CH2CH2
NHCOCH3
MeO
S
CH2CH2

5-Methoxy-2-(β-nitrovinyl) thiophene[16]

1. Freshly distilled 5-methoxythiophene-2-carboxaldehyde (2 g) and nitromethane (0.54 g) in A.R. methanol (2 ml) were cooled to 0°. A solution of sodium hydroxide (0.4 g) in water (2 ml) was added dropwise (T < 5°) after which the solution was left to stand for ½ hr. Water (2 ml) was added, the solution was poured into dilute hydrochloric acid and extracted with methylene chloride. None of the desired product was obtained and all the starting material had decomposed.

2. Sodium (0.2 g) in A.R. methanol (5 ml) was cooled in ice, and a solution of 5-methoxythiophene-2-carboxaldehyde (1.17 g) and nitromethane (0.45 ml) in A.R. methanol (2.5 ml) was added. The mixture was left at room temperature for 15 min, during which time a precipitate formed. This was filtered off, added to dilute hydrochloric acid and the acidic solution was extracted with methylene chloride. Again no product was obtained and no starting material recovered.

3. 5-Methoxythiophene-2-carboxaldehyde (1.4 g) was mixed with nitromethane (4.54 g), ammonium acetate (0.88 g) and glacial acetic acid (9.1 ml) and heated under reflux for 4 hr. The cooled solution was poured into water and extracted with ether. The extract was washed with water, sodium hydrogen carbonate solution, water and brine, dried ($MgSO_4$) and concentrated. This method gave the desired product as yellow crystals m.p. 131-132° but in only 19% yield.

4. A mixture of 5-methoxythiophene-2-carboxaldehyde (6.0 g), nitromethane (3.0 g) and benzylamine (0.4 ml) was allowed to stand at room temperature in the dark for 8 days. The yellow crystals were

filtered off, washed with a little ether and dried at the pump, to give 5-methoxy-2-(β-nitrovinyl) thiophene, 3.5 g (44%), m.p. 131-133° (lit[15] 129.6-130°).

β-(5-Methoxy-2-thienyl) ethylamine[16]

5-Methoxy-2-(β-nitrovinyl) thiophene (19 g) in dry THF (200 ml) was added dropwise to a suspension of lithium aluminium hydride (25 g) in dry THF (200 ml), under nitrogen, at such a rate that there was gentle reflux. When all had been added the mixture was stirred at room temperature for one hour. The excess lithium aluminium hydride was destroyed by the cautious addition of wet THF and the complex was broken down with sodium hydroxide solution. The liquor was decanted, and the solid residue was washed well with THF. All extracts were combined and evaporated, the residue was taken up in ether, dried ($MgSO_4$) and concentrated. Distillation of the residue gave a colourless liquid, b.p. 87-89°/0.1 mm (7 g 50%) (lit[16] b.p. 78-80°/0.6 mm).

N-Formyl-β-(5-methoxy-2-thienyl) ethylamine

β-(5-Methoxy-2-thienyl) ethylamine (10 g) was dissolved in methanol (100 ml), and chloral hydrate (10.5 g) was added. The solution was warmed on the steam bath then left to stand overnight. Removal of the methanol under reduced pressure gave an oil which on distillation yielded 9.7 g (81%) of the title compound, b.p. 147-148°/0.1 mm (lit[16] 152-155°/0.4 mm).

N-Acetyl-β-(5-methoxy-2-thienyl) ethylamine

Dicyclohexylcarbodiimide (1.32 g) was dissolved in methylene chloride (5 ml) and a solution of glacial acetic acid (0.4 ml) in methylene chloride (5 ml) was added. Heat was produced and a precipitate formed. A solution of β-(5-methoxy-2-thienyl) ethylamine (1 g)

in methylene chloride (5 ml) was added and the reaction mixture was left at room temperature for 2 days. The solid was filtered off, the filtrate was washed with dilute hydrochloric acid, then with saturated sodium hydrogen carbonate solution, dried ($MgSO_4$) and the solvent removed giving a yellow oil (1 g, 80%) which solidified on standing m.p. 33° (lit[16] m.p. 37°, b.p. 151-154°/0.5 mm).

Attempts to prepare 2-methoxythieno[3,2-c] pyridine

Method 1[17]

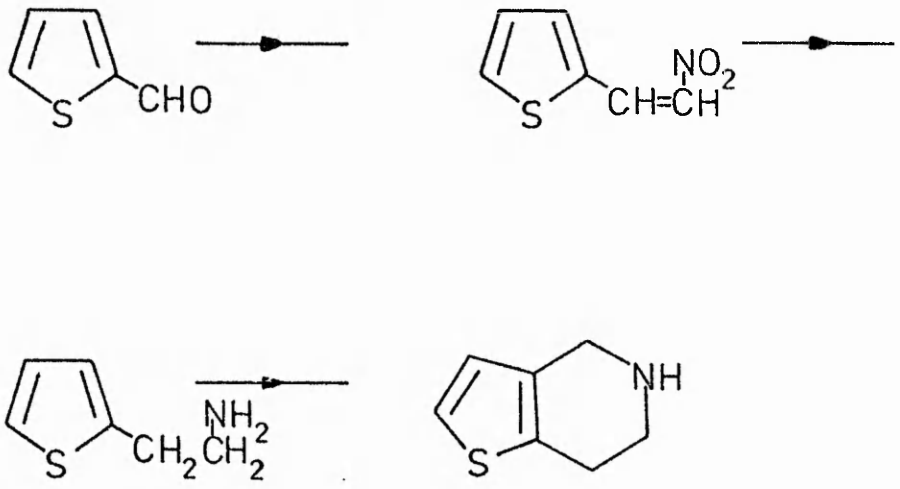
β-(5-Methoxy-2-thienyl) ethylamine (4.7 g) was mixed with 40% formalin solution (2.5 ml, 10% excess), an exothermic reaction taking place. The mixture was heated on a steam bath for 30 min, during which time water had separated out. The water was removed and the residue mixed with hydrochloric acid (22 ml of concentrated acid plus 11 ml of water) and the solution was evaporated to dryness on the steam bath, giving a dark tar. Attempts to extract a product from this failed.

Method 2[18]

Formalin solution (40%, 4g) was added dropwise, with shaking, to β-(5-methoxy-2-thienyl) ethylamine (4 g). A strongly exothermic reaction occurred. The mixture was heated on a steam bath for 3 hr, then left at room temperature for 1 hr. The water was removed by azeotropic distillation with benzene. Removal of the benzene gave an oil which was shaken with hydrochloric acid (6 ml of 5M plus 0.5 ml of concentrated acid) for 2 hr. Water was added and the solution was extracted with ether. The aqueous layer was basified and extracted with chloroform. Tlc (silica/EtOAc) showed that a complex mixture had been formed.

Method 3

The reaction was repeated as in method 2 up to and including the shaking with acid. The mixture was evaporated to dryness to give a red oil, which, on treatment with a little ethanol and ether yielded a solid. However, this too proved to be a complex mixture which was not further investigated.


S
CHO
S
NO2
CH=CH
S
NH2
CH2CH2
NH
S

2-(β-Nitrovinyl-)thiophene[18]

A mixture of thiophene-2-aldehyde (22 g), nitromethane (68 g), ammonium acetate (13.2 g) and acetic acid (200 ml) was heated under reflux for 4 hr. When cool, the solution was poured into water and extracted with ether. The combined extracts were washed with water, saturated sodium hydrogen carbonate solution and brine, dried ($MgSO_4$) and concentrated. The solid produced was recrystallised from methylated spirits to give the product (14 g, 50%) as yellow crystals m.p. 78-80° (lit 88-89°[18], 80-81°[7]).

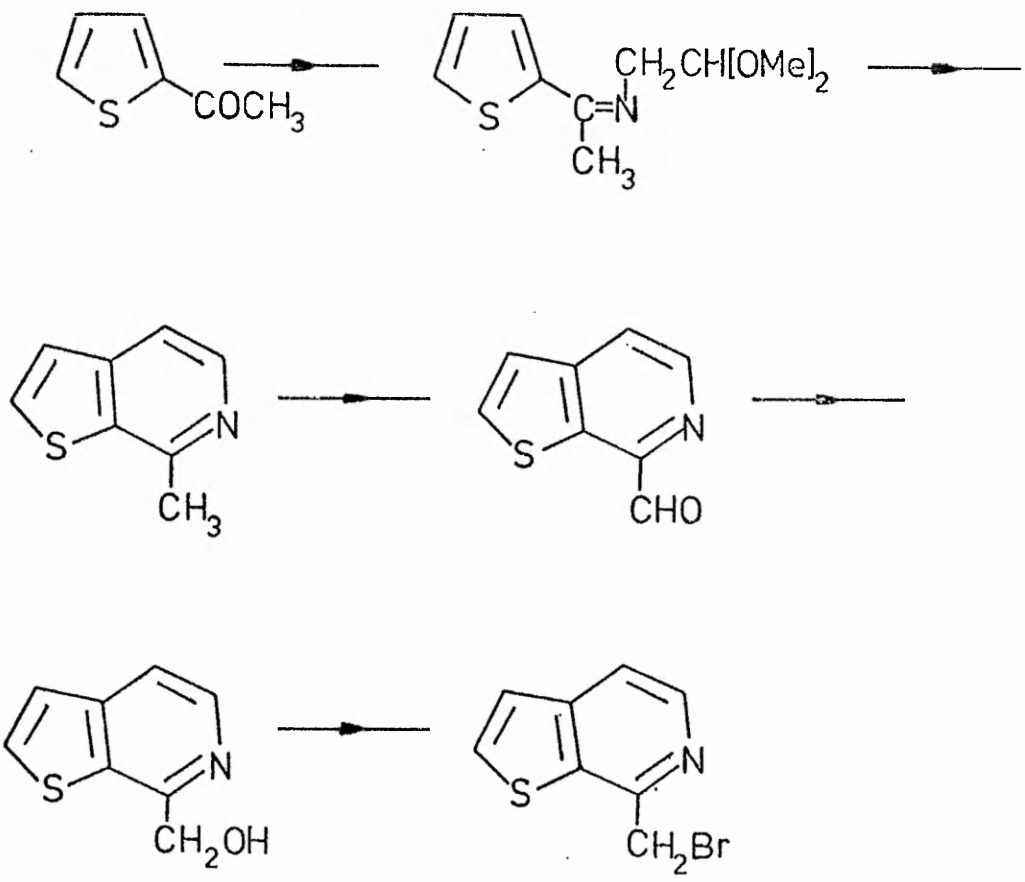
β-(2-Thienyl)ethylamine

This compound was obtained from the foregoing nitro-vinyl compound as a colourless liquid b.p. 55-60°/2 mm (lit[19] 76-78°/7 mm) according to the method of ref. 19.

4,5,6,7-Tetrahydrothieno[3,2-c]pyridine hydrochloride[18]

20% aqueous formaldehyde solution (5.4 g) was added dropwise, with stirring, to β-(2-thienyl)ethylamine (4.6 g). A strongly exothermic reaction occurred. The reaction mixture was stirred for 3 hr on a boiling water bath. After 1 hr at room temperature the aqueous phase was separated and the oil was dissolved in benzene. The benzene layer was washed with water and dried over magnesium sulphate. Removal of the benzene, in vacuo, left 4 g of crude formimine of β-(2-thienyl) ethylamine.

The formimine (4 g) was shaken with 23% hydrochloric acid (5 ml) for 2 hr; an exothermic reaction began immediately. The solution was evaporated to dryness, leaving a red oil. None of the desired product was obtained, since the oil was an unresolvable mixture.


S
COCH3
CH2CH[OMe]2
C=N
CH3
N
CHO
CH2OH
CH2Br

2-Acetyl thiophene

This was prepared in 79% yield as a yellow liquid b.p. 118°/18 mm (lit[20] 77°/4 mm) by the method of ref. 20.

[(α-Methyl-2-thenylidene) amino] acetaldehyde dimethyl acetal

To a solution of 2-acetyl thiophene (57.2 g) in toluene (100 ml) was added aminoacetaldehyde dimethyl acetal (66.6 g). The flask was fitted with a Dean and Stark trap and the solution was heated under reflux until no more water was produced. The mixture was cooled, dried ($MgSO_4$) and concentrated. [α-Methyl-2-thenylidene) amino] acetaldehyde dimethyl acetal (65 g, 68%) was obtained on distillation as a yellow liquid b.p. 132-136°/1 mm.

τ ($CCl_4$):

3.37, 3.60 (m 3-thiophene H), 5.60 (t $-CH_2-\underline{CH}-$ J = 4.5 Hz)

6.57 (d $-\underline{CH_2}-CH-$ J = 4.5 Hz) 6.70 (s 2x$-CH_3$)

7.83 (s $-\underset{\underset{CH_3}{|}}{C}=N$)

$\nu_{max}$ (thin film):

1630 $cm^{-1}$ -C=N-

7-Methylthieno[2,3-c]pyridine

This was prepared in 60% yield by the method of Dressler and Joullié[21] as a colourless liquid b.p. 100°/2.5 mm (lit[21] 102-103°/2.5 mm). The methiodide of this compound was also prepared and had m.p. 198-201° (lit[21] 201-202°).

Thieno[2,3-c]pyridine-7-carboxaldehyde

Selenium dioxide (3 g, sublimed immediately after preparation[22]) was dissolved in dioxan (150 ml) and water (6 ml). The thienopyridine (4 g) was added in one portion and the solution was boiled under reflux for 7 hr. When cool, the solution was filtered, the dioxan was removed under reduced pressure, the residue was treated with sodium hydroxide solution (2M) and extracted with ether. The combined

extracts were dried and concentrated giving a semi-solid mass which, when treated with light petroleum (b.p. 60-80°) gave the pure aldehyde as a crystalline solid m.p. 72-73° (lit[21] 73-74°). The overall yield was 50% based on unrecovered starting material.

7-Hydroxymethyl thieno[2,3-c] pyridine

Thieno[2,3-c] pyridine-7-carboxaldehyde (1 g) was dissolved in ethanol (35 ml) and treated with an excess of sodium borohydride (2 g). When reaction was complete, the solvent was removed and the residue was treated with water. Extraction with methylene chloride followed by drying ($MgSO_4$) and removal of the solvent gave a yellow oil which was taken up in light petroleum (b.p. 60-80°). On cooling, white crystals were deposited, which were identified as 7-hydroxymethyl thieno[2,3-c] pyridine (0.6 g 60%), m.p. 73-74°.

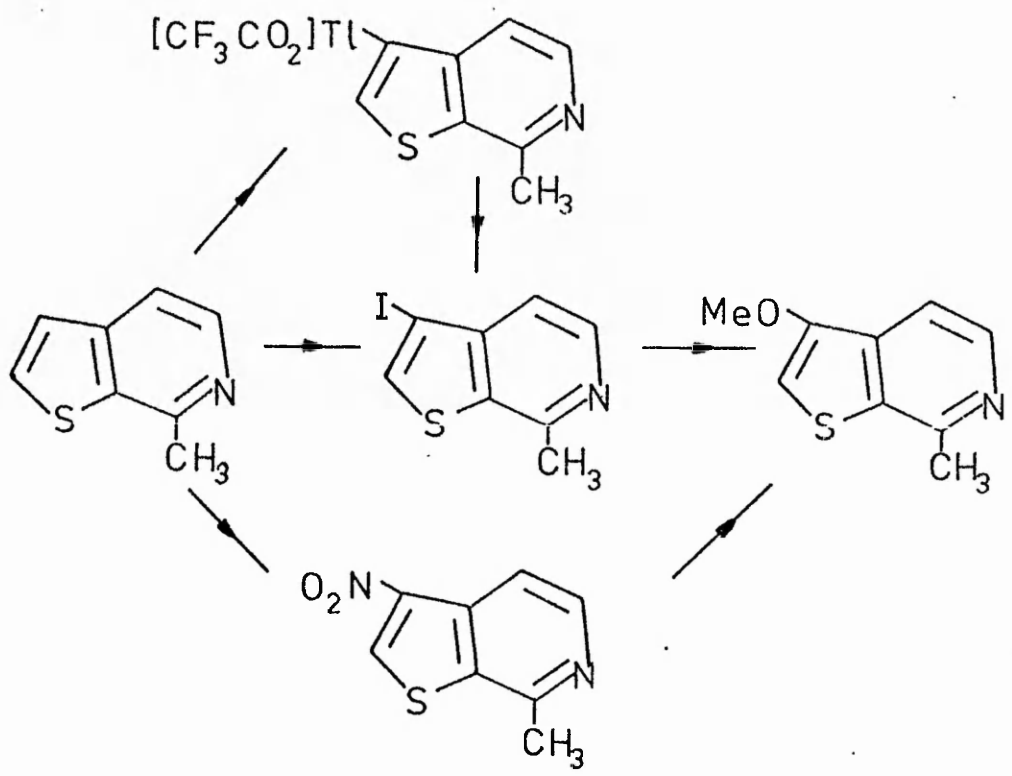
(Found; C, 58.18; H, 4.24; N, 8.49; $C_8H_7NOS$ requires C, 57.98; H, 4.42; N, 8.29%)

$\tau$ ($CDCl_3$):

1.6 (d pyridine H J = 6 Hz), 2.5 (m - aromatics)

5.0 (s $-CH_2-$) 5.5 (s -OH)

$\nu_{max}$ (nujol): 3200 $cm^{-1}$ (OH)


[CF3CO2]Tl
S
N
CH3
I
MeO
O2N

7-Bromomethylthieno[2,3-c]pyridine

The foregoing alcohol (1 g) was treated with phosphorous tribromide (0.6 ml) after dissolution in chloroform (30 ml) and heated under gentle reflux for 1¼ hr, during which time a solid separated out. The solid was filtered off and the chloroform removed from the filtrate producing more solid. This was identified by spectroscopy as the hydrobromide of 7-bromomethyl thieno[2,3-c]pyridine, the yield being quantitative. The picrate of the free base had m.p. 174-175°.

(Analysis of picrate

Found: C, 36.76; H, 1.97; N, 12.25; $C_{14}H_9BrN_4O_7S$ requires C, 36.7; H, 1.9; N, 12.2%.)

τ($CDCl_3$) (free base):

1.47 (d pyridine H J = 6Hz), 2.5 (m aromatics), 5.15 (s $-CH_2-$).

Attempt to prepare 3-iodo-7-methylthieno[2,3-c]pyridine

7-Methylthieno[2,3-c]pyridine (1.5 g) was stirred in acetonitrile (10 ml) and thallium trifluoroacetate (5 g) was added in one portion. The mixture was stirred at room temperature for 10 mins, when tlc (silica/EtOAc) indicated that there was no starting material present. The solution was stirred for a further 20 min then treated with a solution of potassium iodide (1.9 g) in water (5 ml), whereupon an orange/brown solid formed. The mixture was stirred at room temperature for 3½ hr, treated with sodium hydroxide solution and diluted with ether. The solid was filtered off and the ether layer was separated from the filtrate. Removal of the ether, after drying ($MgSO_4$) gave an oil (1.3 g) which proved to be unchanged 7-methylthieno[2,3-c]pyridine.

3-Iodo-7-methylthieno[2,3-c]pyridine

7-Methylthieno[2,3-c]pyridine (5 g) was dissolved in concentrated sulphuric acid (75 ml) and silver sulphate (10.4 g) was added. The

solution was brought to 120° when iodine (10.5 g) was added in portions with stirring. As soon as all the iodine had dissolved the solution was poured onto ice, made basic with sodium hydroxide solution and steam distilled. Extraction of the distillate with methylene chloride gave the crude product, which was crystallised from chloroform-hexane to yield 3-iodo-7-methylthieno[2,3-c]pyridine (1.5 g, 16%) as white crystals m.p. 150-152°.

(Found: C, 34.90; H, 2.18; N, 5.1; I, 46.16; $C_8H_6INS$ requires C, 35.10; H, 2.10; N, 5.0; I, 45.40%.)

$\tau(CDCl_3)$;

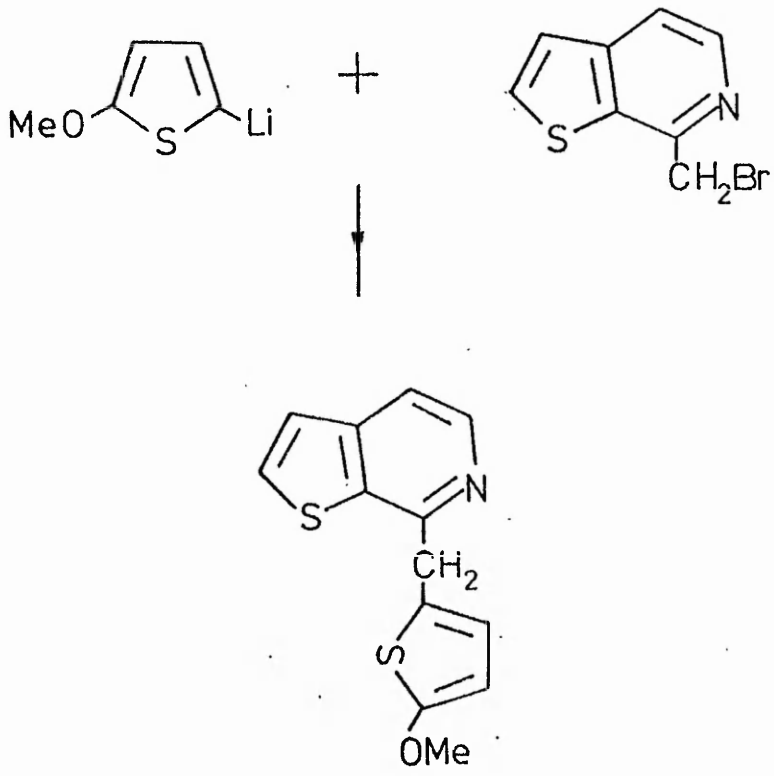
1.45 (d pyridine H J = 6 Hz), 2.2 (s thiophene H), 2.55 (d pyridine H J = 6Hz), 7.17 (s $-CH_3$).

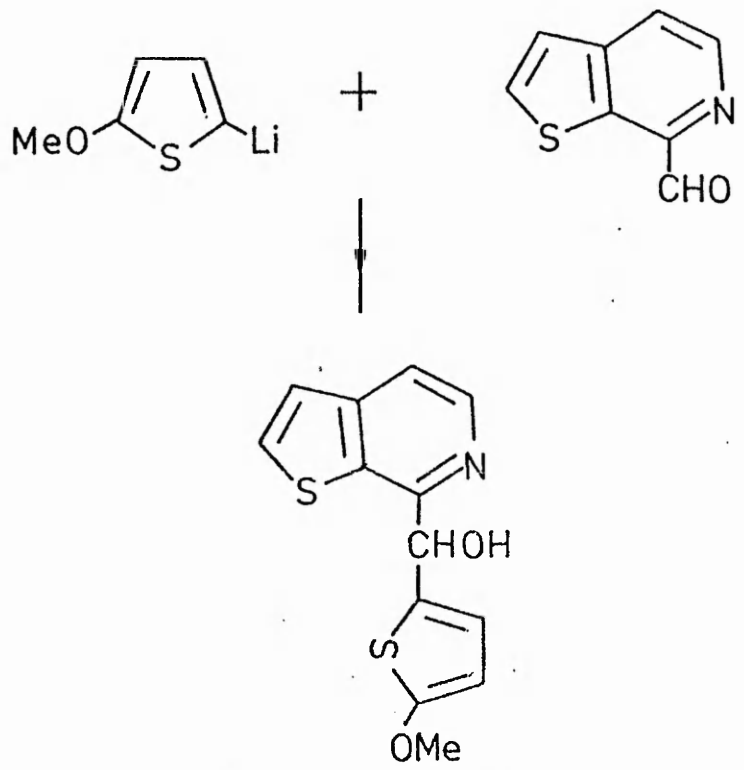
Attempt to prepare 3-methoxy-7-methylthieno[2,3-c]pyridine

Dried copper (II) oxide (0.24 g) was added to a solution of sodium metal (0.43 g) in A.R. methanol (6 ml) and to this was added 3-iodo-7-methylthieno[2,3-c]pyridine (1.5 g) in A.R. methanol (2 ml). The mixture was heated under reflux, with stirring, for 36 hr, after which it was filtered, poured into water and extracted with ether. The extract was washed with water and brine, dried ($MgSO_4$) and concentrated, giving a pale yellow liquid (0.6 g). Although this ran as a single spot on tlc (silica/EtOAc) its nmr spectrum showed that it was a mixture of the starting iodo compound and the desired 3-methoxy-7-methylthieno[2,3-c]pyridine.

3-Nitro-7-methylthieno[2,3-c]pyridine

The method of Dressler and Jouillé[21] was followed for the preparation of this compound. The yield obtained (3%) however, was much smaller than that claimed (40%).


MeO
S
Li
+
S
N
CH2Br
S
N
CH2
S
OMe

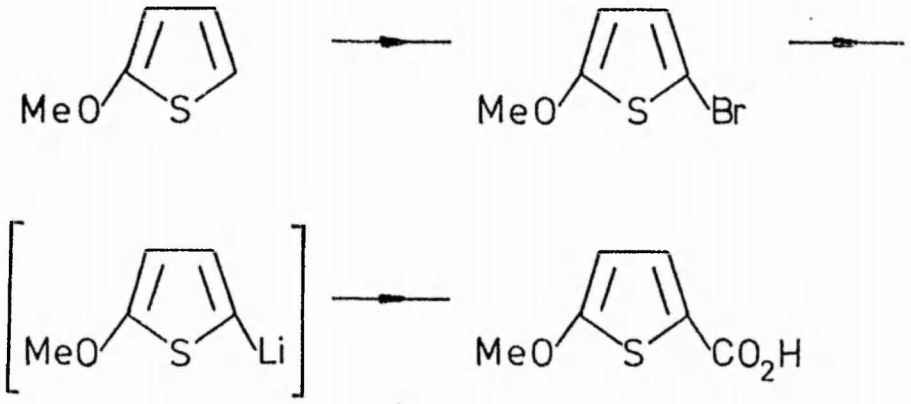

MeO
S
Li
+
S
N
CHO
S
N
CHOH
S
OMe

Attempts to couple 2-methoxythiophene with thieno[2,3-c]pyridine -7-carboxaldehyde

a) 2-Methoxythiophene (0.35 g) in dry ether (10 ml) was treated under nitrogen with n-butyllithium (1.9 ml of a 1.6M solution in hexane), then stirred at room temperature for 15 min, whereupon a yellow colour developed.

Thieno[2,3-c]pyridine-7-carboxaldehyde (0.8 g) in dry ether (10 ml) was added in small portions to the above solution; on addition of the first few drops a pink precipitate formed, whilst on further addition the solution became an intense red colour, there being no significant change in temperature throughout. The reaction mixture was poured into dilute acid and the ether layer was separated and washed with dilute acid; all the acid washes were combined, basified and extracted with methylene chloride. No reaction had occurred, however, since 2-methoxythiophene and the aldehyde were recovered unchanged from the ether and methylene chloride solutions respectively.

b) n-Butyllithium (1.9 ml of a 1.6M solution in hexane) was added to 2-methoxythiophene (0.3 g) in dry ether (25 ml) under nitrogen, with stirring. The solution was stirred at room temperature for 15 min, then treated with a solution of the aldehyde (0.5 g) in dry ether (20 ml). Again a precipitate was formed, but there was no intense colouration during the addition. However, whilst stirring at room temperature for 1 hr, a salmon pink colour developed. Tlc ($CHCl_3$/ silica) of the material obtained by quenching a sample in acid and extraction of the basified solution, showed both starting materials to be present. The reaction mixture was therefore heated under reflux for 20 min, but again only starting materials were observed on tlc. To try to produce a homogeneous reaction mixture tetramethylethylene-diamine (0.25 ml) was added; however, it did not appear to have any effect since, after a further 10 mins under reflux, tlc indicated


MeO
S
MeO
S
Br
MeO
S
Li
MeO
S
CO2H

that the starting materials were still present. The reaction mixture was therefore worked up as before, but none of the desired product was obtained.

2-Bromo-5-methoxythiophene

2-Methoxythiophene (4.4 g) in carbon tetrachloride (50 ml) was treated with 1,3-dibromo-5,5-dimethylhydantoin (5.6 g) and left at room temperature until the reaction was complete. The solid was filtered off, the filtrate was washed with 10% sodium carbonate solution and water, dried ($MgSO_4$) and concentrated. Distillation of the residual oil gave a pale yellow oil (4.2 g, 55%) b.p. 60-62°/1.5 mm (lit[7] b.p. 92-93°/10 mm).

5-Methoxy-2-thenoic acid

2-Methoxythiophene (1.14 g) in dry ether (20 ml) under nitrogen was treated with 4.9 ml of a 1.67M solution of n-butyl lithium in hexane, when a clear yellow solution was produced. The solution was stirred at room temperature for 35 min then poured onto solid carbon dioxide and ether. The mixture was treated with dilute acid, the ether layer was separated and washed with 10% sodium carbonate solution. Acidification of the carbonate washes afforded the desired acid, which was recrystallised from benzene and had m.p. 163-4° (1 g, 64%) (lit[7] m.p. 162-163° (dec)).

Attempts to couple 2-methoxythiophene with 2-bromomethylthieno[2,3-c] pyridine

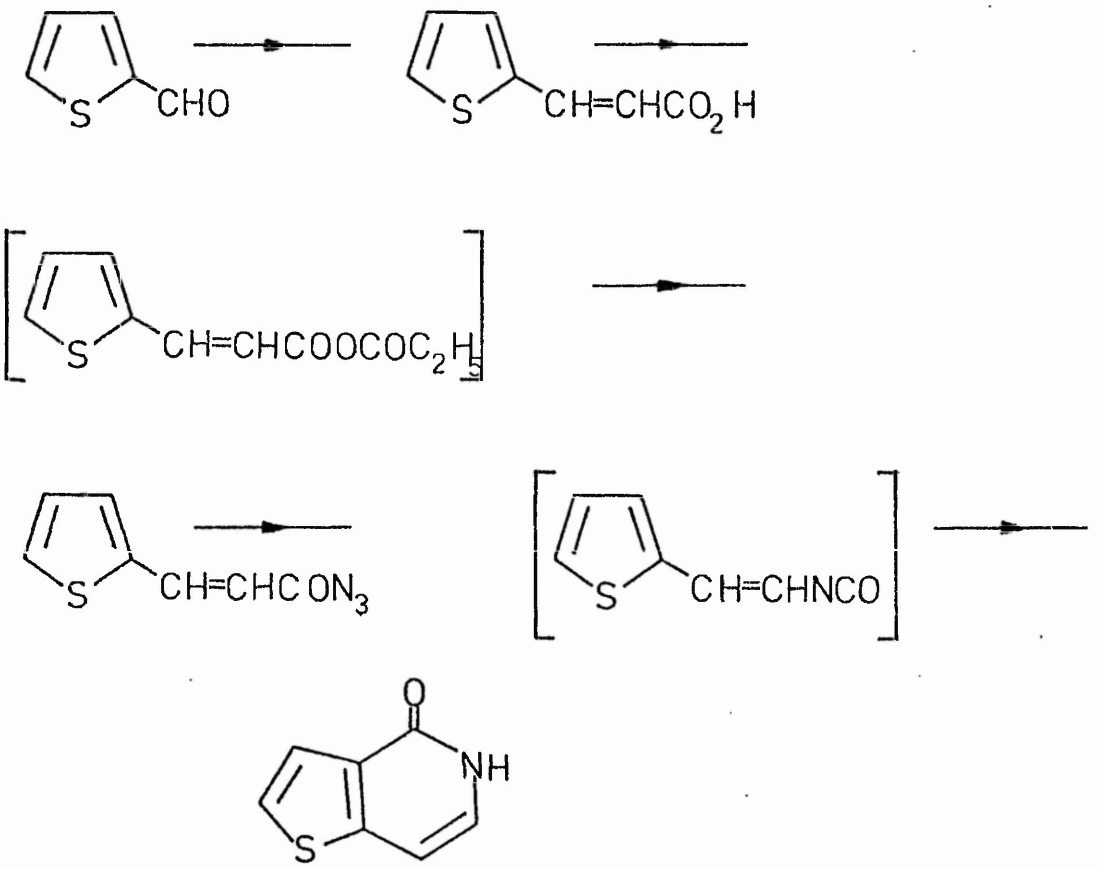
a) n-Butyllithium (2.4 ml of 1.67M solution in hexane) was added dropwise, with stirring, to 2-bromo-5-methoxythiophene (0.77 g) in dry ether (5 ml) under nitrogen. A brown colouration was observed, the solution becoming very turbid. The ether solution was stirred at room temperature for 15 min and then cooled in an ice-bath.

The bromomethylthienopyridine (generated from 1.2 g of its hydrobromide) in dry ether (20 ml) was added in small portions to the above cooled solution, but there was no apparent reaction. Hexamethylphosphoramide (0.5 g) was added in case insolubility was preventing reaction, and more bromomethylthienopyridine was added, but again tlc (EtOAc/silica) confirmed that no reaction had occurred, since only the spot due to the bromo compound was visible. The reaction was left at room temperature for 4 hrs during which time a black solid formed. The reaction mixture was poured into water and the ether layer was separated, and concentrated, to give a very small amount of oil. Nmr showed this to be hexamethylphosphoramide. No other product was isolated.

b) 2-Methoxy-5-bromothiophene (1.93 g) was stirred in dry ether (10 ml) under nitrogen at $10^{\circ}$ to give a yellow solution. n-Butyl lithium (4.9 ml of a 1.67 M solution in hexane) was added dropwise, with stirring; the first few drops changed the solution to a green colour with an immediate rise in temperature. The temperature was kept at $18^{\circ}$, by cooling, throughout the addition of the remaining n-butyl lithium solution. The solution was stirred for 15 min at $15^{\circ}$, then treated with the bromomethylthienopyridine (0.7 g) in dry ether (20 ml). Again, a temperature rise was noted, the solution darkening in colour. However, work up as described above after 1 hr at room temperature gave only unreacted bromomethylthienopyridine.

c) 2-Methoxythiophene (1 g) was stirred in dry ether (10 ml) under nitrogen and n-butyllithium (5.6 ml of a 1.6 M solution in hexane) was added, whereupon an immediate yellow colouration was produced, which darkened on stirring. After 10 mins an ethereal solution of bromomethylthienopyridine (2 g) was added in portions; the solution became very dark, and a rise in temperature occurred when the first drops were added, so external cooling was applied for the remainder of the addition. When addition was complete, the mixture was stirred

at room temperature for 30 min. On pouring into water, a dark precipitate was formed; the ether layer was separated and the aqueous layer re-extracted with ether, the solid being insoluble in both water and ether (further inspection showed it to be polymer). The combined ether extracts were dried ($MgSO_4$) and the solvent was removed to furnish a dark oil which was shown to be a mixture by tlc ($CHCl_3$/silica). Purification of the oil by column chromatography ($CHCl_3$/silica)produced 2-methoxythiophene as the major component, with a very small amount of recovered bromocompound.

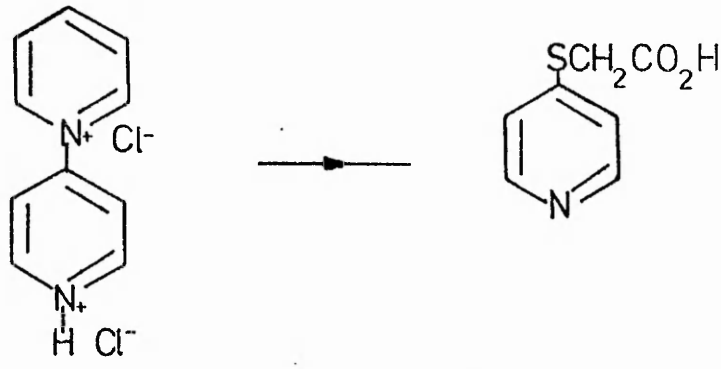

CHO
CH=CHCO2H
CH=CHCOOCOC2H5
CH=CHCON3
CH=CHNCO
O
NH
S

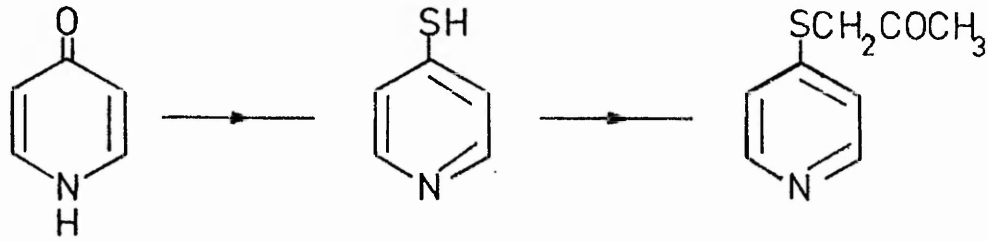
β-(2-Thienyl)acrylic acid[23]

This compound was obtained as white fibrous crystals, m.p. 145° (5.8 g, 77%) according to the method of ref. 23(lit[23] m.p. 144-145°).

4-Oxo-5H-thieno[3,2-c]pyridine

This compound was prepared according to the method of Eloy and Deryckere[24], and had m.p. 209-210° (lit[24] 213-214°). However, the yield obtained (23%) was considerably lower than that claimed by these authors (70%).


N+ Cl-
N+
H Cl-
SCH2CO2H
N


O
N
H
SH
N
SCH2COCH3
N

Pyridylpyridinium chloride hydrochloride

This was prepared according to ref. 25 and had m.p. 150-154°.

(4-Pyridylthio)acetic acid

This was prepared by a literature method[25] (in 80% yield) as a white solid m.p. 268-270° (dec) (lit[25] 268-270°(dec)).

Attempts to cyclise (4-pyridylthio)acetic acid

1. (4-Pyridylthio)acetic acid (2 g) was added to polyphosphoric acid (4.2 g) at 120°, then kept at this temperature for 3 hrs. The solution was poured onto ice, basified with sodium carbonate solution and extracted with methylene chloride. On removal of the solvent, however, no product was obtained. On acidification of the aqueous phase it was noticed that at pH 6 a solid was deposited, which was collected and identified as the starting material.

The reaction was repeated at 170° and at 220° for various periods of time. In all cases, only starting material was recovered, an increase in reaction time resulting in a lower recovery.

2. Phosphoryl chloride (0.5 g) was added dropwise to the acid (0.5 g) in dry pyridine (5 ml). Intense heat was produced with immediate darkening of the solution. The reaction mixture was cooled, treated with water and brought to pH 6, no starting material being recovered. On basification a dark oil was produced which proved to be only basic polymer.

This reaction was repeated at -20°. However, at this temperature only impure starting material was recovered.

4-Mercaptopyridine

This compound was prepared in 80% yield using the method of ref. 26, and had m.p. 182-184° (lit[26] 186°).

1-(4-Pyridylthio)propan-2-one

4-Mercaptopyridine (8 g) was dissolved in a mixture of 4M sodium hydroxide solution (25 ml) and water (10 ml); slight warming was necessary to effect solution. The solution was treated with chloroacetone (8 g), added dropwise at such a rate that the temperature never exceeded 30°. Then it was stirred at room temperature for 3 hr, during which time an oil separated; the liquor was decanted and the oil was treated with dilute sodium hydroxide solution and extracted with methylene chloride. After removal of the solvent 1-(4-pyridylthio)propan-2-one was obtained as an oil (8.5 g, 70%) b.p. 110°/0.3 mm, m.p. 38°.

(Found: C, 57.60; H, 5.50; N, 8.10; $C_8H_9NOS$ requires C, 57.48; H, 5.38; N, 8.31%)

$\tau(CCl_4)$:

1.7, 2.95 (2 doublets of doublets, 4 pyridine H, J = 6 Hz, J = 1.5 Hz) 6.29 (s $-CH_2-$), 7.8 (s $-CH_3$).

$\nu_{max}$ (thin film): 1720 $cm^{-1}$ ($\geq C=O$)

The picrate had m.p. 145-147°. Found: C, 42.80; H, 3.30; N, 14.40; $C_{14}H_{12}N_4O_8S$ requires C, 42.43; H, 3.03; N, 14.14%.

Attempts to cyclise 1-(4-pyridylthio)propan-2-one

a) A solution of the ketone (1 g) in dry chloroform (5 ml) was added to phosphorus pentoxide (2 g) in dry chloroform (20 ml). There were no visible signs of reaction; the mixture was left to stand at room temperature overnight. Tlc (EtOAc/silica) indicated that no reaction had taken place, so the solution was heated under reflux for 3 hr. Again tlc indicated that no reaction had occurred and all the ketone was recoverd.

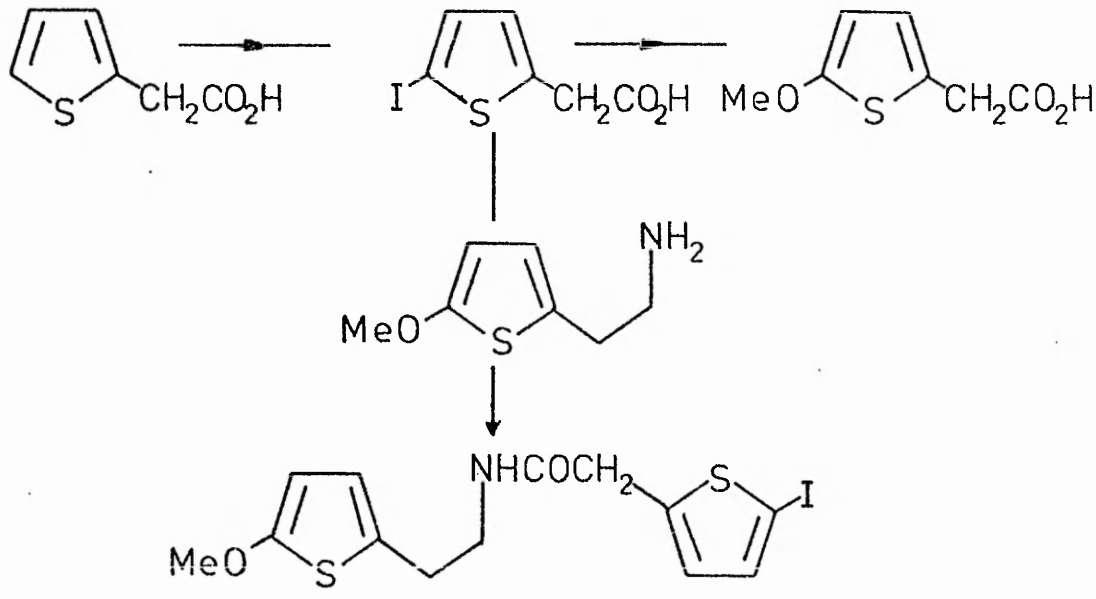
b) A solution of the ketone (0.5 g) in dry toluene (10 ml) was added to phosphorus pentoxide (1 g) in dry toluene (10 ml). After 30 min at room temperature, during which time no reaction had taken place, the mixture was warmed on a steam bath for 4 hrs. Tlc (EtOAc/silica) again indicated that no change had occurred.

c) Phosphoryl chloride (0.5 g) was added dropwise to a solution of the ketone (0.5 g) in dry pyridine (10 ml). After standing at room temperature for 30 min the solution was heated under reflux for 30 min during which time it became quite dark. Tlc (EtOAc/silica) indicated that all the starting material had disappeared. The mixture was poured into water and extracted with ether; removal of the ether left only polymer, however.

The reaction was repeated at $100^{\circ}$ and at $70^{\circ}$; in both cases polymerisation occurred and none of the desired product was obtained. It should be noted that standing at room temperature appeared to have no effect at all over a short period of time, therefore, the optimum reaction temperature must be somewhere between $\sim 15^{\circ}$ and $70^{\circ}$.

d) The ketone (0.84 g) was added to a mixture of triphenylphosphine (1.64 g) in dry chloroform (5 ml) and dry carbon tetrachloride (0.8 g) and the mixture was heated under reflux for 1 hr. The solution was washed with dilute hydrochloric acid and the acid extract was basified with dilute sodium hydroxide solution, then extracted with chloroform.

The basic extract contained recovered starting material whereas the acid wash contained triphenylphosphine oxide; no cyclised product could be detected.


S
CH2CO2H
I
S
CH2CO2H
MeO
S
CH2CO2H
NH2
MeO
S
NHCOCH2
S
I
MeO
S

5-Iodo-2-thienylacetic acid

Iodine (12.5 g) was added in portions to a vigorously stirred solution of 2-thienylacetic acid (21.1 g) in methylene chloride (50 ml). A mixture of concentrated nitric acid-water (1:1, 18 ml) was added dropwise, whereupon the reaction mixture boiled spontaneously. The mixture was stirred at room temperature for 2 hrs, the methylene chloride layer was separated, washed with water, dried and concentrated, to yield a dark coloured solid. Recrystallisation from light petroleum (b.p. 60-80°) gave pale brown crystals of 5-iodo-2-thienylacetic acid m.p. 86-87° (16 g 48%).

$\tau(CDCl_3)$:

2.3 (broad peak -OH); 2.85, 3.3 (2d 2 thiophene H, J = 4 Hz); 6.1 (s $-CH_2-$)

Attempt to prepare 5-methoxy-2-thienylacetic acid

Sodium (4.3 g) was dissolved in Analar methanol (60 ml) and copper oxide (2.4 g) was added, followed by 5-iodo-2-thienylacetic acid (15 g). The mixture was heated and stirred under reflux for 25 hrs after which time tlc (EtOAc/silica) showed that no change had taken place. The solution was filtered and the filtrate was poured into water and extracted with chloroform. The nmr spectrum of the residue, after removal of the solvent, showed no methoxy group to be present; the material appeared to be rather impure 5-iodo-2-thienylacetic acid.

Preparation of N-(5-iodothienylacetyl)-2-(5-methoxy-2-thienyl) ethylamine

A solution of 2-(5-methoxy-2-thienyl) ethylamine (0.93 g) in chloroform (3 ml) was added to a solution of 5-iodo-2-thienylacetic acid (1.6 g) in chloroform (10 ml), when a slight temperature rise was observed. A solution of dicyclohexylcarbodiimide (1.2 g) in

chloroform (3 ml) was then added. After approximately 5 mins a precipitate was formed (dicyclohexylurea) with evolution of heat. The mixture was left at room temperature for 30 mins, filtered, and the filtrate was washed with dilute hydrochloric acid, 10% sodium carbonate solution and water, dried ($MgSO_4$) and evaporated to leave a dark oil. This oil was purified by column chromatography (silica/$CHCl_3$), the slowest running product being collected. Recrystallisation from light petroleum (b.p. 60-80°) gave N-(5-iodothienylacetyl)-2-(5-methoxy-2-thienyl) ethylamine as a cream solid, m.p. 54-57°

$\tau(CDCl_3)$:

2.95, 3.45, 3.75, 4.05 (all doublets 4 thiophene H, J = 4 Hz); 6.18 (s -OMe), 6.34 (s $-CH_2-$); 4.65 (t $-NH-CH_2-$, J = 6.0 Hz), 7.2 (t $-CH_2-Ar$, J = 6.0 Hz).

N-2-thienylacetyl-β-(2-methoxy-5-thienyl)ethylamine

Dicyclohexylcarbodiimide (1.32 g) was dissolved in dry methylene chloride (5 ml) and to this was added a solution of 2-thienylacetic acid (0.9 g) in dry methylene chloride (5 ml). An exothermic reaction occurred and a precipitate formed. β-2-Methoxythienylethylamine (1 g) in dry methylene chloride (5 ml) was added, more heat being produced. Dry methylene chloride (10 ml) was added to the reaction mixture to produce a suspension of the solid. After 5 hrs at room temperature the mixture was filtered, the filtrate was washed with dilute acid and 10% sodium carbonate solution, dried ($MgSO_4$) and concentrated, giving a yellow oil, which solidified. Recrystallisation from ethylacetate-light petroleum (b.p. 60-80°) gave a cream solid, N-2-thienyl-β-(2-methoxy-5-thienyl)ethylamine (0.5 g, 30%), m.p. 50-51°. ← acetyl

This product, however, did not give the expected analytical figures,

(Found: C, 58.4; H, 6.3; N, 5.6; $C_{13}H_{15}NO_2S_2$ requires C, 55.51; H, 5.34; N, 4.98%)

although the nmr spectrum was consistent with the required amide:-

$\tau(CDCl_3)$:

2.8 (m 3 thiophene H)

3.75 (d thiophene H, J = 4 Hz)

4.05 (d thiophene H, J = 4 Hz)

6.17 (s -OMe), 6.25 (s $-CH_2-CO$)

6.65 (t $-\underline{CH_2}-NH$, J = 6 Hz)

7.2 (t $Ar\underline{CH_2}-CH_2$ J = 6 Hz)

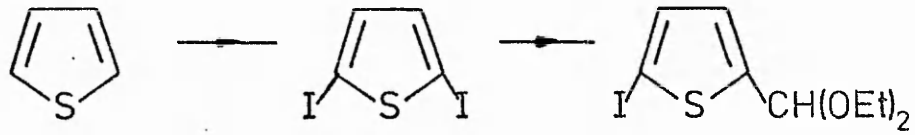
7.85 (s -NH-)

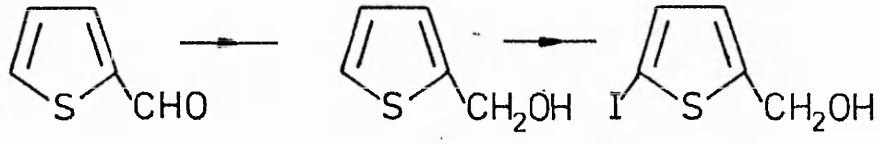
Attempts to cyclise N-2-thienylacetyl-β-(2-methoxy-5-thienyl)ethylamine

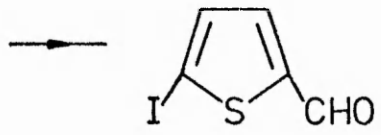
a) The amide (0.5 g) in dry pyridine (30 ml) was kept under gentle reflux whilst an intimate mixture of phosphorus pentoxide (5 g) and sand (30 g) was added in portions with stirring. The mixture was then heated under reflux for 6 hr, the pyridine was removed under reduced pressure and the residue taken up in benzene. The extract was washed with dilute acid. Basification and re-extraction with benzene of the aqueous layer gave a yellow oil. However, this would not form a picrate or a hydrochloride and so was discarded. No other product was obtained.

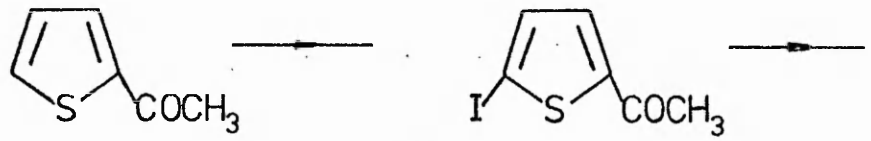
b) The amide (0.7 g) in dry chloroform (5 ml) was added to triphenylphosphine (0.82 g) in chloroform (5 ml) containing carbon tetrachloride (0.4 g) and the resulting mixture was heated under reflux for $2\frac{1}{2}$ hr. during which time the solution became dark red, although tlc (silica/$CHCl_3$) showed the presence of starting material. After refluxing for a further hour the mixture was left at room temperature for 2 days. The chloroform solution was washed with dilute acid, the aqueous layer

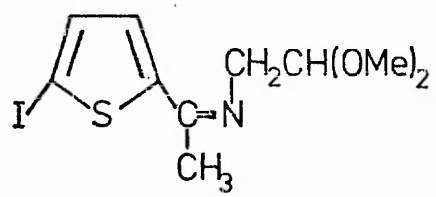
was separated, basified and extracted with chloroform. Removal of the dried ($Na_2SO_4$) solvent gave an oil which solidified. Attempts to prepare a picrate or a hydrochloride of part of this failed. Recrystallisation from light petroleum gave a solid which proved to be triphenylphosphine oxide.











2,5-Diiodothiophene

Thiophene (50 g) in methylene chloride (150 ml) was treated with iodine (150 g) at room temperature. When all the halogen had dissolved a 1:1 mixture of nitric acid-water (100 ml) was added dropwise whereby an exothermic reaction occurred. A further 10 mls of nitric acid was added and the solution was heated under reflux for 18½ hr. After cooling, the aqueous layer was removed, the organic layer was washed with water, 10% sodium hydroxide solution and water, dried ($MgSO_4$) and concentrated. The residue was distilled under reduced pressure, yielding the desired product as a red liquid, b.p. 128°/7 mm (175 g, 87%), (lit[6] b.p. 67-70°/0.05 mm).

Attempted preparation of 2-diethoxymethyl-5-iodothiophene[27]

A Grignard reagent was prepared from 2,5-diiodothiophene (11.2 g) and magnesium (0.8 g) in dry ether (20 ml). Triethylorthoformate was added dropwise and the mixture was heated under reflux for 8 hrs. Water (50 ml) was added and the ethereal layer was separated. Removal of the ether gave an oil which was identified as 2,5-diiodothiophene. As this is a published method[27] for the preparation of 2-diethoxymethyl-5-iodothiophene the lack of reaction suggests that the Grignard reagent did not form.

Thiophene-2-aldehyde

This was prepared in 50% yield by the method of ref. 28.

2-Thenylalcohol

Thiophene-2-aldehyde (14.0 g) in ethanol (40 ml) was treated with sodium borohydride until no further reaction occurred. After 30 min at room temperature, water was added and the aqueous solution was extracted with ether. The residue, after removal of the solvent, was distilled yielding a colourless liquid (10 g, 70%) b.p. 94-96°/12 mm (lit[29] 102-5°/20 mm). The alcohol turns green on standing.

2-Iodo-5-thenylalcohol

The compound was prepared according to the method of ref. 30 in 60% yield.

2-Iodo-5-thiophenecarboxaldehyde

Two methods were used, neither being very successful.

a) 2-Iodo-5-thenylalcohol (8.5 g) was added to nickel peroxide (12 g) in benzene (75 ml) and the mixture was stirred at 50° for 5 hrs. The solid was filtered off, the solvent was removed by distillation and the residue was chromatographed on silica. Elution with pentane-ether (10:1) gave the desired aldehyde (1.75 g) m.p. 48-50° (lit 51-52°). Further elution gave unreacted alcohol (2 g). However, the yield (26%) was far lower than that reported in the literature (70%).

b) (Following a published procedure[31]) A solution of the alcohol (2.4 g) in a mixture of 1,2-dimethoxyethane (20 ml) and 70% aqueous nitric acid (2 ml) was heated under reflux until oxidation was complete (approximately 45 min). The cooled reaction mixture was extracted with benzene and the organic layer was separated and washed with saturated sodium hydrogen carbonate solution and water. Evaporation of the solvent gave crude aldehyde, but the yield (0.3 g, 12%) was even poorer than in the previously described experiment.

2-Iodo-5-acetyl thiophene

2-Iodothiophene (21 g) and acetyl chloride (8 g) in toluene (100 ml) were treated with stannic chloride (26 g) at 0°. The mixture was stirred in cold water for 1 hr, then at room temperature for 1 hr, poured onto ice and the resulting solution was acidified. The toluene layer was separated, washed with sodium hydrogen carbonate solution and water and the solvent was removed, giving a solid. Recrystallisation from light petroleum (b.p. 60-80°) gave the product (11.4 g, 45%), m.p. 130-132° (lit[32] m.p. 129°).

Attempted preparation of [(α-methyl-5-iodo-2-thenylidene)amino]acetaldehyde dimethyl acetal

a) 2-Iodo-5-acetyl thiophene (6.3 g) in toluene (100 ml) was heated under reflux with aminoacetaldehyde dimethyl acetal for 4½ hr using a Dean and Stark trap. The reaction was followed by t.l.c. (EtOAc/silica) and after this period starting material was still present. After a total of 16 hr reflux, 2-iodo-5-acetyl thiophene was still present. However, the solvent was evaporated and the residue was chromatographed ($CHCl_3$/silica). Pure starting material was recovered and, in addition, a very small amount of solid which appeared to be the desired compound. The percentage conversion, however, was so low that the reaction was not worthwhile from the preparative point of view.

b) [(α-Methyl-2-thenylidene)amino]acetaldehyde dimethyl acetal (4.3 g) in benzene (25 ml) was treated with alternate portions of iodine (5.4 g) and yellow mercuric oxide (4.6 g) over a period of 45 min, then stirred at room temperature for 2½ hr. The solution was filtered and the solvent removed from the filtrate, to give a dark coloured oil which t.l.c. showed to be a mixture. Attempts to isolate any product from this mixture failed, nor was any Schiff's base recovered.

Attempts to prepare 2-methoxythienyl-5-methyl ketone

a) 2-Methoxythiophene (1.7 g) was stirred with acetic anhydride (2.6 ml), the temperature of the mixture being maintained at $7^{o}$ (ice bath). Phosphoric acid (0.7 ml) was added dropwise; an initial rise in temperature was contained by adding salt to the ice bath ($T = 13^{o}$). The red solution was stirred in the ice bath for 15 min then poured onto ice and the whole was made basic with sodium hydroxide solution and extracted with ether. The combined extracts were washed with sodium carbonate solution, dried ($Na_2SO_4$) and evaporated, giving a yellow oil which solidified. Recrystallisation from light petroleum (b.p. $60-80^{o}$) gave white crystals m.p. $52-54^{o}$; however, the nmr spectrum of this material showed that it was not the desired ketone.

b) 2-Methoxythiophene (2.5 g) and acetic anhydride (3.5 ml) were mixed and left to stand overnight. It was found that no reaction had occurred.

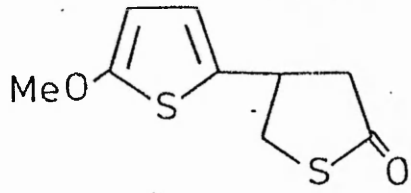
c) The reaction was repeated several times using the same proportions of 2-methoxythiophene and acetic anhydride but varying the amounts of phosphoric acid used. The unknown product was obtained in all cases, the yield being greater the more acid present.

d) 2-Methoxythiophene (0.5 g) and phosphoric acid (0.5 ml) were left overnight. The unknown product was obtained which indicates that the acetic anhydride has no part in the reaction.

e) Dimethylacetamide (1.7 g) was stirred in an ice bath whilst phosphoryl chloride (2 ml) was added dropwise. Methylene chloride (5 ml) was added after 5 min, followed by a solution of 2-methoxythiophene (2.28 g) in methylene chloride (5 ml). The resulting solution was stirred for 1 hr in the ice bath, for 2 hr at room

temperature and then left overnight in the dark. The dark solution was poured into sodium hydroxide solution (4M) and ice, and the aqueous layer was separated and extracted with methylene chloride. All extracts were combined, washed with water, 4M hydrochloric acid and brine, dried ($Na_2SO_4$) and concentrated. The oil remaining was made to solidify by treatment with light petroleum (b.p. 60-80°). Recrystallisation from light petroleum (b.p. 60-80°) gave white crystals m.p. 51-52°, identical to those produced in the previous experiments.

Spectral data suggests that the product is a thiolactone, probably




This was confirmed by analysis.

(Found: C, 50.77; H, 4.79; $C_9H_{10}O_2S_2$ requires C, 50.47; H, 4.67%)

τ ($CDCl_3$):

3.5 (d thiophene H J = 4 Hz)

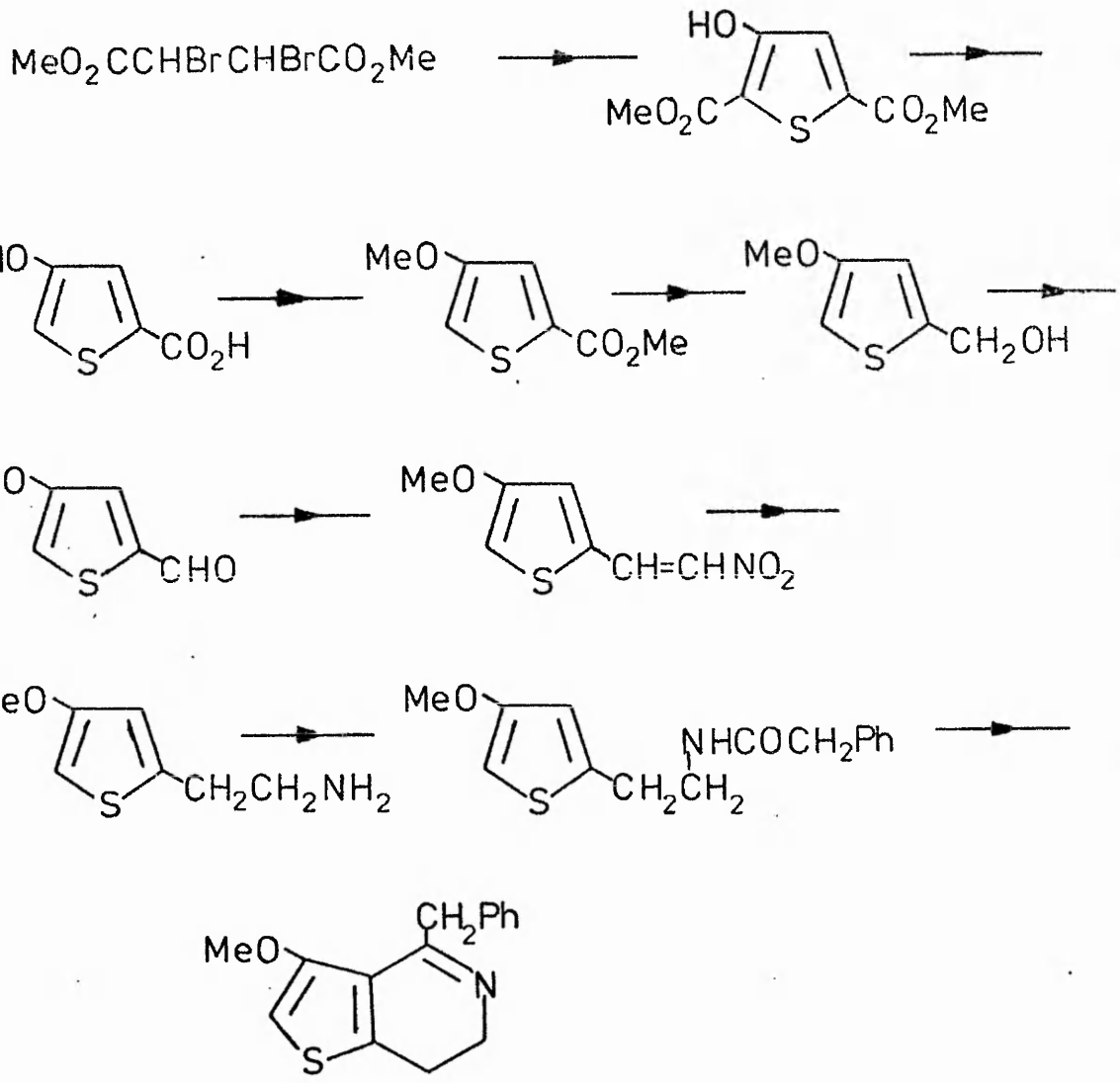
4.0 (d thiophene H J = 4 Hz)

6.15 (s -OMe), 6.55 (m $-CH_2-$, $-CH=$)

7.25 (m $-CH_2-$)

$\nu_{max}$ (KBr disc)

1720 $cm^{-1}$ (  )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MeO2C
S
CO2Me
HO
CO2H
MeO
CO2Me
MeO
CH2OH
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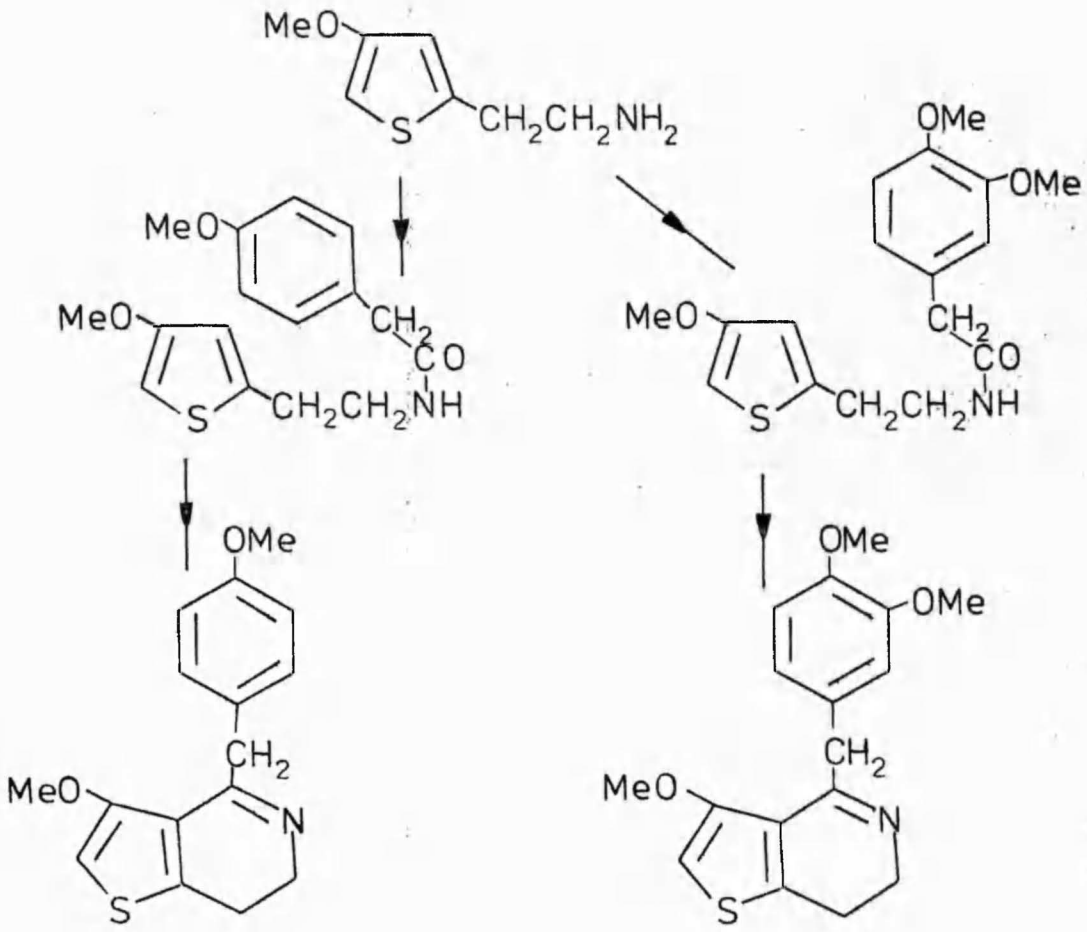
MeO
NHCOCH2Ph
CH2CH2
CH2Ph
MeO
N
S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S
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MeO
MeO
CH2
CO
S
CH2CH2NH
OMe
CH2
MeO
N
S
OMe
OMe
MeO
CH2
CO
S
CH2CH2NH
OMe
OMe
CH2
MeO
N
S

4-Hydroxy-2,5-bismethoxycarbonyl thiophene [33]

Meso dimethyl 1,2-dibromosuccinate (144 g) was dissolved in methanol (308 ml) at 28-30°, then methanolic potassium hydroxide (2M, 237 ml) was added dropwise with stirring and cooling so that the temperature remained at 28-30°. The mixture was then allowed to stand at room temperature until the total time elapsed was 1 hr, after which the solution was filtered and the filtrate was mixed with methyl thioglycollate (50.2 g). To this mixture was added, over a period of 40 min, methanolic potassium hydroxide (2M, 592 ml), the maximum temperature during the addition being 28°. After standing at room temperature for 4½ hrs the reaction mixture was poured into water (1137 ml) and acidified to Congo Red paper. The mixture was cooled in ice for one hour, when the precipitate was filtered off and dissolved in methylene chloride. Evaporation of the dried solution gave 4-hydroxy-2,5-bismethoxycarbonyl thiophene m.p. 103-106° (lit[33] m.p. 111°) (60 g).

The filtrate was extracted with methylene chloride and the extract was washed with sodium hydrogen carbonate solution. Evaporation of the dried methylene chloride solution gave a yellow oil (8 g) which solidified on standing. The solid, however, was very low melting; it was later identified as methyl 3-hydroxythiophene-2-carboxylate (lit m.p.[34] 40°).

The sodium hydrogen carbonate washings were combined and acidified to litmus paper with dilute hydrochloric acid. The precipitate which formed was filtered off, and was found to be the half-ester of the desired product, m.p. 185-186° (lit[35] m.p. 192°) (7 g).

The yield of the desired diester based on the possible amount of bromoester reacted was 71%.

Methyl 4-methoxythiophene-2-carboxylate[36]

4-Hydroxythiophene-2-carboxylic acid (21 g), dichloroethane (96 ml), methanol (25 ml) and concentrated sulphuric acid (4.5 ml) were heated under reflux for 10 hr. When cool, the solution was washed with water and 10% sodium carbonate solution, dried and concentrated. Distillation of the residue under reduced pressure gave methyl 4-methoxythiophene-2-carboxylate b.p. 92°/0.2 mm (lit[36] m.p. 38-39°) in 71% yield (11.4 g).

The basic washings were brought to pH 8 and extracted with methylene chloride. Removal of the solvent gave a solid which was identified as methyl 4-hydroxythiophene-2-carboxylate (0.7 g) m.p. 85-86° (lit[36] 89.5-90.5°). Further reduction of the pH of the basic solution caused a solid to be precipitated. This was collected and identified as 4-methoxythiophene-2-carboxylic acid (7.7 g) m.p. 167° (lit[36] 170-171°).

4-Hydroxythiophene-2-carboxylic acid

This was prepared according to Fiesselmann and Schipprak[37] in quantitative yield, m.p. 197-199° (lit[37] m.p. 204°).

2-Hydroxymethyl-4-methoxythiophene

Methyl 4-methoxythiophene-2-carboxylate (7.3 g) in dry ether (25 ml) was added dropwise with stirring to a suspension of lithium aluminium hydride (2 g) in dry ether (50 ml) under nitrogen, at such a rate that there was gentle reflux. When the addition was complete the mixture was stirred at room temperature for 1 hr. The excess of lithium aluminium hydride was destroyed by the cautious addition of wet ether and the complex was broken down by pouring the reaction mixture into a saturated solution of ammonium chloride. The mixture was filtered and the solid residue was washed well with ether. The

aqueous layer was separated and was re-extracted with ether. All ether solutions were combined, dried ($MgSO_4$) and concentrated, to give a pale yellow oil. Distillation of this oil yielded pure 2-hydroxymethyl-4-methoxythiophene b.p. 96°/0.3 mm (5.3 g 88%).

$\tau(CDCl_3)$:

3.47, 3.95 (2s thiophene H)

5.5 (s $-CH_2$), 6.05 (s -OH)

6.35 (s -OMe)

$\nu_{max}$ (thin film):

3400-3500 $cm^{-1}$ (OH).

The compound did not give satisfactory elemental analysis results so the phenyl urethane was prepared, m.p. 89-90°:

(Found: C, 59.50; H, 5.0; N, 5.0; $C_{13}H_{13}NO_3S$ requires C, 59.31; H, 4.94; N, 5.32%)

4-Methoxythiophene-2-carboxaldehyde

This aldehyde was prepared by oxidation of 2-hydroxymethyl-4-methoxythiophene. Details of unsuccessful, as well as successful experiments are given below.

a) Attempted oxidation with ceric ammonium nitrate[38]

2-Hydroxymethyl-4-methoxythiophene (0.27 g) in water (4 ml) was treated with a 1M solution of ceric ammonium nitrate (4 ml), to give a dark red solution. This was warmed at 50° for approximately 5 mins, during which time the colour of the solution changed to yellow. However, at the same time a dark oil was deposited. The dark oil was taken up in methylene chloride; the solution was washed with sodium hydrogen carbonate solution and water, dried ($MgSO_4$) and concentrated. The ir spectrum of the dark oil obtained showed that it was impure alcohol and no aldehyde was detected. Examination (via methylene chloride extraction) of the original aqueous phase showed that it, too, contained no aldehyde.

b) Attempted oxidation by nickel peroxide[39]

To the alcohol (0.3 g) in benzene (10 ml) was added nickel peroxide (0.7 g, 100% excess). The mixture was kept at 50° and the reaction was followed by tlc [silica/ether-light petroleum (b.p. 60-80°) 1:1]. After only a short time, tlc indicated the formation of a new product; however, after 5 hrs some starting material was still present. The mixture was filtered and the filtrate was concentrated under reduced pressure, to give a yellow oil, which was shown by ir and nmr spectroscopy to be essentially alcohol. Although the presence of aldehyde was indicated, the proportion of alcohol oxidised was very small.

c) Attempted oxidation using Seloxcette (chromium trioxide intercalated in graphite)[40]

Seloxcette (1.5 g) was added to a solution of the alcohol (0.67 g) in toluene (20 ml) under nitrogen. The mixture was heated under reflux, with stirring, and the reaction was followed by tlc [silica/ether-light petroleum (b.p. 60-80°) 1:1]. After a reflux time of 7 hrs, tlc indicated that starting material was still present. The mixture was filtered and the solvent was removed from the filtrate to leave an oil. Again ir and nmr spectroscopy indicated the presence of aldehyde, but the oil was essentially alcohol.

d) Attempted oxidation using silver carbonate on Celite[41]

A mixture of the alcohol (0.14 g) and silver carbonate on Celite (0.6 g) in benzene (15 ml) was stirred and heated under reflux. After 9 hrs, tlc [silica/ether-light petroleum (b.p. 60-80°) 1:1] indicated that the alcohol was still present. The mixture was filtered, and the filtrate was concentrated to yield an oil which proved to be mainly alcohol, although some aldehyde was present.

e) Oxidation using pyridinium chlorochromate[42]

A solution of the alcohol (12.5 g) in dry methylene chloride (50 ml) was added to a suspension of pyridinium chlorochromate (26.8 g) in dry methylene chloride (120 ml). After a short time the reaction mixture began to reflux spontaneously and a dark tar was formed. After 2 hrs at room temperature the reaction mixture was diluted with 5 volumes of dry ether, the solvent was decanted off and the black solid was washed with dry ether. Filtration of this mixture, followed by evaporation of the filtrate gave a yellow oil. Distillation of the oil gave pure 4-methoxythiophene-2-carboxaldehyde, b.p. $92^{o}/0.2$ mm, which solidified and had m.p. 35-37° (6.4 g, 50%).

$\tau(CDCl_3)$:

2.55, 3.2 (2s thiophene H)

6.14 (s -OMe) 0.14 (s-CHO)

$\nu_{max}$ (Thin film): 1670 $cm^{-1}$ (CHO)

The 2,4-dinitrophenylhydrazone had m.p. 164-166°.

(Found: C, 44.4; H, 3.40; N, 17.1; $C_{12}H_{10}N_4O_5S$ requires C, 44.7; H, 3.10; N, 17.39%)

4-Methoxy-2-(β-nitrovinyl)thiophene

a) 4-Methoxythiophene-2-carboxaldehyde (2.5 g), nitromethane (1.26 g) and benzylamine (0.3 ml) were mixed and left at room temperature in the dark. After 5 days the crystals formed were filtered off, giving 4-methoxy-2-(β-nitrovinyl)thiophene m.p. 114-115° (0.3 g). The unreacted aldehyde was recovered by distillation. This method was not used routinely as the waiting time was too long and the yield too low.

b) A mixture of glacial acetic acid (51 ml), ammonium acetate (5.8 g), nitromethane (37 ml) and the aldehyde (9 g) was heated under reflux

for 30 min, then allowed to cool. The crystals formed were filtered off. Treatment of the filtrate with a little water caused more product to crystallise out; this was collected and washed with a little ethanol, to give a total yield of nitrostyrene of 6.4 g (55%).

Although this method was quite successful and easy to use the product was not completely pure, which caused problems in the next stage of the reaction sequence.

c) A solution of sodium hydroxide (2.1 g) in water (3 ml) was added to a solution of the aldehyde (7.1 g) and nitromethane (3 g) in methanol (10 ml), with stirring in an ice-salt bath, at such a rate that the temperature did not exceed 15°. A bulky white precipitate formed when all the alkali had been added. The mixture was stirred in the ice-salt bath for 15 mins and then it was diluted with ice-water (30 ml). The basic solution produced was added dropwise to a solution of concentrated hydrochloric (10 ml) in water (15 ml). The yellow precipitate was filtered off, washed with a little ethanol and dried at the pump. Recrystallisation from ethanol gave yellow crystals of the nitrostyrene, m.p. 114-115° (5 g, 53%).

(Found: C, 45.1; H, 3.80; N, 7.3; $C_7H_7NO_3S$ requires C, 45.40; H, 3.78; N, 7.57%.)

$\tau(CDCl_3)$:

1.8 (d -CH=, J = 13 Hz)

2.55 (d -CH=, J = 13 Hz)

2.85, 3.42 (2d thiophene, J = 1.75 Hz)

6.14 (s -OMe)

$\nu_{max}$ (KBr): 1620 $cm^{-1}$ (Ar-C=C-)

1540, 1320 $cm^{-1}$ ($C-NO_2$)

β-(4-Methoxy-2-thienyl)ethylamine

A solution of 4-methoxy-2-(β-nitrovinyl)thiophene (3.3 g) in dry THF (50 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (3 g) in dry THF (50 ml) under nitrogen, at such a rate that there was gentle reflux. When the addition was complete the reaction mixture was stirred at room temperature for 1 hr. The excess of lithium aluminium hydride was destroyed by cautious addition of wet THF and the complex was broken down by treatment with 4M sodium hydroxide solution. The liquor was decanted off and the solid residue was washed several times with THF. All extracts were combined and evaporated, the residue was taken up in ether, dried ($MgSO_4$) and concentrated, giving impure β-(4-methoxy-2-thienyl) ethylamine. Attempts to distil the amine resulted in polymer formation, therefore it was purified by formation of the hydrochloride (by treatment of an ethereal solution of the amine with hydrogen chloride gas), m.p. 138-140° (1.9 g, 54%).

(Found: C, 43.5; H, 6.4; N, 7.3; $C_7H_{12}ClNOS$ requires C, 43.6; H, 6.2; N, 7.3%)

The spectroscopic data for the free amine is as follows:

τ($CDCl_3$):

3.46 (d thiophene H, J = 1.75 Hz)

3.96 (d thiophene H, J = 1.75 Hz)

6.25 (s -OMe)

7.14 (t $-CH_2-CH_2-$ J = 3Hz)

8.15 (broad peak $-NH_2$)

$\nu_{max}$ (thin film): 3380, 3300 $cm^{-1}$ ($NH_2$)

1560 $cm^{-1}$ ($NH_2$)

N-phenylacetyl-β-(4-methoxy-2-thienyl)ethylamine

Dicyclohexyl carbodiimide (0.65 g) was dissolved in dry methylene chloride (10 ml) and to this was added a solution of phenylacetic acid (0.43 g) in dry methylene chloride (5 ml). An exothermic reaction occurred and a precipitate formed. β-(4-methoxy-2-thienyl)ethylamine (0.5 g) in dry methylene chloride (5 ml) was added (further exothermic reaction), and the mixture was left to stand at room temperature overnight. The reaction mixture was filtered, the filtrate was washed with dilute acid and 10% sodium carbonate solution, dried ($MgSO_4$) and concentrated to afford a yellow mobile oil, which solidified. Recrystallisation from benzene-light petroleum (b.p. 40-60°) gave white crystals of N-phenylacetyl-β-(4-methoxy-2-thienyl) ethylamine, m.p. 76-77° (0.8 g), 92%.

(Found: C, 65.90; H, 6.93; N, 5.34; $C_{15}H_{17}NO_2S$ requires C, 65.45; H, 6.56; N, 5.09%.)

τ($CDCl_3$):

2.7 (s benzene H)

3.6 (broad peak thiophene H)

3.99 (d thiophene H, J = 1.75 Hz)

4.35 (hump -NH)

6.24 (s -OMe), 6.45 (s $-CH_2CO-$)

6.61 (t $-CH_2-$, J = 6 Hz)

7.17 (t $-CH_2-$, J = 6 Hz)

$\nu_{max}$ (KBr): 3280 $cm^{-1}$ (NHCO)
1640, 1560 $cm^{-1}$ (CONH)

3-Methoxy-4-benzyl-6,7-dihydrothieno[3,2-c]pyridine

A mixture of the above amide (0.1 g) and phosphoryl chloride (0.06 g) in dry toluene (5 ml) was heated under reflux for 15 min. During this time formation of an oil was observed. The toluene was removed under reduced pressure and the residual oil was treated with 2M sodium

hydroxide solution and extracted into ether. The extract was dried ($MgSO_4$) and concentrated to give a yellow viscous oil which solidified. Nmr spectroscopy showed this to be impure 2-methoxy-4-benzyl-6,7-dihydrothieno[3,2-c]pyridine (0.1 g 100%). This amine was converted into the picrate m.p. 163-164°.

(Found: C, 52.0; H, 3.7; N, 11.4; $C_{21}H_{18}N_4O_8S$ requires C, 51.85; H, 3.7; N, 11.5%.)

τ($CDCl_3$) for the free base:

2.7 (s benzene H)

4.15 (s thiophene H)

6.0 (s $-CH_2-$ phenyl)

6.3 (s -OMe)

6.3 (t $-CH_2-$ J = 6 Hz)

7.4 (t $-CH_2-$ J = 6Hz)

N-(4-methoxyphenyl acetyl)-β-(4-methoxy-2-thienyl)ethylamine

A solution of 4-methoxyphenylacetic acid (1.1 g) in dry methylene chloride (10 ml) was added to dicyclohexyl carbodiimide (1.4 g) in dry methylene chloride (10 ml), an exothermic reaction occurring with formation of a precipitate. To this stirred suspension was added a solution of β-(4-methoxy-2-thienyl)ethylamine (1.1 g) in dry methylene chloride (10 ml) and the reaction was then stirred at room temperature for 1 hr. Filtration, followed by concentration of the filtrate gave an oil which solidified. Recrystallisation from benzene-light petroleum (b.p. 40-60°) gave white crystals of N-(4-methoxyphenyl acetyl)-β-(4-methoxy-2-thienyl)ethylamine m.p. 99-100° (1.1 g, 52%).

(Found: C, 63.5; H, 6.3; N, 4.5; $C_{16}H_{19}NO_3S$ requires C, 62.95; H, 6.23; N, 4.59%.)

τ($CDCl_3$):

2.78, 2.83, 3.1, 3.23 (q benzene H, J = 9 Hz)

3.65 (broad peak thiophene H)

4.0 (d thiophene H, J = 1.75 Hz)

4.4 (hump -NH-)

6.2, 6.25 (2s 2-OMe)

6.55 (s $-CH_2-CO-$)

6.65, 7.2 (2xt 2x$-CH_2-CH_2-$, J = 6 Hz)

$\nu_{max}$(KBr): 3280 $cm^{-1}$ (NHCO)

1640 $cm^{-1}$ (CONH)

3-Methoxy-4-(4'-methoxybenzyl)-6,7-dihydrothieno[3,2-c]pyridine

The foregoing amide (0.5 g) in dry toluene (20 ml) was treated with phosphoryl chloride (0.3 g) and the mixture was heated under reflux for 15 mins, during which time an oil was formed. The toluene was decanted off and left to cool. The oil was treated with 2M sodium hydroxide solution and extracted into ether. The extract was dried ($MgSO_4$) and evaporated, to yield a pale yellow oil the ir spectra of which suggested it to be the desired product. On cooling, the toluene solution deposited crystals, m.p. 146-150°. The nmr spectrum of this material showed it to be the hydrochloride of 3-methoxy-4-(4'-methoxybenzyl)-6,7-dihydrothieno[3,2-c]pyridine (0.1 g).

$\tau(CDCl_3)$:

2.6 (d benzene H, J = 9 Hz)

3.1 (d benzene H, J = 9 Hz)

3.7 (s thiophene H)

5.35 (s $-CH_2-$)

6.0, 6.2 (2s 2x -OMe)

6.9 (t $-CH_2-CH_2-$, J = 6 Hz)

$\nu_{max}$ (thin film): 1620 $cm^{-1}$ (C=N)

The picrate of the dihydrothienopyridine had m.p. 169-170°. Unfortunately, the product did not give the expected elemental analysis results.

(Found: C, 50.0; H, 3.3; N, 10.2; $C_{22}H_{20}N_4O_9S$ requires C, 51.2; H, 3.9; N, 10.9%.)

N-(3,4-dimethoxyphenylacetyl)-β-(4-methoxy-2-thienyl)ethylamine

A solution of 3,4-dimethoxyphenyl acetic acid (1.24 g) in dry methylene chloride (20 ml) was added to dicyclohexyl carbodiimide (1.3 g) in dry methylene chloride (20 ml); an exothermic reaction occurred and a precipitate was formed. To this was added β-(4-methoxy-2-thienyl)ethylamine (1 g) in dry methylene chloride (20 ml) and the mixture was stirred at room temperature for 1 hr. The reaction mixture was filtered and the filtrate was concentrated, giving a yellow oil which solidified. Recrystallisation from benzene-light petroleum (b.p. 40-60°) gave white crystals of N-(3,4-dimethoxyphenylacetyl)-β-(4-methoxy-2-thienyl)ethylamine m.p. 91-92° (1.8 g 86%).

(Found: C, 60.89; H, 6.93; N, 4.28; $C_{17}H_{21}NO_4S$ requires C, 60.89; H, 6.58; N, 4.18%.)

τ($CDCl_3$):

2.7 (hump -NH), 3.2 (m benzene H)

3.6 (broad peak thiophene H)

3.99 (d thiophene H, J = 1.75 Hz)

6.1 (s 2x -OMe)

6.24 (s -OMe (thiophene) )

6.5 (s $-CH_2CO-$)

6.6 (t $-CH_2-$, J = 6 Hz)

7.15 (t $-CH_2-$, J = 6Hz)

$\nu_{max}$ (KBr): 3300 $cm^{-1}$ (NHCO)

1640 $cm^{-1}$ (CONH)

3-Methoxy-4-(3',4'-dimethoxybenzyl)-6,7-dihydrothieno[3,2-c]pyridine

To the above amide (2.1 g) in dry toluene (100 ml) was added phosphoryl chloride (0.96 g) and the solution was heated under reflux for 40 mins. The toluene was decanted from the dark oil that had separated and was left to cool.

The oil was treated with dry ether and scratched, causing it to solidify; the ir spectrum of the solid indicated that it could be the impure hydrochloride of the desired product.

The crystals deposited by the toluene were identified as the hydrochloride of 3-methoxy-4-(3',4'-dimethoxybenzyl)-6,7-dihydrothieno [3,2-c]pyridine m.p. 146-149° [$\nu_{max}$ (KBr): 1640 $cm^{-1}$ (C=N), 2300 $cm^{-1}$ ($\overset{+}{N}H$)].

A picrate of the dihydrothienopyridine was prepared, and had m.p. 80-84°. Unfortunately, the analytical sample of the picrate decomposed on drying for 2½ hrs at 75° under vacuum.

The overall yield of the reaction was quite low, (1.5 g 33%) which could have been due to the prolonged reflux period. The reaction was repeated with a reflux period of 20 mins, all starting material having disappeared by this time; however, there did not seem to be a significant increase in the yield.

The spectroscopic properties of 3-methoxy-4-(3',4'-dimethoxybenzyl)-6,7-dihydrothieno[3,2-c]pyridine are as follows:

$\tau(CDCl_3)$:

2.5 (m benzene H)

3.2 (d benzene H, J = 9 Hz)

4.05 (s thiophene H)

6.1 (m 2x -OMe, $-CH_2-CH_2-$)

6.15 (s $-CH_2-Ar$)

6.45 (s thiophene -OMe)

7.2 (t $-CH_2-CH_2-$, J = 9 Hz)

$\nu_{max}$ (thin film): 1610 $cm^{-1}$ (C=N)

Attempt to prepare 3-methoxy-4-(3',4'-dimethoxybenzyl)thieno [3,2-c]pyridine

Activated manganese dioxide (0.69 g) in dry benzene (10 ml) was heated under reflux for 2 hrs with azeotropic removal of water. 3-Methoxy-4-(3',4'-dimethoxybenzyl)-6,7-dihydrothieno[3,2-c]pyridine (0.31 g) in dry benzene (2 ml) was added in one portion and the whole was heated under reflux for 40 min. The cooled reaction mixture was filtered through Hyflo and the filtrate was concentrated, to give a viscous oil (0.3 g), the spectrum of which indicated that benzene was still present. On tlc (silica/EtOAc) the product proved to have a very similar $R_F$ value to the starting material. However, the ir spectrum of the oil indicated that it contained a carbonyl group [$\nu_{max}$ (thin film): 1670 $cm^{-1}$ (C=O)].

It was difficult to obtain any conclusive evidence from the nmr spectrum. The integration indicated an increase in the number of protons in the aromatic region, which would be expected if aromatisation had occurred, yet, at the same time, the triplet for the saturated $-CH_2-CH_2-$ was visible.

It would appear, therefore, that the product was 3-methoxy-4-(3',4'-dimethoxybenzoyl)-6,7-dihydrothieno[3,2-c]pyridine. The picrate had m.p. 128-130°(dec).

$\tau$($CDCl_3$:

2.45 (d benzene H, J = 1.75 Hz)

3.15 (s aromatic)

3.25 (d benzene H, J = 1.75 Hz)

4.1 (s thiophene H)

6.15 (broad s -OMe, $-CH_2-$)

6.2 (s -OMe), 6.5 (s thiophene -OMe)

7.25 (t $-CH_2-CH_2-$)

$\nu_{max}$ (thin film): 1670 $cm^{-1}$ (C=O), 1600 $cm^{-1}$ (C=N).

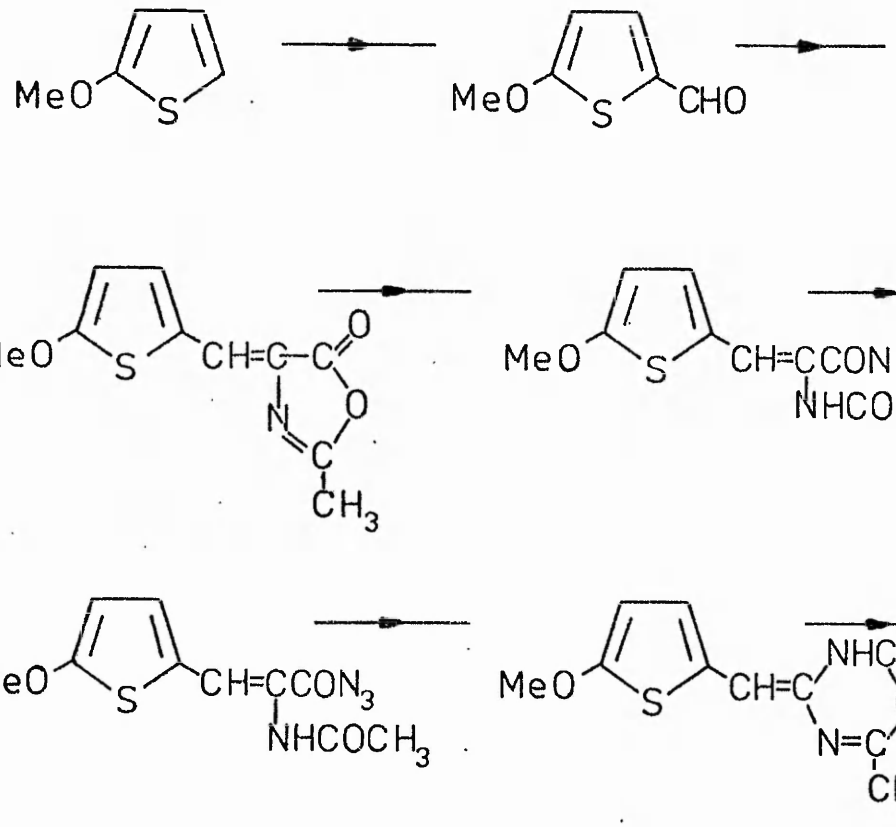
Reduction of the carbonyl group

Boron trifluoride-ether complex (1.2 ml) in diglyme (2.7 ml) was added dropwise with stirring to the suspected 3-methoxy-4-(3',4'-dimethoxybenzoyl)-6,7-dihydrothieno[3,2-c]pyridine (90 mg) in a mixture of sodium borohydride (1.13 g) and diglyme (1 ml). A vigorous reaction occurred, heat being produced. The mixture was stirred at room temperature for $1\frac{1}{2}$ hrs, then the diglyme was removed under reduced pressure at $60^{\circ}$. The white solid residue was treated carefully with methanol (10 ml), a very vigorous reaction taking place. This mixture was boiled under reflux for $\frac{1}{2}$ hr to decompose the excess of sodium borohydride and the complexes formed. The methanol was removed under reduced pressure and the residue was taken up in ether. The ether solution was washed with water, dried ($MgSO_4$) and concentrated giving a very small quantity of oil. The ir spectrum of this showed that diglyme was present; however, it also showed the presence of the alcohol group indicating reduction had occurred, [$\nu_{max}$ (thin film): broad peak 3500 $cm^{-1}$ (-OH), no peak at 1670 $cm^{-1}$ (-C=O)]. The product was therefore suspected to be 3-methoxy-4-(3',4'-methoxyphenyl carbinyl)-6,7-dihydrothieno[3,2-c]pyridine.

3-Methoxy-4-(3',4'-dimethoxybenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine

3-Methoxy-4-(3',4'-dimethoxybenzyl)-6,7-dihydrothieno[3,2-c]pyridine (50 mg) in ethanol (2 ml) was treated with sodium borohydride (0.2 g) and left at room temperature for 1 hr. The reaction mixture was evaporated to dryness and the residue was treated with water and extracted into ether. The extract was dried ($MgSO_4$) and concentrated, giving a very viscous product. The ir spectrum of this showed that the -C=N- peak of the starting material at 1670 $cm^{-1}$ had disappeared; the product was therefore thought to be the tetrahydrothieno[3,2-c]pyridine. A picrate of the product had m.p. 95-100°(dec).

Unfortunately, insufficient of this material was available for analysis.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N
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NHCOCH3
MeO
S
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NHCOCH3
MeO
S
CH=C
NHCO
O
N=C
CH3
MeO
S
CH2CO2H

2-Methyl-4-(5-methoxy-2-thenylidene)oxazol-5-one

5-Methoxythiophene-2-aldehyde (5 g), anhydrous sodium acetate (5.7 g), aceturic acid (4.1 g) and acetic anhydride (11 ml) were heated on a water bath for 3 hrs during which time a solid was formed. Water (17 ml) was added and when the solution was cool, the solid was filtered off, washed with water and ethanol and dried at the pump. Recrystallisation from benzene-light petroleum (b.p. 60-80°) gave pure 2-methyl-4-(5-methoxy-2-thenylidene)oxazol-5-one as yellow crystals m.p. 141-142°, (1.4 g).

Extraction of the filtrate with chloroform gave an oil which proved to be recovered 5-methoxythiophene-2-aldehyde (3 g). Hence, the yield of oxazolone was 31% based on unrecovered aldehyde.

(Found: C, 53.7; H, 4.0; N, 6.0; $C_{10}H_9NO_3S$ requires C, 53.81; H, 4.0; N, 6.28%.)

$\tau$($CDCl_3$): 2.65 (d thiophene H -CH=)

3.65 (d thiophere H, J = 4 Hz)

5.95 (s -OMe), 7.61 (s -Me)

$\nu_{max}$ (KBr): 1640 $cm^{-1}$ (C=N)

1750, 1770 $cm^{-1}$ (C-O-C, C=O)

α-Acetamido-β-(5-methoxy-2-thienyl)acryloylhydrazide

The above oxazolone (1 g) was added to a solution of 100% hydrazine hydrate (0.6 g) in ethanol (9 ml). The deep yellow colour of the oxazolone changed immediately to the light yellow of the product which was filtered off, washed with ethanol and dried. Recrystallisation from ethanol gave pale yellow crystals of the hydrazide m.p. 164-165° (0.8 g, 72%).

(Found: C, 46.7; H, 5.1; N, 16.5; $C_{10}H_9NO_3S$ requires C, 47.05; H, 5.09; N, 16.47%.)

$\nu_{max}$ (KBr): 3350-3450 $cm^{-1}$ (NHCO, $NH-NH_2$)

1650-1680 $cm^{-1}$ (NHC, $NHNH_2$)
‖
O

α-Acetamido-β-(5-methoxy-2-thienyl)acryloyl azide

The hydrazide (0.7 g) was treated with 1N hydrochloric acid (8 ml) and sodium nitrite (0.25 g) in water (5 ml), with stirring. The precipitate which appeared immediately, was filtered off, washed with water and dried in vacuo over silica gel. The pure azide had m.p. 111° (dec) (0.6 g, 90%). Unfortunately, an analysis of this sample could not be obtained due to its instability on drying.

τ($CDCl_3$): 2.15 (s -CH=)

2.85 (m thiophene H NH-)

3.7 (d thiophene H, J = 4 Hz)

4.1 (s Ar-OMe), 7.8 (s $-CH_3$)

$\nu_{max}$ (KBr): 3500 $cm^{-1}$ (NHCO)

2150 $cm^{-1}$ (azide)

1660 $cm^{-1}$ (NHC=O)

3,4-Dihydro-6-methyl-4-(5-methoxy-2-thenylidene)-2-oxo-1,3,5-oxadiazine

The azide (0.55 g) in benzene (8 ml) was heated under reflux for 30 min, after which time the solution was filtered. On cooling, orange crystals of the oxadiazine were deposited (0.32 g, 65%). After several recrystallisations this compound failed to give a sharp m.p. although it darkened rapidly at 160°.

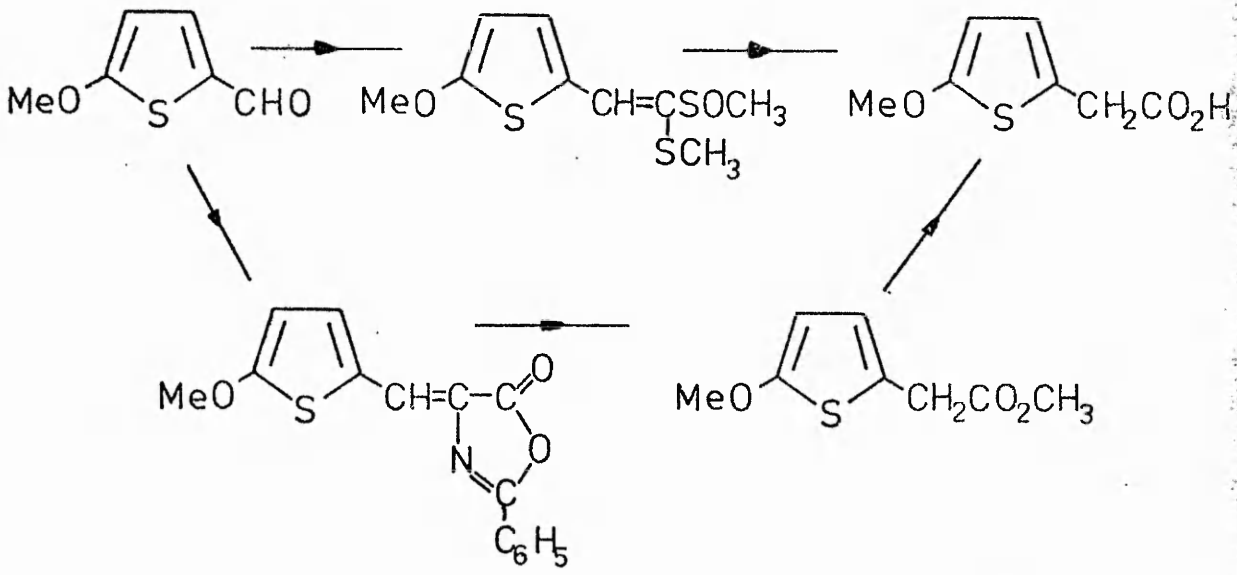
$\nu_{max}$ (KBr): 1750 $cm^{-1}$ (NH-C(=O)-O)

1640 $cm^{-1}$ (C=N)

5-Methoxy-2-thienyl acetic acid

The foregoing oxadiazine (0.20 g) in 4M hydrochloric acid (6 ml) was kept at 80° for 15 min. When cool, the solution was extracted with ether and the extract was washed with base. Acidification and re-extraction with ether gave an oil which solidified when scratched, (0.05 g). Tlc (silica/EtOAc) showed that the $R_f$ of this product and that of the acid obtained by another route to be the same. The ir spectrum of the solid confirmed that it was an acid.

The sequence used in the foregoing experiments was that of ref. 43.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SCH3
MeO
S
CH2CO2H
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S
CH=C–C
O
O
N
C
C6H5
MeO
S
CH2CO2CH3

1-Methylsulphinyl-1-methylthio-2-(5-methoxy-2-thienyl)ethylene

To a solution of methyl methylthiomethyl sulphoxide[44] (2.57 g) and 5-methoxythiophene-2-aldehyde (3.5 g) in THF (5 ml) was added Triton B (2 ml of a 40% solution in methanol) and the resultant mixture was heated under reflux for 4 hrs.

After removal of the solvent the residue was distilled under reduced pressure to yield a pale yellow oil (1.4 g) b.p. 100°/0.2 mm, identified as impure unreacted aldehyde. It was suspected, however, that some decomposition accompanied this distillation. The large pot residue was chromatographed (alumina/EtOAc) yielding more aldehyde (1.4 g), a solid (0.8 g) and unreacted methyl methylthiomethyl sulphoxide (0.5 g).

The solid was recrystallised from benzene-light petroleum (40-60) to give crystals which were identified as 1-methylsulphinyl-1-methylthio-2-(5-methoxy-2-thienyl)ethylamine m.p. 87-89°, (0.8 g, 62% based on reacted aldehyde).

(Found: C, 43.74; H, 5.23; $C_9H_{12}O_2S_3$ requires C, 43.55, H, 4.8%.)

nmr $\tau$($CDCl_3$):

2.25 (s Ar-CH=)

2.9, 3.76 (d thiophene H, J = 4 Hz)

6.05 (s -OMe)

7.3 (s $-SOCH_3$), 7.63 (s $-SCH_3$)

$\nu_{max}$(KBr): 1080 $cm^{-1}$ (methyl sulphinyl)

The reaction was repeated using an increased reflux time; after a total of 11 hrs tlc indicated that aldehyde was still present and separation by column chromatography (alumina/EtOAc) gave approximately the same proportions of products as was obtained after 4 hrs reflux.

2-Phenyl-4-(5-methoxy-2-thenylidene)oxazol-5-one

A mixture of 5-methoxythiophene-2-aldehyde (3 g), hippuric acid (6.2 g) and anhydrous sodium acetate (1.9 g) in acetic anhydride (11 ml) was heated on a water bath for 3 hr during which time a solid was formed. After cooling, the solid was filtered off and washed with water and ethanol; thus 2-phenyl-4-(5-methoxy-2-thenylidene)oxazol-5-one was obtained as yellow crystals, m.p. 168-169° (4.4 g, 74%).

(Found: C, 63.3; H, 3.8; N, 4.7; $C_{15}H_{11}NO_3S$ requires C, 63.15; H, 3.86; N, 4.91%.)

$\tau$($CDCl_3$): 1.8 (m benzene 2H)

2.5 (m benzene 3H + thiophene H -CH=)

3.66 (d thiophene H, J = 4 Hz)

5.95 (s -OMe)

$\nu_{max}$ (KBr): 1650 $cm^{-1}$ (C-N=C)

1770, 1790 $cm^{-1}$ (C(=O)-O-C)

5-Methoxy-2-thienylacetic acid

2-Phenyl-4-(5-methoxy-2-thenylidene)oxazol-5-one (7.8 g) in 10% sodium hydroxide solution (50 ml) was heated under reflux, with stirring, until evolution of ammonia had ceased (approximately 10 h), then 40% sodium hydroxide solution (4 ml) was added. The cooled reaction mixture was stirred in an ice bath whilst a mixture of 30% hydrogen peroxide-water (1:1, 6 ml) was added at such a rate that the temperature did not exceed 15°, then the whole was left at room temperature overnight.

The dark yellow solution was acidified by cautious addition of concentrated hydrochloric acid (17.5 ml) which caused a solid to precipitate. This was extracted with chloroform; the extract was

dried and concentrated giving a red solid, which was dissolved in methanol (40 ml) and concentrated sulphuric acid (0.6 ml). The solution was heated under reflux for 45 min, then cooled. After removal of the methanol the residue was treated with water and extracted with methylene chloride. The extract was washed with 10% sodium carbonate solution and water, dried ($MgSO_4$) and concentrated. The oil obtained was purified by column chromatography [alumina/1:1 mixture $Et_2O$-light petroleum (b.p. 60-80°)] giving two products which were identified as methyl benzoate and methyl(5-methoxy-2-thienyl)-acetate. Distillation of the latter gave a pale yellow liquid, b.p. 84°/0.3 mm (1.5 g, 28%).

nmr ($CDCl_3$): 3.5, 4.0 (2d thiophene H, J = 4 Hz)

6.12 (s $-CH_2-$)

6.2 (s $-CO_2Me-$)

6.3 (s -OMe)

$\nu_{max}$ (thin film): 1740 $cm^{-1}$ (ester).

The above ester (1.5 g) in 10% sodium hydroxide solution (8 ml) was heated under reflux for 20 mins during which time the ester layer disappeared. The solution was cooled, poured into concentrated hydrochloric acid (8 ml) and ice and the precipitate formed was filtered off, taken up in ether, dried ($MgSO_4$) and evaporated to give a brown solid. Recrystallisation of this from benzene-light petroleum (b.p. 60-80°) gave 5-methoxy-2-thienyl acetic acid as a tan coloured solid m.p. 47-48° (0.6 g, 46%).

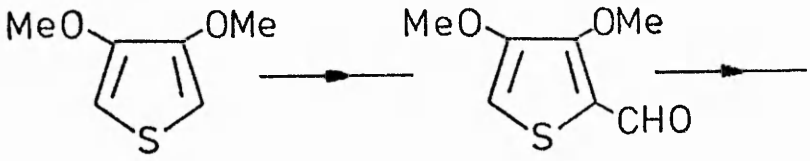
$\tau$($CDCl_3$): 3.4, 3.93 (2d thiophene H, J = 4 Hz)

6.14 (s -OMe)

6.29 (s $-CH_2-$) -1.24 (broad peak -OH)

Attempts to purify this compound to analytical standard failed.

The foregoing two experiments used the methods of ref. 45.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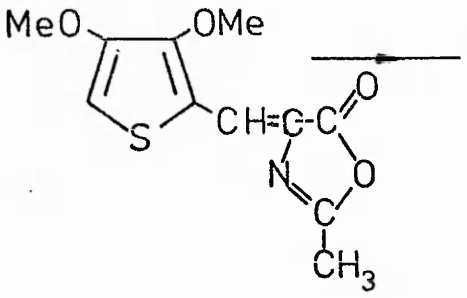
OMe
S
CHO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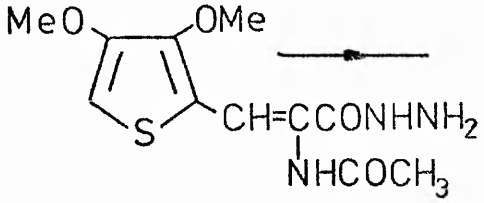
N
O
C
CH3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OMe
S
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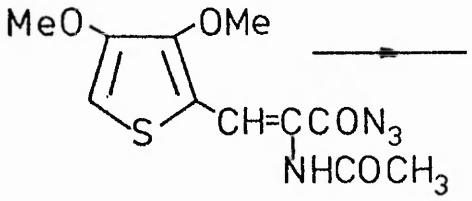
NHCOCH3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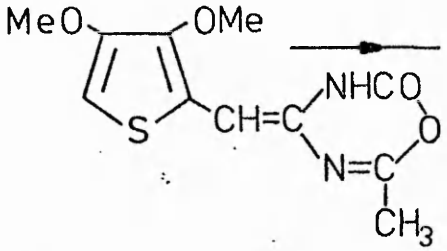
CH=CCON3
NHCOCH3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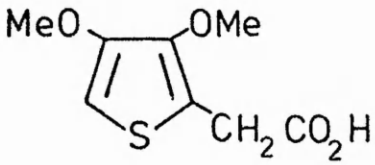
O
N=C
CH3


MeO
OMe
S
CH2 CO2H

3,4-Dimethoxythiophene-2-aldehyde

This compound was obtained in 52% yield by the method of L. H. M. Guindi.[46]

2-Methyl-4-(3,4-dimethoxy-2-thenylidene)oxazol-5-one

3,4-Dimethoxy thiophene-2-aldehyde (2.7 g), fused sodium acetate (2.7g), aceturic acid (1.9 g) and acetic anhydride (5.1 g) were heated on a water bath for 7 hrs during which time a solid was formed. Water (5 ml) was added and when the mixture was cool, the solid was filtered off, washed with water and ethanol, and dried at the pump. Recrystallisation from acetone-ethanol gave the pure oxazolone (1.3 g, 33%), m.p. 140-142°.

(Found: C, 52.6; H, 4.2; N, 5.3; $C_{11}H_{11}NO_4S$ requires C, 52.17; H, 4.35; N, 5.53%)

$\tau(CDCl_3)$:

2.4 (s Ar-CH-), 3.3 (s, thiophene H)

5.93 (s Ar-OMe), 6.07 (s Ar-OMe), 7.6 (s -Me)

$\nu_{max}$ (KBr disc):

1770 $cm^{-1}$ (-$\overset{\downarrow}{C}$O-O- azlactone)

1660 $cm^{-1}$ (-$\overset{\downarrow}{C}$=N-)

Extraction of the filtrate with methylene chloride gave a solid, which on purification, proved to be recovered aldehyde (1 g). Hence, the yield was 52% based on unrecovered aldehyde.

α-Acetamido-β-(3,4-dimethoxy-2-thienyl) acrylyl hydrazide

The above azlactone (1 g) was added to a solution of 100% hydrazine hydrate (0.5 g) in ethanol (7 ml). The deep yellow colour of the azlactone changed immediately to the light yellow of the product, which was filtered off, washed with ethanol and dried. Recrystallisation from ethanol gave pale yellow crystals of the hydrazide m.p. 171-172° (0.9 g 82%).

(Found: C, 46.4; H, 5.3; N, 14.5; $C_{11}H_{15}N_3O_4S$ requires C, 46.31; H, 5.26; N, 14.73%)

τ(DMSO):

2.38 (s Ar-CH=), 3.11 (s thiophene H)

5.6 (mound -NH), 6.1 (d 2x Ar-OMe)

6.55 (s $-NH_2$, -NH), 7.95 (s $-COCH_3$)

$\nu_{max}$ (KBr disc):

1670, 1650 $cm^{-1}$ (amide)

α-Acetamido-β-(3,4-dimethoxy-2-thienyl) acryloyl azide

The hydrazide (0.9 g) was treated with 1M hydrochloric acid (9 ml) and 95% sodium nitrite (0.3 g) in water (6 ml) with stirring. The precipitate, which appeared immediately, was filtered off, washed with water and dried in vacuo over silica gel. The pure azide had a melting point of 119-121° (dec) (0.9 g, 95%).

Unfortunately, an analysis of this sample could not be obtained due to its instability when drying.

τ($CDCl_3$):

2.0 (s Ar-CH=), 2.5 (mound -NH)

3.45 (s thiophene H), 5.96 (s Ar-OMe)

6.1 (s Ar-OMe), 7.8 (s $-CH_3$)

$\nu_{max}$ (KBr disc):

2150 $cm^{-1}$ (azide).

3,4-Dihydro-6-methyl-4-(3,4-olimethoxy-2-thenylidene)-2-oxo-1:3:5-oxadiazine

The azide (0.7 g) in benzene (9 ml) was heated under reflux for 30 min, after which the solution was filtered. On cooling orange crystals of the oxadiazine were deposited, (0.35 g 56%). The pure compound, recrystallised from benzene had m.p. 157-159°.

(Found: C, 49.1; H, 4.4; N, 10.1; $C_{11}H_{12}N_2O_4S$ requires C, 49.25; N, 10.45%)

τ(DMSO):

3.8 (s thiophene H), 4.15 (s Ar-CH=)

6.15 (s 2x Ar-OMe), 6.7 (mound -NH)

7.75 (s $-CH_a$)

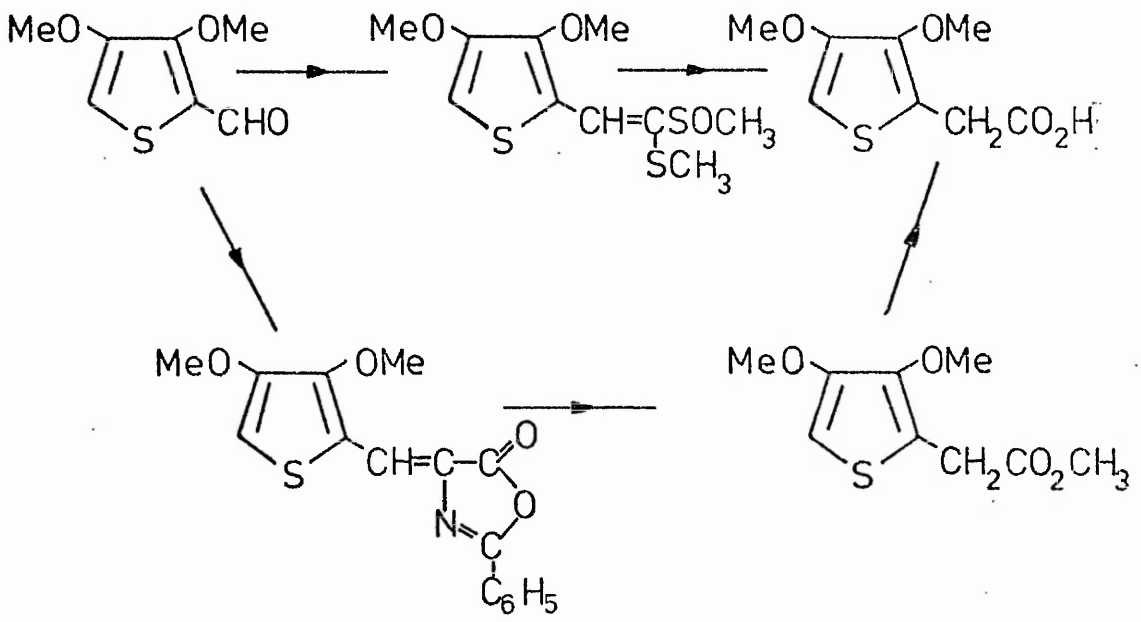
$\nu_{max}$ (KBr disc):

1760 $cm^{-1}$ (-NH-C=O)

3,4-Dimethoxy-2-thienylacetic acid

The oxadiazine (0.23 g) in 4M hydrochloric acid (6 ml) was kept at 80° for 30 min during which time the solution darkened considerably. After cooling, the solution was extracted with ether and the extract was washed with base. Acidification and re-extraction with ether gave an oil which tlc (EtOAc/alumina) showed to contain a substance of high $R_F$ and a material which remained on the baseline. Ir confirmed that the product was an acid, but no conclusions could be drawn from the nmr as the sample was too impure.

The sequence used in the foregoing experiments was that of ref. 43.


MeO
OMe
CHO
S
CH=CSOCH3
SCH3
CH2CO2H
CH=C
C
O
N
C6H5
CH2CO2CH3

1-Methylsulphinyl-1-methylthio-2-(3,4-dimethoxy-5-thienyl)ethylene

To a solution of methyl methylthiomethyl sulphoxide[44] (1.25 g) and 3,4-dimethoxythiophene-2-aldehyde (2.1 g) in THF (3 ml) was added Triton B (1 ml of a 40% solution in methanol); the mixture was heated under reflux for 4 hrs. The solvent was removed and the viscous residue was purified by column chromatography (silica/$CHCl_3$) giving 3 g of a yellow oil. Attempts to distil this resulted in polymer formation and decomposition but a small amount of distillate was obtained, b.p. 200°/0.2 mm (0.7 g, 20%). The nmr spectrum of this showed that it was the desired 1-methylsulphinyl-1-methylthio-2 (3,4-dimethoxy-5-thienyl)ethylene.

$\tau$($CDCl_3$): 1.95 (s Ar-CH=), 3.55 (s thiophene H)
6.02 (s -OMe), 6.11 (s -OMe)
7.26 (s $-SOCH_3$), 7.60 (s $-SCH_3$)

$\nu_{max}$ (thin film): 1050 $cm^{-1}$ (methylsulphinyl)

Attempt to prepare 3,4-dimethoxy-5-thienylacetic acid

[44]1-Methylsulphinyl-1-methylthio-2(3,4-dimethoxy-5-thienyl) ethylene (0.5 g) in 1,2-dimethoxy ethane (10 ml) was treated with concentrated hydrochloric acid (1 ml), whereupon some heat was produced and the solution darkened considerably. After 30 min at room temperature the solution was extracted with dilute sodium hydroxide solution. This basic extract was acidified and re-extracted with methylene chloride. However, no product was obtained on evaporation of the solvent.

2-Phenyl-4-(3,4-dimethoxy-2-thenylidene)oxazol-5-one

3,4-Dimethoxythiophene-2-aldehyde (3 g), hippuric acid (4.5 g), anhydrous sodium acetate (1.5 g) and acetic anhydride (8 ml) were heated on a steam bath for 1 hr during which time a solid was formed. When cool, the solid was filtered off, washed well with water and a little methylated spirit and dried at the pump. Recrystallisation from light petroleum (b.p. 80-100°) gave pure 2-phenyl-4-(3,4-dimethoxy-2-thenylidene)oxazol-5-one m.p. 167-168° (5 g, 90%).

(Found: C, 60.8; H, 4.2; N, 4.5; $C_{16}H_{13}NO_4S$ requires C, 60.95; H, 4.1; N, 4.4%.)

$\tau$($CDCl_3$): 1.8 (m benzene 2H)

2.4 (m benzene 3H + -CH=)

3.3 (s thiophene H)

5.95 (s -OMe), 6.1 (s -OMe)

$\nu_{max}$ (KBr): 1640 $cm^{-1}$ (N=C)

1780 $cm^{-1}$ (C-O-C, C=O)

Attempt to prepare (3,4-dimethoxy-2-thienyl)acetic acid

2-Phenyl-4-(3,4-dimethoxy-2-thenylidene)oxazol-5-one (4.5 g) in 10% sodium hydroxide (30 ml) was heated under reflux until ammonia evolution ceased. During this time the solution became very dark and viscous. 40% Sodium hydroxide solution (2 ml) was added and the reaction mixture was cooled in an ice bath. A mixture of 30% hydrogen peroxide-water (1:1, 3ml) was added to the cooled, stirred solution at such a rate that the temperature never exceeded 15°; it was then left at room temperature overnight.

Acidification of the solution by cautious addition of concentrated hydrochloric acid (10 ml) caused deposition of a dark tar. This was extracted with benzene; the extract was dried and concentrated, giving a dark oil. This was treated with methanol (23 ml) and concentrated sulphuric acid (0.35 ml) and heated under reflux for 5 hrs. The solvent was removed and the residue was treated with water and then extracted with chloroform. The extract was washed with 10% sodium carbonate solution and water, dried ($MgSO_4$) and concentrated. Distillation of the oil obtained gave a small amount of product which was identified as methylbenzoate contaminated by what could have been the desired ester, methyl(3,4-dimethoxy-2-thienyl) acetate. However, the yield was too small to make this a worthwhile route to the acid.

The foregoing two experiments used the methods of ref. 45.

Attempt to prepare 2-methoxy-5-thienylacetic acid

The Mannich base from 2-methoxythiophene and dimethylamine was prepared in good yield by the method of ref. 6.

The methiodide (3.68 g) of the Mannich base was added to a suspension of sodium cyanide (1.2 g) in ethanol (40 ml). The mixture was heated under reflux for 12 hrs, cooled and concentrated. The residue was treated with water (10 ml) followed by concentrated hydrochloric acid until the solution was acidic. Isolation by ether extraction gave 2-methoxy-5-thienylacetonitrile (1.7 g) as a viscous oil.

The nitrile (1.7 g) was dissolved in a solution of potassium hydroxide (8 g) in water (6 ml) and ethylene glycol (50 ml). Following an 18 hr period of reflux the solution was concentrated, the residue was treated with water, the solution was acidified and extracted with ether, but no acidic product was obtained.

The above experiments used the methods of ref. 47.

## Experimental References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