D. Holmes: STUDIES OF THIENO[b]PYRIDINE DERIVATIVES

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Several routes to thienopyridine analogues of furoquinoline alkaloids were investigated. The preparation of angularly fused tricyclic systems was quite straightforward but linear fusion was more difficult to achieve.

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TRENT POLYTECHNIC

in collaboration with

IMPERIAL CHEMICAL INDUSTRIES PLC,
PHARMACEUTICALS DIVISION

STUDIES OF THIENO[b]PYRIDINE DERIVATIVES

being a thesis submitted to
the Council for National Academic Awards
for the degree of

DOCTOR OF PHILOSOPHY

by

DAVID HOLMES, BSc, MRSC CChem

October 1985

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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 October 1982 and October 1985. During this period the author has not been a registered candidate for another award of the CNAA or other academic institution; also no material contained in this thesis has been used in any other submission for an academic award.

A programme of advanced studies has been undertaken during this work. This included postgraduate lectures at Trent Polytechnic on n.m.r. spectroscopy and colloid and polymer chemistry together with attendance at many academic lectures at Nottingham, Loughborough and Sheffield universities, and at Fisons Pharmaceuticals, Loughborough. The RSC annual congress (Exeter 1984) and an SERC summer school on n.m.r. spectroscopy (Sheffield 1983) have also been attended.

The author wishes to express his gratitude to Dr J M Barker for his supervision and encouragement throughout this work; many thanks are also due to Dr P R Huddleston for his helpful advice.

The author is indebted to Dr N F Elmore of ICI Pharmaceuticals Division, Alderley Edge for helpful discussions and advice. The provision of chemicals and micro-analytical facilities by ICI is gratefully acknowledged.

The help of the SERC for financial support in the form of an Instant Award is appreciated.

Thanks are also extended to the technical staff at Trent Polytechnic over this period for their support, in particular to Mr M L Wood and Miss E D Woodland for their technical assistance. Particular gratitude is extended to Miss J Reeder for her patience and perseverance in the typing of this thesis.

Part of this work has been published in the Journal of Chemical Research. Copies of the synopses of these papers are included at the end of this thesis.

DAVID HOLMES

Trent Polytechnic

D. Holmes: STUDIES OF THIENO[b]PYRIDINE DERIVATIVES

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The use of isatoic anhydrides in the preparation of quinolines has been applied to the synthesis of some related thienopyridines. The novel thiophene analogues of isatoic anhydrides were prepared and used to produce analogues of several 2-aryl-4-quinolone alkaloids.

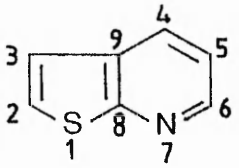
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CHAPTER ONE

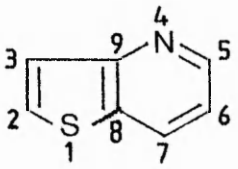
INTRODUCTION

This work concerns studies on thieno[b]pyridines, which are isosteres of quinoline, from two aspects; studies of the reactions of novel compounds (and of known compounds where relevant) and preparation of analogues of quinoline alkaloids in which the benzene ring has been replaced by thiophene. This introduction thus consists of two parts. Firstly a review of the synthesis, physical properties and reactions of thieno[b]pyridines (including the rare [3,4-b] system where appropriate, although no work on this system was carried out by the author) with reference to some relevant aspects of quinoline chemistry. Secondly, a review of the synthesis and properties of the quinoline alkaloids whose analogues were prepared.

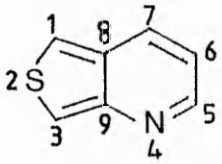
1.1 THIENO[b]PYRIDINES



[2,3-b] (1)



[3,2-b] (2)

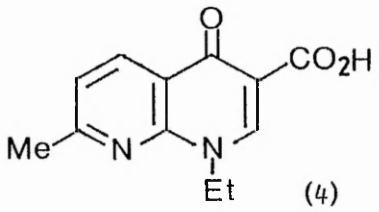


[3,4-b] (3)

The six possible thienopyridine systems can be split into two groups, isosteres of quinoline and of isoquinoline. The quinoline isosteres, subjects of the present work, are shown above.

These ring systems are of interest from two main aspects; firstly the theoretical interest in having π-excessive and π-deficient rings fused together, and secondly the analogy with quinoline compounds exhibiting biological activity. The parent compounds in all three ring systems have been prepared although thieno[3,4-b]pyridine (3) was found to be less stable than the others[1] and has been little studied.

Although the first preparation of a thieno[b]pyridine was reported in 1913[2], most of the work on these systems has been carried out since 1965. Unlike quinolines, these compounds do not occur widely in nature although certain thieno[2,3-b] and [3,2-b]pyridines have been discovered in oils[3,4]. The early work on thieno[b]pyridines was largely concerned with the preparation of analogues of indigo dyes by Russian workers[5,6]. Recently a large number of publications have been devoted to the sythesis of analogues of nalidixic acid (4), a known bactericide.



(4)

Thieno[b]pyridines have also been reported in antibacterial agents of the cephalosporin type[7] and, in one case, in antitumour agents[8].

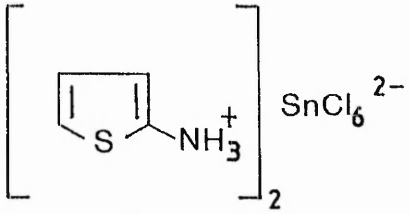
Thienopyridine chemistry has been reviewed by Schneller[9] and by Barker[10]. Comparisons of the chemistries of thieno[2,3-b] and [3,2-b]pyridines with those of quinoline and benzo[b]thiophene have also been made[11].

1.1.1 Synthesis

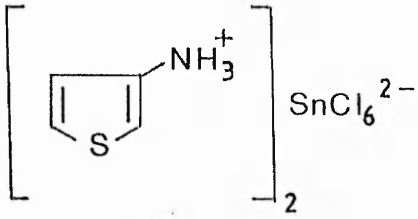
It is convenient to divide the methods of synthesis into two groups, depending on whether the thiophene ring or the pyridine ring is formed.

1.1.1.1 Synthesis by Formation of the Pyridine Ring

Generally these are adaptations of syntheses of quinolines. The major difficulty in this approach is the instability of aminothiophenes to atmospheric oxidation. A common procedure is to use the tin double salts (5) and (6) which are stable and can be formed by reducing the appropriate nitro-compound with tin in hydrochloric acid.



(5)



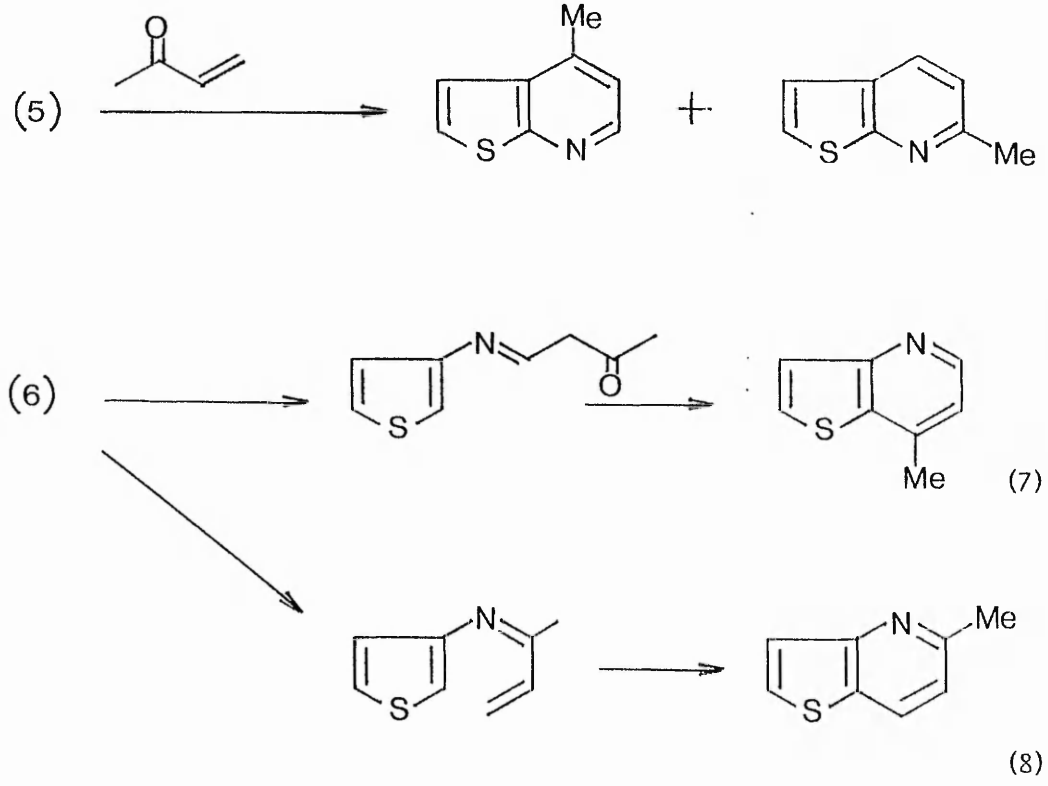
(6)

a) The Skraup Synthesis

The Skraup quinoline synthesis[12] was adapted for the first thieno[b]pyridine synthesis by Steinkopf[2,13] who prepared thieno[2,3-b]pyridine (1) from the tin salt (5).

The proposed intermediacy of acrolein in this synthesis (formed by in situ dehydration of glycerol) led to the use of other α,β-unsaturated carbonyl compounds. This has been applied to thieno[2,3-b] and [3,2-b]pyridines using

methyl vinyl ketone and the tin salts (5) and (6)[14,15]. In each case the compound with methyl γ- to the nitrogen atom (arising from Michael addition) predominated over that with the methyl α- to the nitrogen atom (arising from the Schiff's base). (Scheme 1)

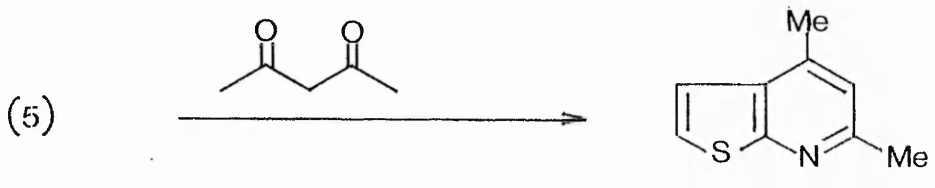


Scheme 1

Compound (8) has also been prepared from (5) and paraldehyde[16].

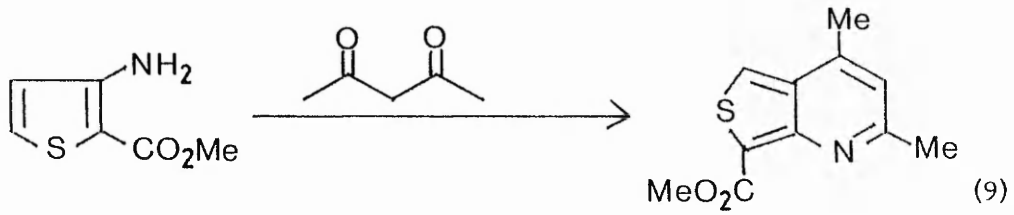
b) **Reaction of aminothiophenes with 1,3-dicarbonyl compounds**

This approach has been used in all three systems. 4,6-Dimethylthieno[2,3-b]-pyridine was formed from pentan-2,4-dione and (5)[16,17,18]. (Equation 1)



Equation 1

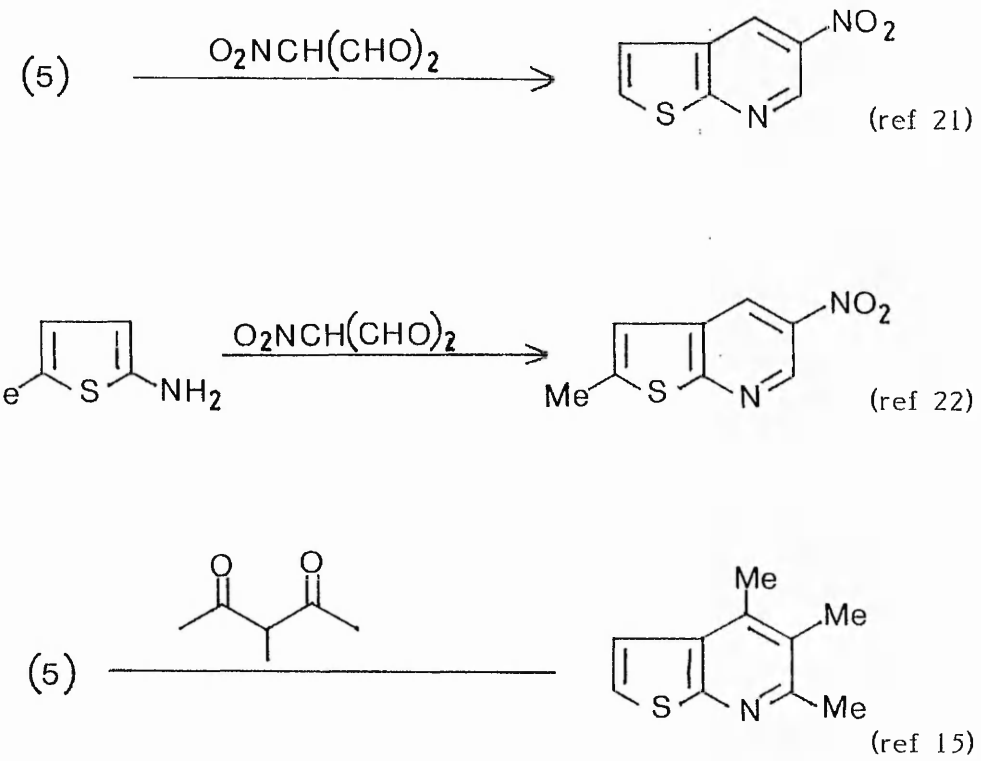
The thieno[3,2-b]pyridine analogue was produced similarly from (6)[19]. In the [3,4-b] series pentan-2,4-dione reacted with a free amine to form (9)[20]. (Equation 2)



(9)

Equation 2

The use of other 1,3-dicarbonyl compounds has been of limited value, often only tars being formed. Successful preparations are shown in Scheme 2.

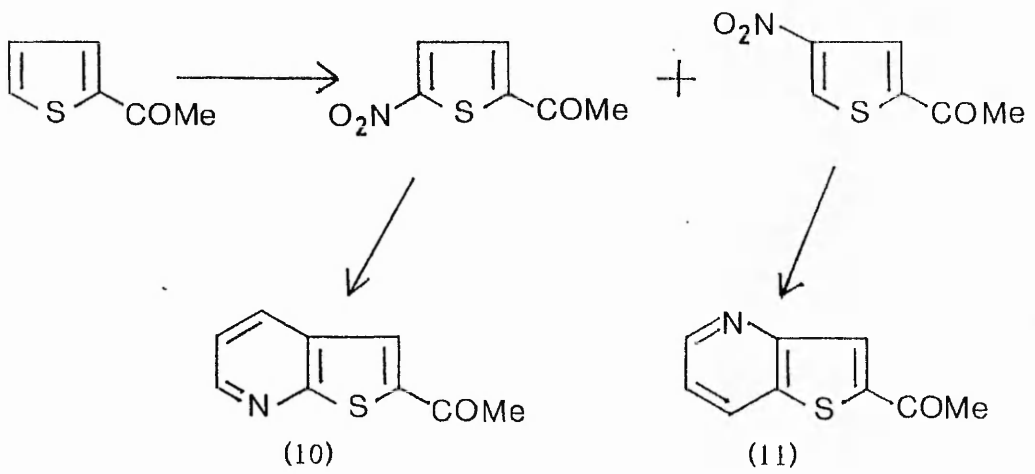


Scheme 2

Acetals and ketals have also been used in this synthesis. Thus thieno[3,2-b]-pyridine (2) was prepared from malondialdehyde tetraethylacetal (MTA) and either (6)[15] or 3-aminothiophene hydrochloride[23]. Thieno[2,3-b]pyridine (1) may be prepared similarly[15,24].

The presence of electron-withdrawing groups does not hinder the reation, since Klemm[15] showed that the mixture of amines formed on nitration and reduction

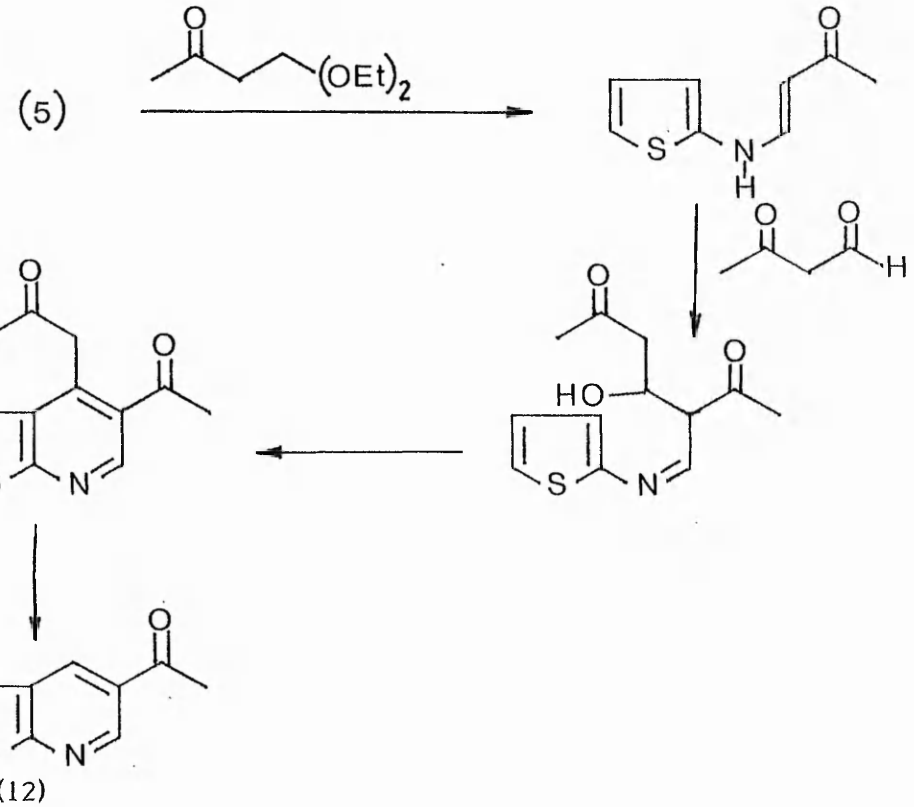
of 2-acetylthiophene gave the corresponding thieno[2,3-b] (10) and [3,2-b] (11) pyridines with MTA. (Scheme 3)



(10) (11)

Scheme 3

Klemm[15] also reacted (5) with the diethyl acetal of 3-ketobutanal to give mainly 5-acetylthieno[2,3-b]pyridine (12) together with small amounts of 4- and 6-methylthieno[2,3-b]pyridines. The mechanism shown in Scheme 4 was proposed.

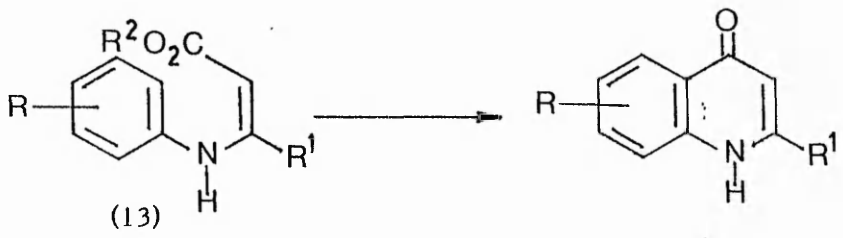


(12)

Scheme 4

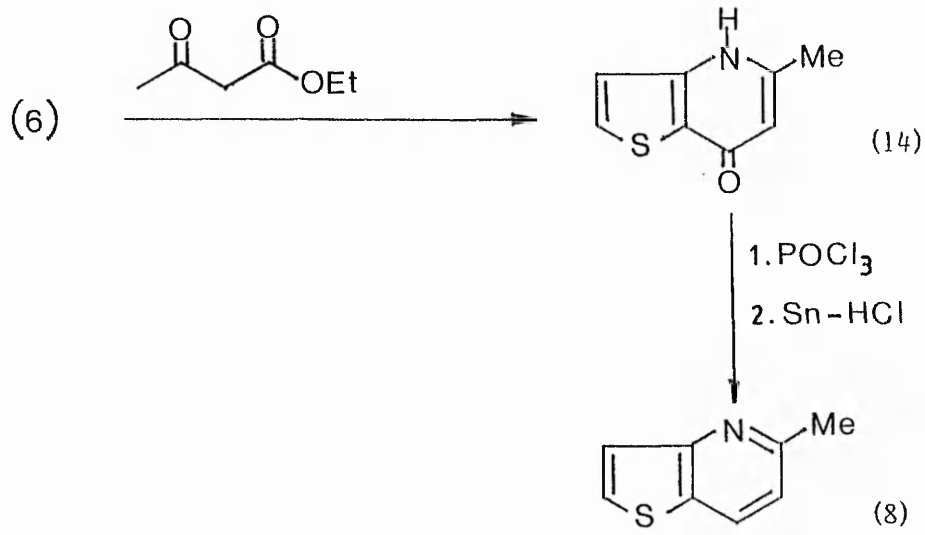
c) The Conrad-Limpach and Gould-Jacobs reactions

The Conrad-Limpach synthesis of 4-quinolones involves the thermal cyclisation of compounds of type (13), derived from aromatic amines. (Equation 3)



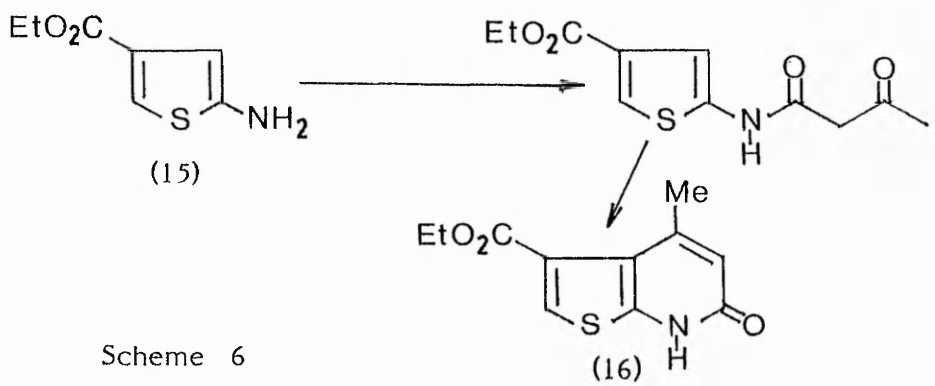
Equation 3

3-Aminothiophene was claimed[18] to react with ethyl acetoacetate to give the thieno[3,2-b]pyridone (14) which was converted into (8), described earlier. (Scheme 5)



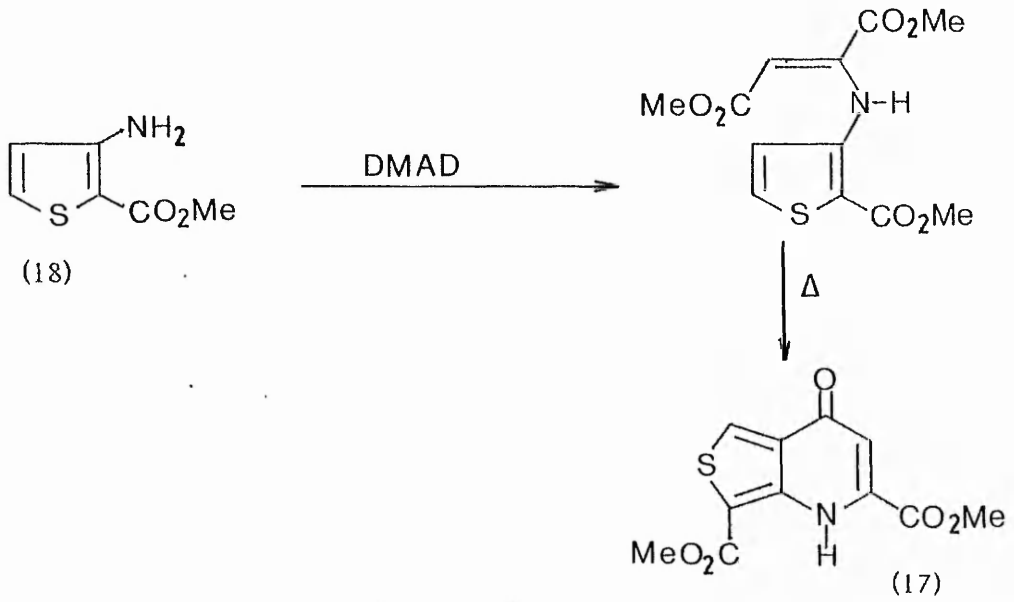
Scheme 5

Difficulty in repeating this work has been reported[25]. Under similar conditions (15) gave (16), suggesting that the ester group, rather than the keto group, of ethyl acetoacetate condensed with the amino group. (Scheme 6)



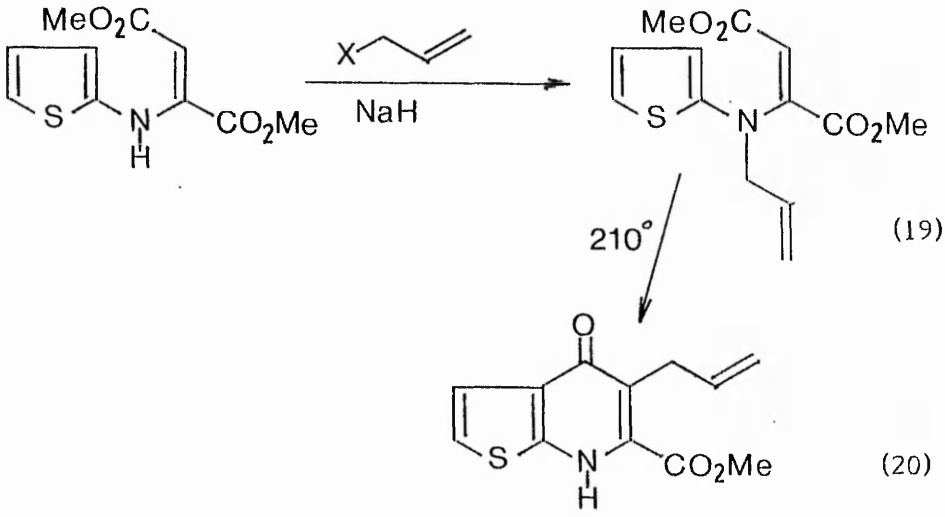
Scheme 6

A thieno[3,4-b]pyridine (17) has been prepared from dimethyl acetylenedicarboxylate (DMAD) and the amino ester (18)[20]. (Scheme 7)



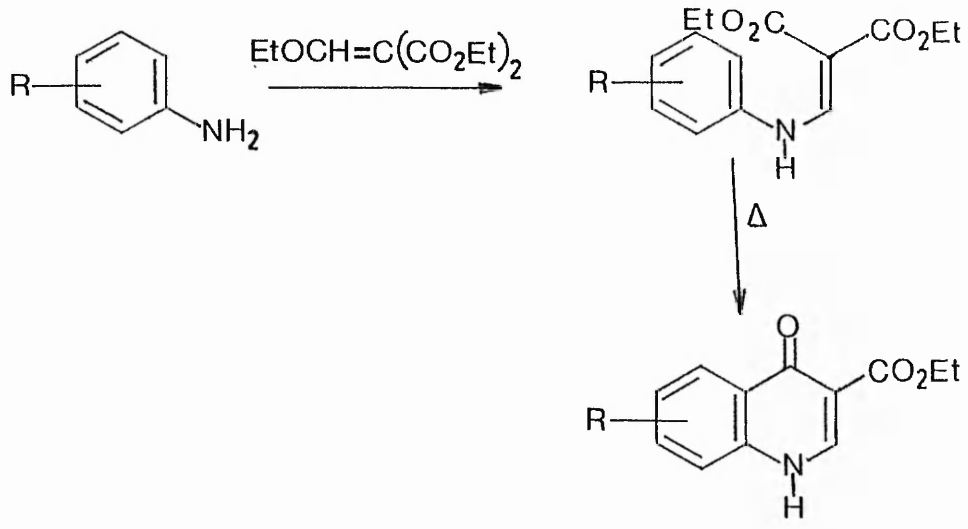
Scheme 7

An elaborate thieno[2,3-b]pyridine was synthesised by Blechert et al[26], the DMAD adduct of 2-aminothiophene was alkylated with an allyl halide to give (19) which, on heating, cyclised and underwent a hetero-Cope rearrangement to give (20). (Scheme 8)



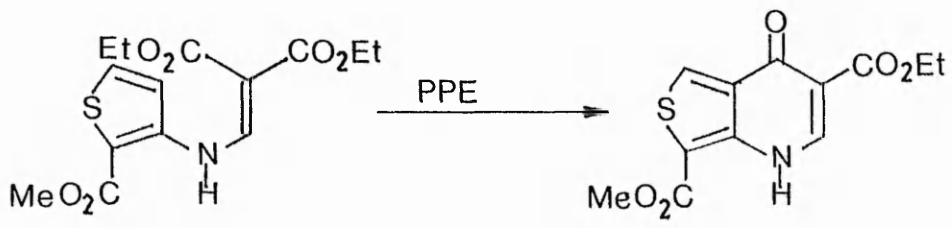
Scheme 8

A variation of the Conrad-Limpach synthesis is the Gould-Jacobs reaction. An aromatic amine is condensed with ethoxymethylenemalonate and the resulting vinylamine cyclised by heating. (Scheme 9)



Scheme 9

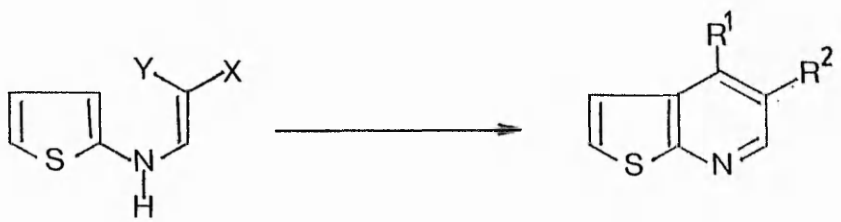
This synthesis has been applied to the production of thieno[3,4-b]pyridines[20]. (Equation 4)



Equation 4

Various thieno[2,3-b] and [3,2-b]pyridines have been prepared in this way, starting from either the free amine or the double salts[27-30].

The use of other compounds in place of ethoxymethylenemalonate gives rise to a variety of substitutions in the pyridine ring as shown in Table 1.

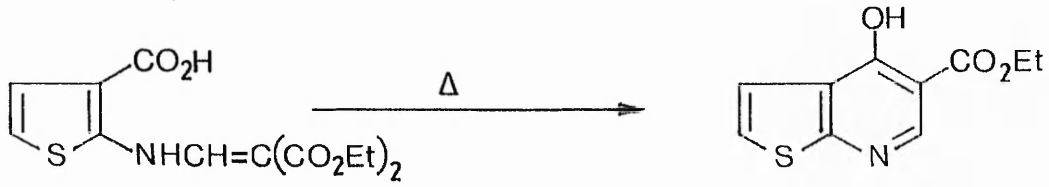


X	Y	R^1	R^2	Ref	
CN	CO_2Et	OH	CN	27	
CN	CN	NH_2	CN	31	(2-Me or Ph)
MeCO	CO_2Et	OH	COMe	27	
MeCO	MeCO	Me	COMe	27	

Table 1

Similar preparations of thieno[3,2-b]pyridines have been reported[27].

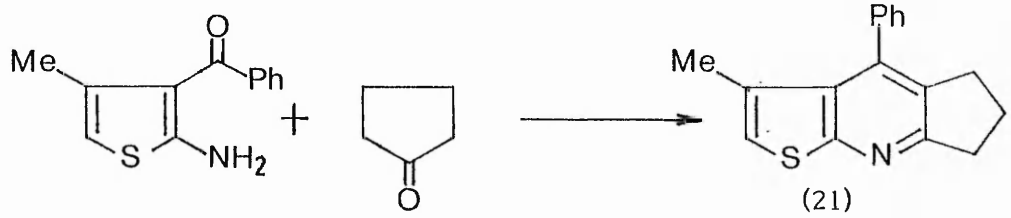
Aminothiophenecarboxylic acids have been used to prepare both the [2,3-b] and [3,2-b] systems[25,28,32]. On heating, decarboxylation occurs giving a vacant site for cyclisation. (Equation 5)



Equation 5

d) **From ortho-amino carbonylthiophenes**

The Friedlander synthesis of quinolines from o-amino aldehydes or ketones has been recently applied to the production of thieno[2,3-b]pyridines from 2-amino-3-benzoylthiophenes[33]. Compound (21) is an example of the products prepared by this route. (Equation 6)

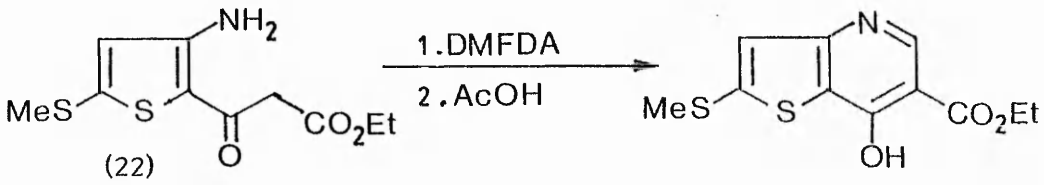


(21)

Equation 6

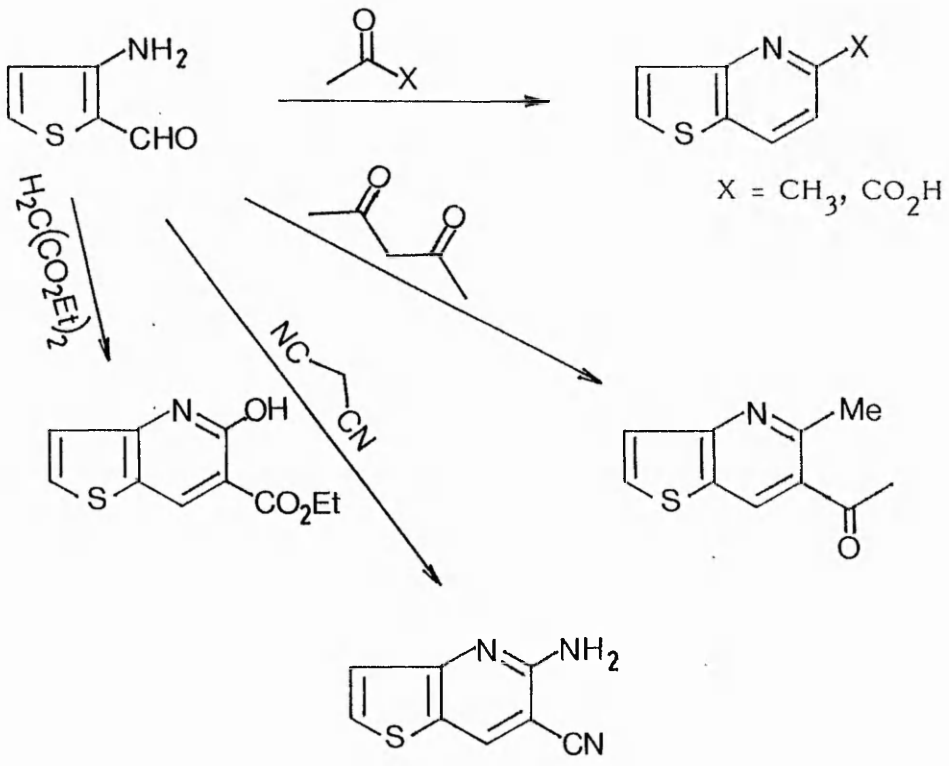
Similarly various thieno[3,2-b]pyridines have been prepared by perchloric acid catalysed reaction of 3-amino-2-benzoylthiophenes with ketones[34].

A good yield of the thieno[3,2-b]pyridine was obtained when (22) was reacted with dimethylformamide dimethylacetal (DMFDA) followed by acetic acid[35]. (Equation 7)



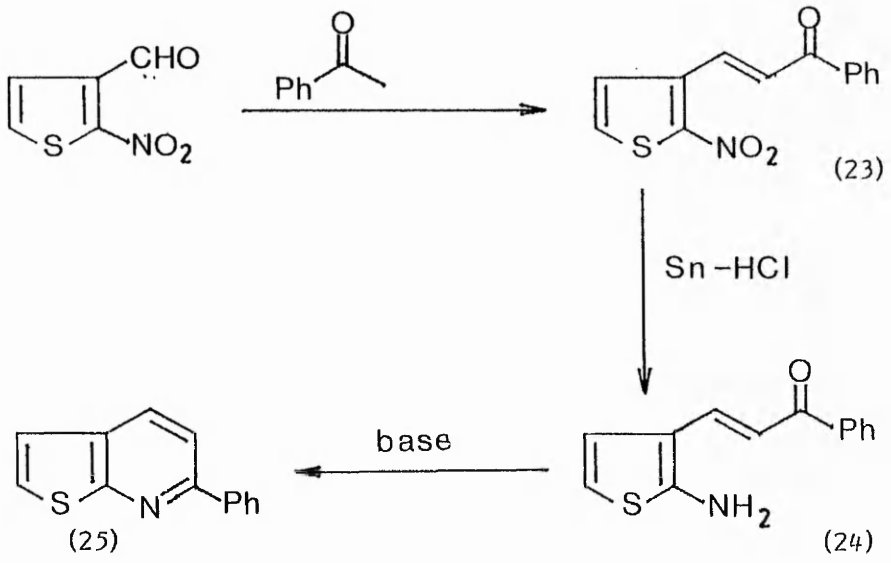
Equation 7

3-Amino-2-formylthiophene has been used to prepare the thieno[3,2-b]-pyridines depicted in Scheme 10[36,24].



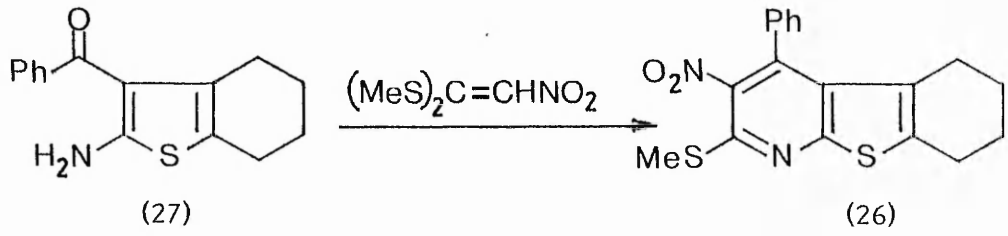
Scheme 10

In an early paper Raich and Hamilton[37] described the condensation of 3-formyl-2-nitrothiophene with acetophenone to give an intermediate (23) which was reduced to the amino-compound (24). On addition of base this cyclised, giving the thieno[2,3-b]pyridine (25). (Scheme 11)



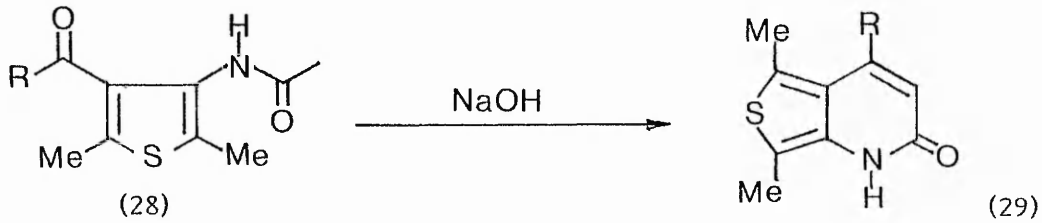
Scheme 11

The methylthio compound (26) was prepared from the benzo[b]thiophene (27) and 1,1-bis(methylthio)-2-nitroethylene[38]. (Equation 8)



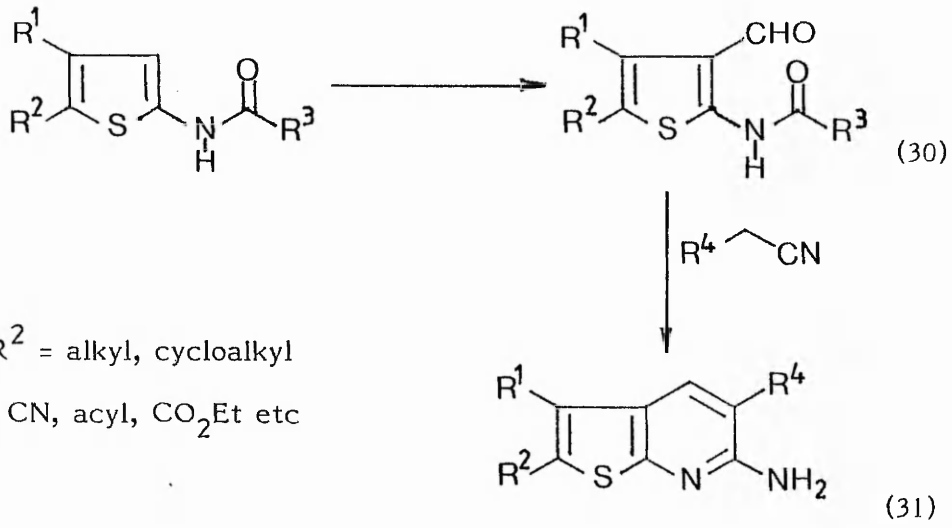
Equation 8

Base catalysed cyclisation of acetamidothiophenes (28) gave the thieno[3,4-b]-pyridines (29)[39]. (Equation 9)



Equation 9

Shvedov et al[40,41] carried out the Vilsmeier reaction on various 2-acylamino-thiophenes and cyclised the resulting aldehydes (30) with substances containing active methylene groups to give thieno[2,3-b]pyridines (31). (Scheme 12)



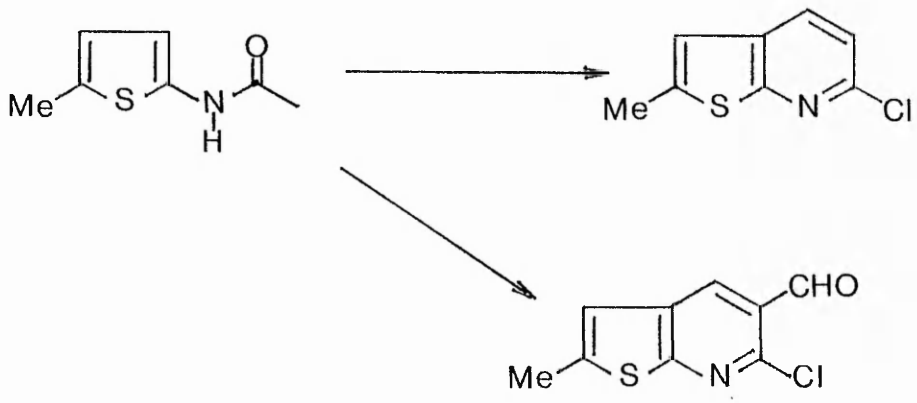
R^1, R^2 = alkyl, cycloalkyl

R^4 = CN, acyl, CO_2Et etc

Scheme 12

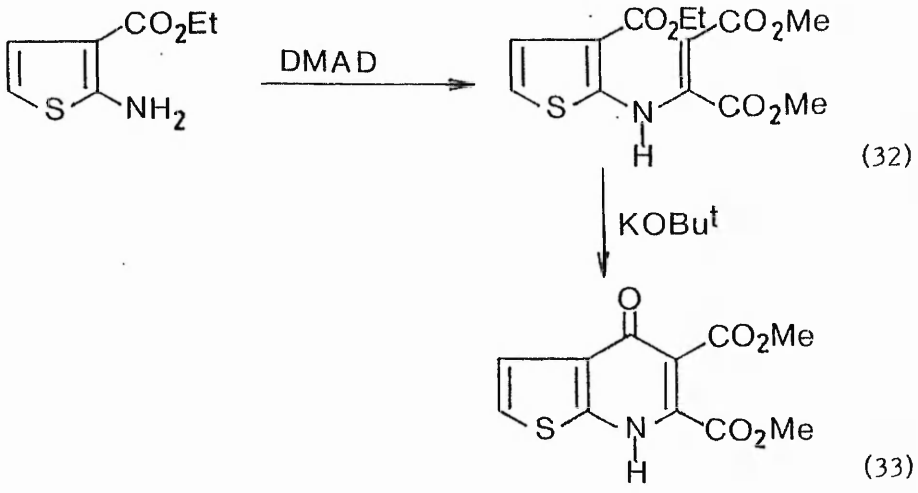
A similar approach was used by Meth-Cohn et al[42,43] who applied the Vilsmeier reaction to acetamidothiophenes and produced all three ring systems, the products obtained depending on the reaction conditions used.

2-Acetamidothiophenes gave thieno[2,3-b]pyridines (Scheme 13), while 3-acetamidothiophenes gave either thieno[3,2-b] or [3,4-b]pyridines depending on the thiophene ring substituents.



Scheme 13

The use of o-aminothiophene carboxylic acid derivatives has found wide application in the synthesis of thieno[b]pyridines. The adduct (32) was formed by reaction of ethyl 2-aminothiophene-3-carboxylate with DMAD. This was then cyclised with potassium t-butoxide in t-butanol to give the thieno[2,3-b]-pyridine (33) shown in Scheme 14[44].



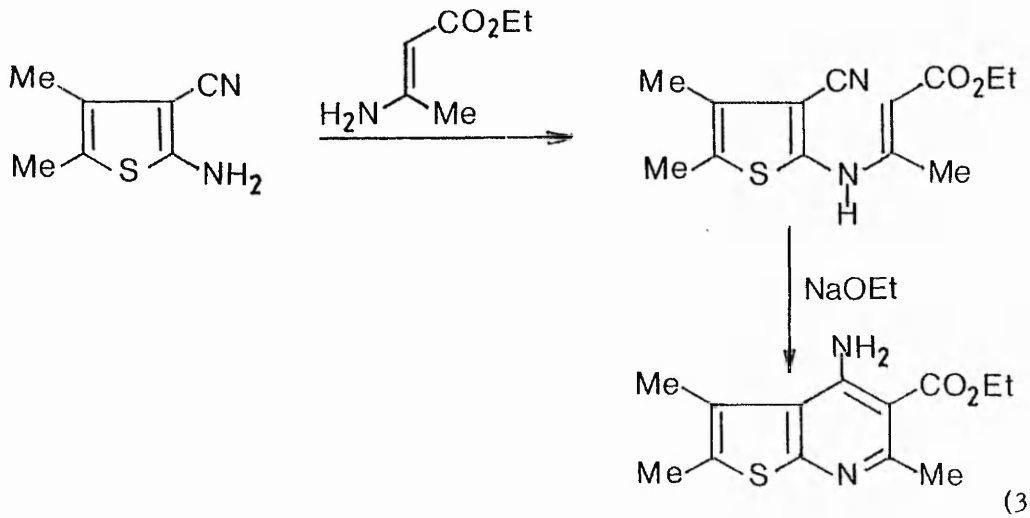
(32)

(33)

Scheme 14

Thieno[3,2-b]pyridines have been prepared similarly, in this case cyclisation was effected with sodium hydride in dimethylformamide (DMF)[32].

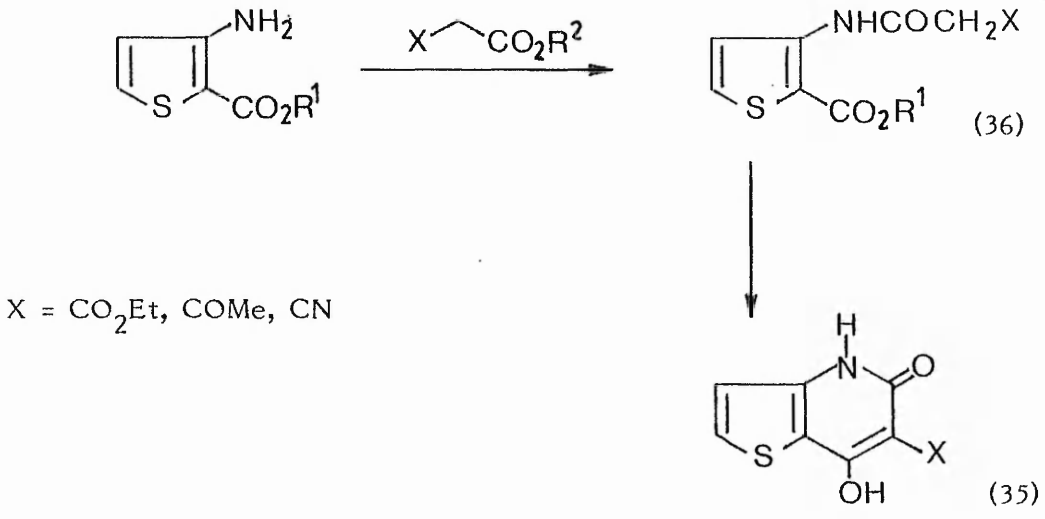
Ethyl β-aminocrotonate condensed with 2-aminothiophenes with loss of ammonia to give vinylamines which were then cyclised with base to give thieno[2,3-b]pyridines (34)[45]. (Scheme 15)



(34)

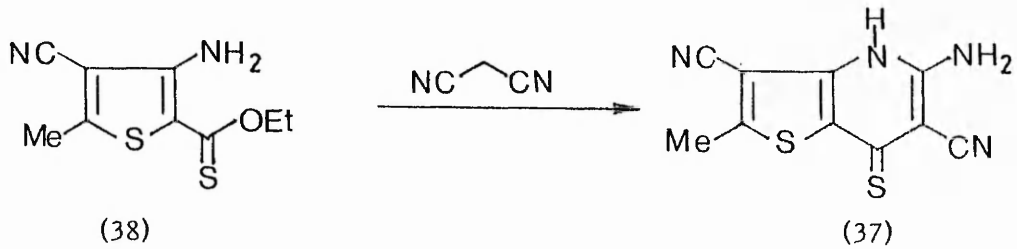
Scheme 15

Various thieno[3,2-b]pyridines (35) have been prepared by reaction of 3-amino-2-alkoxycarbonylthiophenes with acetic acid derivatives and cyclisation of the resulting amides (36) with base[46] as illustrated in Scheme 16.



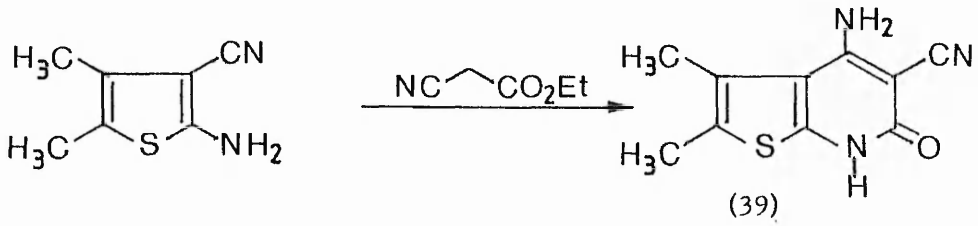
Scheme 16

Similarly the thione (37) was prepared from the thionoester (38) and malononitrile[47]. (Equation 10)



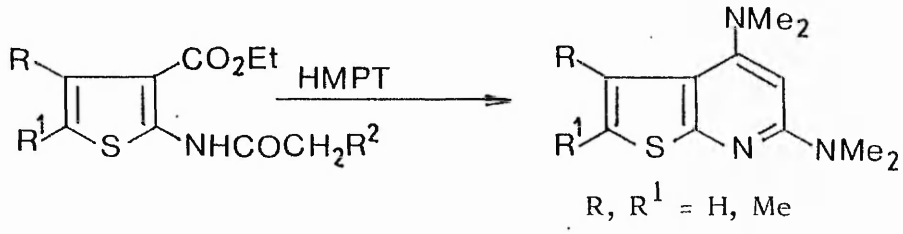
Equation 10

Thieno[2,3-b]pyridines (eg (39)) have been prepared by similar methods[31,48]. (Equation 11)



Equation 11

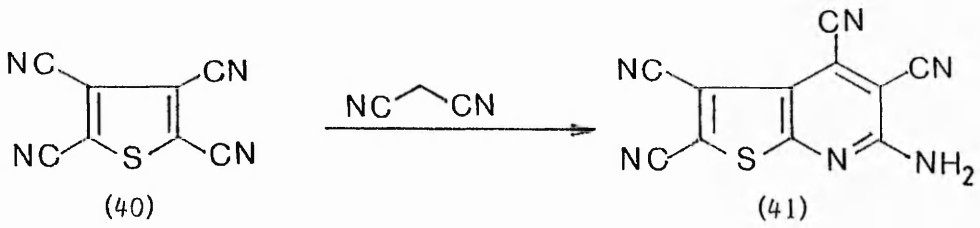
The preparation of 2,4-bis(dimethylamino)quinolines from N-acylanthranilic esters and hexamethylphosphoric triamide (HMPT)[49] has been applied to the production of thieno[2,3-b]pyridines from 2-aminothiophene-3-carboxylic acid derivatives[50]. (Equation 12)



Equation 12

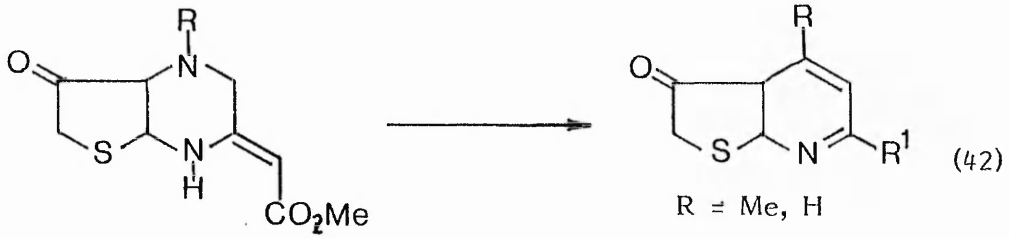
c) **Miscellaneous**

The tetracyanothiophene (40) was condensed with compounds containing active methylene groups to give thieno[2,3-b]pyridines (eg (41))[51]. (Equation 13)



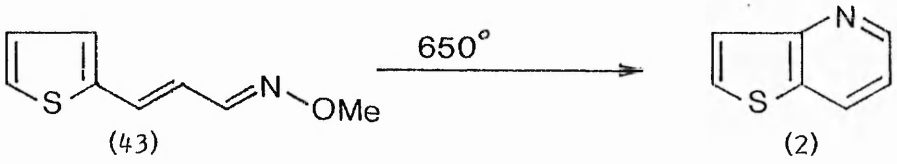
Equation 13

A transformation of thieno[b]piperazines into thieno[2,3-b]pyridines (42) has recently been reported[52]. (Equation 14)



Equation 14

The parent thieno[3,2-b]pyridine (2) has been prepared by a ring closure in which the attacking atom was nitrogen rather than carbon by pyrolysis of the O-methyloxime (43)[53]. (Equation 15)



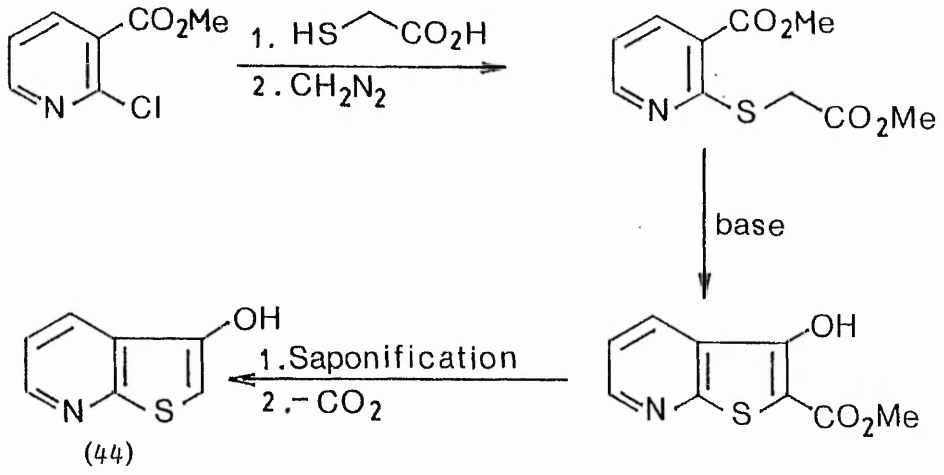
Equation 15

1.1.1.2 Synthesis by Formation of the Thiophene Ring

This approach has been less common than the construction of the pyridine ring and has been mainly applied to the synthesis of thieno[2,3-b]pyridines

a) **From pyridinecarboxylic acid derivatives**

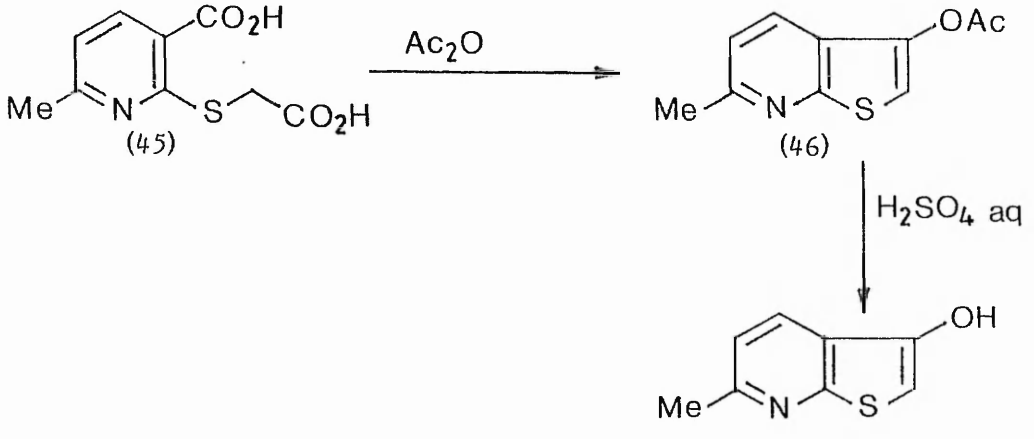
Chichibabin and Vorozhtov[54] prepared 3-hydroxythieno[2,3-b]pyridine (44) by the route depicted in Scheme 17. An earlier claim that this compound had been obtained from 2-pyridylthioacetic acid[55] was shown to be incorrect.



(44)

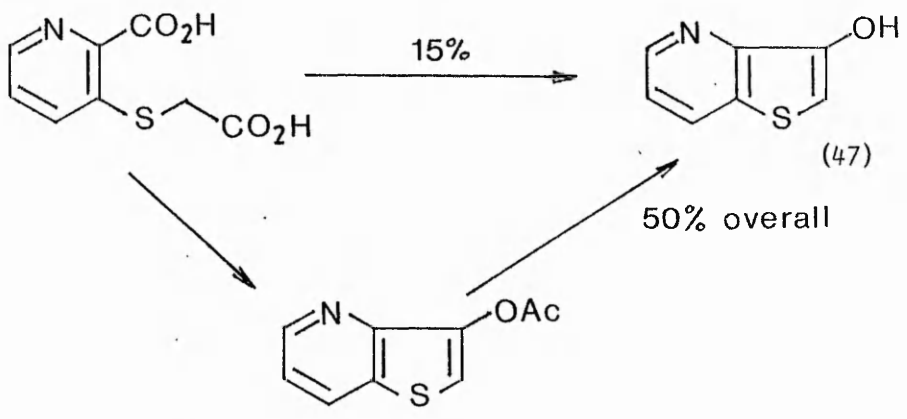
Scheme 17

The 6-methyl analogue of (44) was synthesised from the di-acid (45) and acetic anhydride followed by hydrolysis of the acetoxy compound (46) as shown in Scheme 18[56].



Scheme 18

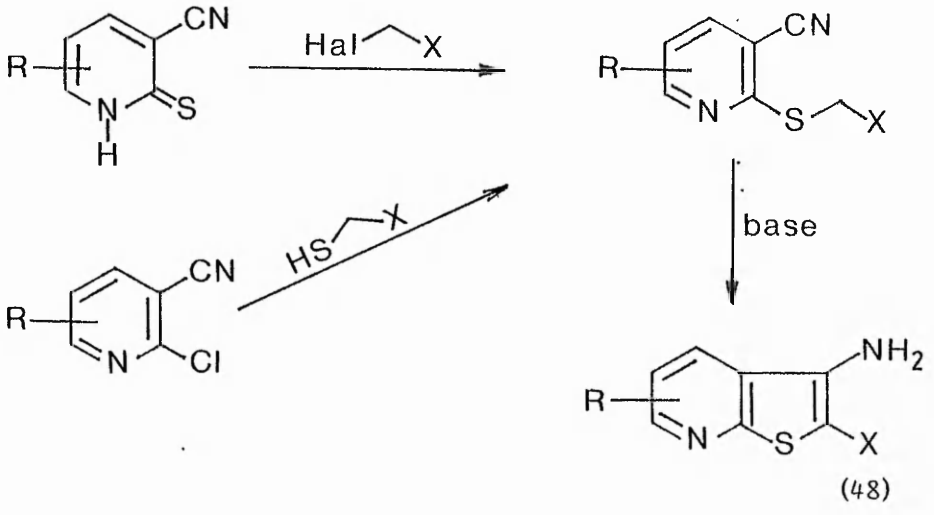
Thieno[3,2-b]pyridines may be produced similarly[57]. The yield of the hydroxy compound (47) is increased if the acetoxy intermediate is isolated. (Scheme 19)



Scheme 19

b) **From other pyridin-2-thiol derivatives**

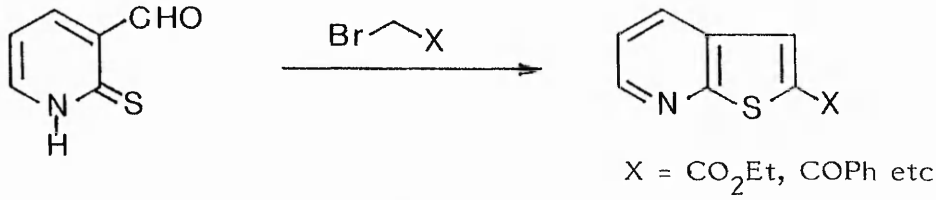
2-Alkylthio-3-cyanopyridines containing an active methylene group α-to the sulphur atom may be prepared by two methods. In the first the appropriate 3-cyanopyridin-2-thione is reacted with an alkyl halide[58-61], and in the second a 2-halo-3-cyanopyridine and a thiol are combined[62]. Cyclisation with base then leads to thieno[2,3-b]pyridine derivatives (48) as outlined by Scheme 20.



X = CO_2Et, COPh, CN etc

Scheme 20

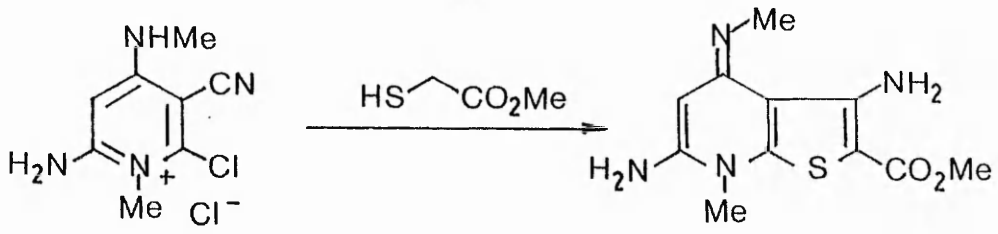
Thieno[2,3-b]pyridines unsubstituted at C-3 can be obtained by use of 3-formyl, rather than 3-cyanopyridinethiones[63]. (Equation 16)



X = CO_2Et, COPh etc

Equation 16

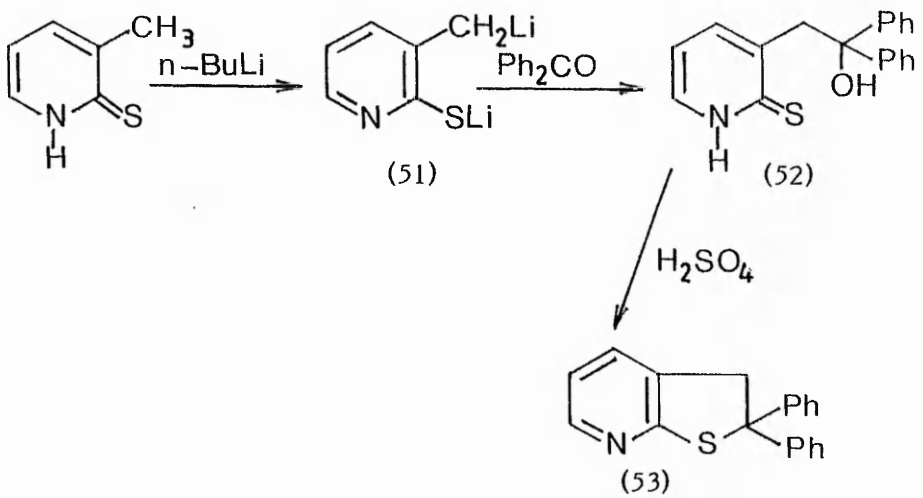
In a related approach the 2-chloro-3-cyanopyridinium salt (49) was reacted with methyl thioglycolate to give the N-methylthieno[2,3-b]pyridine (50)[64]. (Equation 17)



(49) (50)

Equation 17

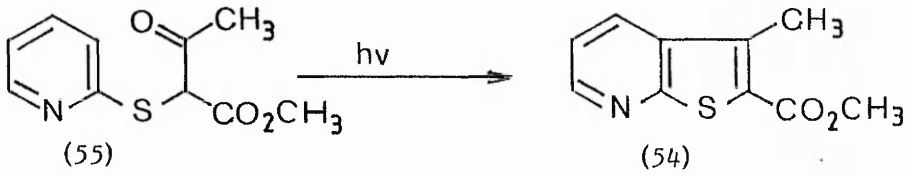
Reaction of 3-methylpyridin-2-thione with n-butyllithium gives the dilithio derivative (51); condensation with benzophenone (giving (52)) and cyclisation with sulphuric acid then leads to the dihydro compound (53)[65] as shown in Scheme 21.



(51) (52) (53)

Scheme 21

Methyl 3-methylthieno[2,3-b]pyridine-2-carboxylate (54) was prepared by a photochemical ring closure from the keto ester (55) in moderate yield[66]. (Equation 18)



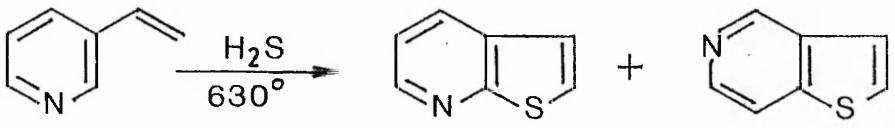
(55) (54)

Equation 18

c) <u>High Temperature Cyclisation Methods</u>

Klemm and his co-workers have developed high temperature catalytic processes for the preparation of thienopyridines. Although yields have generally been poor, in one case reported recently the yield was sufficient for the process to be synthetically useful.

Thieno[2,3-b]pyridine (1) and its 6-methyl derivative were prepared by heating the appropriate 3-vinylpyridine with hydrogen sulphide over an iron(II)sulphide-alumina catalyst at 630°[67] (Equation 19). Similar results were obtained using 3-ethylpyridines.

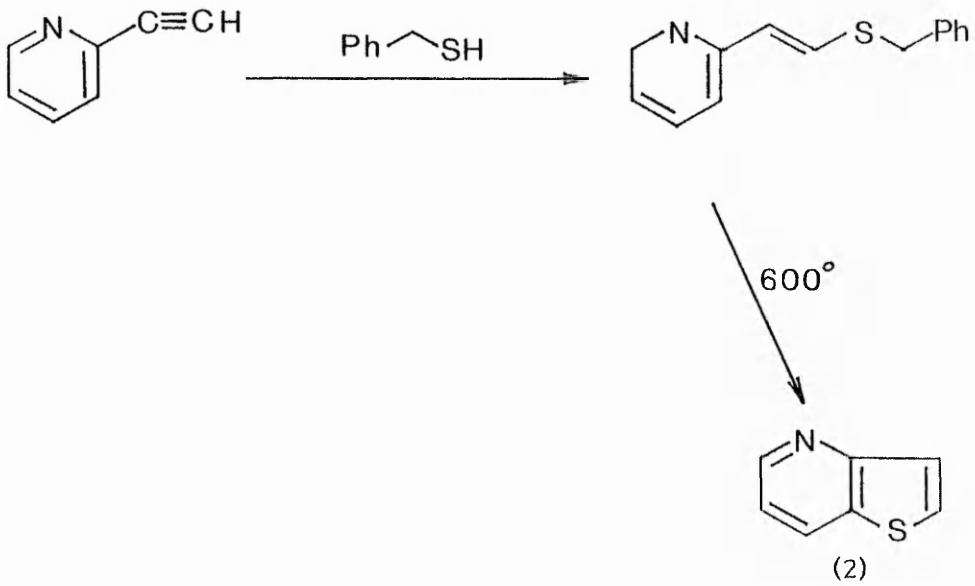


(1)

Equation 19

Under these conditions 2-vinylpyridine gave thieno[3,2-b]pyridine (2) in 1.6% yield[68]. Better results were obtained if the vinylpyridine were first condensed with benzyl mercaptan to give the benzyl pyridylethylsulphide. Pyrolysis of this material then gave (2) as 28% of the basic fraction[69].

A much improved synthesis of (2) from 2-ethynylpyridine was described recently[70]. (Scheme 22)

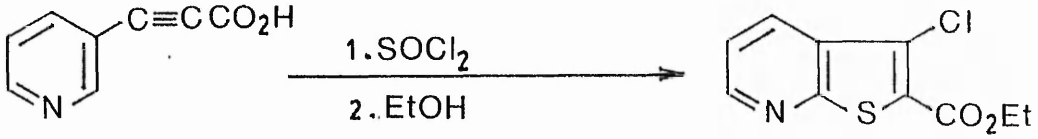


(2)

Scheme 22

d) Miscellaneous

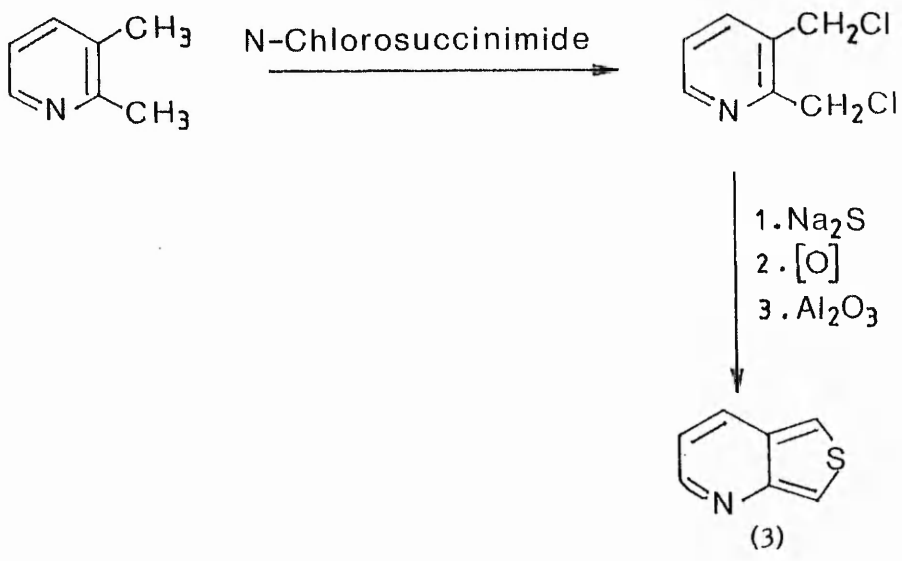
A low yield of the chloro-compound (56) was obtained from pyridin-3-ylpropiolic acid and refluxing thionyl chloride[71]. (Equation 20)



(56)

Equation 20

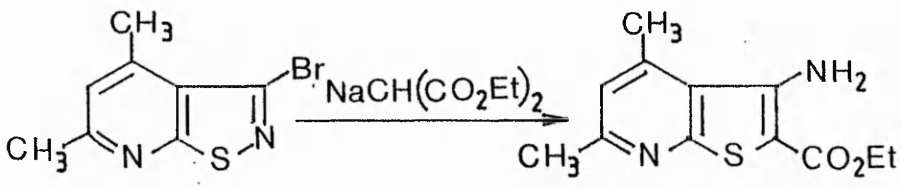
Thieno[3,4-b]pyridines have also been prepared by syntheses involving construction of the thiophene ring. Klemm and his co-workers prepared the parent (3) by the sequence shown in Scheme 23[1,72,73].



Scheme 23

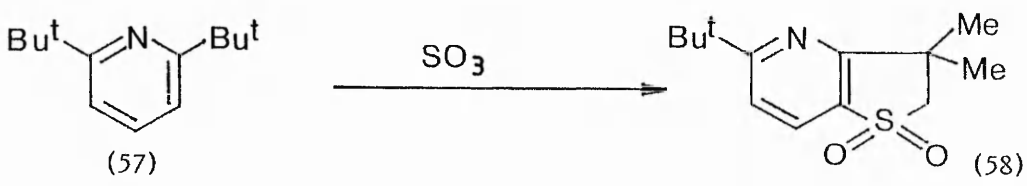
Spinner and Yeoh[74] have synthesised a number of 1,3-dihydro derivatives of (3) from similar starting materials.

Transformation of isothiazolopyridines into thieno[2,3-b]pyridines has been reported[58]. (Equation 21)



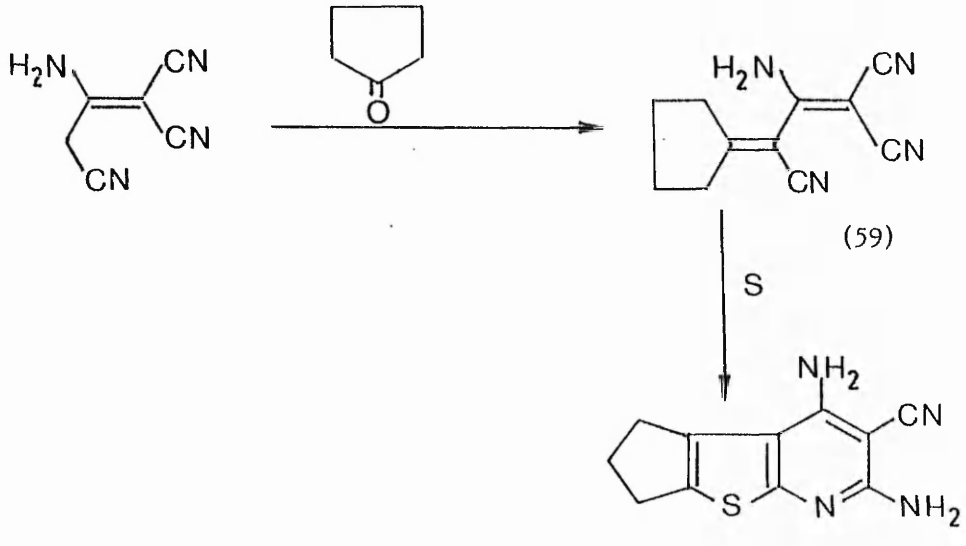
Equation 21

Heating the di-t-butylpyridine (57) with sulphur trioxide gave the sulphone (58)[75]. (Equation 22)



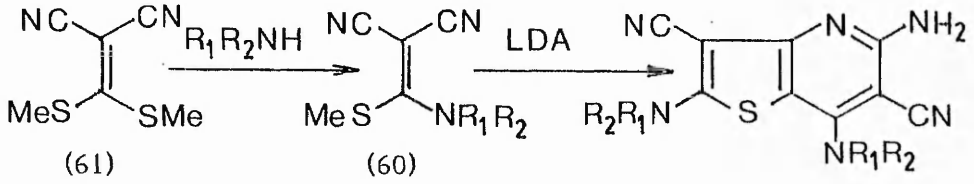
Equation 22

An interesting recent synthesis in which both rings were formed together involved reaction of the tricyano-compound (59) with sulphur[76]. (Scheme 24)



Scheme 24

Another preparation in which both rings are formed together involves cyclisation of cyano-compounds (60), produced from (61) and a variety of secondary amines[77]. (Scheme 25) In one case a substituted thiophene was isolated from the reaction mixture.



Scheme 25

1.1.2 Physical Properties

1.1.2.1 Electron Distribution

Since an important consideration in the chemistry of thieonpyridines is the theoretical interest in the fusion of a π-excessive thiophene ring and a π-deficient pyridine ring it is not surprising that attempts have been made to calculate electron densities and indices of reactivity for these systems. An interesting consideration is how the method of ring fusion affects the site and degree of various reactions (eg electrophilic and nucleophilic substitution).

Quinoline has been the subject of a number of theoretical studies[78]. The

figures given below are π-electron densities at each ring position obtained by Huckel molecular orbital (HMO) calculations. Klemm and co-workers[15,73,79] have use a similar approach to calculate electron densities for thieno[b]-pyridines. They also calculated superdelocalisability values for electrophilic and nucleophilic substitution. The electron density values thus obtained for thieno[b]pyridines and for quinoline are given in Figure 1.

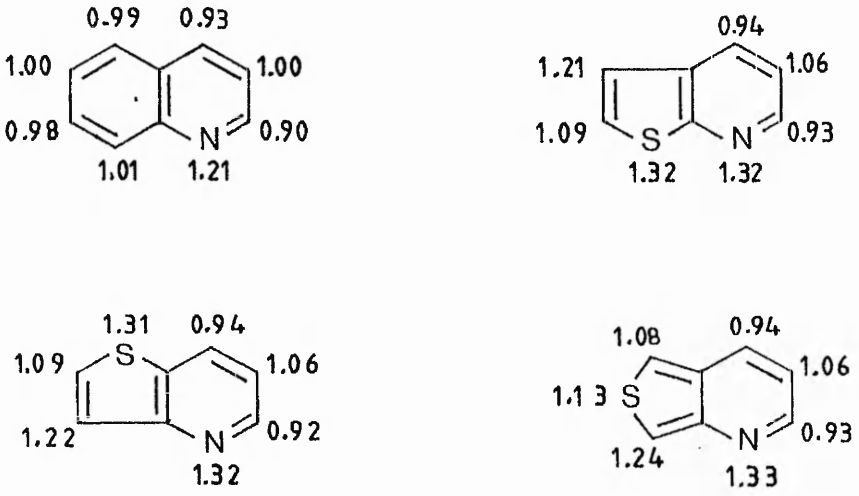


Figure 1. π-Electron densities in quinoline and thieno[b]pyridines

These figures indicate an increase in electron densities in the pyridine ring with respect to quinoline. However, the relative distribution (ie electron deficiency at positions α- and γ- to the nitrogen) is maintained. This electron deficiency suggests that nucleophilic substitution will take place at positions α- and γ- to the nitrogen. This is in accordance with the known reactions of thieno[b]pyridines.

For thieno[2,3-b] and [3,2-b]pyridines electrophilic substitution is predicted to occur at C-3; again this is in accordance with the known chemistries of these systems. The chemistry of thieno[3,4-b]pyridine has been so little studied that it is not possible to compare theoretical predictions with known reactions.

Helland and Skanke[80] used other methods of calculation (Pariser-Parr-Pople [PPP] and complete neglect of differential overlap [CNDO]) to produce electron densities, frontier electron density (FED, for electrophilic substitution), frontier orbital density (FOD, for nucleophilic substitution) and frontier radical density (FRD, for radical substitution). The predictions for electrophilic substitution given by these calculations agree with those produced by the HMO method. However, nucleophilic substitution for thieno[2,3-b] and [3,2-b]pyridines is predicted to occur at C-2 which is not in agreement with

Klemm's electon density figures (which predict nucleophilic subtitution at positions α- and γ- to the nitrogen atom) nor with the known chemistry of these systems (see Section 1.1.3.2).

1.1.2.2 Bond Lengths

Bond lengths in quinoline have been determined by x-ray crystallography[81] whereas those for thienopyridines have only been estimated by calculations[80] based on the values for known compounds. It appears that replacement of the benzene ring by a thiophene ring has little effect on the bond lengths in the pyridine ring.

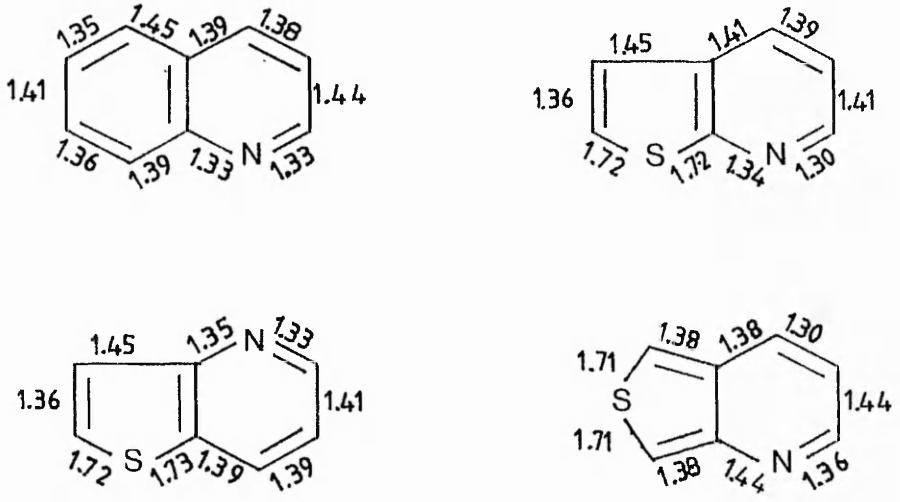


Figure 2. Bond lengths (in Å) for quinoline and thieno[b]pyridines

1.1.2.3 Base Strengths

The pKa values shown below for quinoline and thieno[2,3-b] and [3,2-b]pyridines were determined in water at 25°C[82].

Compound	pKa
Thieno[2,3-b]pyridine	2.75
Thieno[3,2-b]pyridine	4.35
Quinoline	4.87

The differences were interpreted in terms of the inductive effect of the sulphur atom reducing the electron density on the nitrogen. In the [2,3-b] system the sulphur atom is much closer to the nitrogen atom than in the [3,2-b] system; thus thieno[2,3-b]pyridine is considerably less basic than quinoline, whereas thieno[3,2-b]pyridine is only slightly less so.

1.1.2.4 Spectroscopic Properties

The UV spectra of thieno[b]pyridines show considerable similarities to those of quinolines[10]; the i.r. spectra are apparently unremarkable since no detailed discussion of them has appeared.

Both ^{1}H and ^{13}C n.m.r. spectra of a great variety of compounds in the series have been published. The ^{1}H spectra are readily interpreted by considering the systems as a combination of thiophene and pyridine. A summary of the relevant points is given by Barker[10].

Klemm has recorded mass spectroscopic data for a large number of thienopyridines, and explained the fragmentation patterns[83].

1.1.2.5 Other Physical Properties

Dipole moments of thienopyridines have been measured[84] and studies of the behaviour of thienopyridines on gas-liquid[85] and thin-layer[86] chromatography have been made.

1.1.3 Reactions

1.1.3.1 Electrophilic Substitution

The following observations on the electrophilic substitution of quinoline have been made:

a) Electrophiles will co-ordinate with the nitrogen atom, rendering the pyridine ring strongly deactivated to electrophilic attack. In particular, in strong acid media the system will be protonated.

b) When substitution occurs it does so in the benzene ring; the reactivity is less than that of naphthalene but greater than that of pyridine.

c) The general order of reactivity of the ring positions in quinoline is:
C-5 (>phenyl) >C-8 ≏C-6 >C-3 >C-7 >>C-2 >C-4

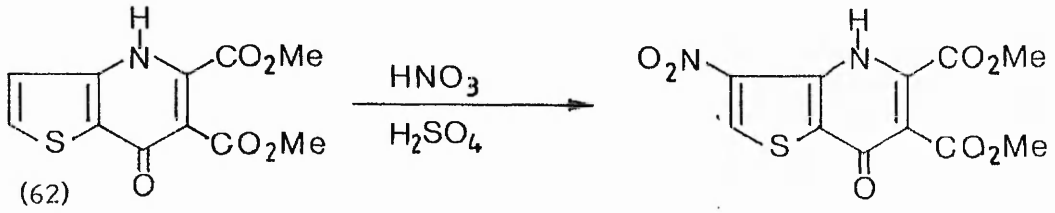
In thieno[b]pyridines the major amount of work on electrophilic substitution has been carried out by Klemm and co-workers, the three reactions most studied being deuteriation, nitration and halogenation.

Deuteriation of thieno[2,3-b] and [3,2-b]pyridine was carried out in D_2SO_4 at 100° and was followed by n.m.r.[87,88]. In both systems it was found that deuterium exchange occurred preferentially at the 3-position but on prolonged heating the 2-proton was also exchanged. The rate constants were calculated and it was found that attack took place on the protonated species; the reactivity was considerably greater than that of quinoline and significantly greater than that of benzene. It was found that the [3,2-b]system was somewhat less reactive than the [2,3-b] system, although in the former case

the C-3 : C-2 selectivity ratio was greater.

The nitration of thieno[2,3-b]pyridine has been studied kinetically[87], and results similar to those obtained for deuteriation have been found (notably attack at C-3, on the protonated species).

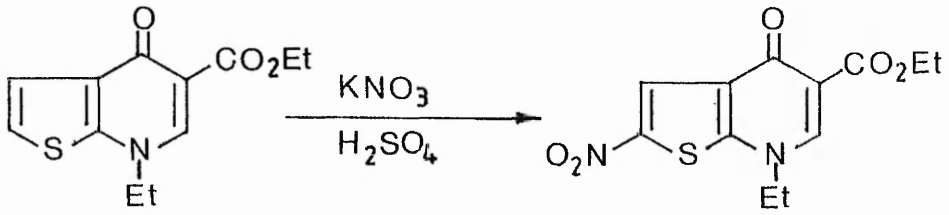
Preparative nitrations have been carried out on both (1) and (2)[79], on 5-ethylthieno[2,3-b]pyridine[89], and on the more elaborately substituted thieno-[3,2-b]pyridine (62)[32]. In all cases reaction took place at C-3 (eg Equation 23).



Equation 23

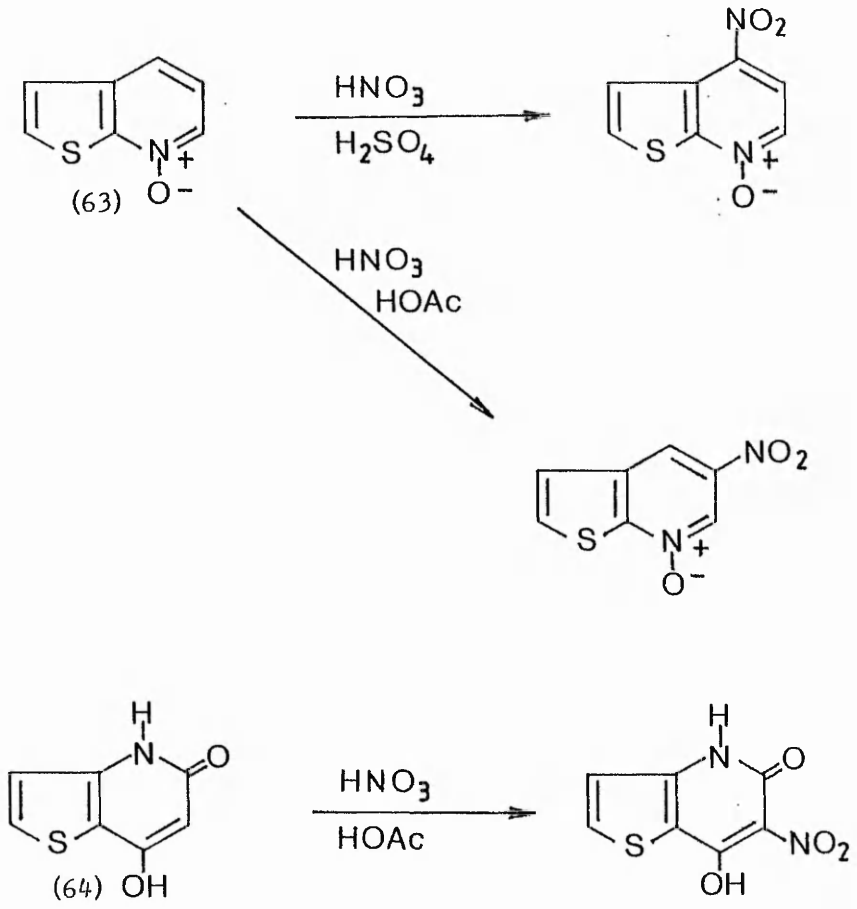
When the 3-position of thieno[2,3-b]pyridine is blocked by halogen nitration by mixed acid occurs at C-2[90].

Certain thieno[2,3-b]pyridines have recently been depicted as undergoing nitration at C-2[91]. (Equation 24)



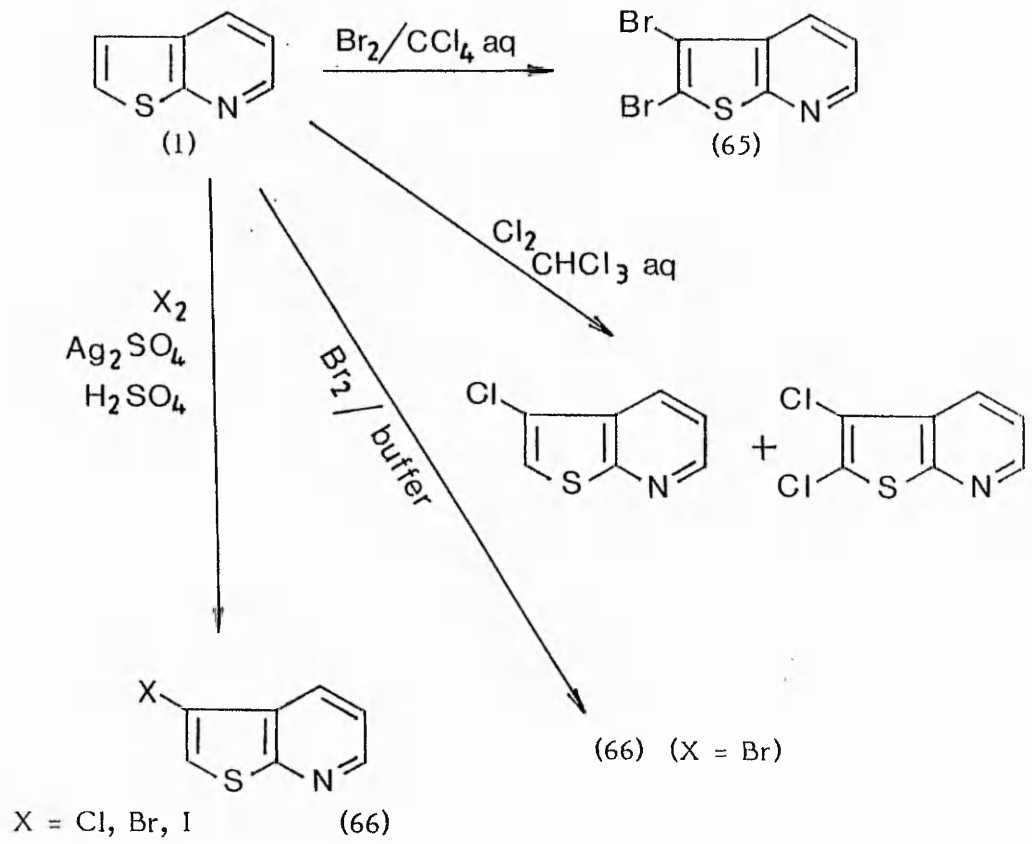
Equation 24

If activating substituents are present nitration can occur in the pyridine ring. Thus the N-oxide (63) can be nitrated at C-4 or C-5 depending on the conditions used[92]. Similar reactions have been reported for quinolines[93,94]. In the di-oxygenated thieno[3,2-b]pyridine (64) the pyridine ring is highly activated and can be nitrated with nitric acid in acetic acid[46]. These reactions are depicted in Scheme 26.



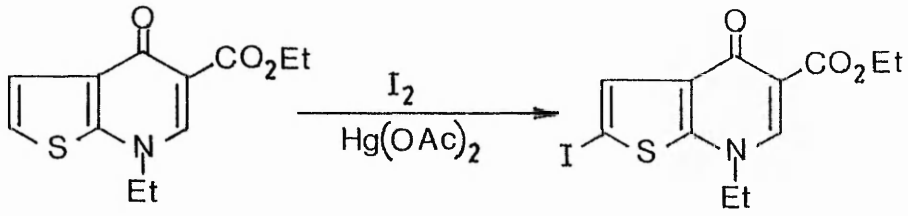
Scheme 26

Halogenation has proved more complex than the reactions just described since oxidation and addition reactions can also occur[90,95]. Bromination of thieno[2,3-b]pyridine (1) with an excess of bromine in carbon tetrachloride-water gave a low yield of the 2,3-dibromo compound (65)[15]. Under similar conditions chlorination gave both 3-chloro and 2,3-dichlorothieno[2,3-b]-pyridines[90]. Moderate yields of the 3-halo derivatives (66) were obtained by treating (1) with elemental halogen in warm concentrated sulphuric acid containing silver sulphate[90]. In an attempt to perform bromination on the unprotonated species bromine in chloroform in the presence of a buffer was employed; in this way improved yields of (66) (X=Br) were obtained[90]. These halogenation reactions are shown in Scheme 27.



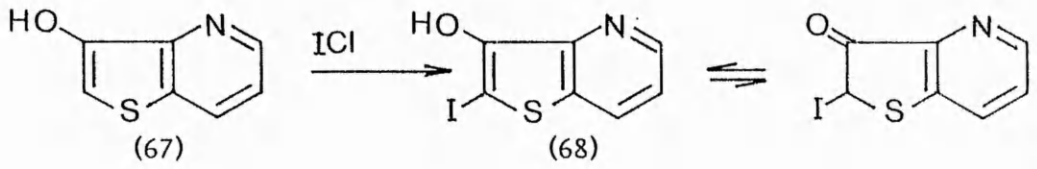
Scheme 27

The introduction of iodine at C-2 of a thieno[2,3-b]pyridone using iodine-mercury (11) acetate has recently been described[96]. (Equation 25)



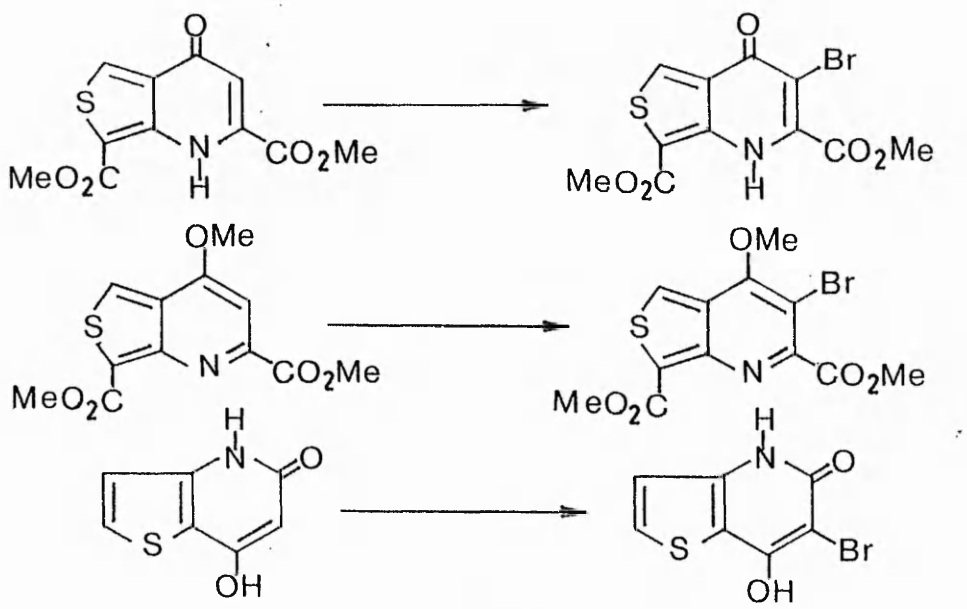
Equation 25

Sheehan and Leitner[57] obtained a labile yellow iodo compound from the hydroxy-compound (67) and iodine monochloride. The identity of the product was not established but was probably the 2-iodo compound (68), the lability of the iodine being explained by its position α- to the carbonyl group in the keto tautomer. (Equation 26)



Equation 26

Recently two thieno[3,4-b]pyridines[20] and a thieno[3,2-b]pyridine[46] containing activating subtituents have been brominated in the pyridine ring on treatment with bromine in acetic acid as shown in Scheme 28.

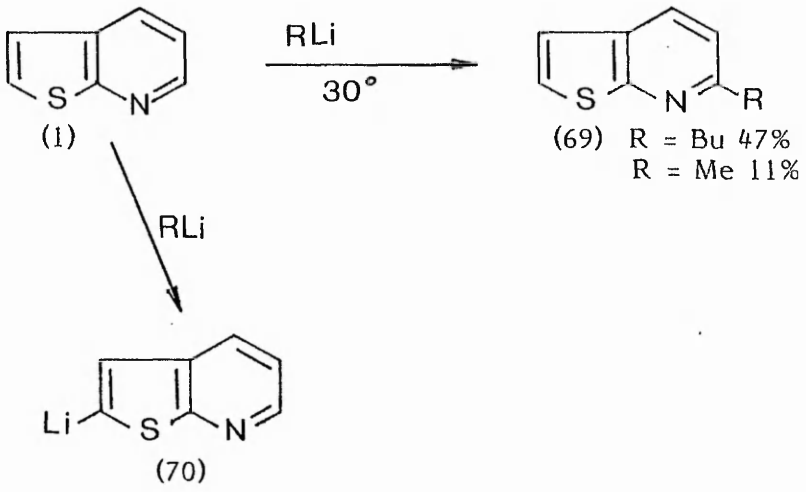


Scheme 28

1.1.3.2 **Nucleophilic Substitution**

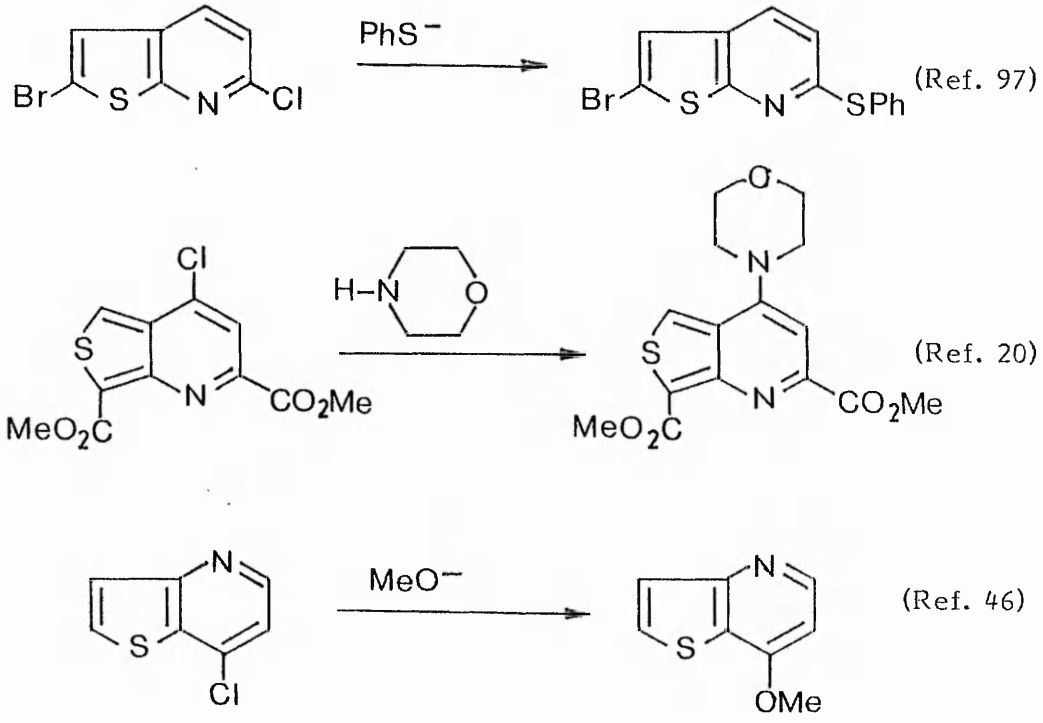
Generally aromatic nucleophilic substitution in quinolines involves the displacement of a hydride or halide ion by a strongly nucleophilic species. Only one example of the former has been reported in thieno[b]pyridines whereas displacements of halogen atoms α- or γ- to the nitrogen atom have been reported in all three systems. Displacement of halogen from less active positions has also been described.

Klemm et al[15] found that thieno[2,3-b]pyridine (1), on treatment with n-butyllithium at 25-35° followed by mild oxidation, gave the 6-butyl derivative (69 R=Bu) together with starting material; methyllithium gave a similar result. It was shown that formation of the 2-lithio compound (70) was a competing process to replacement of H-6, and at lower temperatures was the sole reaction. (Scheme 29)



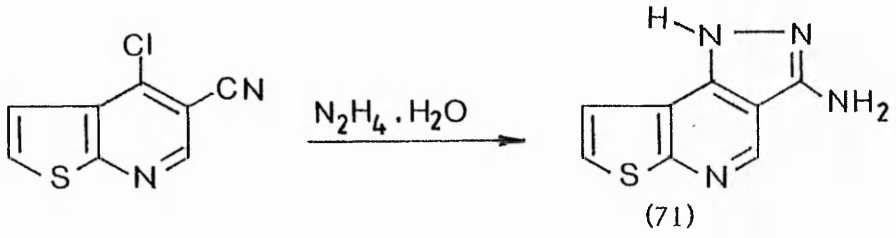
Scheme 29

Displacement of halogen from positions α- or γ- to the pyridine nitrogen atom has been recorded for a variety of thieno[b]pyridines. Scheme 30 shows a few examples of this type of transformation.



Scheme 30

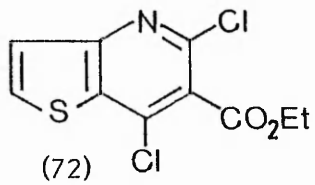
Where suitable substituents exist cyclisation to form tricyclic derivatives is possible, as in the synthesis of the pyrazole (71)[98]. (Equation 27)



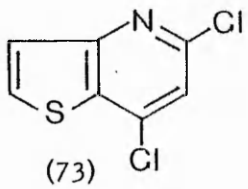
(71)

Equation 27

In the dichloro-ester (72) it was shown that the chlorine atom γ- to the nitrogen was the most readily displaced, forming angularly fused dithieno-pyridines[99]. In the corresponding compound without the ester group (73) it was originally believed that the chlorine atom α- to the nitrogen was the more reactive[46].



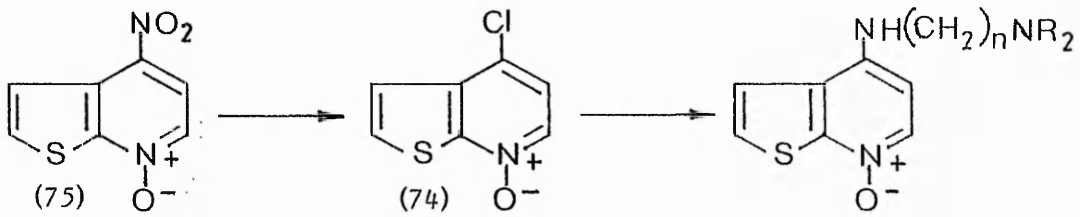
(72)



(73)

However this is incorrect and in (73) it is also the chlorine γ- to the nitrogen atom which is the more reactive (see the discussion section of the present work).

The chlorine atom in the N-oxide (74), formed by reaction of the nitro compound (75) with refluxing acetyl chloride, was displaced, albeit slowly, by a number of amines[92]. (Scheme 31)



(75) (74)

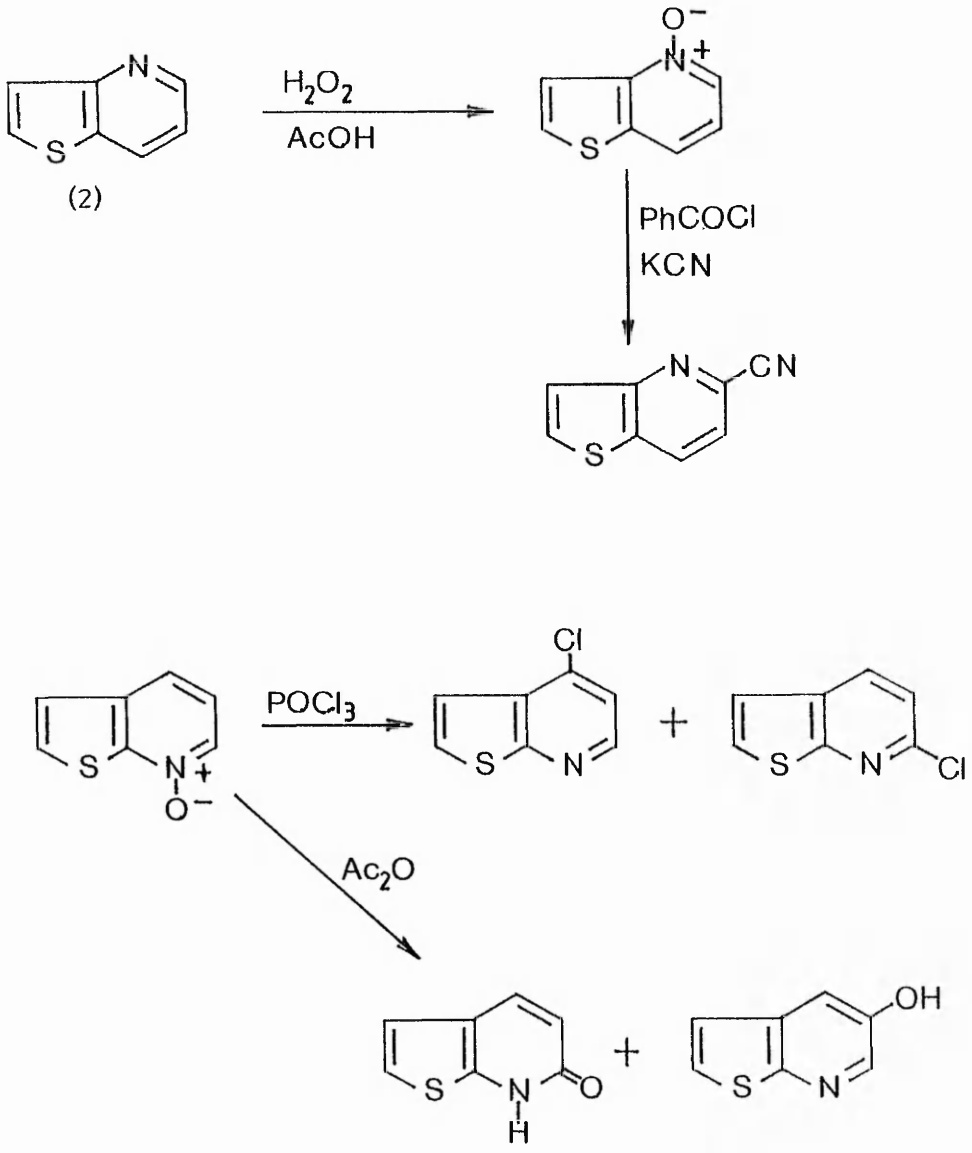
Scheme 31

Under more forcing conditions displacement of halogen from less reactive sites can be accomplished. Both 3-bromo[90] and 5-bromothieno[2,3-b]pyridines[21] form the corresponding nitrile with copper(I)cyanide in refluxing DMF. Iodine

has been displaced from C-2 of thieno[3,2-b][70] and [2,3-b]pyridines[96] using copper(I)cyanide in N,N-dimethylformamide (DMF) and sodium methoxide-copper(II)oxide in methanol, respectively.

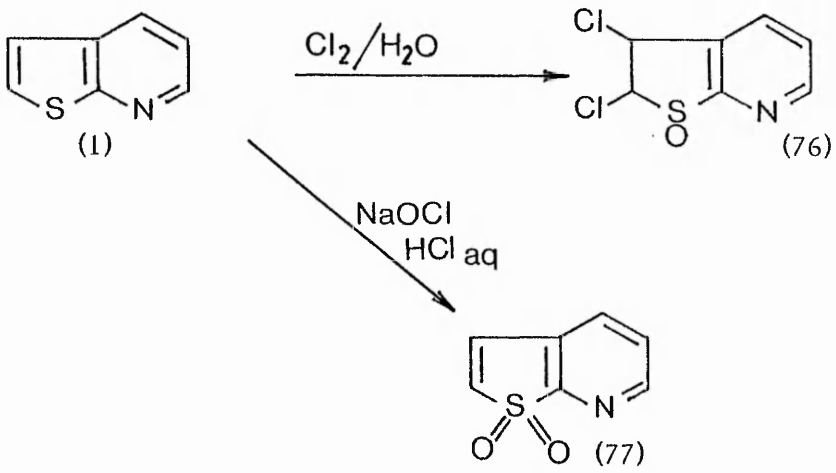
1.1.3.3 **Oxidation**

Thienopyridines can be oxidised at sulphur (giving a sulphoxide or sulphone) or at nitrogen (giving an N-oxide). Thieno[2,3-b][92] and [3,2-b]pyridines[100] are selectively oxidised by per-acids to give N-oxides which have been found to be synthetically useful, undergoing nitration[92] (Section 1.1.3.1), the Reissert-Henze reaction[101] and other transformations[102] similar to those recorded for quinolines. (Scheme 32)



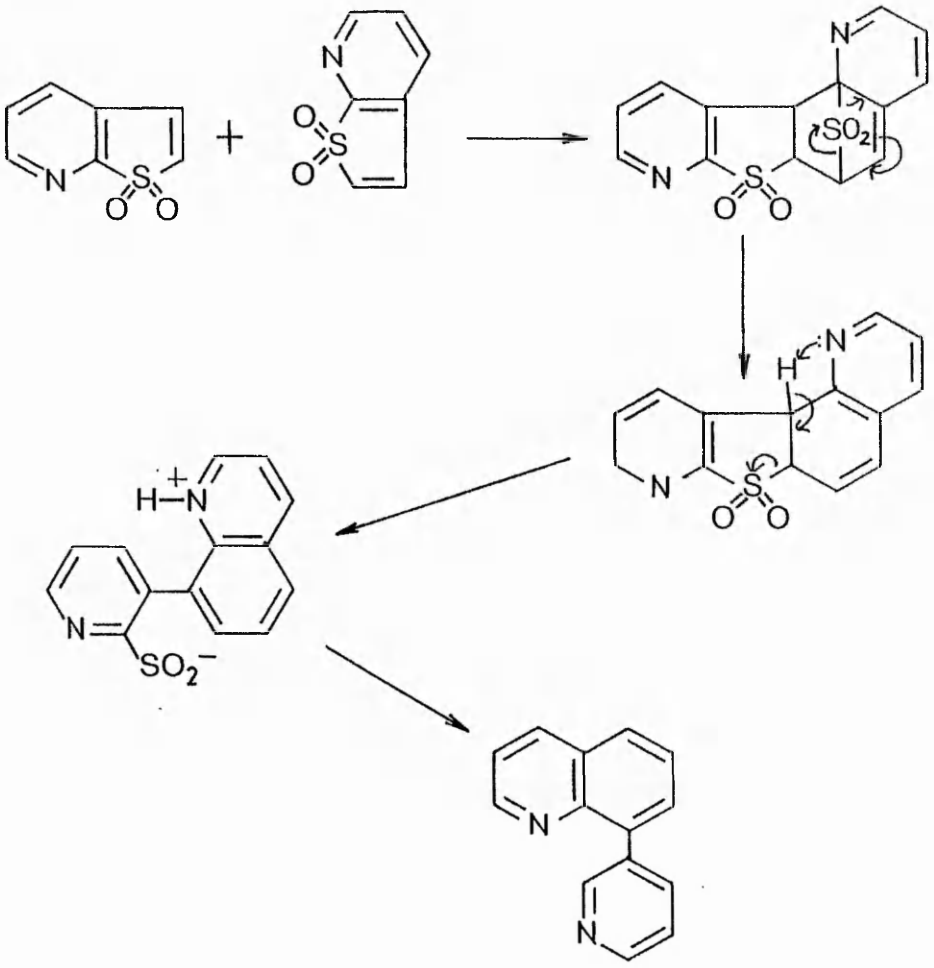
Scheme 32

The preparation of S-oxides is less straightforward; reaction of thieno[2,3-b]-pyridine (1) with chlorine water gave the 2,3-dihydro compound (76)[92], and with sodium hypochlorite and dilute hydrochloric acid the sulphone (77) was formed[95]. (Scheme 33) The sulphone from thieno[3,2-b]pyridine (2) was prepared similarly.



Scheme 33

The sulphone (77) acted as a dienophile in the Diels-Alder reaction, forming adducts with anthracene, with furan and with naphthacene. On heating (77) condensed with itself in a Diels-Alder fashion; sulphur dioxide was then extruded from the adduct to give the quinoline (78) as illustrated by Scheme 34.



(78)

Scheme 34

1.1.3.4 Reduction

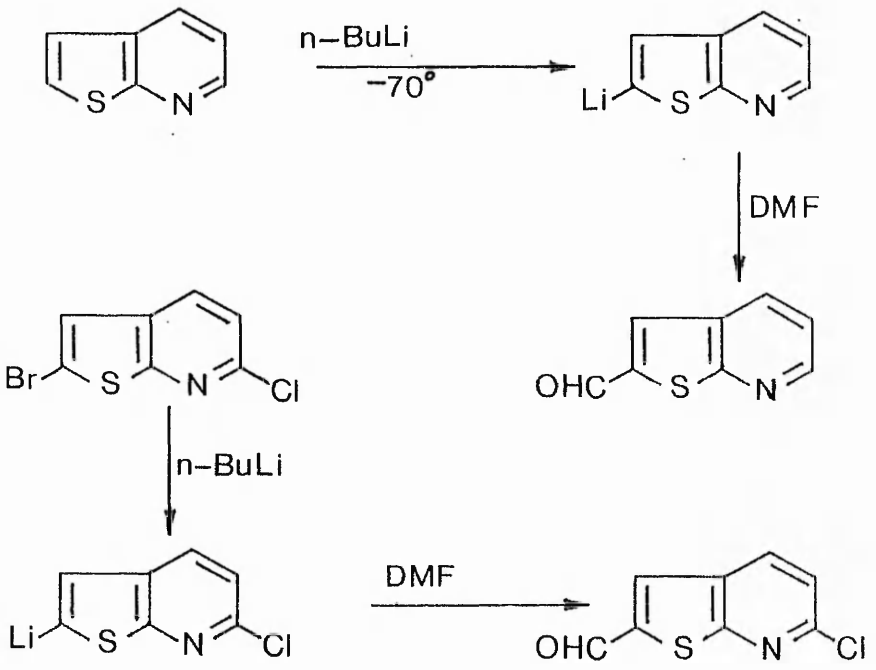
The only report of reduction of a thieno[b]pyridine ring system is the production of ethylpyridines from 4-methyl and 6-methylthieno[2,3-b]pyridines and Raney nickel[3]. The ring systems are stable to tin-hydrochloric acid[92] and iron-acetic acid[89,92] since nitro compounds have been reduced to amines by these reagents. Halogen substituents in either ring are removed by zinc in acetic acid, well illustrated by the production of the parent [2,3-b] system (1) from 2-bromo-6-chlorothieno[2,3-b]pyridine[97].

1.1.3.5 Lithio Compounds

As with thieno itself thieno[2,3-b][103] and [3,2-b]pyridines[70] react with n-butyllithium to give the 2-lithio derivatives, which undergo typical transformations of this type of compound. For example reaction with DMF leads to the aldehyde (79).

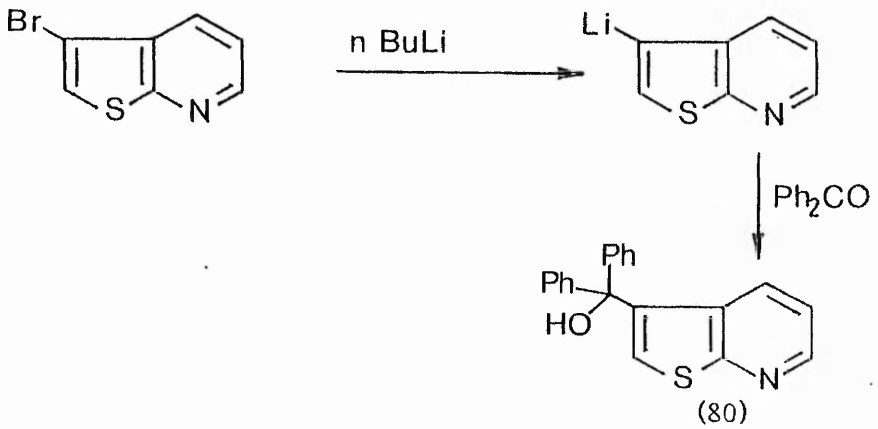
6-Chloro-2-lithiothieno[2,3-b]pyridine was prepared from the corresponding 2-bromo-6-chloro compound by reaction with n-butyllithium. This too reacted

with DMF to form an aldehyde[97]. (Scheme 35)



Scheme 35

3-Lithiothieno[2,3-b]pyridine is prepared by halogen-metal exchange between 3-bromothieno[2,3-b]pyridine and n-butyllithium at -70°[103]. It, too, undergoes typical reactions; for example, reaction with benzophenone yields the carbinol (80). (Scheme 36)



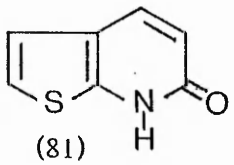
Scheme 36

1.1.3.6 **Reactions of Functional Groups**

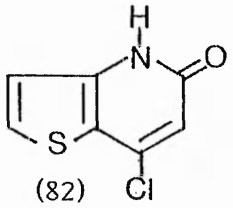
a) **Hydroxy Compounds**

A major point of interest in hydroxythienopyridines is the extent to which they exist in the keto or enol forms. Both 2- and 4-hydroxyquinolines exist in the keto form whilst 3-hydroxyquinoline exists solely in the enol form.

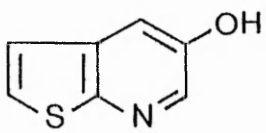
Similar observations can be made for thieno[b]pyridines. Thus (81)[102], (82)[46], (83)[21] and (84)[32] exist in the tautomeric forms shown below.



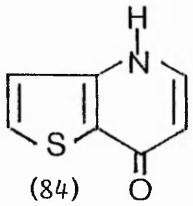
(81)



(82)

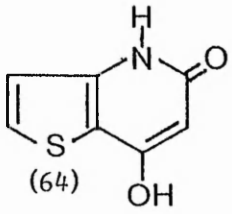


(83)

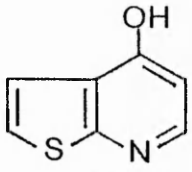


(84)

Like the corresponding quinoline the 5,7-dioxygenated thieno[3,2-b]pyridine (64) exists as the γ-hydroxy-α-keto tautomer[46]. However, unlike its thieno-[3,2-b]pyridine counterpart (84), the 4-oxygenated thieno[2,3-b]pyridine (85) exists as the hydroxy tautomer[27].



(64)

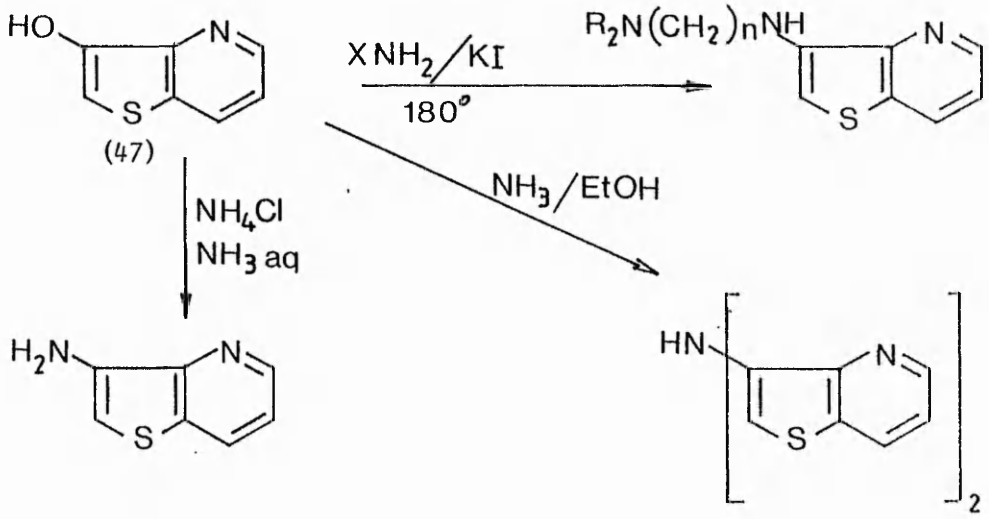


(85)

A more detailed study of tautomerism in these systems will be made in the discussion section of the present work.

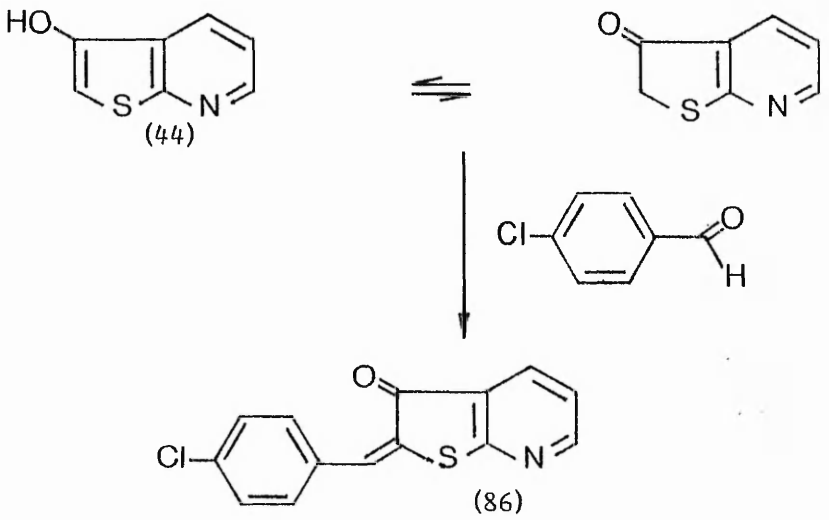
2-Hydroxythieno[b]pyridines are unknown and only a few examples of 3-hydroxy derivatives have been reported. Spectroscopic evidence indicates that 3-hydroxythieno[3,2-b]pyridine (47) exists in the hydroxy form[57]. This

compound also reacts with a variety of amines to form 3-amino derivatives as depicted in Scheme 37[104,105].



Scheme 37

Since nucleophilic substitution is unlikely in such a system it is possible that the products are formed by addition-elimination to the keto form. The involvement of the keto form is also likely to have been involved in the conversion of the thieno[2,3-b]pyridine analogue (44) into the benzylidene derivative (86)[106]. (Scheme 38)



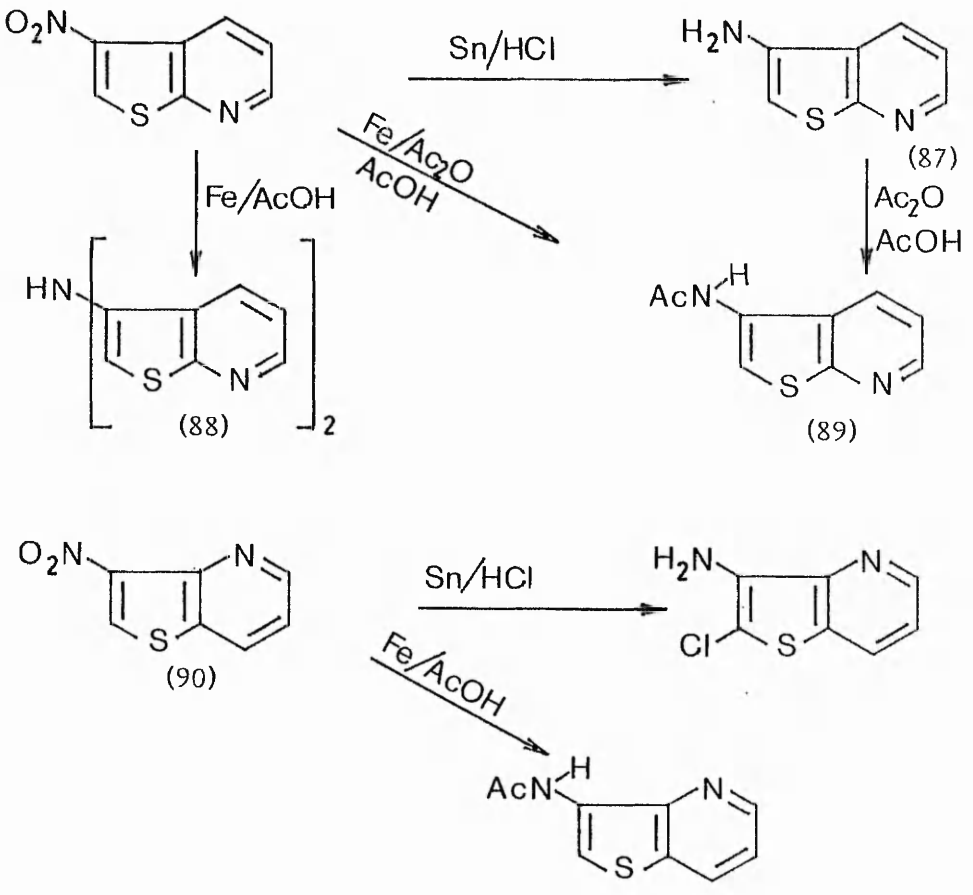
Scheme 38

b) **Amino Compounds**

Amino compounds generally behave in a similar manner to analogous quinoline and thiophene compounds. Thus compounds with the amino group attached to the thiophene nucleus are unstable as the free base but stable as the N-acyl derivatives.

N-Acetyl derivatives of 2-aminothieno[2,3-b] and [3,2-b]pyridines were prepared from the corresponding 2-acetyl compounds by Beckmann rearrangement of the oximes[79].

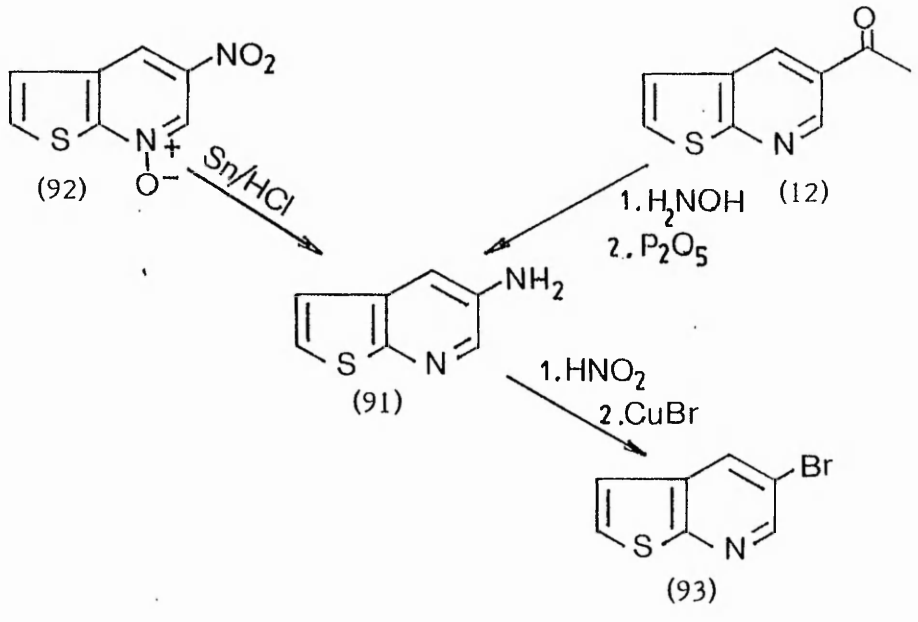
The reduction of 3-nitrothieno[b]pyridines to the amines does not always proceed smoothly. Klemm et al found that tin-hydrochloric acid treatment of 3-nitrothieno[2,3-b]pyridine gave the required amine (87) in moderate yield but that iron-acetic acid gave the dimer (88)[79]. Reduction with iron in a mixture of acetic acid and acetic anhydride gave the N-acetyl derivative (89) in good yield[107]. Scheme 39 shows these results and reductions of 3-nitrothieno-[3,2-b]pyridine (90) under similar conditions.



Scheme 39

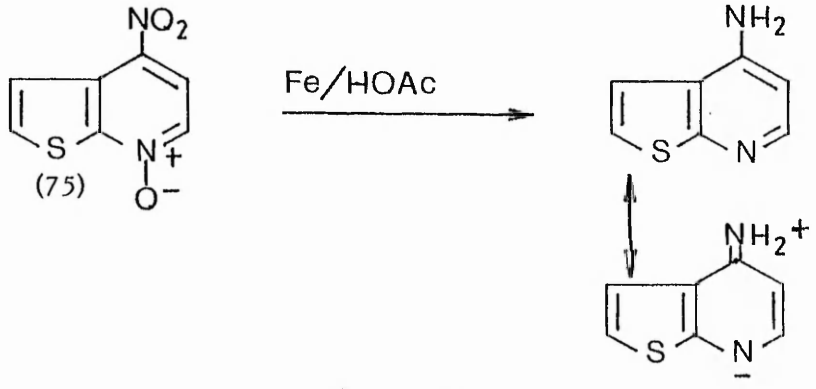
3-Aminothieno[2,3-b]pyridines react as normal aromatic amines. Thus, for example, they can be diazotised; the resulting diazonium salts couple with aromatic amines[108], and are reduced by hypophosphorous acid[109].

5-Aminothieno[2,3-b]pyridine (91) was prepared by Beckmann rearrangement[21] or by reduction of the nitro N-oxide (92)[92]. The amino behaved as a typical aromatic amine, forming Schiffs bases and undergoing diazotisation[21]. The diazonium salt behaved unexceptionally in a number of standard reactions, for example giving the bromo-compound (93) with copper(I)bromide. (Scheme 40)



Scheme 40

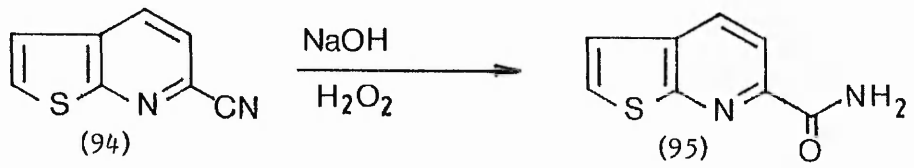
4-Aminothieno[2,3-b]pyridine was prepared similarly from the N-oxide (75)[92]. The amino group in this compound was considerably less nucleophilic than that in (91), only forming Schiffs bases with difficulty. The reduced basicity is presumably due to interaction with the ring nitrogen as shown in Scheme 41.



Scheme 41

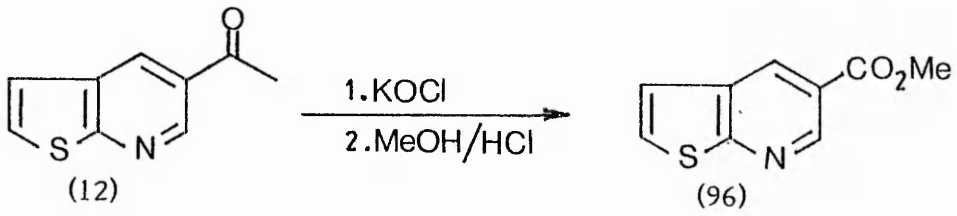
c) **Reactions of other functional groups**

Generally functional groups behave as in other aromatic systems. Thus acetyl groups were reduced to ethyl by the Wolf-Kischner reaction[15,21] and Schiffs bases were reduced to amines with sodium borohydride[21,92]. Cyano groups underwent a number of typical transformations[101, 110], for example, conversion of (94) into the amide (95). (Equation 28)



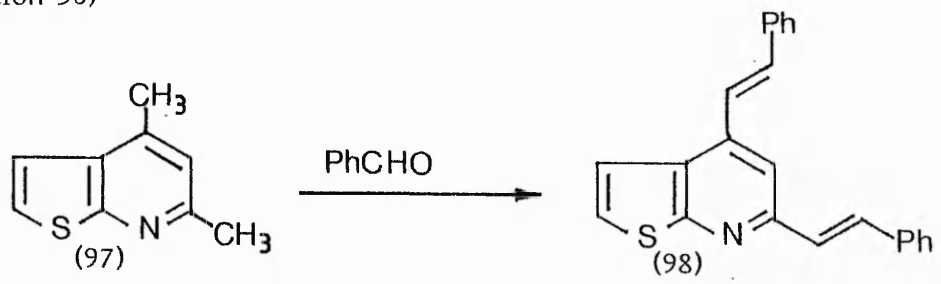
Equation 28

Oxidation of the acetyl compound (12), followed by methylation, gave the ester (96)[21]. (Equation 29)



Equation 29

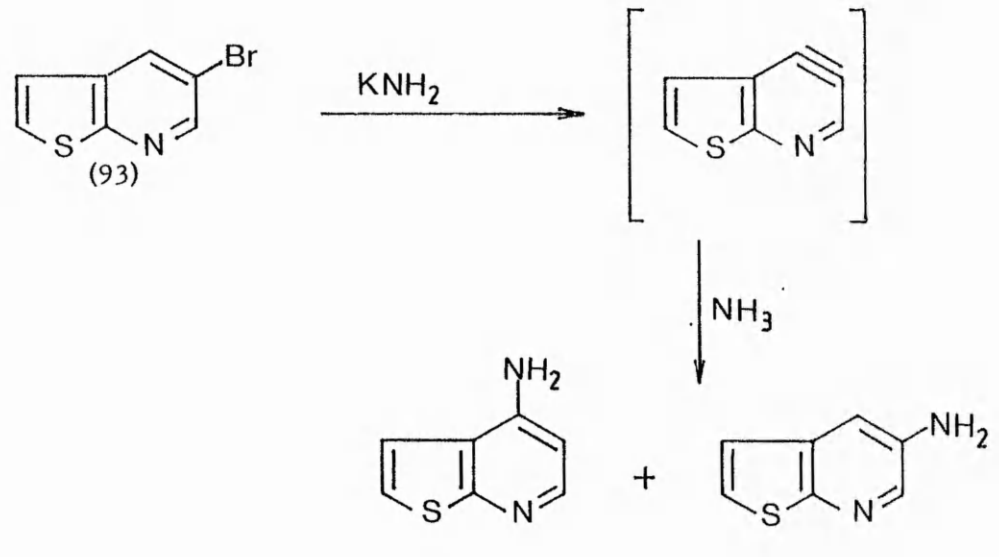
The reactivity of methyl groups in the 2- and 4-positions of quinolines has been observed in analogous thieno[2,3-b]pyridines. For example, the dimethyl compound (97) gave a dibenzylidene derivative (98) with benzaldehyde[17]. (Equation 30)



Equation 30

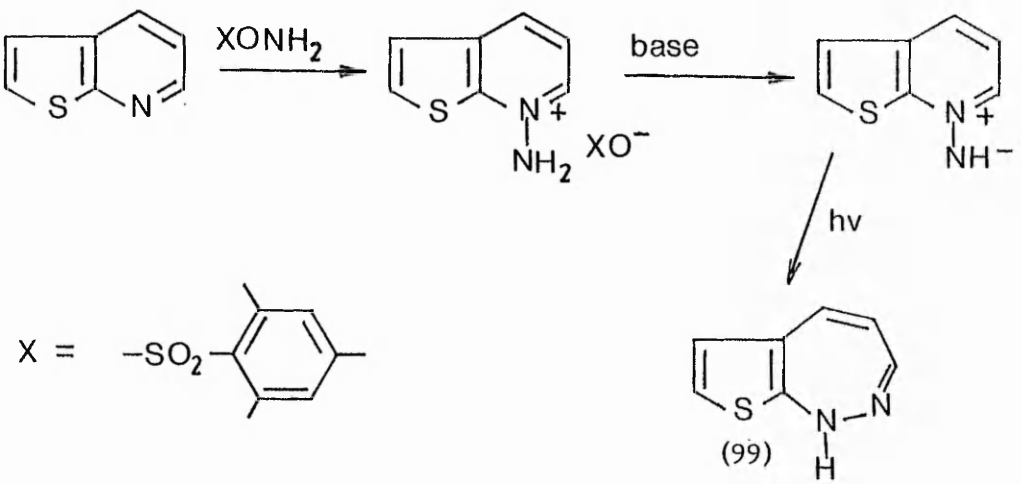
Russian workers produced analogues of indigo dyes by reaction of such active methyl groups with, for example, triethyl orthoformate[5,6].

Reaction of the bromo compound (93) with potassium amide at -70° gave a mixture of amines, presumably via an aryne intermediate[21]. (Scheme 42)



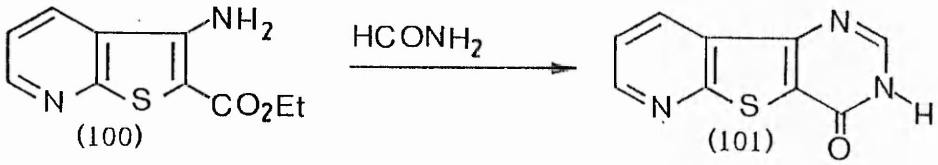
Scheme 42

Both thieno[2,3-b] and [3,2-b]pyridines have been aminated at nitrogen to give products which on irradiation underwent ring expansion to give diazepines[111,112], for example the preparation of (99), depicted in Scheme 43.



Scheme 43

When functional groups are correctly orientated cyclisations to give tricyclic systems are possible. For example, many compounds containing adjacent ester and amino groups have been converted into the related fused pyrimidines[113-5]. The conversion of (100) into (101) is a simple, but typical example. (Equation 31).

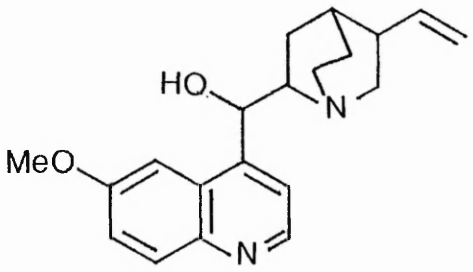


Equation 31

1.2 QUINOLINE ALKALOIDS

It is not possible to define simply what constitutes an alkaloid. In general they are nitrogen containing heterocyclic bases which occur naturally in plants, although some, for example the ergot alkaloids, are produced by micro-organisms and fungi. Particular alkaloids or types of alkaloids are generally only found in a limited group of plants and it is thus possible to classify alkaloids both by structure and by origin. Many alkaloids have been found to have some biological activity, although very few have passed the stringent course of testing and clinical trials to be accepted for pharmaceutical use.

Alkaloids which contain the quinoline nucleus fall into two general types; firstly the Cinchona alkaloids of which quinine (102) is a well known example. These are biosynthesised from tryptophan and are closely related to the indole alkaloids with which they often occur.



Quinine (102)

The second class of quinoline alkaloids is those arising from anthranilic acid which are found in plants of the Rutacea family.

This review will be solely concerned with the second group, the other types being outside the scope of the present work.

Quinoline Alkaloids of the Rutacea Family

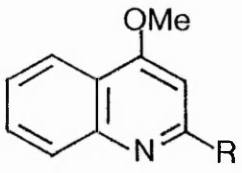
The Rutacea family of plants consists of over one thousand individual species which are abundant suppliers of many alkaloids. Well over one hundred quinoline alkaloids have been isolated from rutaceous plants, and they can be subdivided into several groups.

These compounds are too numerous to be discussed here individually; instead a few representative examples of each class will be presented in terms of structure, synthesis and biogenesis.

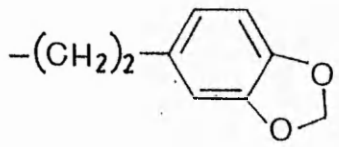
These systems have been covered in many books and reviews, in particular Sainsbury's review in Rodd[116] and the Annual Reports published by the Royal Society of Chemistry[117] to which reference should be made for the origin and isolation of these alkaloids. References to the biosynthesis of quinoline alkaloids may also be found in these publications and also in works dealing specifically with biosynthesis of natural products[118,119,120].

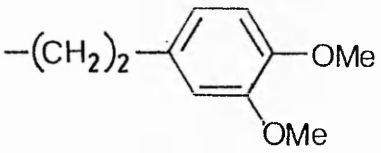
1.2.1 Simple Quinolines

Several simple quinolines, including quinoline itself, have been isolated; for example angostura bark yields, amongst others, quinoline, quinaldine, 4-methoxy-2-n-amylquinoline (103), cusparine (104), galipine (105) and graveolinine (106). (Figure 3)



(103) R = $-(CH_2)_3CH_3$

(104) R = 

(105) R = 

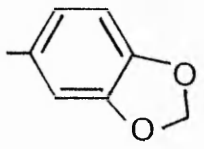
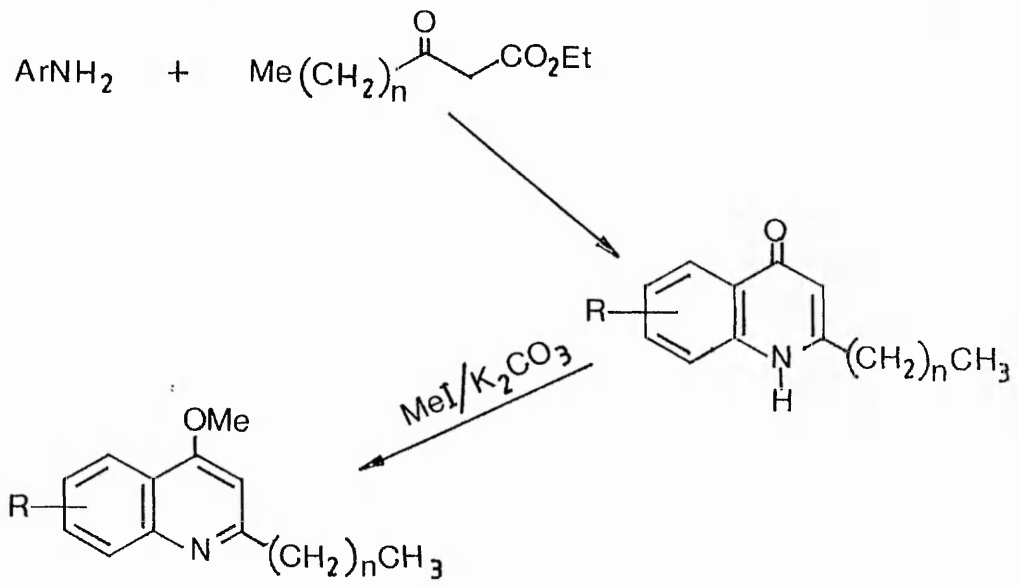
(106) R = 

Figure 3: Simple Quinoline Alkaloids

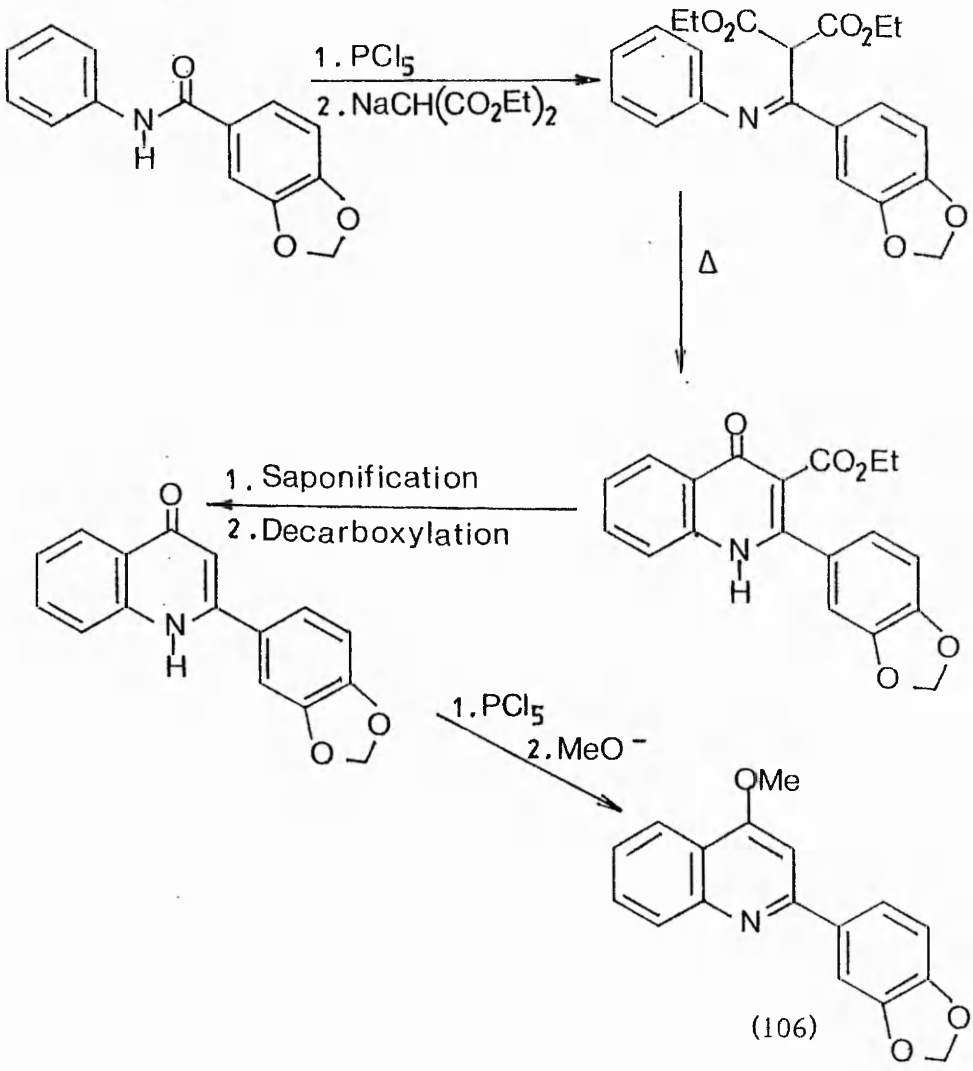
Compounds of type (103), ie 2-alkyl-4-methoxyquinolines may be synthesised via 4-quinolones[121] as shown in Scheme 44.



Scheme 44

Both (104) and (105) have been prepared by condensation of the methyl group of 4-methoxy-2-methylquinoline with the appropriate araldehyde, followed by reduction of the diarylethylene produced[122].

2-Arylquinolines, for example graveolinine (106), may be prepared as outlined in Scheme 45 from N-arylbenzamides[123].



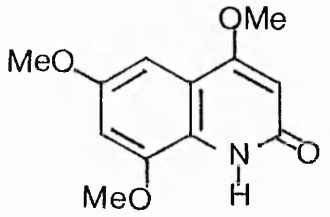
Scheme 45

1.2.2. 2-Quinolones

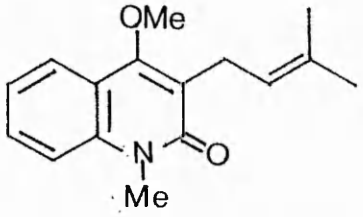
Together with simple quinolines many 2- and 4-quinolones are also found in plants of the family Rutacea. It is possible to distinguish between the two types by spectroscopy. In the u.v. spectrum both show an intense band at λ_{max} 239-258nm and a medium band at λ_{max} 322-331nm but only the 2-quinolones show an extra band at λ_{max} 263-298nm. Also, since 4-quinolones are the more basic, a shift in the absorption maximum occurs when acid is added[124,125]; this shift is not observed with 2-quinolones. The position and intensity of the carbonyl band in the i.r. is also a useful diagnostic tool[126]. In 2-quinolones it occurs at ≏ 1660-1650cm^{-1} whereas in 4-quinolones it is somewhat less intense and occurs at ≏ 1630-1620cm^{-1}; however on occasions this method is unreliable. Proton n.m.r. can also give useful information is appropriate cases[127].

Although 1-methyl-2-quinolone has been isolated, most of the 2-quinolones have a substituent at C-4 (usually methoxy).

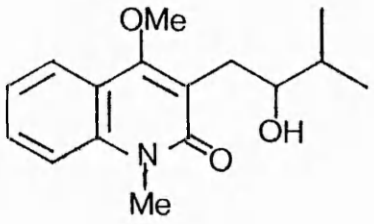
Substitution at C-3, usually by groups arising from a prenyl unit, is also frequently observed as in the compounds illustrated in Figure 4.



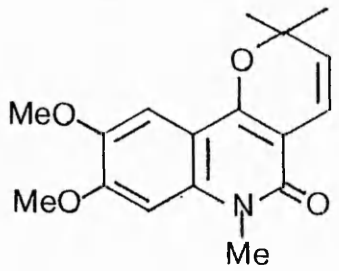
Halfordamine (107)



Atenine (108)



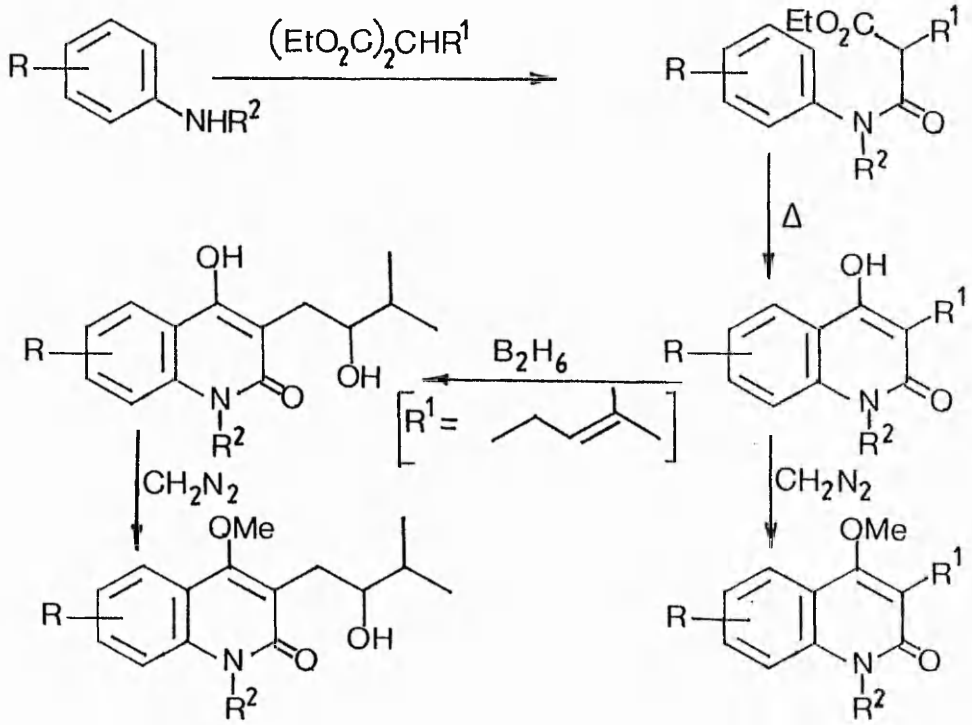
Lunacridine (109)



Oricine (110)

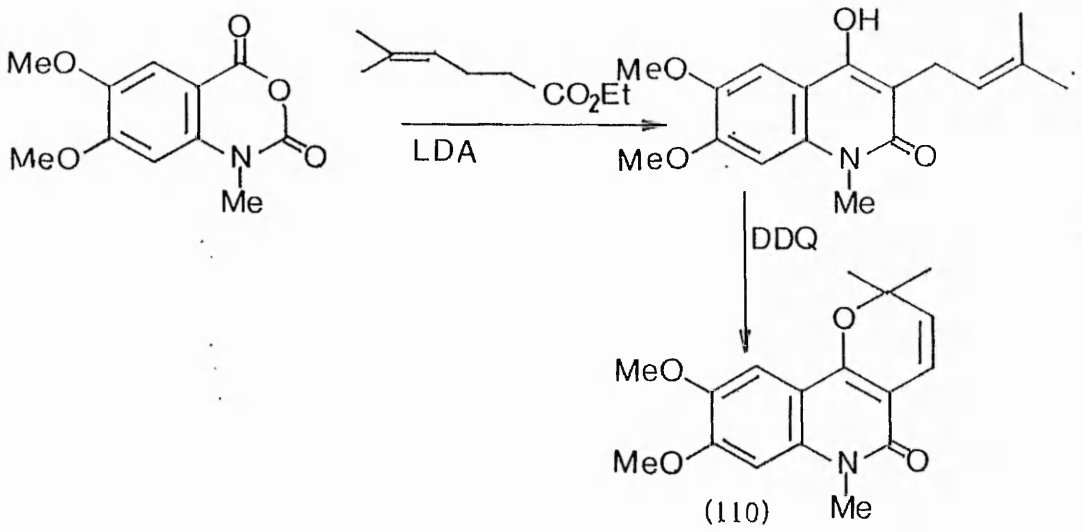
Figure 4: 2-Quinolone Alkaloids

In the case of oricine (110) the 3-prenyl unit has been modified into a pyran ring. A common procedure for the preparation of these compounds involves the reaction of an aniline with a substituted malonic ester as the first step. Subsequent transformations of the general type shown in Scheme 46 give 2-quinolones, for example (107)[128] and (109)[129].



Scheme 46

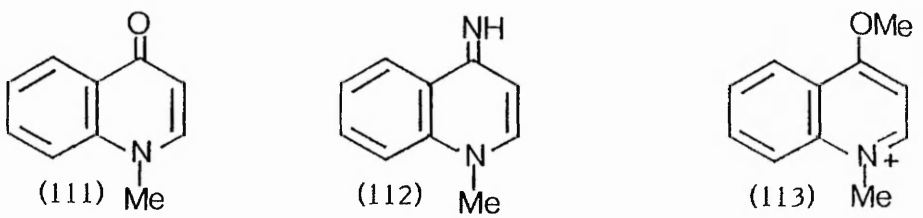
A recent synthesis involves the use of isatoic anhydrides[130]. (Scheme 47)



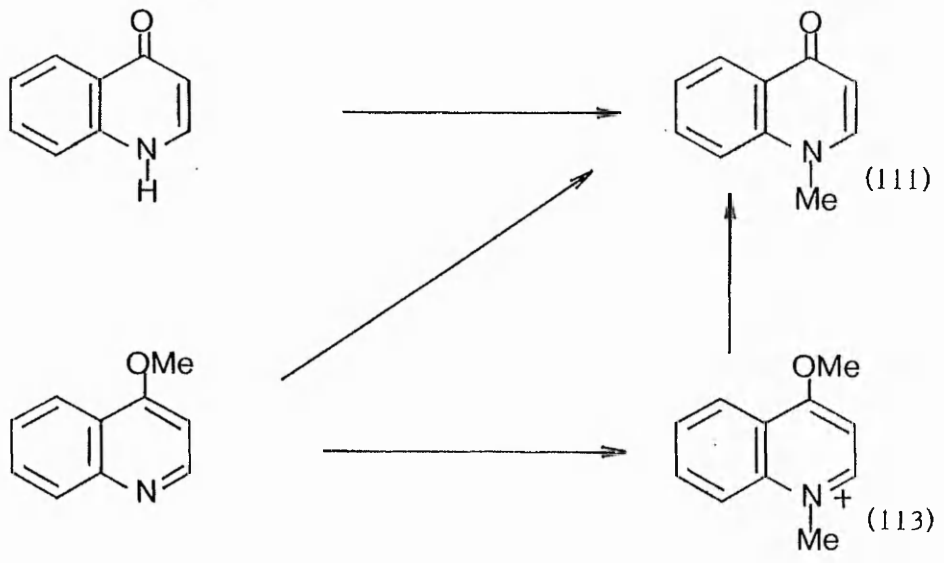
Scheme 47

1.2.3 **4-Quinolones**

Most 4-quinolones have been found to be substituted as C-2 but unsubstituted at C-3, although there are a few exceptions. The simplest 4-quinolone, 1-methyl-4-quinolone (111), has been claimed as an alkaloid (echinopsine)[131]. However, this material, together with the imine echinopsidine (112) are probably artefacts of the salt echinorine (113) arising on isolation by hydrolysis[132] and ammonolysis respectively[133].



Echinopsine (111) may be prepared by alkylation of 4-hydroxyquinoline (which exists mainly as the quinolone)[134] or by heating 4-methoxyquinoline with methyl iodide in a sealed tube[135] or by hydrolysis of (113)[132]. (Scheme 48)

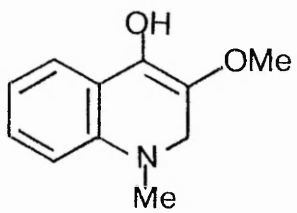


Scheme 48

This Scheme shows the relationship between N-methyl-4-quinolones and 4-methoxyquinolines. Many comparable compounds occur together in nature.

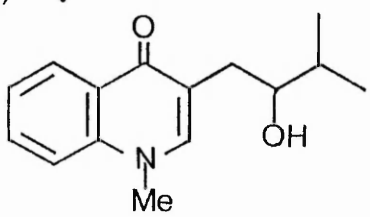
Biological activity has been reported for echinopsine[136]. The synthesis of the thieno[3,2-b]pyridine analogues of (111) and (113) has been described[32].

An oil, known as echinine, has been isolated and the dihydro structure (114) has been proposed for it[137].



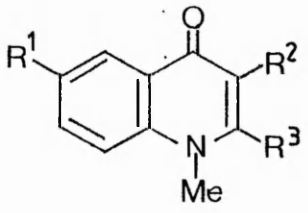
Echinine (114)

The 2-unsubstituted alkaloid pilokeanine has been shown spectroscopically to have the structure (115)[138].

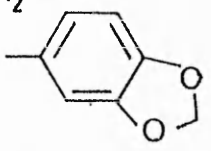


Pilokeanine (115)

Other naturally occurring 4-quinolones are N-methyl counterparts of 4-methoxyquinolines (Section 1.2.1). The typical examples evocarpine (116), graveoline (117) and japonine (118) are shown in Figure 5.



(116) $R_1 = R_2 = H$
$R_3 = -(CH_2)_7CH=CH(CH_2)_3CH_3$

(117) $R_1 = R_2 = H$
$R_3 =$ 

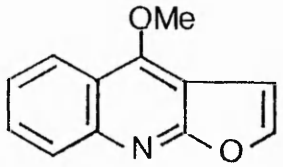
(118) $R_1 = R_2 = -OMe$, $R_3 = Ph$

Figure 5: 4-Quinolone Alkaloids

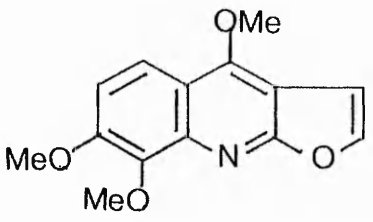
These compounds may be prepared by adaptations of the routes used to prepare 4-methoxyquinolines (see Section 1.2.1). A convenient synthesis of (117) and (118) from isatoic anhydrides has recently been reported[139].

1.2.4 Furoquinolines

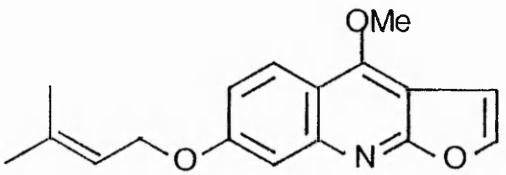
Many alkaloids of the furo[2,3-b]quinoline type have been isolated, the simplest being dictamnine (119). Other derivatives of this type generally carry ring substituents; typical are skimmianine (120), evellerine (121) and platydesmine (122). (Figure 6)



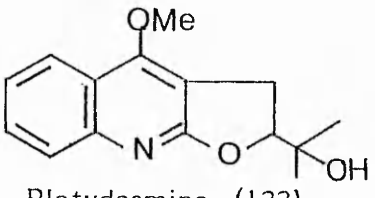
Dictamnine (119)



Skimmianine (120)



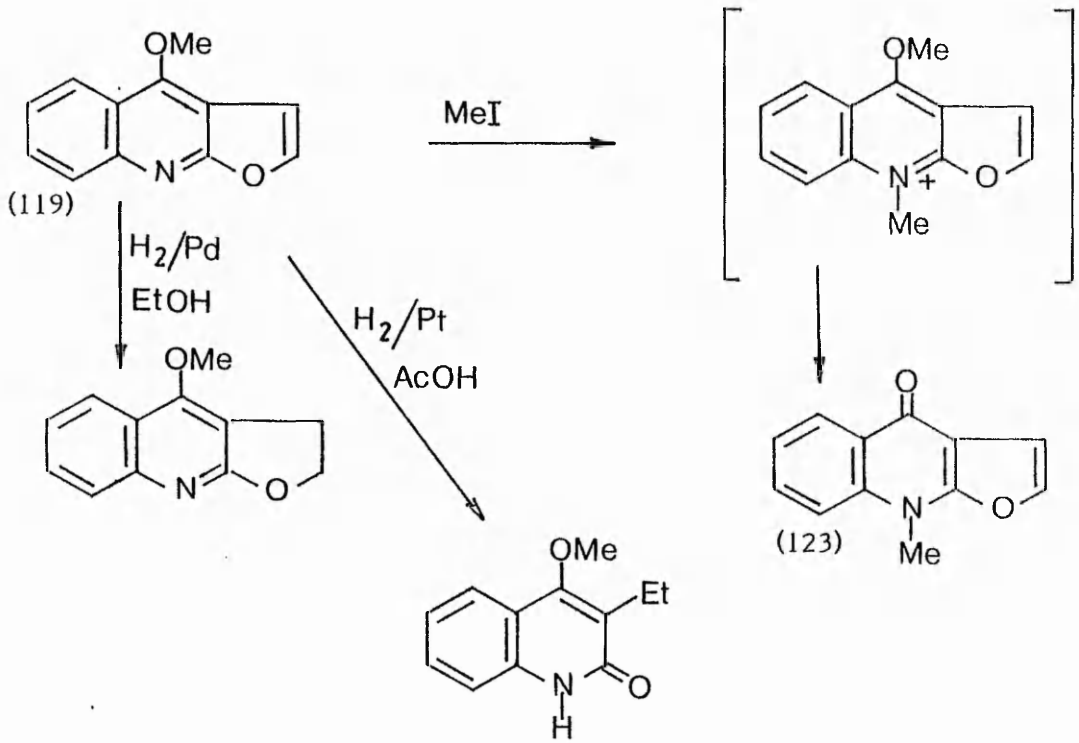
Evellerine (121)



Platydesmine (122)

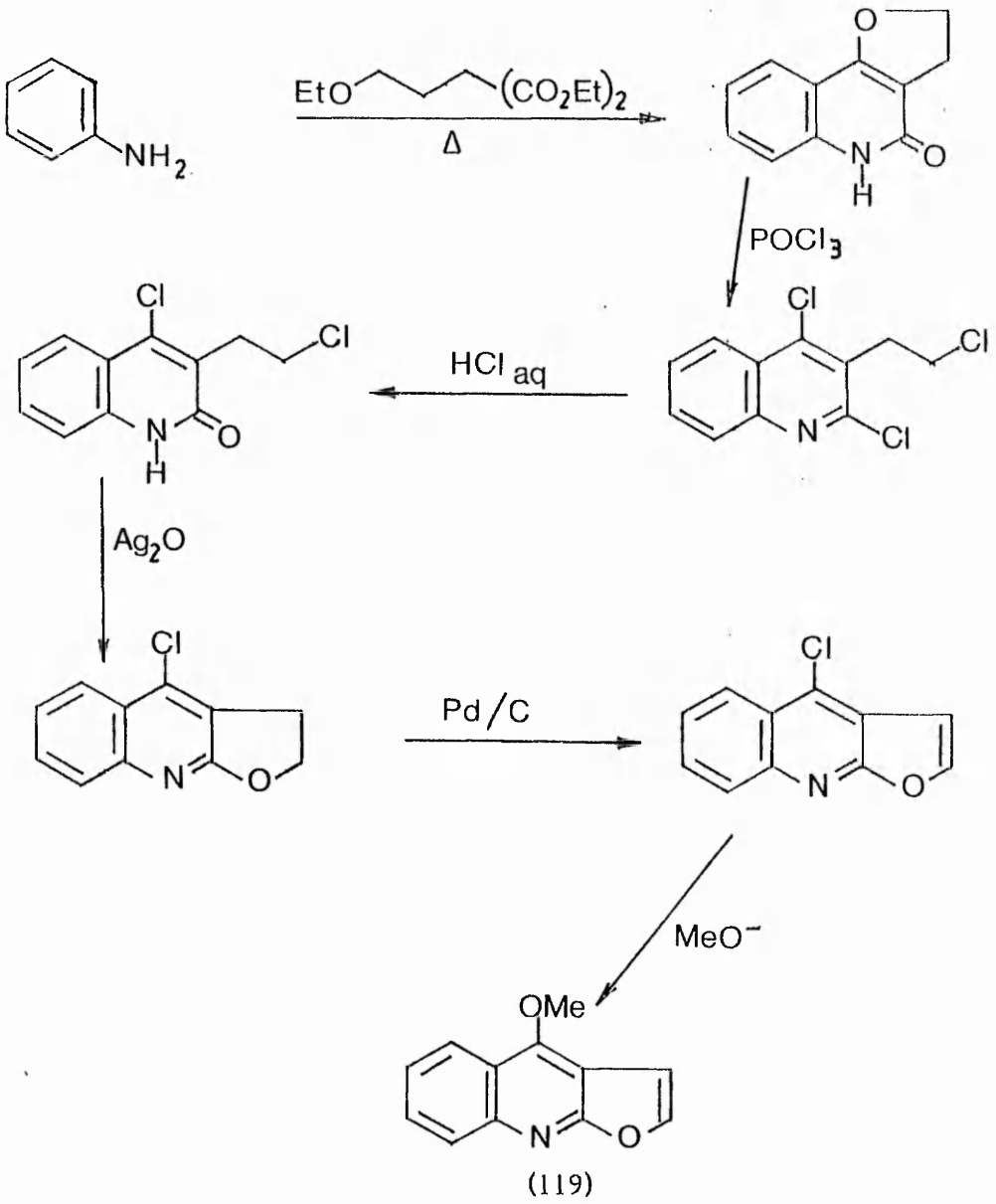
Figure 6: Furo[2,3-b]quinoline alkaloids

Much study has been made of the synthesis and reactions of these compounds, in particular of dictamnine. When heated with methyl iodide, dictamnine forms isodictamnine (123)[140], a compound which has also been isolated from plants. On reduction dictamnine forms different products depending on the catalyst used[141,142]. Scheme 49 shows these reactions of dictamnine.



Scheme 49

Scheme 50 shows the first synthesis of dictamnine[143].

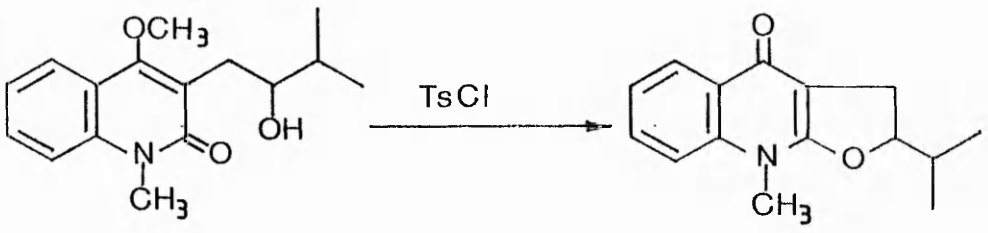


(119)

Scheme 50

More recently syntheses of this type of compound starting from 2,4-dimethoxyquinolines[144] and from 2-anilinofuran-3-carboxylic acid derivatives[145] have been reported.

Furoquinolones also occur in nature; isodictamnine (123) has already been discussed and lunacrine (124) (which has been prepared from lunacridine (109)[146]) is another typical N-methylfuroquinolone. (Equation 32)

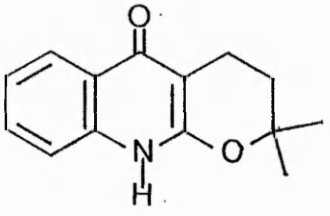


Lunacrine (124)

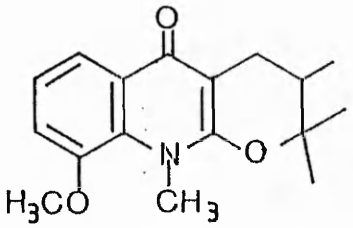
Equation 32

1.2.5 **Pyranoquinolines**

This class of alkaloid is much less common than the furoquinolines. The simplest structure in the class that has been isolated is the N-H compound khaplofoline (125), but in general the pyranoquinolines contain the N-methyl-4-quinolone unit and often have a hydroxy substituent at the 3-position of the pyran ring as, for example, in isobalfourodine (126).

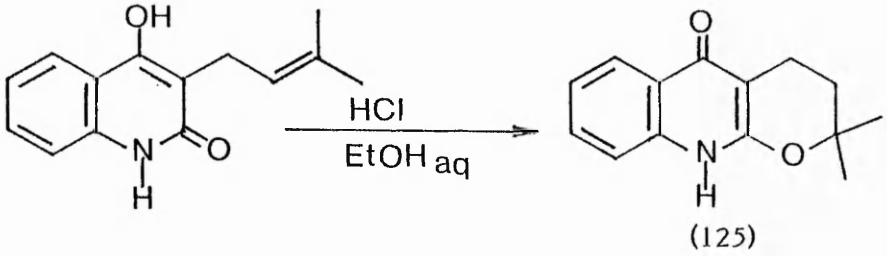


Khaplofoline (125)



Isobalfourodine (126)

Syntheses of this type of compound mainly involve cyclisation of a 3-prenyl-quinolin-2-one as a key step as in, for example, the synthesis of khaplofoline (125), shown in Equation 33[147].

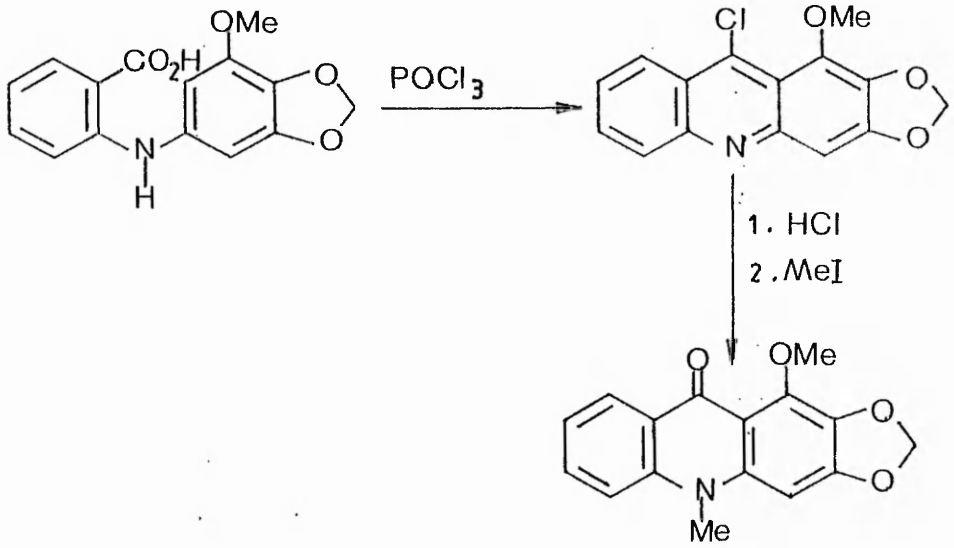


(125)

Equation 33

1.2.6 **Acridones**

Various acridones, including the parent 1-methyl-9-acridone have been isolated. They are usually N-methylated although some N-H compounds are known. Other substituents are generally hydroxy, methoxy and methylenedioxy although in some cases a pyran or furan ring is fused to the system. A typical example is evoxanthine (127) which was synthesised as shown in Scheme 51[148].



Evoxanthine (127)

Scheme 51

1.2.7 **Biosynthesis**

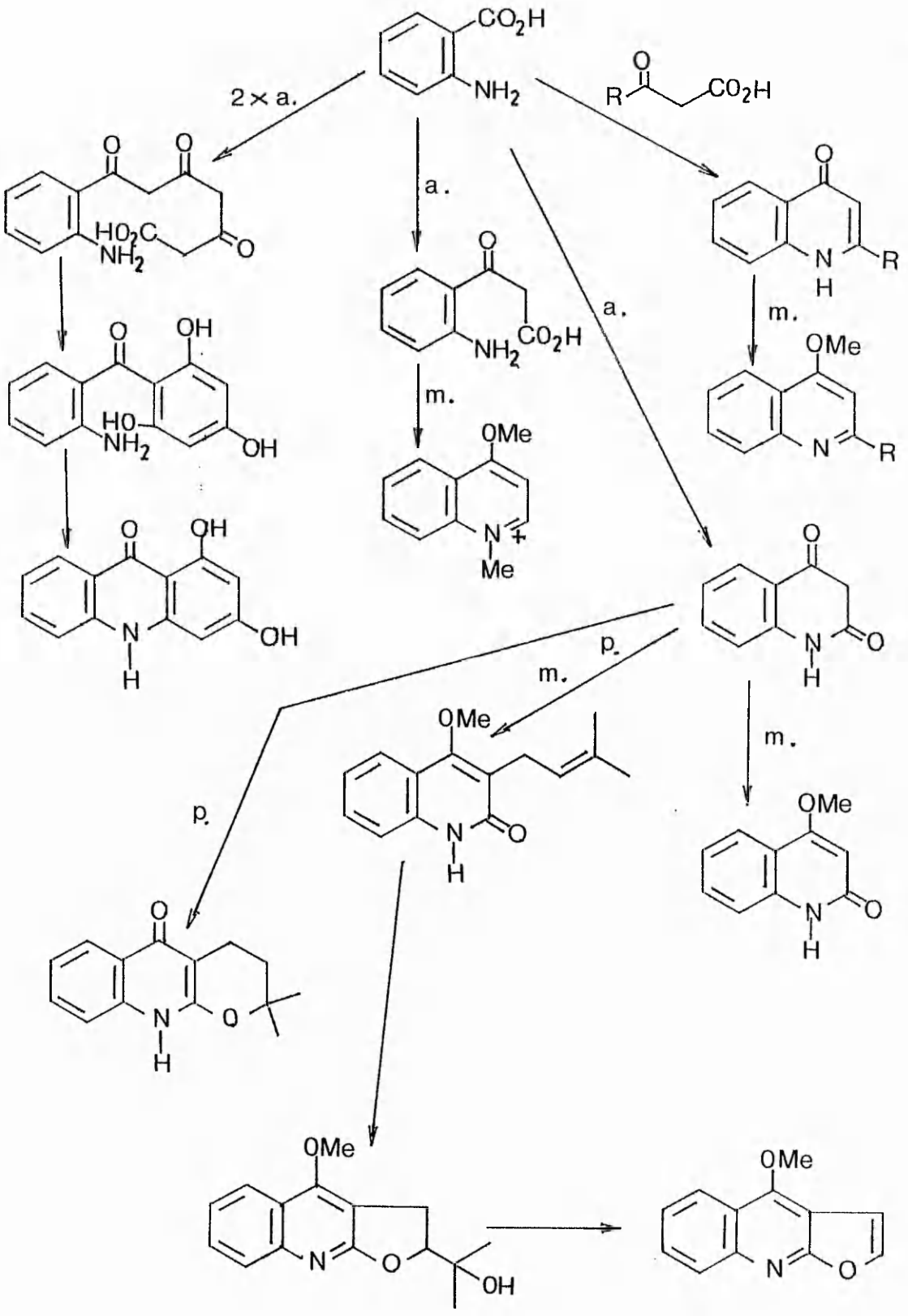
Quinoline alkaloids from plants of the Rutacea family are biosynthesised from anthranilic acid; tryptophan is not involved. The remaining carbon atoms of the pyridine ring are usually provided by "acetate", in some cases (for example 2-alkyl quinolines) extended into a long chain before incorporation. Aryl groups in the C-2 substituent (for example 2-arylquinolines) are provided by a phenylpropane-carboxylic acid unit. Furan or pyran rings arise from γ,γ-dimethylallyl pyrophosphate (derived from mevalonic acid) and methyl groups (for methoxy or N-methyl subtituents) are provided by methionine. Scheme 52 shows the biosynthesis of all types of alkaloids described previously, subsequent modifications, for example ring hydroxylation, are not shown.

Reagents used in Scheme:

a "Acetate"

b Methionine

c γ,γ-Dimethylallyl pyrophosphate



Scheme 52

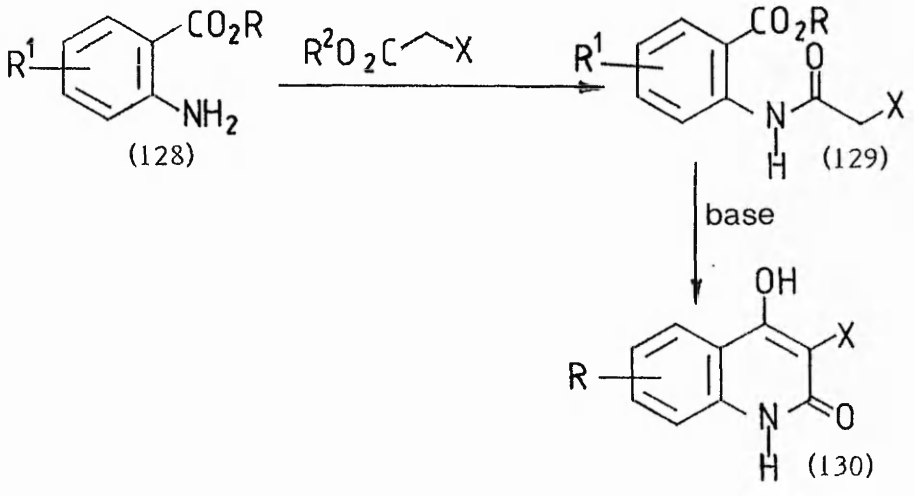
CHAPTER TWO

PREPARATION OF THIENO[2,3-b]PYRIDINES

PREPARATION OF THIENO[2,3-b]PYRIDINES

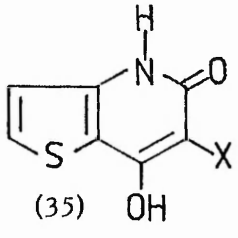
2.1 4,6-Di-oxygenated derivatives

The synthesis of 4-hydroxy-2-quinolones from anthranilic esters has been well documented[149,150]. Reaction of esters (128) with acetic acid derivatives gives amides (129) which are cyclised by base to quinolines (130). (Scheme 53)



Scheme 53

Recently this procedure has been used for the preparation of thieno[3,2-b]-pyridines (35)[151,99,46]. In this case cyclisation was effected by either sodium ethoxide in ethanol or sodium hydride in DMF.

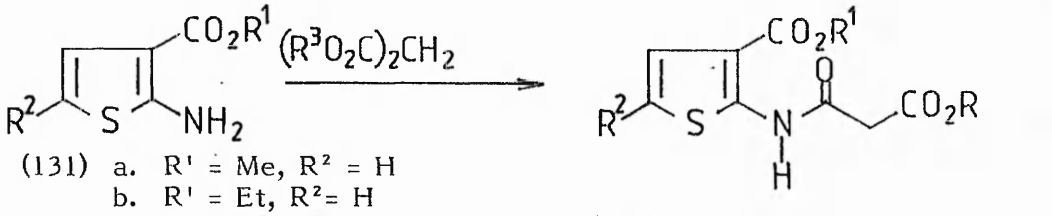


(35) X = CO_2Et, CO_2Me, COMe, CN

This method was used to prepare the thieno[3,2-b]pyridines used in the present work.

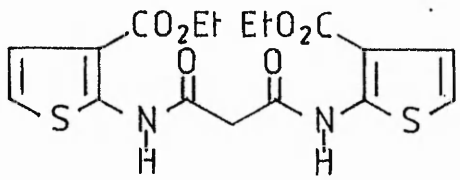
In order to apply this procedure to the production of thieno[2,3-b]pyridines, the 2-aminothiophene-3-carboxylates (131 a-d), required as starting materials, were prepared by the methods reported by Gewald[152,153]. These amines were boiled under reflux with an excess of the appropriate dialkyl malonate giving the required amides (132 a-d). In one case the bis-amide (138), arising from condensation of two molecules of amine with one of malonate, was isolated (Scheme 54).

Presumably in the other cases the corresponding bis-amides were formed but in insufficient quantity to be isolated.



(131) a. R' = Me, R^2 = H
b. R' = Et, R^2 = H
c. R' = R^2 = Et
d. R' = Et, R^2 = Me

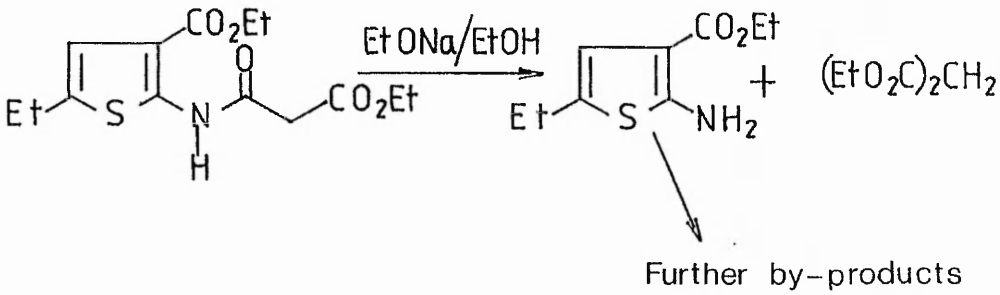
(132) a. R' = R^3 = Me, R^2 = H
b. R' = R^3 = Et, R' = H
c. R' = R^2 = R^3 = Et
d R' = R^3 = Et, R^2 = Me



(138) (from (131b))

Scheme 54

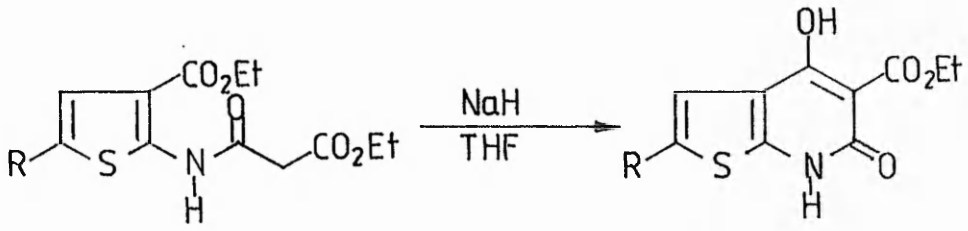
Cyclisation of these amides proved to be more difficult than in the quinoline or thieno[3,2-b]pyridine series. The initial experiments were conducted on the tri-ethyl compound (132c). Use of sodium ethoxide in ethanol, successful in the other series[46], failed in this case and led to complex mixtures (the related compound (132b) behaved similarly with this reagent). The reason for this behaviour is unclear but it is possible that solvolysis of the amide (132c) to the amine (131c) could occur; leading to further by-products. (Equation 34)



Equation 34

With sodium hydride in DMF (successful in the [3,2-b] series[46]) effervescence occurred, indicating the formation of a sodium salt. However, stirring at room temperature followed by aqueous workup led to recovery of starting material and no cyclised product. A similar result was observed when potassium t-butoxide in t-butanol was employed; although a salt was formed no cyclisation occurred. Eventually a successful ring closure was achieved when (132c) was

heated with two equivalents of sodium hydride in tetrahydrofuran (THF) giving (133b). This procedure was also successful with (132b) and (132d) giving thieno[2,3-b]pyridines (133a) and (133c), respectively. These successful cyclisations are shown in Equation 35. Interestingly the bis-methyl ester (132a) did not cyclise under these conditions.



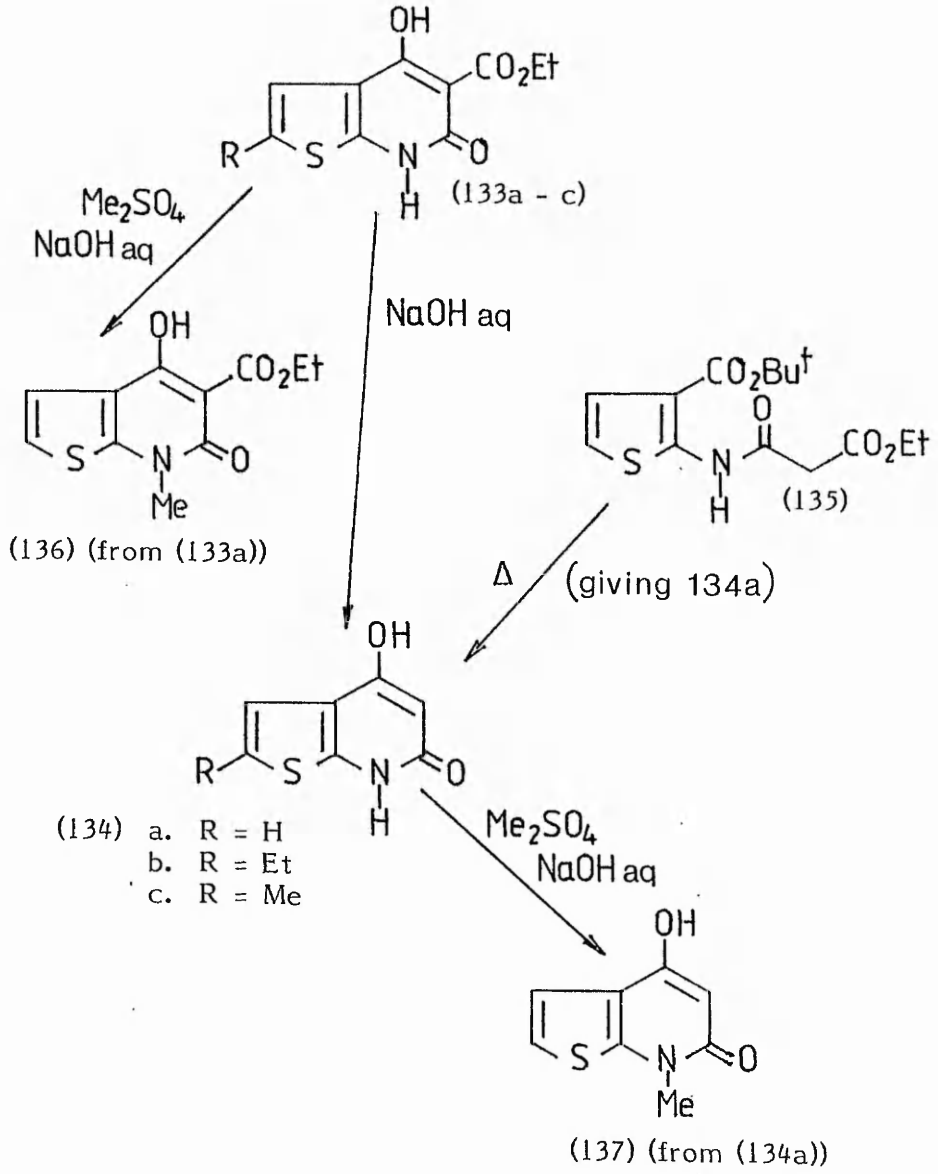
(132) b. R = H
c. R = Et
d. R = Me

(133) a. R = H
b. R = Et
c. R = Me

Equation 35

The thieno[2,3-b]pyridines formed in this manner were shown by ^{13}C n.m.r. (see Chapter 4) and i.r. spectroscopy to exist as the 4-hydroxy-2-pyridone tautomers, as do the corresponding quinolines and thieno[3,2-b]pyridines. The i.r. spectra show broad bands at 1640cm^{-1} with shoulders at 1650cm^{-1}, and the absence of absorption maxima at 1620-1610cm^{-1}; indicating the 2-pyridone tautomer. (2-Pyridones show absorption at 1660-1640cm^{-1}, whereas 4-pyridones absorb at 1620-1610cm^{-1}.)

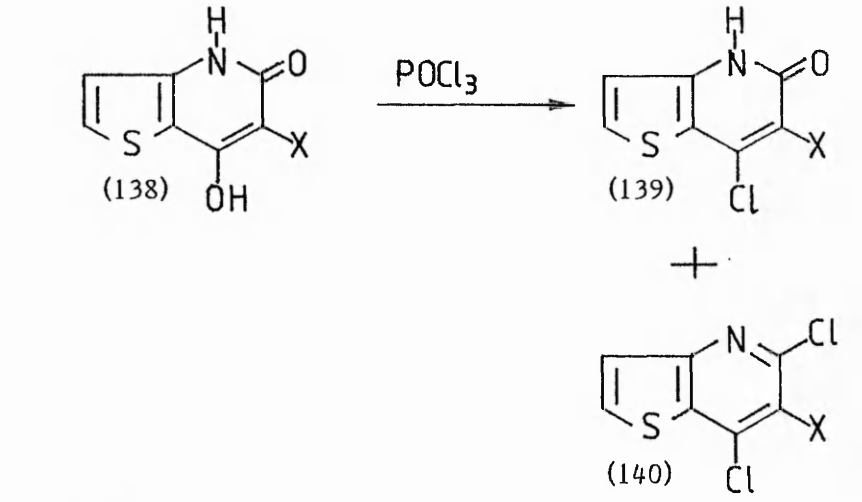
When boiled under reflux with aqueous alkali these esters were saponified and, upon acidic workup, the acids produced spontaneously decarboxylated to give the 5-unsubstituted compounds (134a-c) which were shown by the methods just described to exist as the 4-hydroxy-2-pyridone tautomers also. Compound (134a) was also prepared by thermolysis of the t-butyl ester (135) (obtained from t-butyl 2-aminothiophene-3-carboxylate and diethyl malonate) in diphenyl ether. Both (133a) and (134a) were N-methylated by dimethyl sulphate in aqueous sodium hydroxide giving (136) and (137) respectively. These transformations are illustrated in Scheme 55.



Scheme 55

2.2 Chloro compounds

In order to study nucleophilic substitution in this system it was necessary to prepare chloro compounds. In the [3,2-b] series reaction of various 5,7-dioxygenated compounds with phosphoryl chloride under reflux gave mixtures of monochloro (139) and dichloro (140) compounds[46,99,151]. (Scheme 56)

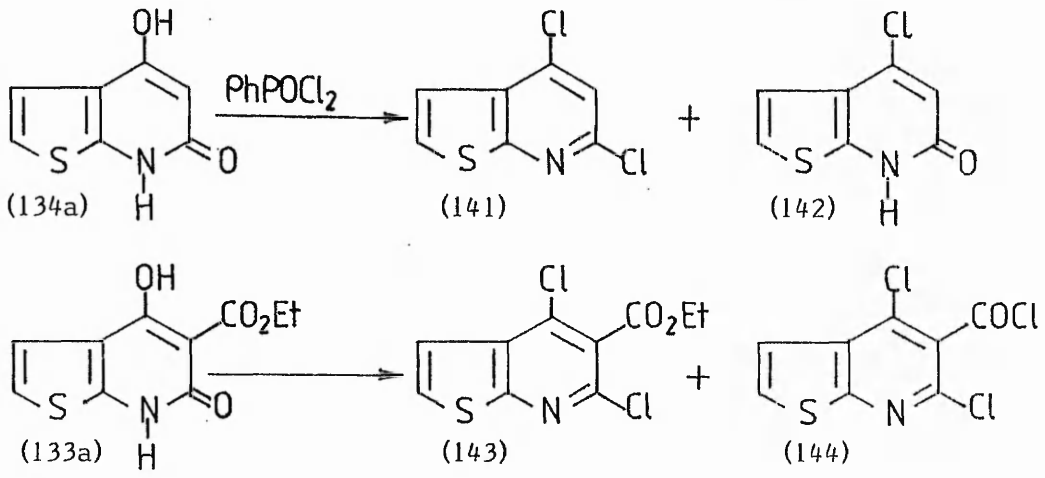


X = CO_2Et, CO_2Me, CN, H

Scheme 56

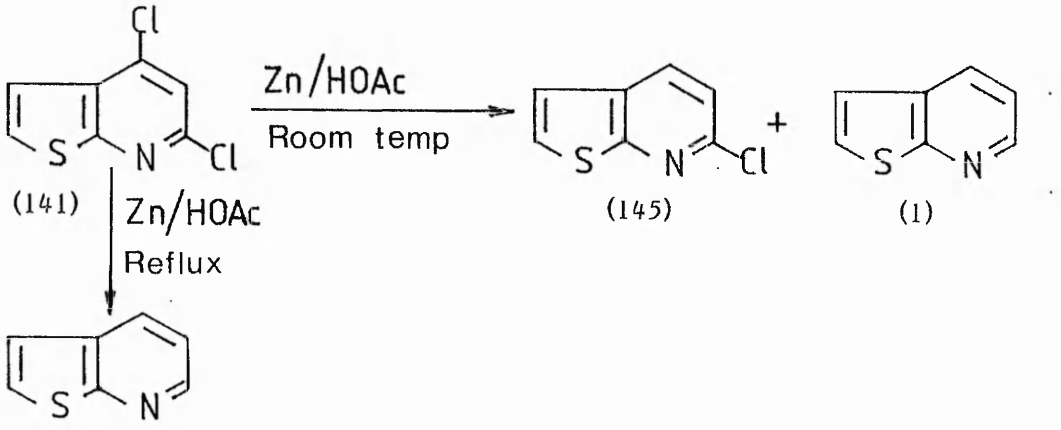
However, under the same conditions with this reagent (133a) and (134a) gave no reaction; (134a) was also unaffected by thionyl chloride. Although (134a) did react with phosphorus pentachloride the product was a complex mixture having no single major component.

The action of phenylphosphonic dichloride on (134a) led to a modest yield of 4,6-dichlorothieno[2,3-b]pyridine (141) which was contaminated with a small amount of a second component, shown by its spectroscopic properties and by chemical transformation (see Chapter 3) to be (142). The same reagent with (133a) gave ethyl 4,6-dichlorothieno[2,3-b]pyridine-5-carboxylate (143), also in rather poor yield; in this case the second (minor) component was the acid chloride (144). These chlorinations are depicted in Scheme 57.



Scheme 57

The preparation of 6-chlorothieno[2,3-b]pyridine (145) has been reported in the literature[97]. Material required for the present work was prepared by selective monodechlorination of (141) using zinc in acetic acid. At reflux temperature thieno[2,3-b]pyridine (1) was the sole product whereas at lower temperatures mixtures of (1) and (145) were formed. At 30° the yield of (145) was 11%; this figure rose to 32% when the reaction was conducted at room temperature. (Scheme 58)



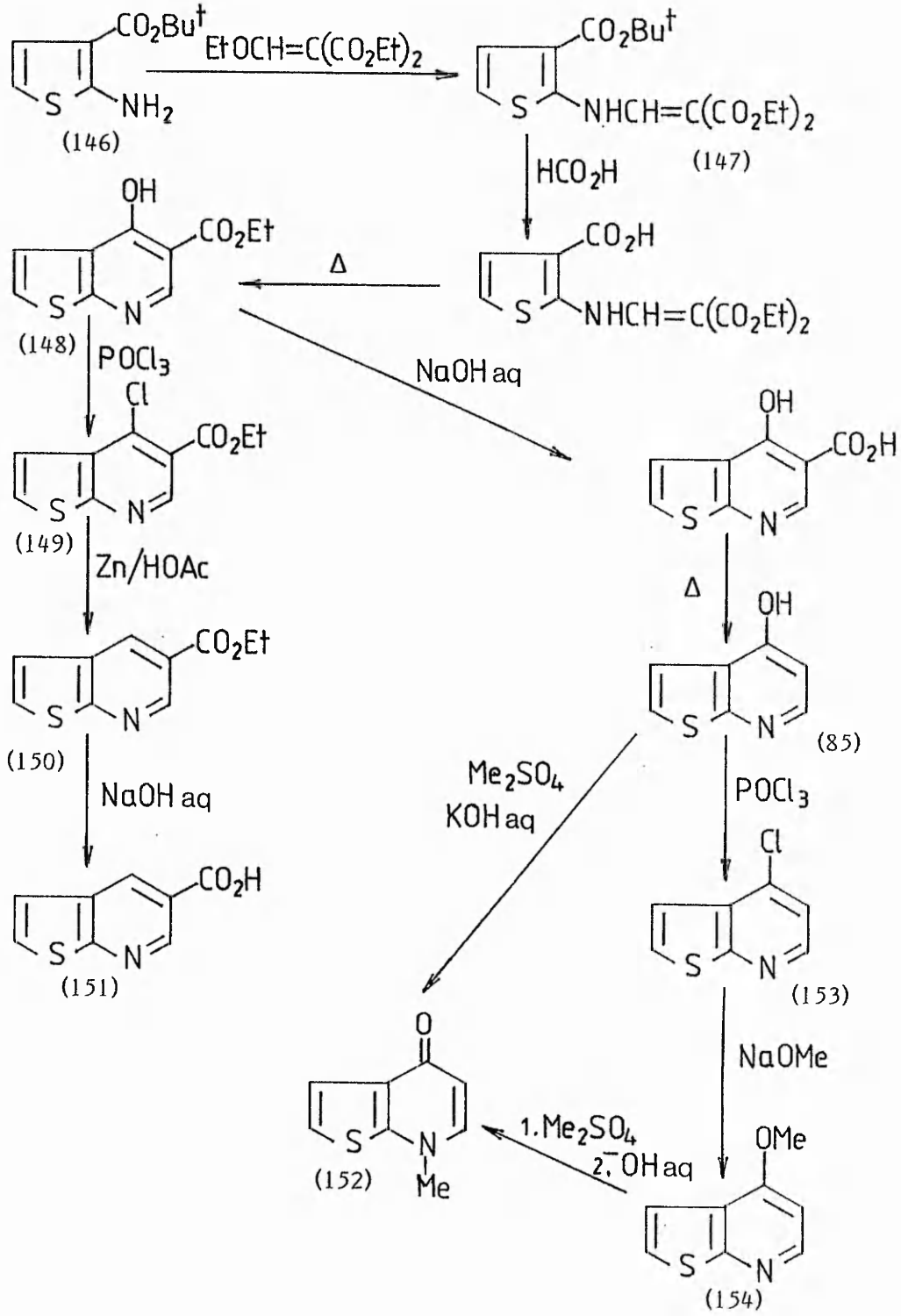
Scheme 58

2.3 Other Thieno[2,3-b]pyridines

The other thieno[2,3-b]pyridines used in this work were mainly prepared by methods described in the literature. Thus reaction of the t-butyl ester (146) with diethyl ethoxymethylenemalonate yielded (147) which was hydrolysed to the acid on treatment with formic acid at room temperature. Ring closure to the thieno[2,3-b]pyridine (148) was effected by boiling in diphenyl ether[96]. Treatment of this material with phosphoryl chloride under reflux afforded the chloro ester (149)[27]; dechlorination of the latter by zinc in acetic acid produced the novel ester (150) which was then hydrolysed to the novel acid (151).

Hydrolysis of the hydroxy-ester (148) gave the acid which underwent decarboxylation in boiling diphenyl ether to yield 4-hydroxythieno[2,3-b]pyridine (85)[27]. N-Methylation of (85) gave the novel thienopyridone (152), which is an analogue of the quinoline alkaloid echinopsine (see Section 1.2.3). Reaction of (85) with phosphoryl chloride yielded 4-chlorothieno[2,3-b]pyridine (153)[27], converted into the methoxy compound (154) by treatment with sodium methoxide in methanol. The thienopyridone (152) was also produced by reaction of (154) with dimethyl sulphate followed by alkaline hydrolysis. These

preparations are shown in Scheme 59.



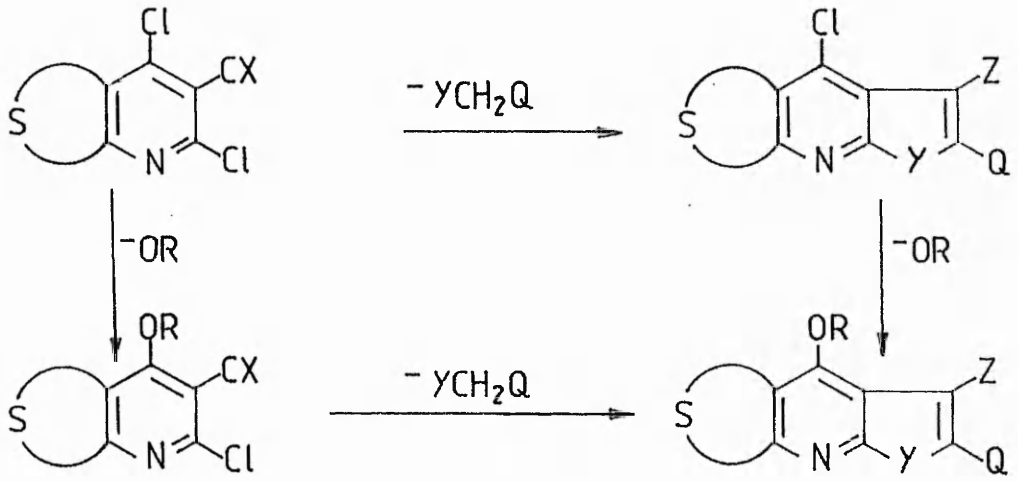
Scheme 59

CHAPTER THREE

NUCLEOPHILIC SUBSTITUTION

NUCLEOPHILIC SUBSTITUTION

The author has studied the displacement of choride ion from positions α- and γ- to the nitrogen atom in both thieno[2,3-b] and [3,2-b]pyridines and in some quinolines. Of interest was whether in the former pair the change in mode of ring fusion would affect the principal site of substitution and degree of reactivity. Particularly attractive was the possibility of preparation of linear tricyclic compounds by the approaches shown in Scheme 60.

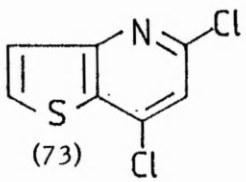


Scheme 60

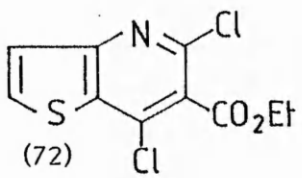
Assuming that the displacements indicated are effective it should be possible to prepare linear compounds (for example analogues of furoquinoline alkaloids) whichever of the two chlorine atoms is the more reactive.

3.1 Thieno[3,2-b]pyridines

It has been reported that in the dichloro compound (73) the chlorine atom α- to the nitrogen atom is displaced preferentially by alkoxide[46] whereas in the dichloro ester (72) it is the chlorine atom γ- to the nitrogen atom which is displaced preferentially by alkoxide[151] and by thioglycolate anion[99] (leading to angularly fused dithienopyridines). In both cases the remaining chlorine atom was very much deactivated and was only replaced with difficulty.



(73)



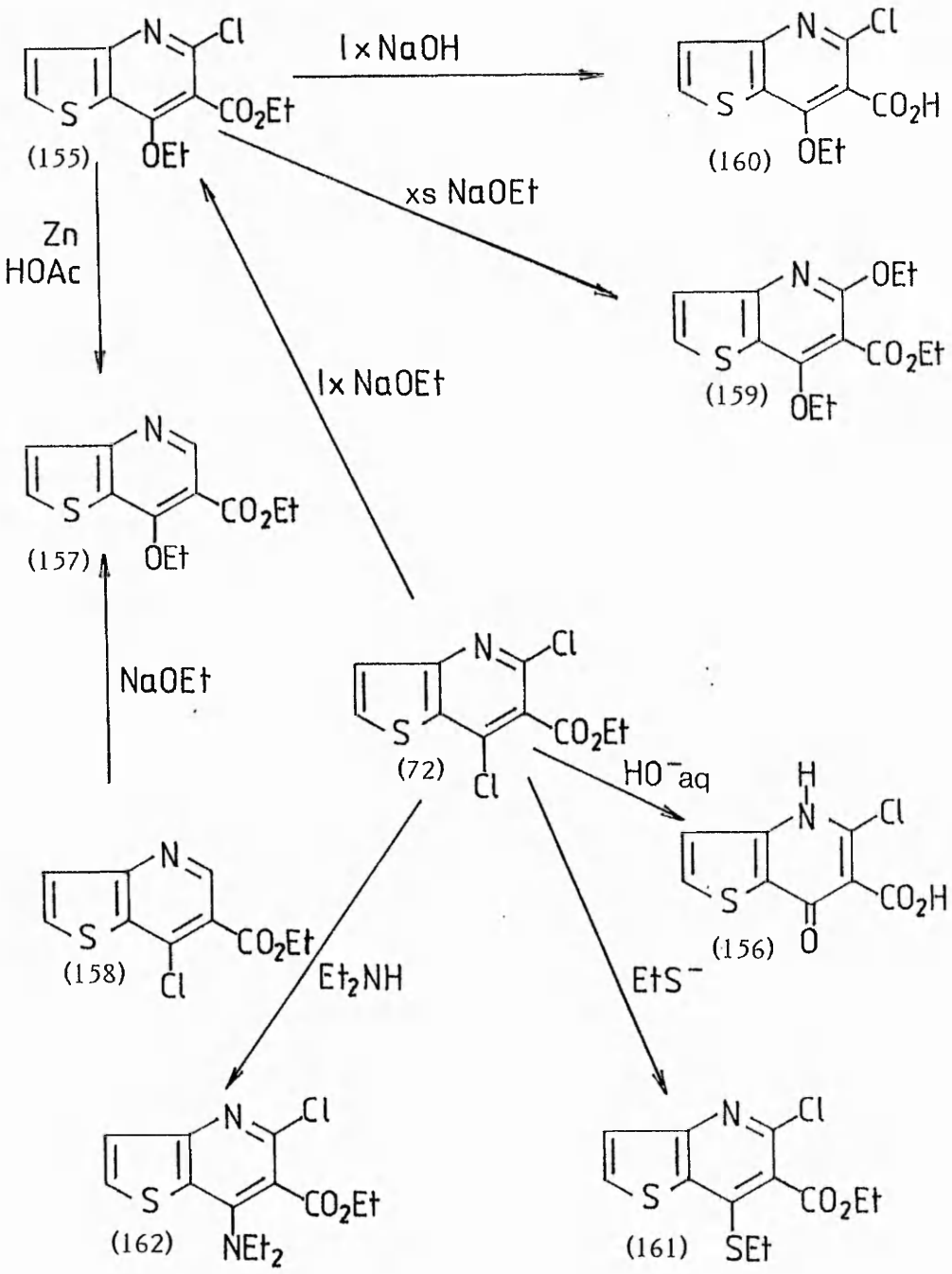
(72)

It is somewhat surprising that the addition of the ester group should cause such a reversal in the reactivities of the chlorine atoms and it was decided to reinvestigate these results to see if the reported findings were correct.

The dithienopyridines produced by reaction of (72) with the anion of methyl thioglycolate had been related by reductive dechlorination to angular compounds prepared by an unambiguous route. Rather than repeat this work a study of the reactions of (72) with other nucleophiles was undertaken, it being considered that the change of nucleophile would cause little change in the pattern of reactivity.

Reaction of (72) with sodium ethoxide in ethanol and with sodium hydroxide in aqueous ethanol gave products whose structures were suggested to be (155) and (156) respectively[151]. This work was repeated and the identity of the products was proved by unambiguous chemical means. With a slight excess of sodium ethoxide (72) yielded the chloroethoxy compound (155) which upon reductive dechlorination by zinc in acetic acid afforded (157), identical to material of unambiguous constitution prepared from the chloro ester (158)[99]. Treatment of (155) with a large excess of sodium ethoxide furnished the diethoxy compound (159).

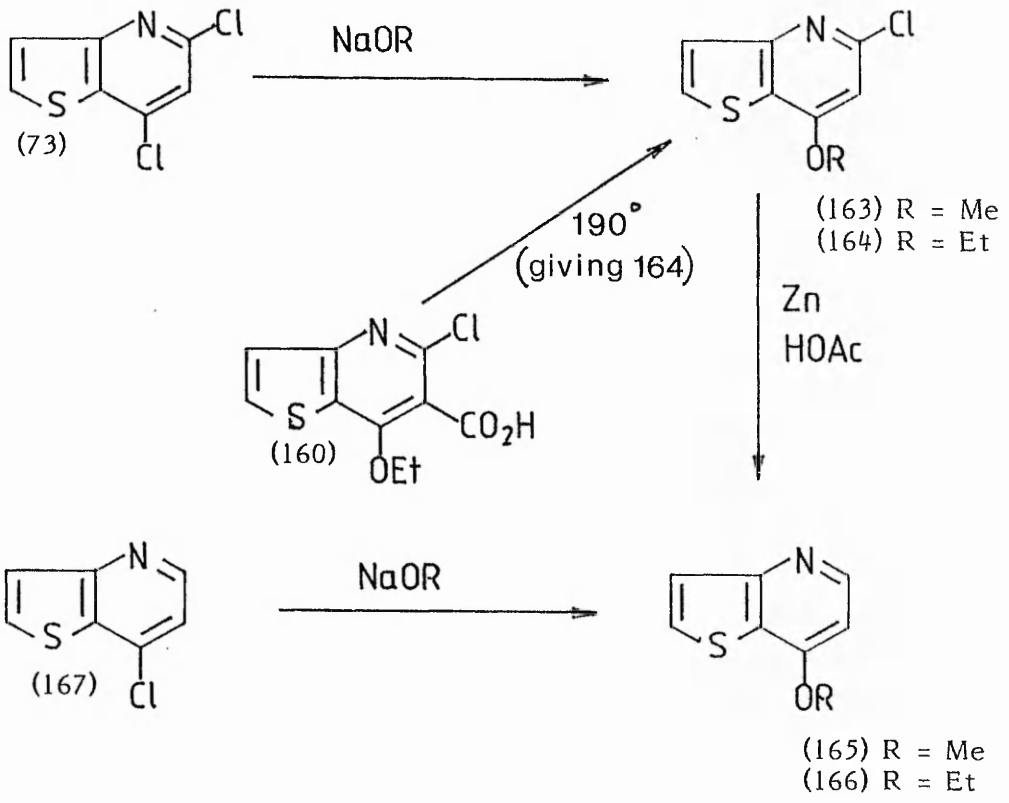
With one equivalent of aqueous sodium hydroxide (155) gave the acid (160) which was related to the products of reaction of (73) by decarboxylation (see later). Reaction of (72) with sulphur and nitrogen nucleophiles (ethanethiol and diethylamine, respectively) gave products (161) and (162), also formed by displacement of the chorine atom γ- to the nitrogen atom. These transformations are illustrated in Scheme 61.



Scheme 61

The reactions of (72) just described are consistent with its previously reported behaviour.

The reactivity of 5,7-dichlorothieno[3,2-b]pyridine (73) towards nucleophiles was then reinvestigated. With one equivalent of sodium methoxide or ethoxide in the appropriate alcohol (73) gave 5-chloro-7-methoxy (163) and 5-chloro-7-ethoxythieno[3,2-b]pyridine (164) respectively, and not (as previously reported[46]) the isomeric 7-chloro-5-alkoxy compounds. The structure of these products was evident by analysis of their ^{13}C n.m.r. spectra (see Chapter 4) and by their reductive dechlorination to 7-alkoxythieno[3,2-b]pyridines (165) and (166), identical to materials prepared from 7-chlorothieno[3,2-b]pyridine (167). A further proof of the structure of (164) was given by decarboxylation of the acid (160) (see Scheme 61) which provided material identical to that formed on reaction of (73) with sodium ethoxide. (Scheme 62)

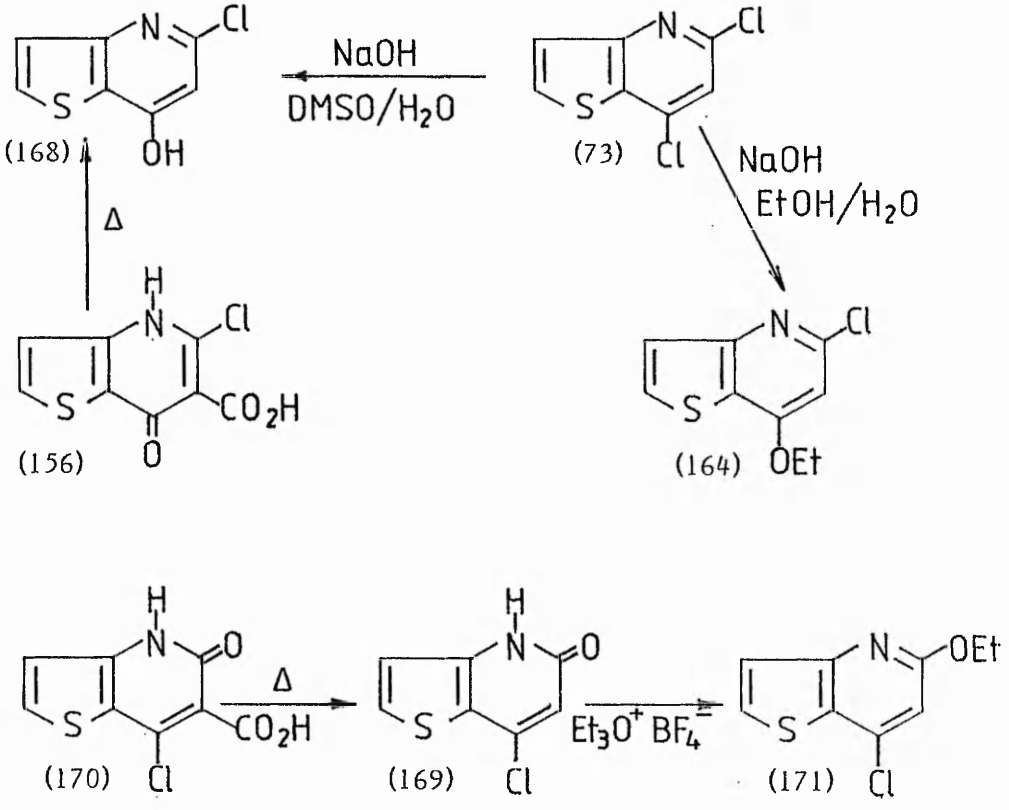


Scheme 62

These transformations show conclusively that the previous conclusions on the reactivity of (73) with alkoxides were wrong and in this case it is also the chlorine atom γ - to the nitrogen atom which is the more reactive.

5,7-Dichlorothieno[3,2-b]pyridine (73) proved to be rather unreactive towards hydroxide ions. No reaction occurred with aqueous sodium hydroxide, and sodium hydroxide in aqueous ethanol gave the ether (164) (similar behaviour has been reported in quinolines[78]). It was found that heating (73) with sodium

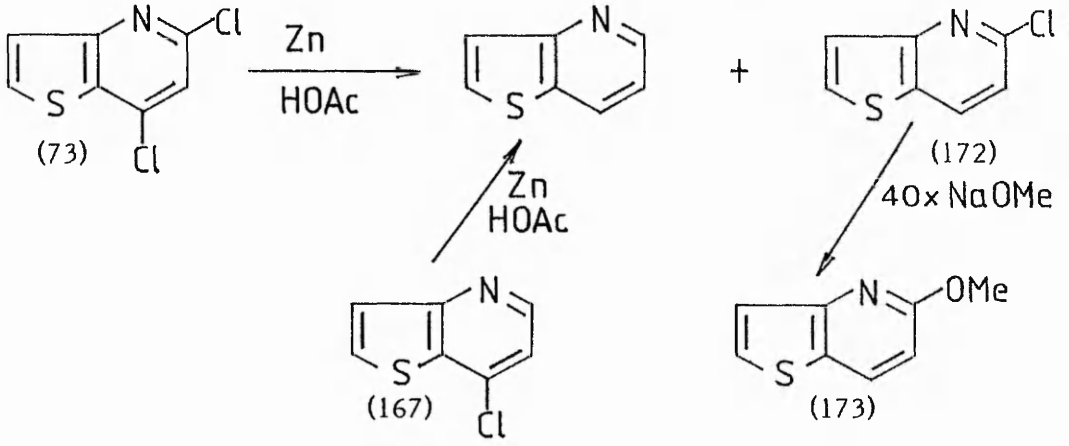
hydroxide in aqueous dimethyl sulphoxide gave 5-chloro-7-hydroxythieno[3,2-b]-pyridine (168); the presence of the hydroxy tautomer was clearly indicated by the i.r. and ^{13}C n.m.r. spectra. This hydroxy compound was also formed by decarboxylation of the acid (156) in boiling diphenyl ether. The isomeric 7-chlorothieno[3,2-b]pyridine-5-one (169), isolated as a by-product in the preparation of (73), was also prepared by thermal decarboxylation of the acid (170) of proven structure[151]. Treatment of (169) with triethyloxonium tetrafluoroborate gave the O-ethyl derivative (171), which was quite different from (164). The ^{13}C n.m.r. spectrum of (171) was also consistent with the 7-chloro-5-ethoxy structure. (Scheme 63)



Scheme 63

It has been shown that replacement of both chlorine atoms in (72)[151] and (73)[46] is very difficult, large excesses of reagent and long reaction times being necessary. To determine whether this behaviour was due to intrinsic lack of reactivity of the second chlorine atom or due to deactivation by the introduced alkoxy group the reaction of 5-chlorothieno[3,2-b]pyridine (172) with sodium methoxide was studied. This chloro compound was prepared by selective monodechlorination of (73) (as for the corresponding thieno[2,3-b]-pyridine, see Section 2.2). Thus treatment of (73) with zinc in acetic acid gave a mixture of (172) and thieno[3,2-b]pyridine (2); (2) was also prepared by

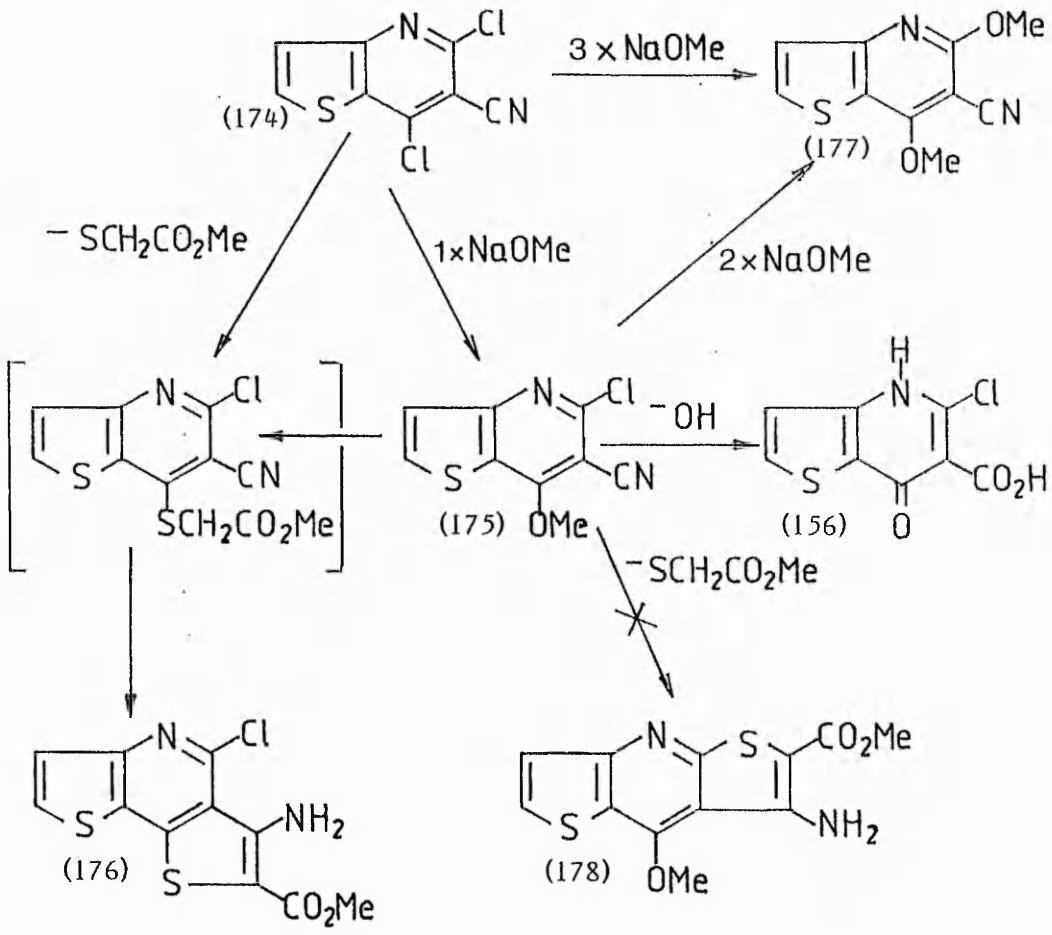
reductive dechlorination of 7-chlorothieno[3,2-b]pyridine (167). 5-Chlorothieno-[3,2-b]pyridine (172) a compound which has previously been reported in the literature[42]) yielded the methoxy derivative (173) only after prolonged reaction with a considerable excess of sodium methoxide. Scheme 64 illustrates these reactions.



Scheme 64

It would thus appear that the low reactivity of chlorine atoms at C-5 in thieno[3,2-b]pyridines is an intrinsic property and is not due to deactivation by the introduction of an alkoxy group at C-7.

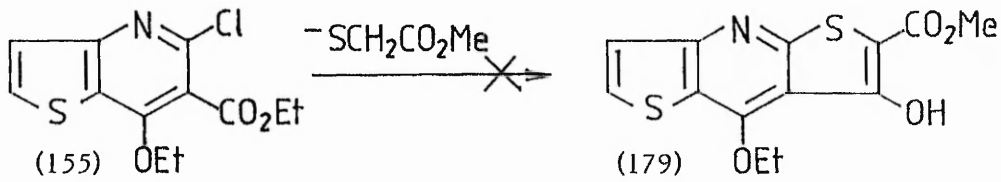
To examine whether the presence of a strongly electron-withdrawing group at C-6 would increase the reactivity of the chlorine atom at C-5 the behaviour of 5,7-dichloro-6-cyanothieno[3,2-b]pyridine (174) towards nucleophiles was examined. Treatment with one equivalent of sodium methoxide gave 5-chloro-6-cyano-7-methoxythieno[3,2-b]pyridine (175), the structure of which was proved by vigorous hydrolysis to the acid (156), identical to previously prepared material (see Scheme 61). With the anion of methyl thioglycolate a dithieno-pyridine was produced, presumably the angular compound (176). The chlorine atom remaining in (175) proved to be less resistant to displacement than observed in the other chloro compounds discussed above, yielding the dimethoxy compound (177) upon reaction with two equivalents of sodium methoxide in methanol; this material was also prepared directly from (174) by treatment with an excess of sodium methoxide. In an attempt to prepare the linear tricycle (178) the chloromethoxy compound (175) was reacted with the anion of methyl thioglycolate; however the methoxy group was displaced and the product was in fact the angular derivative (176). These transformations are depicted in Scheme 65.



Scheme 65

These results suggest that although the cyano group does activate chlorine at C-5 towards nucleophilic displacement it also activates the substituent at C-7 with the result that a poor leaving group (methoxide) is displaced from C-7 in preference to a good leaving group (chloride) from C-5.

It was hoped that the ethoxy group in the ethoxy-ester (155) would be less activated towards nucleophilic displacement and that substitution would occur at C-5 leading to a linear tricycle (179). However, on boiling under reflux with the anion of methyl thioglycolate, no reaction was observed. (Equation 36). Evidently in this case neither the chlorine atom nor the ethoxy group is sufficiently activated to be displaced.



Equation 36

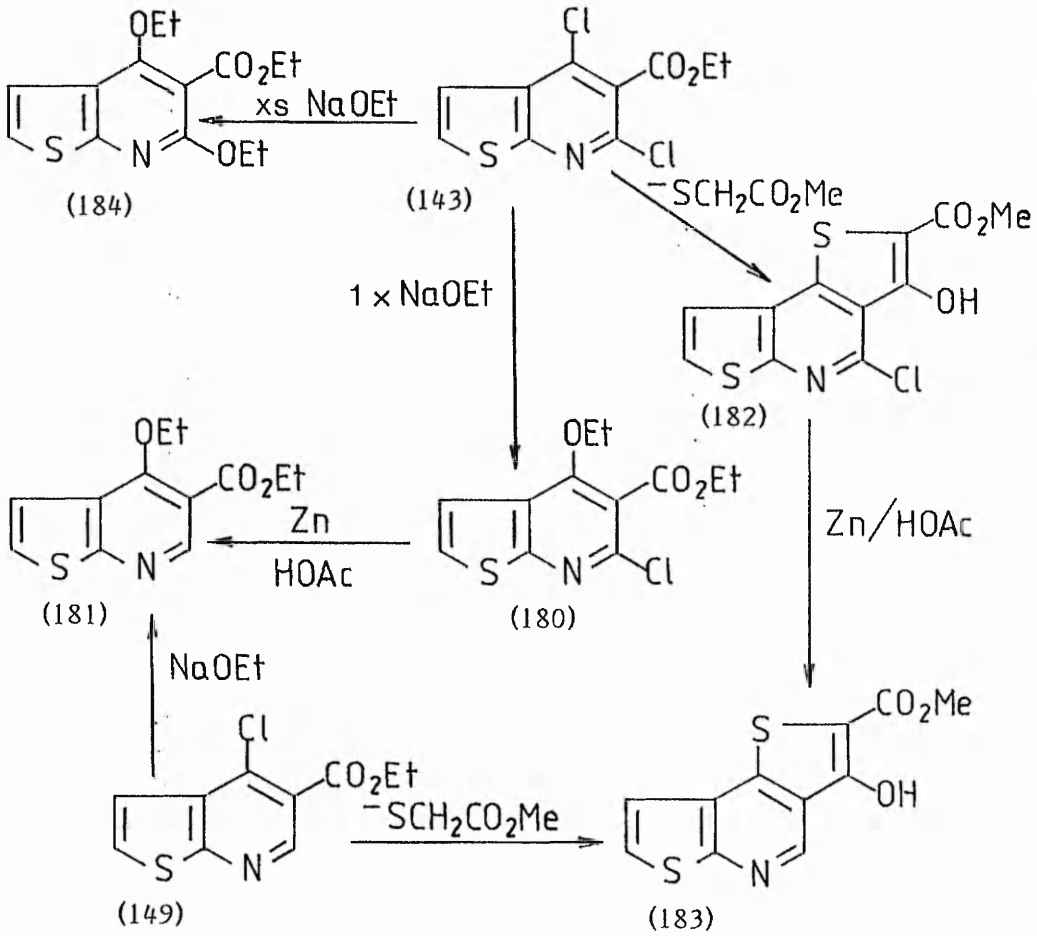
In view of the lack of success in forming linear tricyclic compounds by nucleophilic substitution reactions this aspect of the chemistry of thieno[3,2-b]-pyridines as a route to analogues of furoquinoline alkaloids was abandoned in favour of a study of other potential routes.

3.2 Thieno[2,3-b]pyridines

The studies of nucleophilic displacement in chlorothieno[3,2-b]pyridines just described show that chlorine atoms γ- to the nitrogen atom are easily replaced by nucleophiles whereas those α- to the nitrogen atom are resistant to displacement.

A similar study of thieno[2,3-b]pyridines was undertaken to determine whether the different mode of ring fusion would have any significant effect on the chemistry. Some aspects of the chemistry of the [2,3-b] system, studied in the [3,2-b] series (chiefly reactions of cyano compounds), were not investigated since the appropriate [2,3-b] compounds were not to hand.

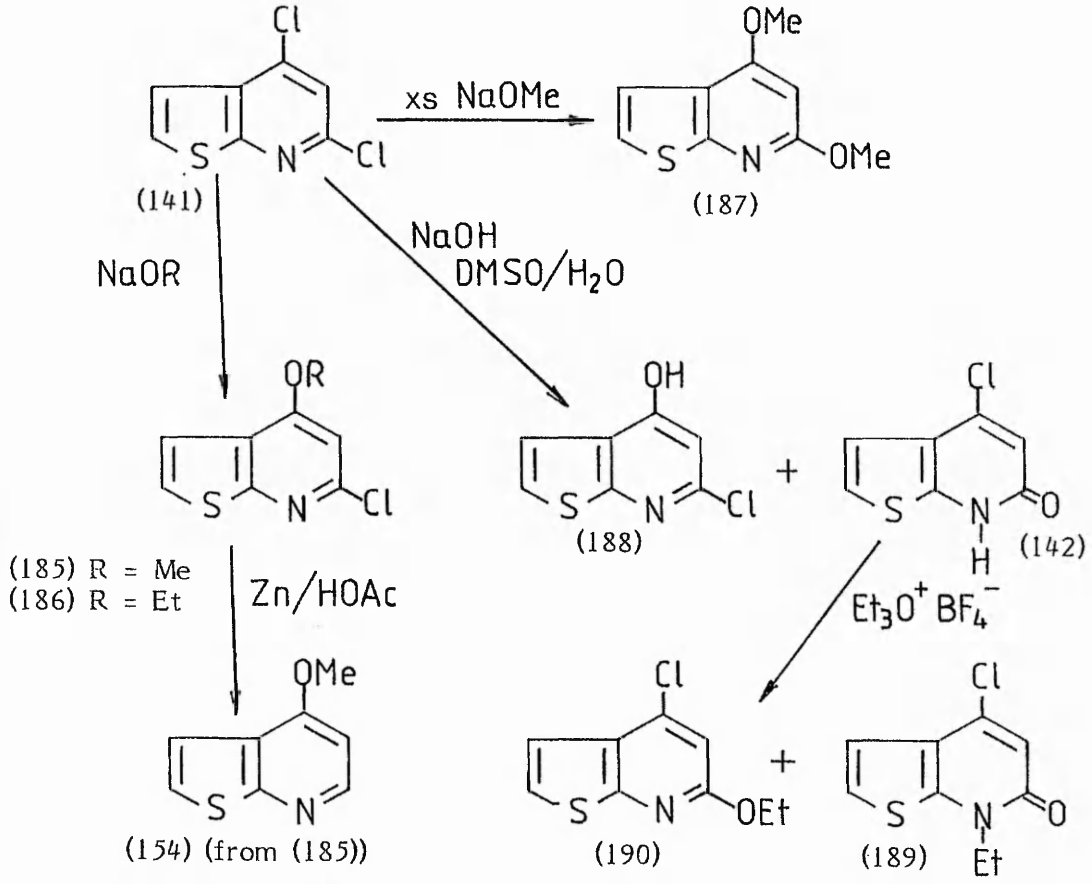
Treatment of the dichloro ester (143) with one equivalent of sodium ethoxide in ethanol gave a single monochloroethoxy thieno[2,3-b]pyridine (180) which on reductive dechlorination yielded ethyl 4-ethoxythieno[2,3-b]pyridine-5-carboxylate (181), identical to material prepared by an unambiguous route from a substance (149) of known constitution[27]. Thus the ethoxydechlorination product of (143) is ethyl 6-chloro-4-ethoxythieno[2,3-b]pyridine-5-carboxylate, ie it is the chlorine atom γ- to the nitrogen atom which is the more reactive. With the anion of methyl thioglycolate (143) gave a dithienopyridine which, in view of the preferential displacement of the C-4 chlorine atom just established, was presumably the angular derivative, ie (182). This was confirmed by reductive dechlorination to a substance of known structure (183), also derived from (149). When (143) was boiled under reflux with three equivalents of sodium ethoxide decomposition occurred. However, partial conversion into ethyl 4,6-diethoxythieno[2,3-b]pyridine-5-carboxylate (184) was achieved using a greater excess of reagent at room temperature over 10 days. These reactions are presented in Scheme 66.



Scheme 66

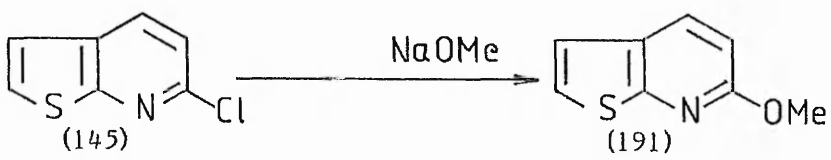
4,6-Dichlorothieno[2,3-b]pyridine (141) gave a single product upon reaction with one equivalent of sodium methoxide; it was shown to be 6-chloro-4-methoxythieno[2,3-b]pyridine (185) by reductive dechlorination to 4-methoxythieno-[2,3-b]pyridine (154), identical to material synthesised by an unequivocal route via 4-chlorothieno[2,3-b]pyridine (153). The related 4-ethoxy-6-chloro compound (186) was obtained in a similar manner. After prolonged reaction with a very considerable excess of sodium methoxide (141) was converted into 4,6-dimethoxythieno[2,3-b]pyridine (187). With sodium hydroxide in aqueous dimethyl sulphoxide the chlorine atom at C-4 in (141) was preferentially replaced, giving 6-chloro-4-hydroxythieno[2,3-b]pyridine (188), but in this case a small quantity of the product arising from the substitution of chloride from the less reactive site [(142)] was also isolated. This minor product was identical to the by-product produced in the chlorination of (134a). The identity of this minor product was confirmed by its reaction with triethyloxonium tetrafluoroborate, which converted it mainly into the N-ethyl derivative (189), but also produced some O-ethylated material. The latter was

isomeric with 6-chloro-4-ethoxythieno[2,3-b]pyridine ((186), of proven constitution, see above) and must therefore be the 4-chloro-6-ethoxy compound (190), arising from (142). These reactions are illustrated in Scheme 67.



Scheme 67

As did the corresponding thieno[3,2-b]pyridine, 6-chlorothieno[2,3-b]pyridine (145) proved to be very resistant to attack by methoxide. Methoxydechlorination was only achieved by using a large excess of sodium methoxide and a long reaction time. Although the product (191) could not be obtained analytically pure its ^{1}H and ^{13}C n.m.r. spectra were sufficient to confirm it as 6-methoxythieno[2,3-b]pyridine (191). (Equation 37)



Equation 37

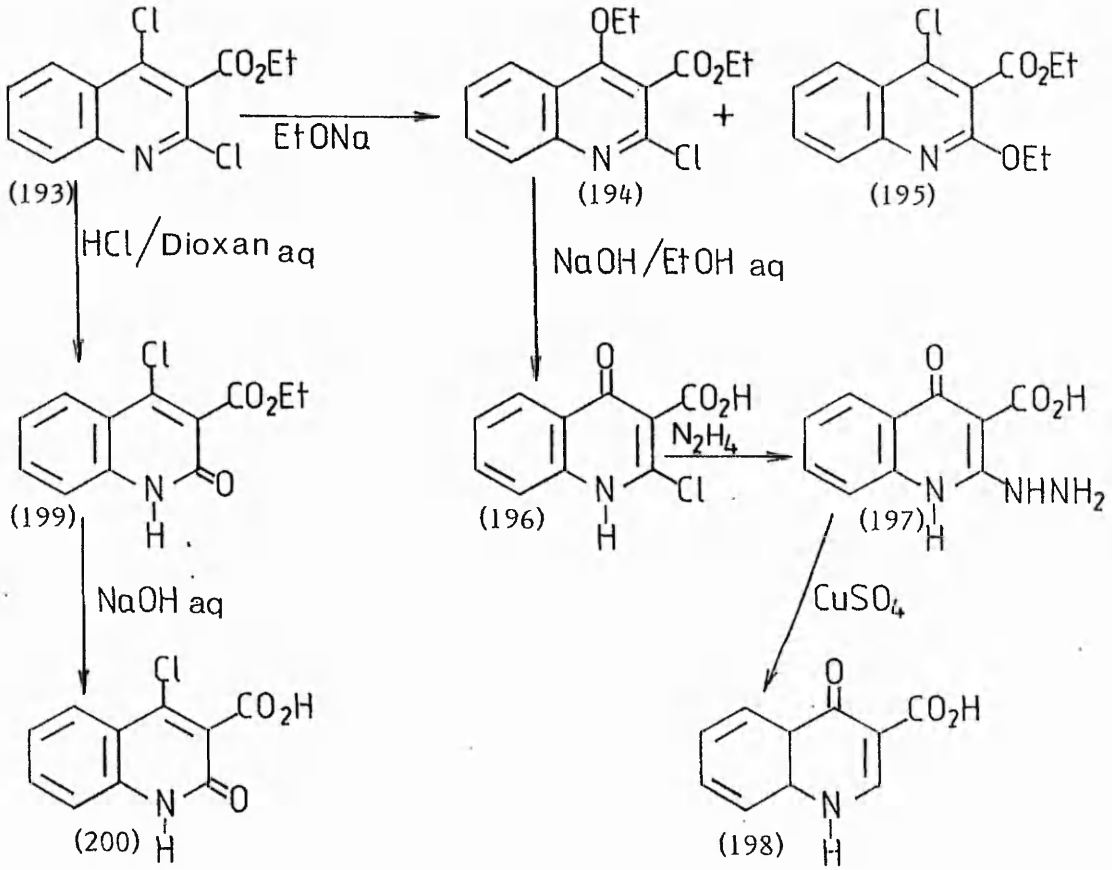
The results just described show that the thieno[2,3-b]pyridine system behaves in a similar manner to the analogous thieno[3,2-b]pyridines, ie the alternative mode of ring fusion has no significant effect upon the relative reactivities of chlorine atoms at the α- and γ- positions in the pyridine ring.

3.3 Comparative Studies Involving Quinolines

The nucleophilic substitution of halogen in 2- and 4-haloquinolines has frequently been referred to in the literature. The methoxydechlorination of a wide variety of 2- and 4-chloroquinolines has been studied and the reaction kinetics have been determined[154,155] (the use of other nucleophiles, eg ethoxide and piperidine, has also been described[156]). Thus, for example, the rate constants for the reactions of 2- and 4-chloroquinolines with sodium methoxide were found to be almost identical. Nucleophilic displacement of chlorine from 2,4-dichloroquinoline (192) has also been studied. With ethanolic potassium hydroxide (192) gives the two isomeric chloroethoxyquinolines in almost equal amounts[157], but with sodium methoxide in methanol 2-chloro-4-methoxyquinoline is the major product by a factor almost 2:1.[154,158] The exact proportion of the isomeric products depends to some extent on the reaction conditions and times but it is clear that both halogen atoms in 2,4-dichloroquinoline (192) are of the same order of reactivity towards nucleophiles under basic conditions.

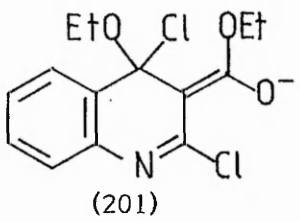
There has been no comparable study of the behaviour of 2,4-dichloroquinoline-3-carboxylic esters. For this reason the author examined the reaction of ethyl 4,6-dichloroquinoline-3-carboxylate (193) with sodium ethoxide. It was found that, as in thienopyridines, the chlorine atom γ-to the nitrogen atom was much more susceptible to nucleophilic substitution than that α- to it. With one equivalent of sodium ethoxide (193) gave a mixture of ethyl 2-chloro-4-ethoxy (194) and 4-chloro-2-ethoxyquinoline-3-carboxylate (195) in yields of 72% and 5% respectively. The major product was identified by its alkaline hydrolysis to the acid (196) and thence by reductive dechlorination *via* the hydrazino compound (197) (in the manner described by Grundon and co-workers[149]) to the acid (198), identical to an authentic sample[159].

Under acidic conditions substituents at C-2 of quinolines are hydrolysed more readily, and in appropriate 2,4-disubstituted quinolines C-2 becomes the more active position. Acid hydrolysis of (193), followed by saponification of the known[149] ester (199) so obtained, gave the novel 4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (200) which was different from the product (196) derived from (194). The reactions just described are presented in Scheme 68.

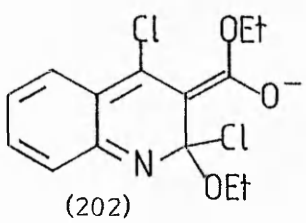


Scheme 68

The preference for attack by ethoxide at C-4 in (193) may at least be partly explained if one assumes that the ability of the ester group to contribute to the delocalisation of the negative charge in the sigma complex is an important factor. Reaction at C-4 permits consideration of a canonical form (201) in which the ester group carries the negative charge and the benzene ring is in its normal configuration. In the equivalent form for attack at C-2 (202) a quinoid structure is required.



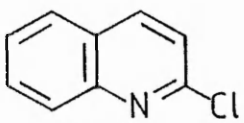
(201)



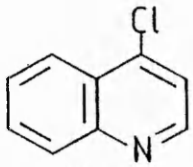
(202)

A similar argument may be used to at least partly explain the lack of reactivity of chlorine α- to the nitrogen atom in the corresponding dichloro-thienopyridine esters.

However, in view of the low reactivity of α-chlorothienopyridines (145) and (172) vis-a-vis their γ-chloro counterparts (153) and (167) (the corresponding quinolines (203) and (204) are of almost equal reactivity) it is apparent that there are also other reasons for the inertness of the α-chlorine atom in thienopyridines.



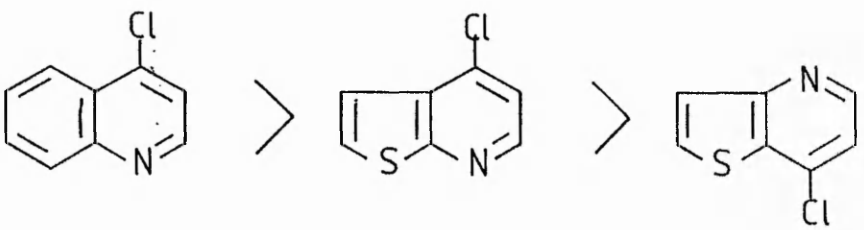
(203)



(204)

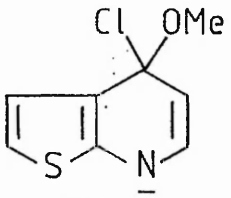
In order to make a direct comparison between the three systems the reactivities of γ-chloro compounds (153), (167) and (204) towards sodium methoxide were investigated. From the simple consideration that the electron-rich thiophene ring in (153) and (167) would feed electron density into the pyridine ring it was thought that the quinoline (204) would be the most reactive.

The three alternative pairs of (153), (167) and (204) were allowed to compete for an insufficiency of sodium methoxide in methanol; reaction mixtures were analysed by both g.l.c. and ^1H n.m.r.* Although these competitive experiments were not carried out under the most rigorous conditions, the results give a clear indication of the relative reactivities of the three chloro compounds. As expected 4-chloroquinoline (204) proved to be the most reactive; however it was not greatly more reactive than the thienopyridines and appreciable amounts of methoxy derivatives were formed from both 4-chlorothieno[2,3-b]pyridine (153) and 7-chlorothieno[3,2-b]pyridine (167) in competition with (204). Of the two thienopyridines the [2,3-b] compound was found to be the more reactive. The overall order of reactivity is thus:

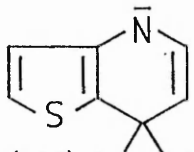


* These competitive experiments were performed with Mr G Bryant, final year undergraduate project student 1983-84.

The relative reactivities of the thienopyridines may be explained by considering the canonical forms (205) and (206) which are the most important contributors to the transition state.



(205)

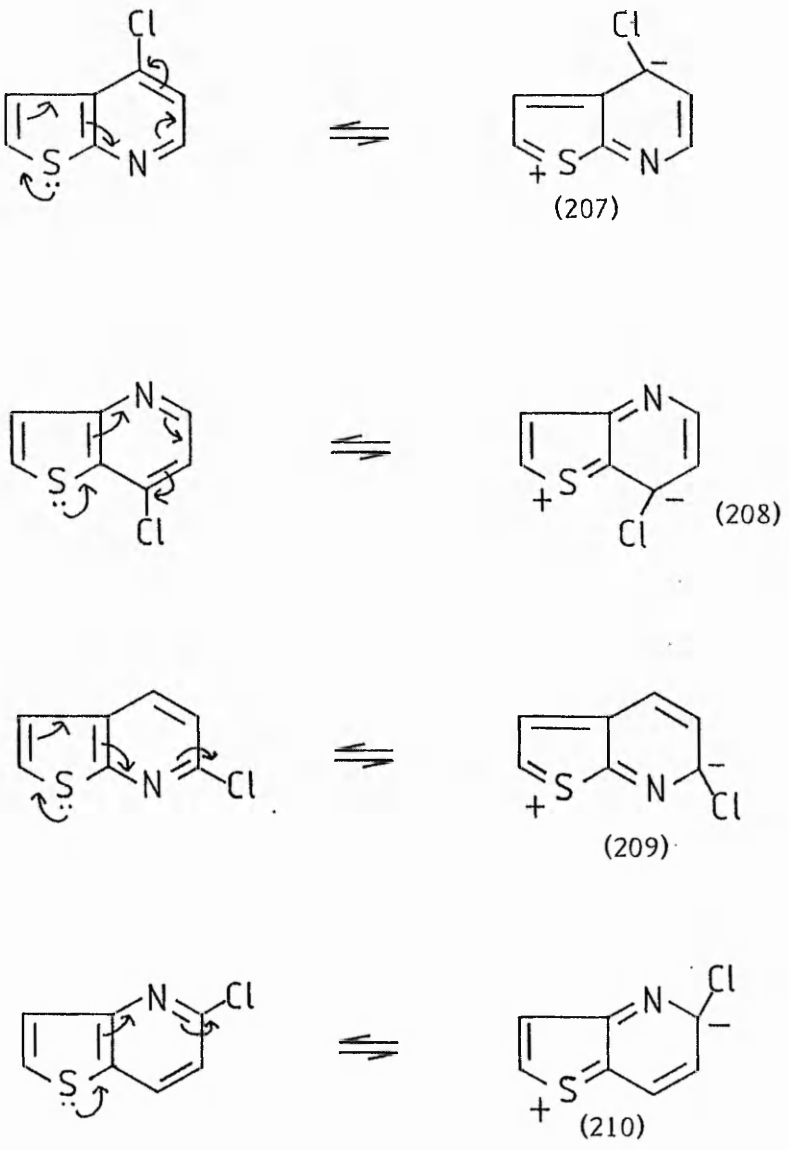


(206) Cl OMe

For (205) it is possible to postulate that the inductive effect of the sulphur atom will operate to reduce the electron density on the nitrogen atom and stabilise the structure whereas in (206) the sulphur atom is further away from the nitrogen atom and thus a much weaker inductive effect will be felt, so stabilisation will be less. A similar argument has been proposed to explain the relative basicities of thieno[2,3-b] (1) and [3,2-b]pyridines (2).[82] Another factor which may have an effect is that in (167) some steric hindrance by the sulphur atom to the approach of the methoxide ion may occur.

In view of their much reduced reactivity towards methoxide, it was felt that a similar investigation of the behaviour of the α-chlorothienopyridines would be inappropriate and in any case to obtain meaningful comparisons a rigorous kinetic study on the lines of those reported for quinolines would be necessary.

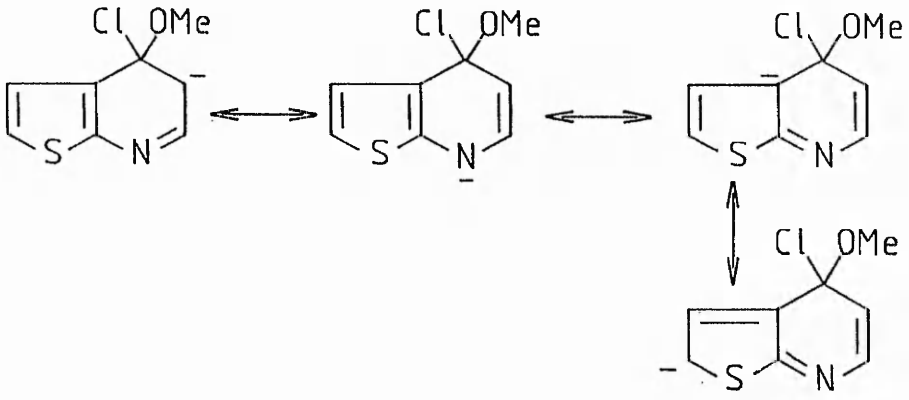
The low reactivity of the α-chlorine atom in the thienopyridines is most probably due to mesomeric electron release from the sulphur atom to positions in the pyridine ring which would either hinder the approach of a nucleophile or destabilise the transition state for the reaction. Considering the first aspect gives the structures shown in Scheme 69.

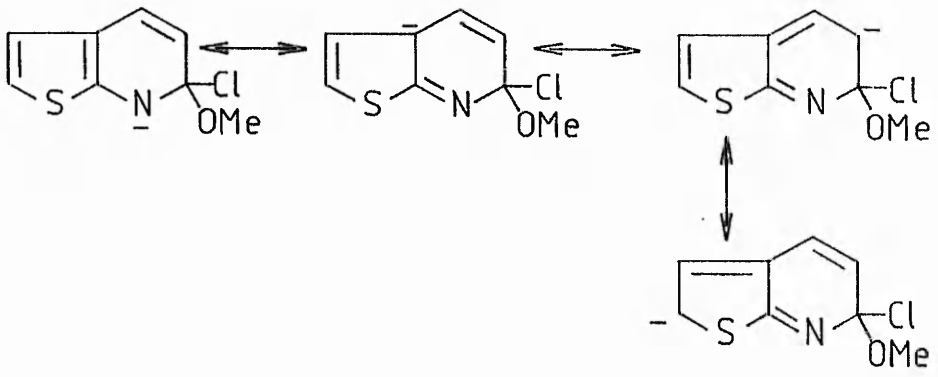


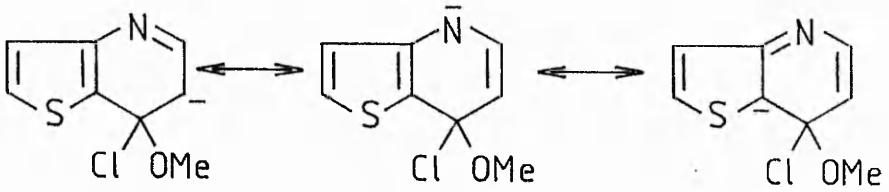
Scheme 69

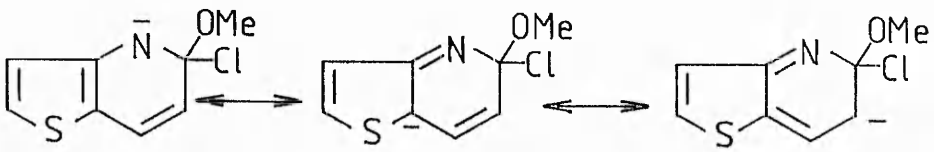
These structures (207) - (210) show that in all cases it is possible to draw canonical forms in which electron release from the sulphur atom increases electron density at the carbon atom bearing the chlorine atom. For related pairs ((207) and (209), and (208) and (210)) it is not possible to identify any significant differences in the structures that might account for the greatly different reactivities.

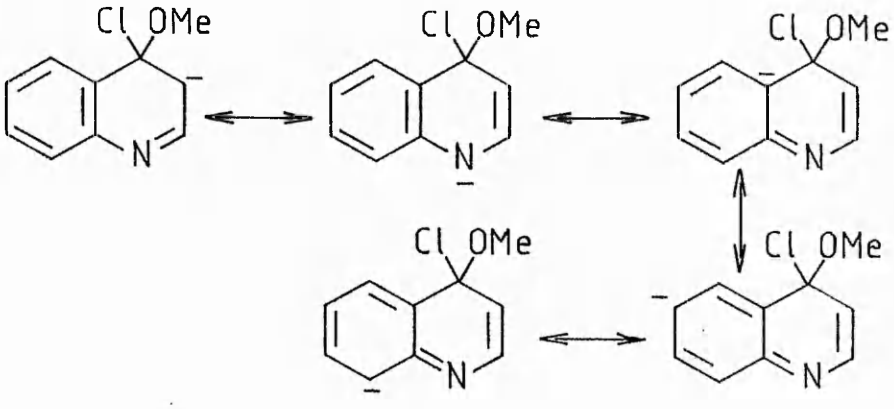
The canonical forms for the transition states for reactions in all the systems (not including structures invoking sulphur d-orbitals) are presented in Scheme 70.

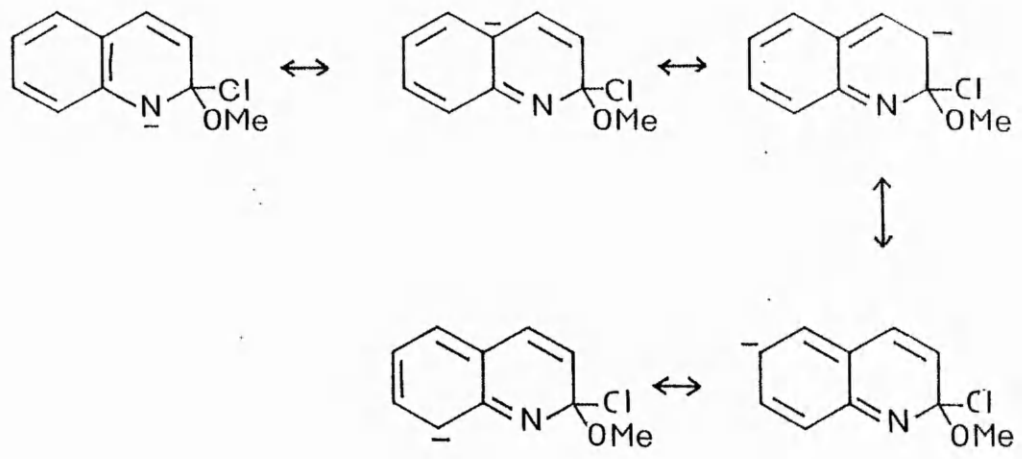

Cl OMe
S
N


S
N
Cl
OMe


N
S
Cl OMe


N
OMe
Cl
S


Cl OMe
N



Scheme 70

It is possible to draw 5 canonical forms for the quinolines, 4 for the thieno-[2,3-b]pyridines and 3 for the thieno[3,2-b]pyridines. This may have some bearing on the reactivity order of the γ-chloro compounds mentioned earlier. Inspection of related pairs of α- and γ-chloro compounds fails to show significant differences. In all cases for the γ-chloro compounds it is possible to draw two canonical structures with the benzene/thiophene ring in its normal configuration whereas for the α-chloro compounds there is only one such form. However, the most important forms, ie those having the negative charge localised on the nitrogen atom, have the ring in the normal (ie not quinoid) configuration. It must be noted that the same observations apply to the quinolines.

It can thus be seen that there is no explanation in terms of simple resonance theory for the nucleophilic substitution behaviour of these compounds. Molecular orbital calculations on the parent compounds suggest that the α- and γ- positions should be of the same order of reactivity towards nucleophiles. To date no similar treatment of chloro compounds has appeared.

CHAPTER FOUR

^{13}C N.M.R. STUDIES

^{13}C N.M.R. STUDIES

The ^{13}C n.m.r. spectra of the compounds prepared in the present work (and of a number of compounds previously synthesised in these laboratories) have been recorded with proton decoupling (for details see Experimental section). Analysis of these spectra has proved useful in determining positions of substitution and, in appropriate cases, the tautomeric forms adopted by the compounds. (All values of δ quoted are in ppm with respect to tetramethylsilane).

4.1 Thieno[3,2-]pyridines

Some general remarks concerning assignments can be made:

a) Carbon atoms carrying hydrogen atoms show large peaks due to the Nuclear Overhauser Effect (NOE).

b) The C-2 and C-3 resonances occur at approximately 130ppm and 124ppm, respectively, and are not shifted appreciably by pyridine ring substituents (except in cases of keto-enol tautomerism - see later).

c) Carbon atoms at positions 8- and 9- give very small signals in the regions 120-135ppm and 140-160ppm, respectively. In the spectra of relatively insoluble compoinds the signal from C-8 is often too small to be observed.

d) The location of the signals due to C-5, C-6 and C-7 vary significantly with substitution.

The resonances were assigned by adding (or subtracting) the increments given in Table 2 to the chemical shift of the carbon atom concerned in thieno[3,2-b]-pyridine itself. The values given in Table 2 are those shifts observed when the substituent in question is introduced into the comparable position in quinoline, pyridine or benzene (depending on which data were available).

Table 2

Chemical Shift Increments (ppm) used in Assignment of Thieno[3,2-b]pyridine ^{13}C NMR Spectra

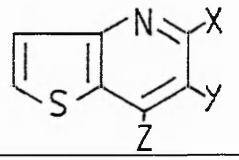
Substituent	Location	Shift produced at C-5 - C-9					Ref
		C-5	C-6	C-7	C-8	C-9	
Cl	C-5	+1.4	+0.3	+3.0	-1.2	0	160[a]
OAlkyl	C-5	+12.5	-14.0	+2.3	-7.8	-4.0	161[a]
=O (4H)	C-5	+11.7	-4.7	+4.4	-19.7	-15.4	161[a]
CO_2H	C-5	+2.1	+1.5	0	+5.1	0	162[b]
CO_2Alkyl	C-5	+1.3	-0.5	-0.5	+3.5	-0.5	162[b]
CO_2Alkyl	C-6	+2.9	+6.1	+1.4	+1.4	-1.3	163[c]
CN	C-6	+3.1	-13.3	+4.1	+0.2	+3.1	160[a]
Cl	C-7	-0.5	+0.1	+6.4	-1.9	+0.8	163[d]
OAlkyl	C-7	+0.1	-14.7	+28.5	-14.7	+0.1	161[a]
OH	C-7	+1.4	-12.7	+26.9	-12.7	+1.4	162[b]
=O (4H)	C-7	-10.8	-8.6	+39.3	-8.6	-10.8	161[a]
NEt_2	C-7	-1.0	-14.7	+19.9	-14.7	-1.0	160[e]
SAlkyl	C-7	+0.4	-1.8	+10.2	-1.8	+0.4	162[b]

Notes: a: shifts derived from those in the related pyridine.
b: shifts derived from those in the corresponding substituted benzene.
c: shifts derived from those in nicotinamide.
d: shifts derived from those in the related quinoline.
e: shifts derived from those in 4-aminopyridine.

In the great majority of cases the calculated and observed values for C-5 - C-9 differed by less than 5ppm, and it was possible to assign the resonances due to the ring carbon atoms with confidence. The data are presented in Tables 3 - 5.

Table 3

^{13}C NMR Spectra of Thieno[3,2-b]pyridines



No[a]	X	Y	Z	Ref.	Sol[b]	Chemical Shift						
						C-2	C-3	C-5	C-6	C-7	C-8	C-9
1	H	H	H	164	P	130.2	125.1	147.1	118.4	130.2	133.0	156.0
1	H	H	H	53	P	130.2	124.7	146.9	118.2	130.0	132.7	155.7
-	H	CO_2Et	H	99	P	134.5	125.2	148.4	121.3	132.1	131.1	158.6
167	H	H	Cl	32	P	131.3	125.7	147.9	118.4	138.2	132.9	157.3
172	Cl	H	H	164	P	132.1	124.4	149.0	119.2	132.6	131.5	155.8
172	Cl	H	H	42	P	124.3	118.1	139.8	123.1	131.7	130.6	154.5
165	H	H	OMe	164,32	P	129.8	125.3	149.5	100.0	161.1	c	158.1
166	H	H	OEt	164	P	129.8	125.3	149.4	100.6	160.4	122.5	158.1
173	OMe	H	H	164	P	129.7	124.3	162.8	108.6	132.4	126.1	153.4
73	Cl	H	Cl	46	P	132.7	125.1	149.1	118.8	139.5	131.6	156.2
163	Cl	H	OMe	164,46	P	130.9	124.6	150.5	100.6	162.1	121.8	156.4
164	Cl	H	OEt	164,46	P	130.8	124.7	150.4	100.1	161.4	121.7	156.4
168	Cl	H	OH	164	P	131.1	123.8	149.0	104.8	162.1	121.6	155.7
171	OEt	H	Cl	164	P	130.0	124.8	163.2	108.2	139.0	126.0	154.1
-	OMe	H	OMe	46	P	128.9	124.4	162.5	89.7	165.1	117.1	154.3
-	OEt	H	OEt	46	P	128.7	124.5	161.7	89.5	164.2	117.8	154.5
-	Cl	CO_2Et	H	99	P	134.7	124.4	147.4	121.6	135.7	131.0	156.9

continued/

Table 3 (continued)

No[a]	X	Y	Z	Ref	Sol[b]	Chemical Shift						
						C-2	C-3	C-5	C-6	C-7	C-8	C-9
158	H	CO_2Et	Cl	99	P	134.8	125.9	150.0	120.0	136.9	c	161.3
-	H	CO_2H	Cl	165	P+Q	136.0	125.4	149.7	120.4	137.6	133.8	158.0
-	Cl	CO_2Me	CO_2Me	32	P	134.7	127.0	144.0	125.6	136.5	135.6	155.8
-	H	CO_2Me	OMe	165	P	133.3	125.6	151.3	112.6	161.6	123.9	162.2
159	H	CO_2Et	OEt	164	P	133.1	125.6	151.4	113.6	160.8	c	161.3
72	Cl	CO_2Et	Cl	99	P	134.2	124.7	145.2	124.1	136.5	131.5	155.8
-	Cl	CO_2Me	Cl	165	P	134.5	125.1	145.6	124.2	135.3	c	155.6
-	Cl	CO_2Me	OMe	165	P	133.2	125.1	146.8	115.0	160.0	120.6	158.7
-	Cl	CO_2H	OMe	165	P+Q	133.4	124.3	156.9	119.2	166.0	120.8	159.1
155	Cl	CO_2Et	OEt	164	P	132.9	125.1	146.6	116.0	159.5	121.3	157.8
160	Cl	CO_2H	OEt	164	P+Q	133.0	124.3	156.9	c	166.9	c	158.6
162	Cl	CO_2Et	NEt_2	164	P	131.6	124.9	146.9	119.8	152.8	127.3	156.3
161	Cl	CO_2Et	SEt	164	P	133.8	125.0	145.0	129.6	137.2	133.3	154.8
-	OMe	CO_2Me	OMe	165	P	131.0	124.7	160.0	104.3	161.1	c	155.7
159	OEt	CO_2Et	OEt	164	P	130.8	124.9	159.4	105.5	161.3	117.5	155.9
175	Cl	CN	OMe	164	P+Q	136.8	124.8	150.2	93.2	165.0	119.0	158.8
177	OMe	CN	OMe	164	P+Q	134.3	124.8	164.0	79.0	165.2	114.2	157.4

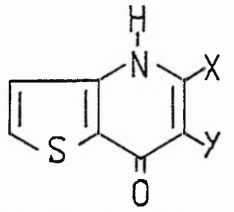
Notes: a: No. of compound in this Thesis

b: Sol. = solvent; P = $CDCl_3$, Q = $(CD_3)_2SO$

c: No signal observed

Table 4

^{13}C NMR Spectra of Thieno[3,2-b]pyridin-7(4H)-ones



No[a]	X	Y	Ref	Sol[b]	Chemical Shift						
					C-2	C-3	C-5	C-6	C-7	C-8	C-9
-	H	H	32	P+Q	131.7	118.4	137.3	109.3	173.4	127.8	144.3
-	H	CO_2H	165	P+Q	135.7	118.6	142.6	108.8	174.2	127.8	145.4
156	Cl	CO_2H	164	P+Q	134.3	117.8	143.6	105.6	169.3	123.4	145.1
-	CO_2H	CO_2H	32	P+Q	135.8	118.6	142.4	108.7	174.1	127.7	145.4

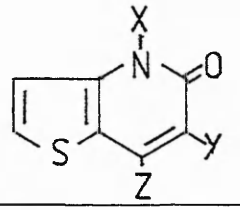
Notes: a: No. of compound in this Thesis

b: Sol. = solvent; P = $CDCl_3$, Q = $(CD_3)_2SO$

c: No signal observed

Table 5

^{13}C NMR Spectra[b] of Thieno[3,2-b]pyridin-5-(4H)-ones



No[a]	X	Y	Z	Ref	Chemical Shift						
					C-2	C-3	C-5	C-6	C-7	C-8	C-9
169	H	H	Cl	46	131.4	117.7	162.1	115.4	140.5	117.7	143.0
170	H	CO_2H	Cl	164	137.2	117.6	163.3	112.4	142.5	122.3	145.8
-	H	CO_2Me	Cl	165	133.1	117.7	159.7	120.8	138.8	c	142.7
-	H	CO_2Me	OH	165	135.6	117.1	160.7	95.0	169.1	c	146.4
-	H	CO_2Et	OH	46	135.3	117.1	160.8	95.1	169.5	c	146.1
-	H	CN	OH	46	134.7	117.4	167.1	83.7	162.6	110.9	145.5
-	Me	H	OH	46	129.4	116.6	164.2	95.6	160.6	112.3	144.5
-	Me	CO_2Et	Cl	99	133.3	117.2	159.5	110.8	c	c	143.7

Notes: a: No. of compound in this Thesis

b: all run in $CDCl_3$ + $(CD_3)_2SO$

c: no signal observed

By noting the chemical shifts at C-2 and C-3 in these compounds it was possible to deduce the approximate shifts from the values in thieno[3,2-b]-pyridine. These shifts are presented in Table 6. The most interesting feature is the comparitively large shift at C-3 arising from the conversion of C-5 or C-7 into a carbonyl group. An alkoxy group at these positions has a very small effect, so that the appearance of the C-3 signal at 117-188ppm is diagnostic for the keto tautomer. Another feature diagnostic of the conversion of C-7 into a carbonyl group is the appearance of the signal for C-7 at 172-174ppm, a much higher figure than is observed for any other ring carbon atom.

Table 6

Shifts produced at C-2 and C-3 by Substituents in the Pyridine Ring of Thieno[3,2-b]pyridines

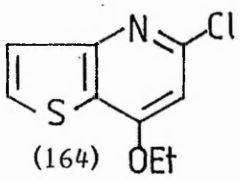
Substituent	Location	Shift produced at	
		C-2	C-3
Cl	C-5	-0.2	-0.8
OAlkyl	C-5	-2.0	-0.8
=O (4H)	C-5	+0.2	-8.0
CO_2H	C-6	+5.0	-0.4
CO_2Alkyl	C-6	+5.0	+0.3
CN	C-6	+5.4	+0.3
Cl	C-7	-1.5	+0.3
OAlkyl	C-7	+0.5	+0.5
OH	C-7	+0.5	+0.5
=O (4H)	C-7	-0.4	-6.6
NEt_2	C-7	-0.2	+0.4

There follows a few examples to illustrate the use of ^{13}C n.m.r. spectroscopy in structure elucidation problems encountered in the present work.

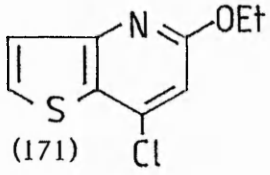
4.1.1. **Differentiation between 5-chloro-7-alkoxy and 7-chloro-5-alkoxy isomers**

The product of reaction of 5,7-dichlorothieno[3,2-b]pyridine (73) with one equivalent of sodium ethoxide could be either the 5-chloro-7-ethoxy-(164) or 7-chloro-5-ethoxy-(171) isomer. The structure has been shown by chemical means to be (164) and the isomer (171) has been synthesised independently (see

Chapter 3). The resonances of the pyridine ring carbon atoms are presented below:



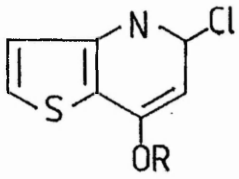
(164)



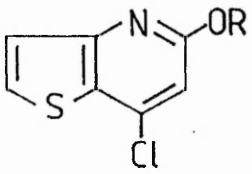
(171)

C-5	150.4	C-5	163.2
C-6	100.1	C-6	108.2
C-7	161.4	C-7	139.0
C-8	121.7	C-8	126.0
C-9	156.4	C-9	154.1

These values were then compared with the predicted values (using the values given in Table 2) and the differences between observed and predicted values may be calculated.



	Predicted	Difference from (164)	Difference from (171)
C-5	148.6	1.8	9.6
C-6	104.0	3.9	4.2
C-7	161.7	0.3	1.5
C-8	117.1	4.6	8.9
C-9	156.1	0.3	2.0
	Total	10.9	26.2

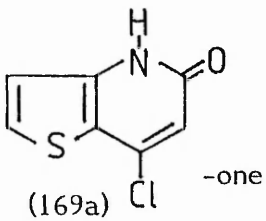


	Predicted	Difference from (164)	Difference from (171)
C-5	159.1	2.3	4.1
C-6	104.5	4.4	3.7
C-7	138.9	11.5	0.1
C-8	123.3	1.6	2.7
C-9	152.8	3.6	1.3
	Total	23.4	11.8

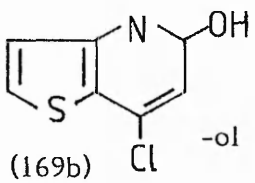
Although the observed and predicted values do not agree precisely a much better fit is obtained for the correct structures than for their isomers.

4.1.2 Keto-enol tautomerism

The 7-chloro-5-oxygenatedthieno[3,2-b]pyridine (169) could exist either in the keto (169a) or enol (169b) forms shown below:



(169a)



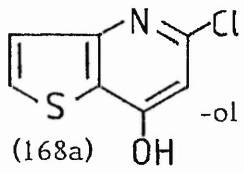
(169b)

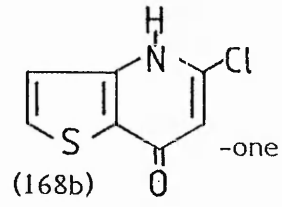
The calculated resonances for these two forms, and the observed values, are as shown on the following page:

	Observed (169)	Calculated for (169a)	Diff. from obs.	Calculated for (169b)	Diff. from obs.
C-2	131.4	128.9	2.5	126.7	4.7
C-3	117.7	117.4	0.3	124.6	6.9
C-5	162.1	158.3	3.8	159.1	3.0
C-6	115.4	113.8	1.6	104.5	10.9
C-7	140.5	141.2	0.7	138.9	1.6
C-8	131.3	124.1	7.2	125.3	6.0
C-9	143.0	140.1	2.9	151.5	8.5
		Total	19.0	Total	41.6

A much better fit is obtained for the keto tautomer, and this preference is confirmed by the i.r. spectrum of the compound which shows a broad band at 1650cm^{-1}, due to a carbonyl group.

A similar treatment of the isomeric 5-chloro-7-oxygenatedthieno[3,2-b]pyridine (168) is given below. In this case it is evident that the hydroxy tautomer (168a) is the preferred form.

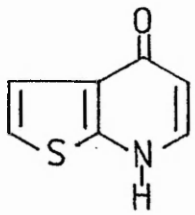




	Observed	Calculated for (168a)	Diff. from obs.	Calculated for (168b)	Diff. from obs.
C-2	131.1	130.5	0.6	129.6	1.5
C-3	123.8	124.8	1.0	117.7	6.1
C-5	149.0	149.9	0.9	137.7	11.3
C-6	104.8	106.0	1.2	110.1	5.3
C-7	162.1	160.1	2.0	172.5	10.4
C-8	121.6	119.1	2.5	123.2	1.6
C-9	155.7	157.4	1.7	145.2	10.5
		Total	9.9	Total	46.5

4.2 Thieno[2,3-b]pyridines

The ^{13}C n.m.r. spectra of the thieno[2,3-b]pyridines prepared in this work were assigned by the means just described for thieno[3,2-b]pyridines. The data are presented in Tables 7 and 8 and Figure 7.

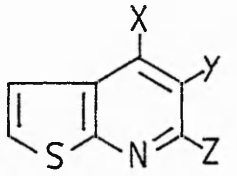


δ ($CDCl_3$)						
	C-2	123.8	C-5	113.7	C-8	151.2
	C-3	117.1	C-6	140.0	C-9	130.1
	C-4	174.7				

Figure 7: ^{13}C n.m.r. Spectrum of 7-Methylthieno[2,3-b]pyridin-4-one

Table 7

^{13}C NMR Spectra of Thieno[2,3-b]pyridines



No.	Solvent[a]	X	Y	Z	Chemical Shift (ppm) C-2	C-3	C-4	C-5	C-6	C-8	C-9
1	P	H	H	H	126.9	119.3	131.0	121.5	146.4	c	132.5
153	P	Cl	H	H	127.8	119.7	138.5	119.7	146.8	162.5	131.5
154	P	OMe	H	H	124.3	118.2	161.1	100.9	148.5	163.1	123.5
85	P+Q	OH	H	H	121.9	119.3	163.3	107.0	145.1	159.7	124.6
145[b]	P	H	H	Cl	127.3	120.4	133.0	121.0	147.8	161.0	131.3
191	P	H	H	OMe	122.3	121.3	133.2	108.6	162.1	159.2	126.9
141	P	Cl	H	Cl	128.0	119.9	139.9	119.5	147.8	161.3	130.5
190	P	Cl	H	OEt	122.8	119.7	139.7	108.6	162.3	c	125.7
185	P	OMe	H	Cl	124.7	118.2	162.1	101.3	149.5	161.5	122.9
186	P	OEt	H	Cl	124.4	118.2	161.3	101.7	149.4	161.3	123.0
188	P+Q	OH	H	Cl	123.6	118.5	161.0	105.4	148.4	161.7	122.5
187	P	OMe	H	OMe	120.3	118.2	164.3	88.7	162.7	159.9	119.5
151	P+Q	H	CO_2H	H	128.6	122.2	132.3	122.8	146.9	164.5	131.7
150	P	H	CO_2Et	H	128.3	121.9	132.3	122.3	147.3	165.6	131.8
149	P	Cl	CO_2Et	H	128.8	120.8	138.9	121.5	148.4	164.3	132.1
181	P	OEt	CO_2Et	H	126.1	119.3	161.2	115.1	150.0	165.2	126.7
-	P+Q	OH	CO_2H	H	122.5	121.0	151.3	110.3	142.6	167.3	129.4
143	P	Cl	CO_2Et	Cl	129.2	119.9	144.1	125.7	c	160.8	130.2

continued/

Table 7 (continued)

No.	Solvent[a]	X	Y	Z	Chemical Shift (ppm) C-2	C-3	C-4	C-5	C-6	C-8	C-9
180	P	OEt	CO_2Et	Cl	126.1	118.8	159.1	117.4	145.1	162.8	123.7
184	P	OEt	CO_2Et	OEt	121.5	119.0	159.9	105.9	159.3	161.3	120.2

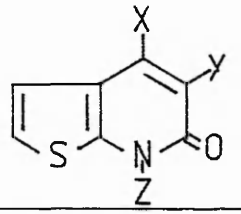
Notes: a: P = $CDCl_3$, Q = $(CD_3)_2SO$

b: lit.[97] values126.7, 119.1, 130.8, 121.4, 146.3, 161.6 and 132.3 ppm

c: no signal observed

Table 8

^{13}C NMR Spectra of Thieno[2,3-b]pyridin-6-ones



No.	Solvent[a]	X	Y	Z	Chemical Shift (ppm) C-2	C-3	C-4	C-5	C-6	C-8	C-9
134a	P+Q	OH	H	H	119.3	115.8	164.6	94.5	162.2	149.6	115.9
137	P+Q	OH	H	Me	120.9	115.9	163.0	95.0	161.2	149.6	115.1
142	P+Q	Cl	H	H	120.0	111.5	140.5	120.0	161.9	153.1	122.3
189	P	Cl	H	Et	122.7	116.3	141.3	116.7	160.7	148.2	120.3
133a	P+Q	OH	CO_2Et	H	120.0	116.6	170.0	95.2	160.5	152.3	114.3
136	P	OH	CO_2Et	Me	122.1	116.0	169.7	95.5	159.7	154.4	114.0

Note: a: P = $CDCl_3$, Q = $(CD_3)_2SO$

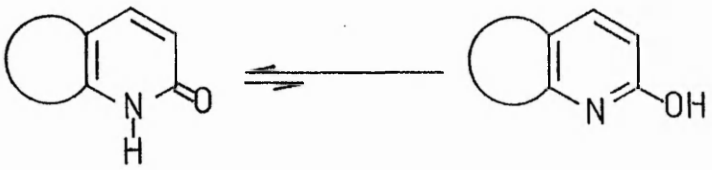
As is the case for thieno[3,2-b]pyridines these spectra give a good indication of the tautomeric form preferred under the conditions of measurement. For example, the resonances of 4-hydroxythieno[2,3-b]pyridine (85) lie very close to those of the 4-methoxy compound (154), and differ considerably from those of 7-methylthieno[2,3-b]pyridin-4-one (152).

The presence of a 6-one group causes a shift in the resonance of C-3, which lies in the region 115.8-116.3ppm in all but one of the thieno[2,3-b]pyridines in Table 8, but occurs at consistently higher values (118.2-121.3ppm) in all the enolic 6-oxygenated compounds listed in Table 7.

4.3 Keto-enol tautomerism

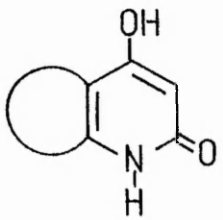
The use of i.r. and the ^{13}C n.m.r. methods just discussed allow some comments to be made concerning keto-enol tautomerism in quinolines, thieno[3,2-b] and [2,3-b]pyridines.

a) α-Pyridones



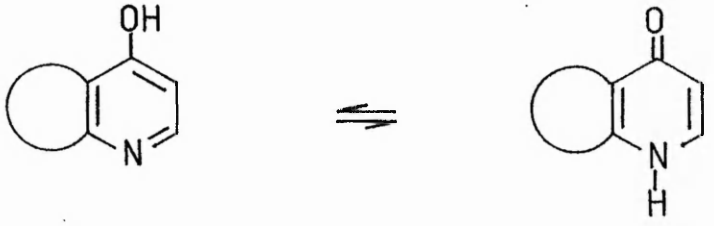
In all cases where there is an oxygen functionality α-to the pyridine nitrogen atom, the keto form is preferred. This is observed in both thienopyridine systems and in quinolines.

b) α, γ-dioxygenated pyridines



Again, the same tautomeric form is preferred in all three systems, namely the γ-hydroxy-α-pyridone form illustrated above.

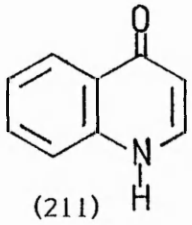
c) γ-hydroxypyridines / γ-pyridones



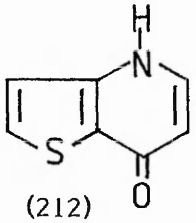
In this case the situation is somewhat more complex, the tautomeric form preferred being dependent on the system and on the substituents present.

In quinolines and thieno[3,2-b]pyridines the parent systems and most derivatives exist in the pyridone form; the hydroxy form is however preferred when a strongly electron-withdrawing substituent (for example chlorine) is situated α- to the nitrogen atom.

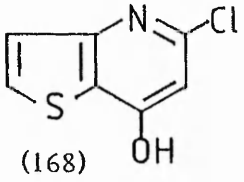
Thus the following forms are preferred:



(211)

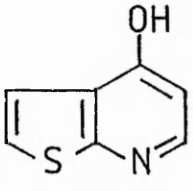


(212)



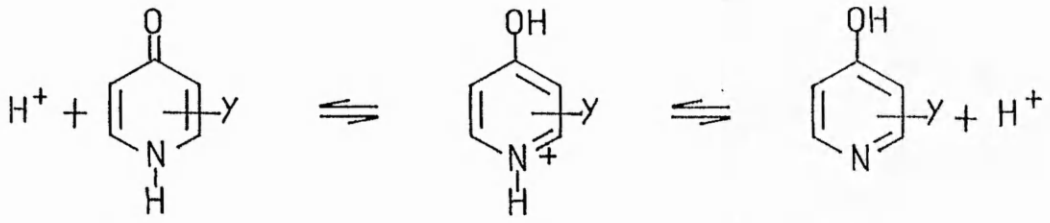
(168)

All thieno[2,3-b]pyridines, including the parent 4-hydroxythieno[2,3-b]pyridine exist in the hydroxy form, eg



(85)

The reasons for the different tautomeric preferences may be explained by considering the equilibrium shown in Equation 38. (A more detailed treatment of this approach is given in Reference 166)



(213) (214) (215)

Equation 38

The position of the tautomeric equilibrium (213) ⇌ (215) is determined by the relative acidities of the -OH and -NH protons in the conjugate acid (214); if the -OH proton is more acidic than the NH proton then (213) will predominate and vice versa. In most cases the OH proton is the more acidic and thus the pyridone form (213) is preferred. The hydroxy form is only preferred when the substituent Y is capable of exerting a strong enough electron-withdrawing effect to make the NH proton in (214) the more acidic. This is most likely to occur when Y is an electronegative atom α- to the nitrogen atom.

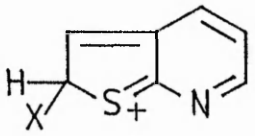
This explains the change in tautomeric preference between (212) and (168), caused by the -I chlorine atom in (168). The preference for the hydroxy form in thieno[2,3-b]pyridines [for example (85)] is explained by considering the sulphur atom of the thiophene ring as a -I substituent on the pyridine ring [In thieno[3,2-b]pyridines the sulphur atom is further away from the nitrogen atom and the inductive effect is much less. A similar argument has been used to explain the low basicity of thieno[2,3-b]pyridine (1) with respect to thieno[3,2-b]pyridine (2).[82]]

CHAPTER FIVE

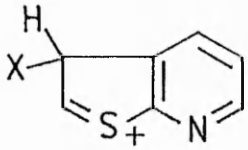
ELECTROPHILIC SUBSTITUTION

ELECTROPHILIC SUBSTITUTION

The electrophilic substitution of the parent compounds, thieno[2,3-b]pyridine (1) and thieno[3,2-b]pyridine (2), has been studied in detail (see Section 1.1.3.1.). In both cases reaction takes place at C-3; if this position is occupied then attack occurs at C-2. Reaction in the electron-rich thiophene ring is understandable, the preference for attack at the β-position, rather than the α-position as in thiophene itself, is explained by consideration of the canonical forms (216) and (217) for attack on (1) at C-2 and C-3 respectively, in which the positive charge is stabilised by the sulphur atom.



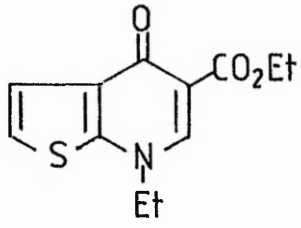
(216)



(217)

In (217) the pyridine ring has the normal bond configuration whereas in (216) a less favourable quinoid structure is necessary.

There are few reports of electrophilic substitution of other compounds in either series. For the types of compound examined in the present work relevant reports are those concerning 5-ethoxycarbonyl-7-ethylthieno[2,3-b]-pyridin-4-one (218), which has been depicted as undergoing nitration[91] and iodination[96] at C-2.



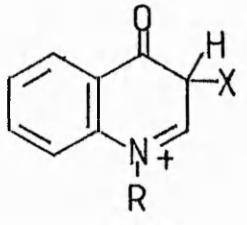
(218)

It was of interest to investigate the reactions of compounds containing activating substituents in the pyridine ring for two reasons; firstly, as potential routes to quinoline alkaloid analogues, and secondly to study the degree and position of activation by a given substituent. Of particular interest was whether a substituent would have the same effect in the [3,2-b] and [2,3-b]-fused systems.

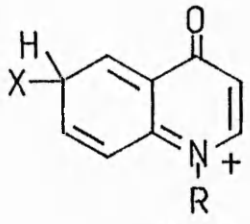
Many electrophilic substitution reactions of related quinolines have been reported. Substitution of 4-oxygenated quinolines can often be effected by mild reagents, reaction almost invariably occurring at C-3 if that position is

vacant. Nitration of 4-quinolone[167] and of 1-methyl-4-quinolone[168] by nitric acid alone gives the 3-nitro derivative in each case, and 4-quinolones are halogenated at C-3 by sulphuryl chloride in acetic acid[169,170], N-chloro-succinimide[171], sodium hypochlorite[172], bromine in acetic acid[170,173], iodine monochloride in acetic acid[169] and by iodine-potassium iodide in aqueous sodium hydroxide[172]; 1-alkyl-4-quinolones are also brominated[174] and iodinated[175] at C-3. 2-Methyl-4-quinolone readily undergoes the Mannich reaction[176,177] and hydroxymethylation with formaldehyde (either alone[178] or in the presence of acid[179]) at C-3 and the Riemer-Tiemann reaction[180,181] and coupling with diazonium salts[180] also take place at this position in 4-quinolones. Under conditions where the 4-oxygenated quinoline is protonated the pyridine ring is deactivated to electrophilic attack, which takes place in the benzene ring, mainly at C-6, but to some extent at C-8 also. This is well illustrated by the mixed acid nitration of 4-quinolone[167,182], N-substituted-4-quinolones[182,183] and 4-methoxyquinoline[182].

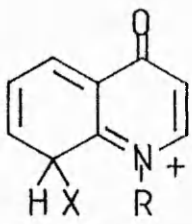
That C-3, C-6 and C-8 are preferred positions of electrophilic attack may be explained by the ability of the activating substituent to delocalise the incoming positive charge in these cases (canonical forms (219), (220) and (221) for 4-quinolones; (222), (223) and (224) for 4-hydroxyquinolines).



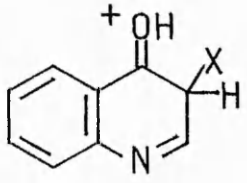
(219)



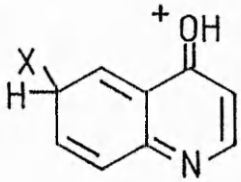
(220)



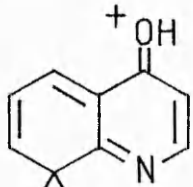
(221)



(222)



(223)



(224)

Such delocalisation is not possible for attack at C-2, C-5 or C-7. The reason for the preferential attack at C-3 over that at C-6 and C-8 is probably that in the canonical forms for attack at C-3 the benzene ring is in the normal configuration whereas reaction elsewhere requires quinoid forms.

4-Hydroxy-2-quinolones similarly undergo electrophilic attack at C-3 by weak

electrophiles. Thus 3-substituted derivatives are produced by the Mannich reaction[184], bromine in acetic acid[185] and nitric acid in acetic acid.[186,187] 4-Hydroxy-2-quinolone also forms 3-acyl derivatives by either Friedel-Crafts acylation[188,189] or Riemer-Tiemann formylation.[190] Coupling with diazonium salts[191] and alkylation[184,192] (under basic conditions) at C-3 has also been reported. Under more vigorous conditions further substitution occurs at C-6; thus nitration of 4-hydroxy-2-quinolone with mixed acid leads to the 3,6-dinitro derivative.[193]

In these dioxygenated systems the hydroxy group activates C-3 and the 2-quinolone function can activate at C-3, C-6 and C-8; the canonical forms depicted in Figure 8 demonstrate these points.

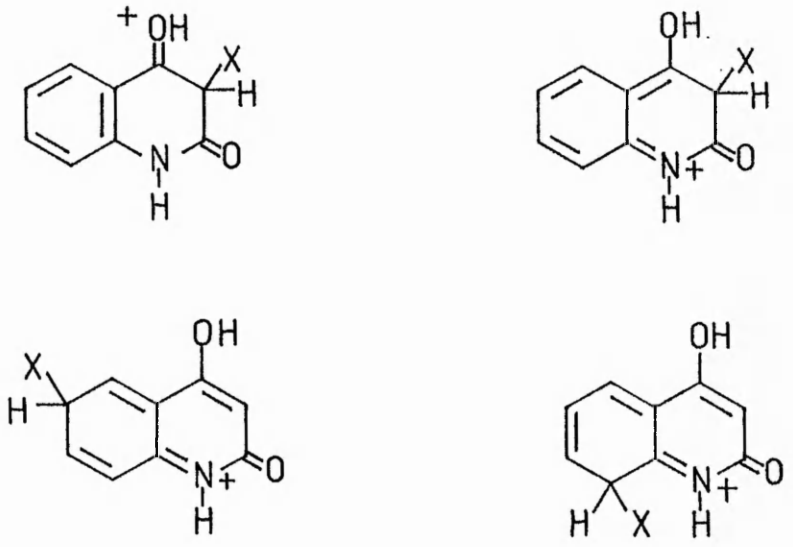


Figure 8

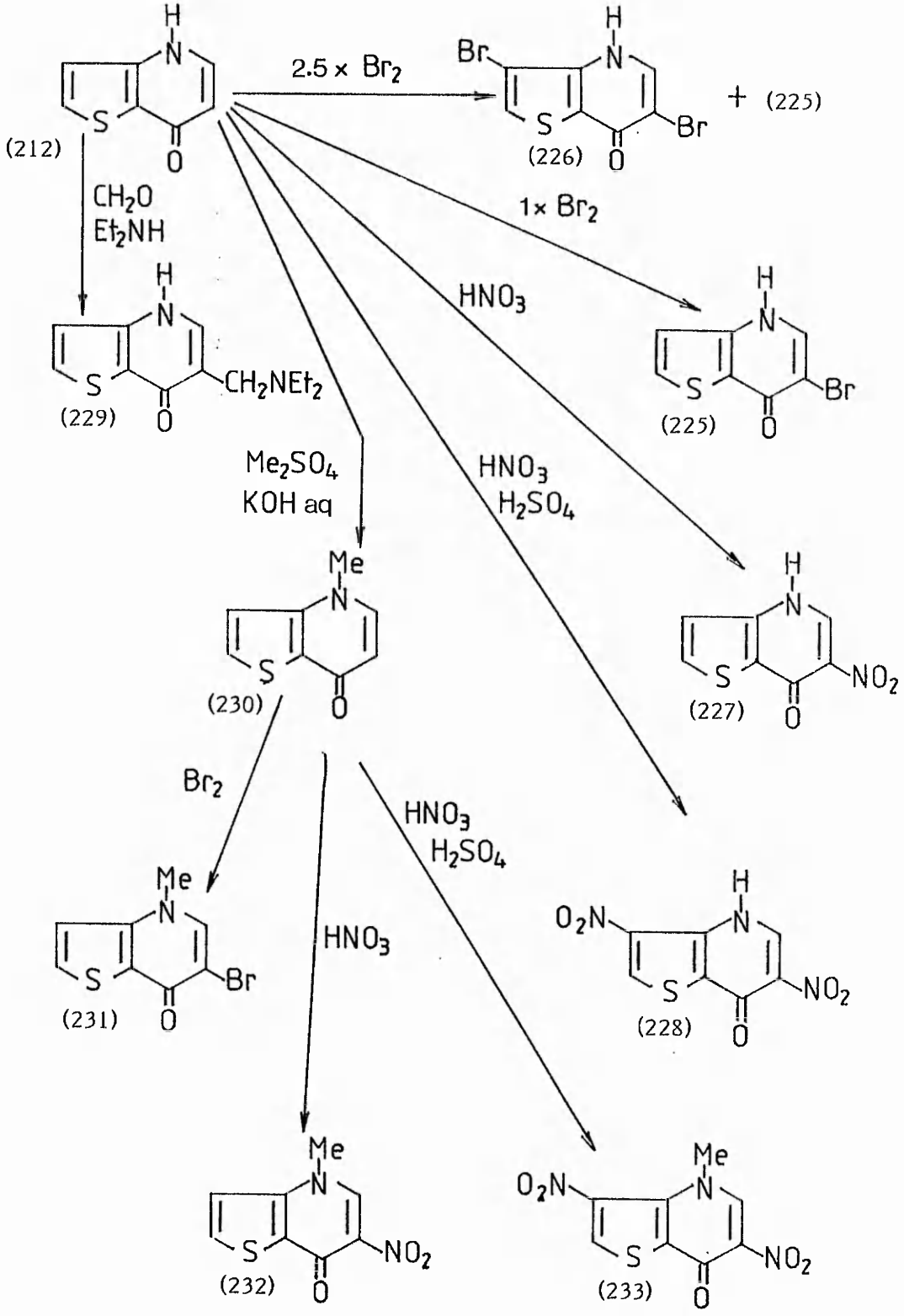
When the only activating substituent present is the 2-quinolone group the situation is less simple. The preference for attack at C-3 is less marked, and in some cases reaction accurs preferentially at C-6. Reactions with weak electrophiles (for example diazo coupling, the Mannich, and Riemer-Tiemann reactions) have not been described. Nitration of 2-quinolones by nitric acid alone gives the 6-nitro derivatives, whilst warm mixed acid affords the 3,6,8-trinitro compounds.[194] The position of halogenation depends on the substituents and the reagent used. A range of 4-methyl-2-quinolones was brominated at C-3[195] whilst 2-quinolone itself is brominated at C-6[196]. With chlorine in acetic acid 2-quinolone gives the 3,6-dichloro derivative[196], whereas iodine monochloride in the same solvent leads to the 3-iodo compound.[197] Friedel-Crafts acylations have been reported for a variety of 1-alkyl-2-quinolones[198,199,200]; mixtures of 3- and 6-substituted products were formed, the ratio depending on the reaction conditions, although overall yields

were generally low.

5.1 Thieno[3,2-b]pyridines

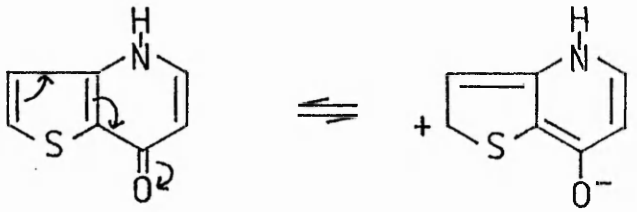
The 7-oxygenated thieno[3,2-b]pyridine (212), like its quinoline counterpart, exists in the keto form. Bromination with one equivalent of bromine in warm acetic acid gave the 6-bromo derivative (225); with an excess of bromine in acetic acid at reflux temperature further reaction took place, albeit slowly, to yield the 3,6-dibromo compound (226). As in the corresponding quinoline, (212) was attacked in the pyridine ring by nitric acid at 100° producing 6-nitrothieno[3,2-b]pyridin-7-one (227); nitric acid in acetic acid led to the formation of the nitrate salt of (212). Mixed acid treatment of (212) afforded the 3,6-dinitro derivative (228) (this is in contrast to the quinoline series, where this reagent does not give substitution in the pyridine ring). A slow Mannich reaction occurred when (212) was boiled under reflux in ethanol with formaldehyde-diethylamine, forming (229).

The N-methyl compound (230) derived from (212) was less reactive than (212) towards electrophiles. In this case the Mannich reaction failed and only monobromination could be achieved. The latter reaction, and nitration with nitric acid at 100°, both took place at C-6, furnishing (231) and (232) respectively; treatment of (212) with mixed acid led to (233). In all the reactions just described (shown in Scheme 71) the position of attack was evident from the ^{1}H n.m.r. spectra.

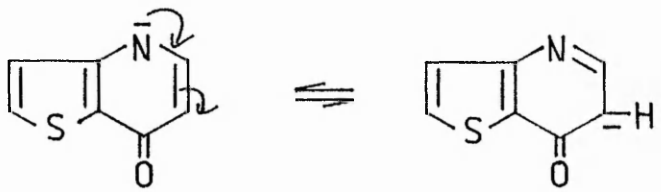

(212)
2.5 × Br2
(226)
+ (225)
CH2O
Et2NH
(229)
CH2NEt2
1× Br2
HNO3
(225)
Me2SO4
KOH aq
HNO3
H2SO4
(230)
(227)
NO2
Br2
HNO3
H2SO4
(231)
HNO3
(228)
O2N
NO2
(232)
NO2
(233)
O2N
NO2

Scheme 71

To sum up: the results are similar to those observed in the comparable quinolines, ie reaction occurs preferentially in the pyridine ring at the position α- to the oxygen atom, and only under more vigorous conditions does attack take place in the other ring. Since there is no activating conjugative interaction between the pyridine ring substituents and positions C-2 and C-3 in the thiophene ring, the site of attack in the thiophene ring is the same as in thieno[3,2-b]pyridine itself. In fact the only interaction possible is deactivation at C-2, reinforcing the preference for reaction at C-3, ie



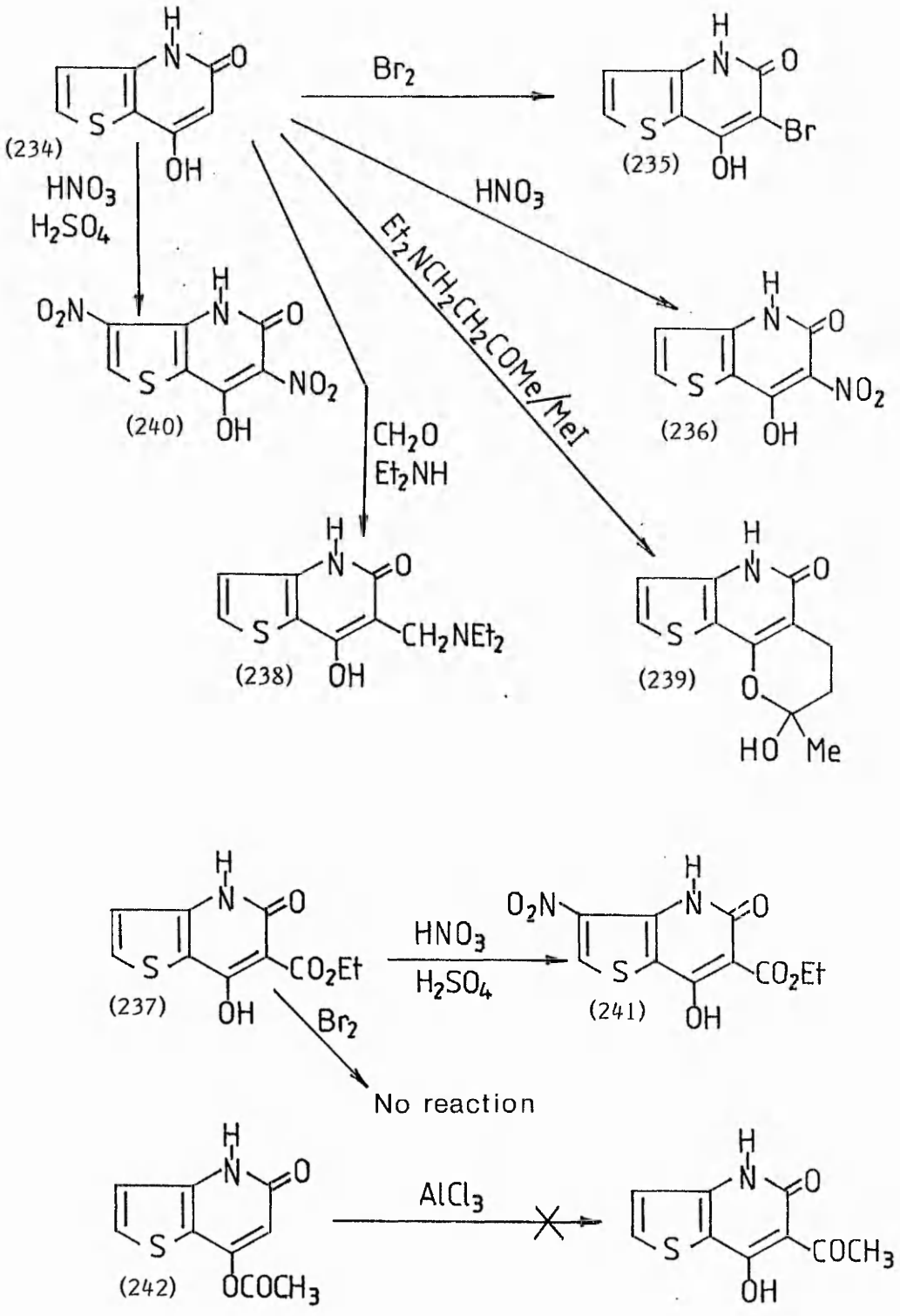
The reduced reactivity of the N-methyl compound (230) with respect to (212) is most probably due to the absence of an acidic proton in the former. The Mannich reaction takes place under basic conditions and it is likely that the anion of (212) is the reacting species. An anion cannot readily be formed from (230) and the neutral compound is not sufficiently active to react with the very weak electrophile concerned.



The fact that (212) and (230) give dinitro compounds with mixed acid whereas the quinoline analogues are only nitrated in the benzene ring may be a result of the lower basicity of the thienopyridines with the result that a small amount of the free base is present in the reaction mixture allowing reaction in the pyridine ring. It has been argued that in the quinolines the system is completely protonated under these conditions, preventing reaction in the pyridine ring.[182]

The thieno[3,2-b]pyridine isostere (234) of 4-hydroxyquinolin-2-one is also highly reactive towards electrophiles. Bromination by bromine in acetic acid and nitration by nitric acid in acetic acid have been reported to give the 6-substituted products [(235) and (236)].[46] Several other reactions of (234)

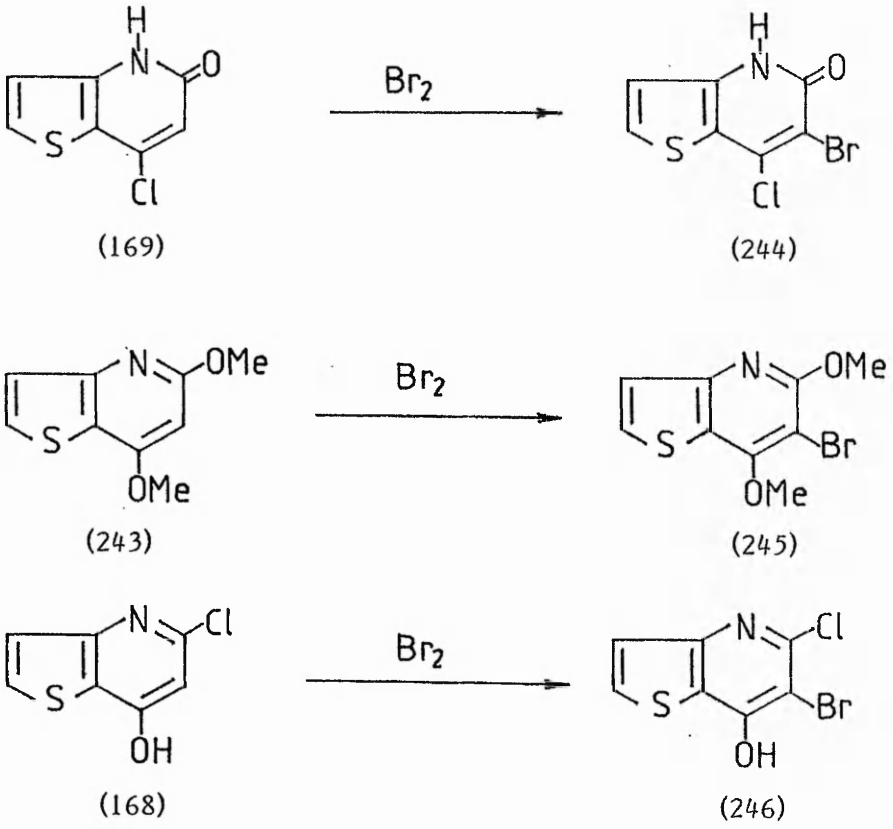
have now been investigated. With an excess of bromine in acetic acid under reflux only (235) was formed, and no disubstitution was observed; similarly the ester (237), in which C-6 is blocked, did not undergo bromination. The Mannich reaction of (234) proceeded at room temperature affording the amine (238) whilst reaction with 4-diethylaminobutan-2-one and methyl iodide in the presence of potassium hydroxide (successful in the corresponding quinoline[184]) produced the tricyclic compound (239). Reaction in the thiophene ring only occurred when mixed acid was used as reagent. Thus (234) gave the 3,6-dinitro compound (240), and (237) yielded the 3-nitro derivative (241) with this reagent. However, efforts to induce (234) to undergo Friedel-Crafts acetylation[188,189] and Riemer-Tiemann formylation[190] resulted in decomposition, and attempts to bring about Fries rearrangement of the acetate (242)[46] were equally unsuccessful. The reactions just described are depicted in Scheme 72.



Scheme 72

The activation of C-6, and the attack at C-3 rather than C-2 of the thiophene ring, are explicable by the same reasoning as that given above for the orientation of substitution in thieno[3,2-b]pyridin-7-ones.

Further variation of the groups in the pyridine ring of thieno[3,2-b]pyridines has revealed more about the effect of substituents on the electrophilic substitution of the system. In both 7-chlorothieno[3,2-b]pyridin-5-one (169) and 5,7-dimethoxythieno[3,2-b]pyridine (243) the reactivity of the pyridine ring was below the level at which the Mannich reaction would occur. Both these compounds and 5-chloro-7-hydroxythieno[3,2-b]pyridine (168) were brominated at C-6 by bromine in acetic acid giving (244), (245) and (246), respectively but neither 7-methoxy (165) not 5,7-dichlorothieno[3,2-b]pyridine (73) were affected by this reagent. (Scheme 73)



(169) (244)

(243) (245)

(168) (246)

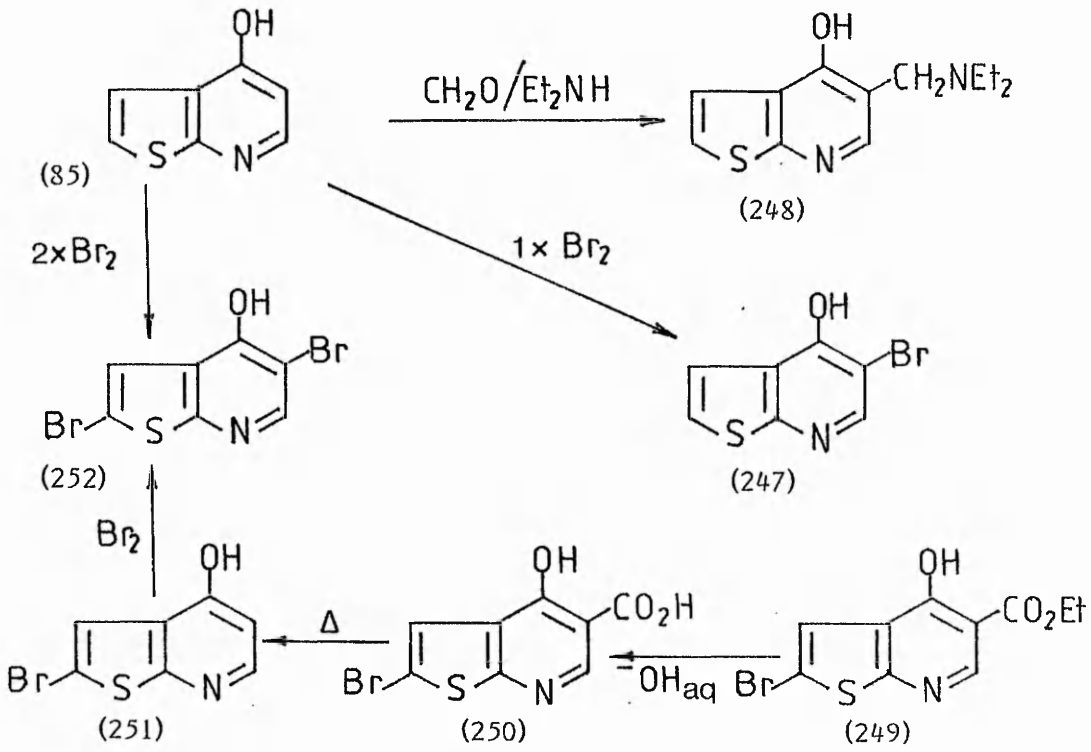
Scheme 73

The foregoing reactions indicate that electron donating substituents ar C-5 and C-7 in thieno[3,2-b]pyridines only promote attack at C-6. When attack does occur in the thiophene ring, it takes place at the same position as in thieno-[3,2-b]pyridine itself, ie at C-3.

5.2 Thieno[2,3-b]pyridines

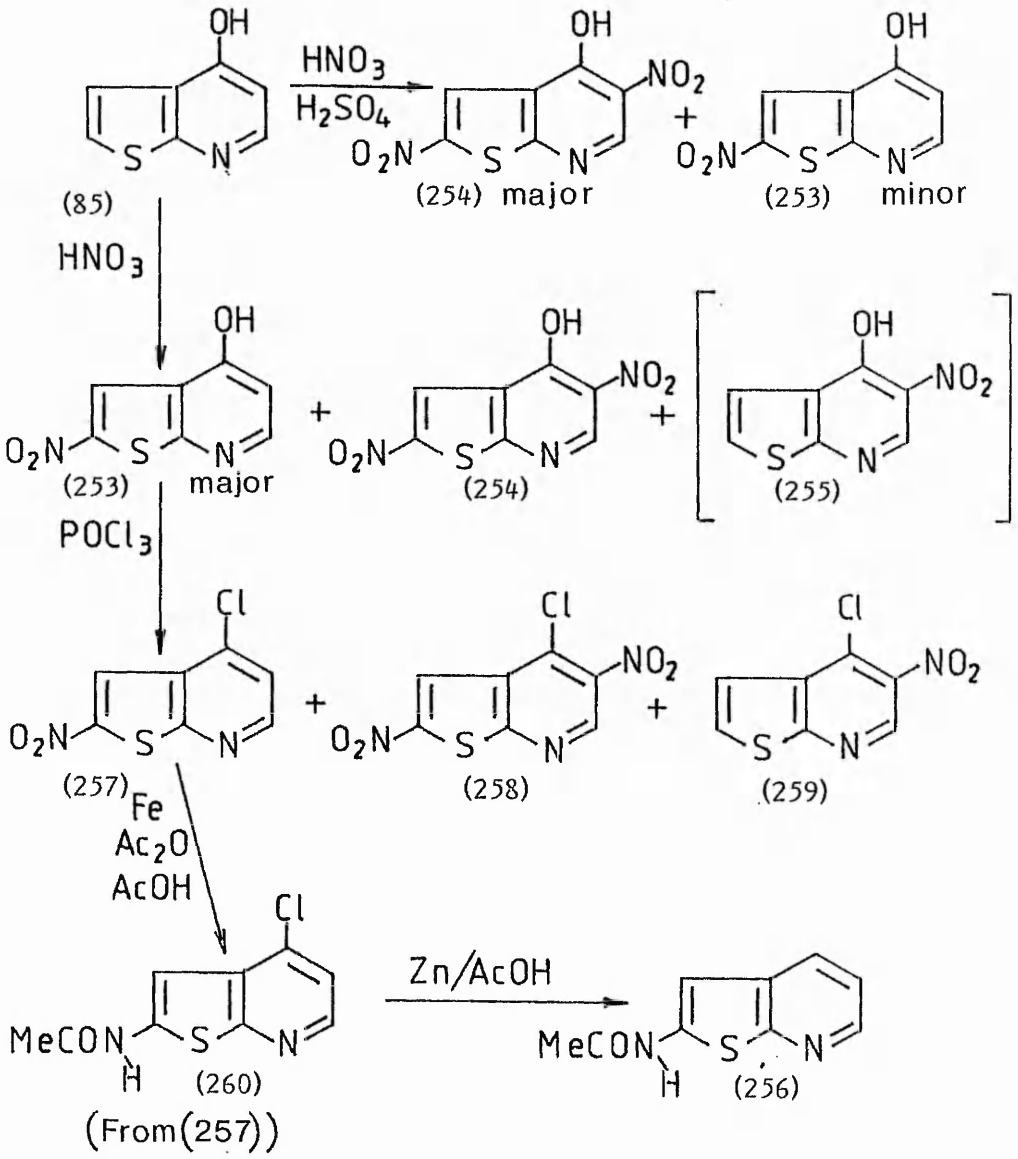
Unlike its thieno[3,2-b]pyridine and quinoline counterparts, the 4-oxygenated-thieno[2,3-b]pyridine (85) exists in the hydroxy form; it, also, reacts readily with electrophiles, however. Upon treatment of (85) with one equivalent of bromine in acetic acid containing sodium acetate the 5-bromo compound (247)

was rapidly formed (more quickly than its [3,2-b]-counterpart). When the sodium acetate was omitted reaction ceased after half of the bromine had been added; presumably the hydrogen bromide formed as a by-product caused protonation of (85), halting the reaction. Diethylamine-formaldehyde reacted with (85) on standing at room temperature to afford the Mannich base (248) (in the [3,2-b] series this reaction only proceeded at reflux temperature). However, (85) failed to react in boiling acetic acid with either nitric acid or iodine. It is also of interest that 4-methoxythieno[2,3-b]pyridine resisted attack by bromine in acetic acid under conditions more forcing than those required for the conversion of (85) in (247). With an excess of bromine in boiling acetic acid containing sodium acetate (85) was converted into a dibromo compound; one of the bromine atoms was clearly placed at C-5 but the position of the second, which was located in the thiophene ring, could not be deduced from the ^{1}H n.m.r. spectrum of the compound. It was finally established to be at C-2 by an unambiguous synthesis from the known[201] ester (249) and acid (250). Decarboxylation of the latter afforded 2-bromo-4-hydroxythieno[2,3-b]pyridine (251) which, upon treatment with bromine in acetic acid containing sodium acetate, furnished the 2,5-dibromo compound (252), identical in all respects to the material formed by bromination of (85). These transformations are depicted in Scheme 74.



Scheme 74

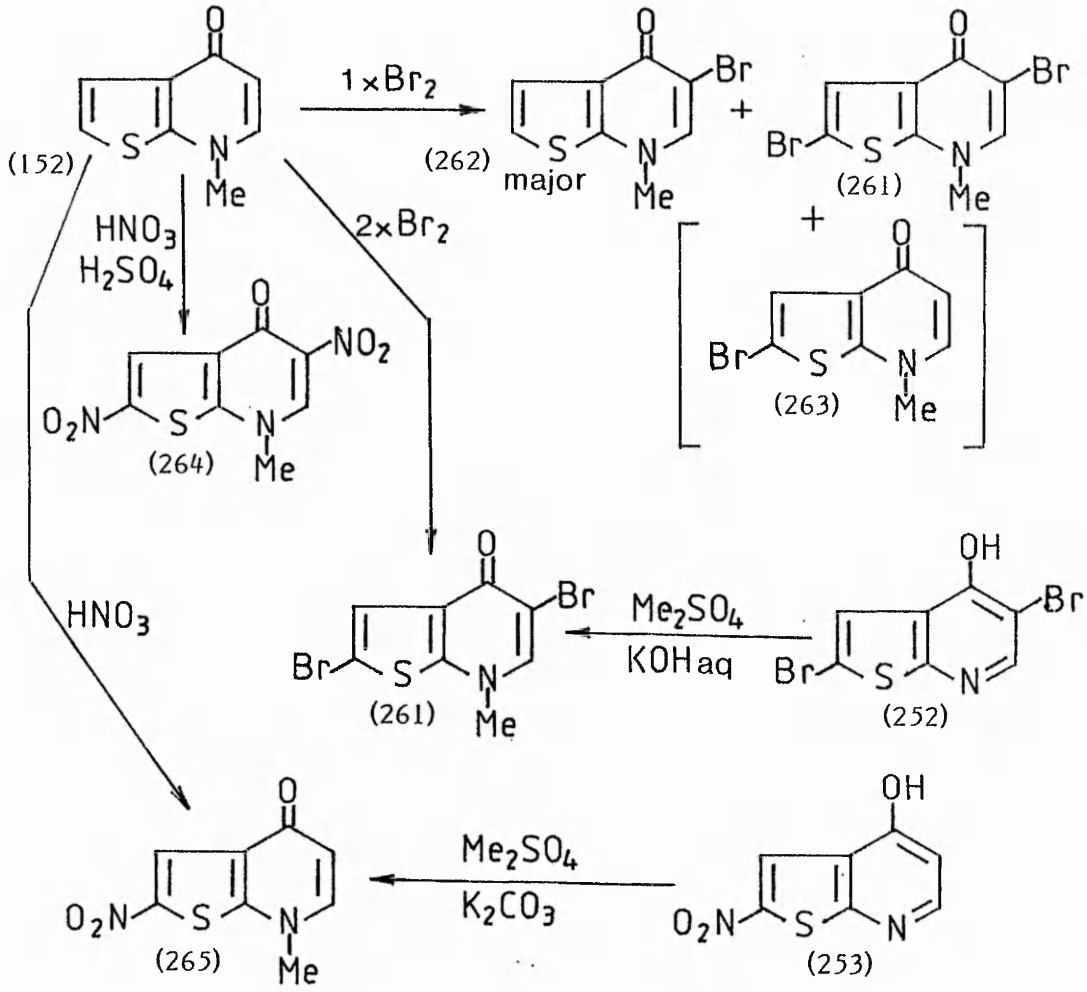
Treatment of (85) with nitric acid alone at 100° gave a mixture containing three components, the major being 2-nitro-4-hydroxythieno[2,3-b]pyridine (253), the second most abundant was the 2,5-dinitro compound (254) and a third, which was not isolated, was presumably the 5-nitro compound (255) (see later). When mixed acid was used a mixture of (253) and (254) was formed but in this case the relative amounts of the products were reversed and the dinitro compound (254) was the major product. The position of substitution in the thiophene ring seemed likely to be C-2 [by analogy with the bromination product (252)] but the possibility could not be discounted that the change in orientation on monosubstitution (pyridine ring on bromination, thiophene ring with nitric acid) might also be accompanied by a change in the preferred site of attack in the thiophene ring. The ^{13}C n.m.r. spectrum of the major product (253) was consistent with it being the 2-nitro compound but an unambiguous chemical proof was desired. The matter was put beyond doubt by the conversion of the product into the known[79] 2-acetylaminothieno[2,3-b]-pyridine (256). Treatment of the crude product of reaction of (85) and nitric acid with phosphoryl chloride furnished a mixture of chloro compounds (257)-(259) which was separated by flash-column chromatography. The isolation of (259) indicated the presence of 4-hydroxy-5-nitrothieno[2,3-b]pyridine (255) in the nitration product. Reduction of (257) with iron in acetic acid - acetic anhydride in the manner described by Klemm[107] afforded the 2-acetamido-4-chloro compound (260). Reductive dechlorination of this material by zinc in acetic acid proved to be very slow (presumably electron release from the amide nitrogen is the cause of this behaviour) but conversion into (256) was finally achieved. The acetamido compound had melting point and i.r. and ^{1}H n.m.r. spectra characteristic of the 2-acetylamino compound[79] (the properties of the 3-acetylamino compound are quite different).[107] An attempt to bring about the transformation of (257) into (256) in one step by reduction with zinc in acetic acid - acid anhydride resulted in decomposition. Scheme 75 summarises these nitration reactions and subsequent transformations of the products.



Scheme 75

7-Methylthieno[2,3-b]pyridin-4-one (152) was subjected to the same set of substitution reactions as those just described for (85). Overall (152) proved to be less reactive than (85); the Mannich reaction failed and bromination was considerably slower. Use of an excess of bromine in hot acetic acid containing sodium acetate produced a dibromo compound. This material was identical to that produced on N-methylation of the 2,5-dibromo-4-hydroxy compound (252) and thus was 2,5-dibromo-7-methylthieno[2,3-b]pyridin-4-one (261). Monobromination of (152) proved to be considerably slower than for (85) and the crude product was shown by t.l.c. to contain several components. A small amount of starting material was present, together with some dibromo

compound (261). The major compound was isolated by flash-column chromatography and was shown to be the product of 5-substitution, ie (262); the remaining component, which was only present in small amount, was not isolated but was tentatively assigned the 2-bromo structure (263). Nitration of (152) proceeded in a manner similar to (85); ie mixed acid afforded the 2,5-dinitro compound (264) (albeit in rather poor yield) whilst nitric acid alone yielded a mixture which consisted mainly of the 2-nitro derivative (265). The latter was also produced by N-methylation of the 4-hydroxy-2-nitro compound (253). The reactions just described are presented in Scheme 76.

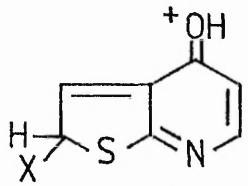


Scheme 76

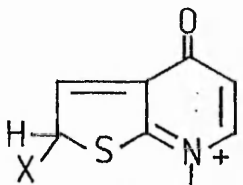
It is interesting to note that the change in mode of ring fusion from [3,2-b] to [2,3-b] causes both an increase in the reactivity of the thiophene ring and a change in the preferred site of attack.

The 4-hydroxy compound (85) is effectively a phenol, which explains its increased reactivity with respect to its [3,2-b] analogue (212) (which exists in the keto form). It is probable that (85) is more acidic than (212) (although no measurements have been made) and the increased likelihood of anion formation explains the increased reactivity of (85) in the Mannich reaction and the high rate of monobromination. In the N-methyl compound (152) the possibility of anion formation does not exist and so the reactivity is lowered.

The reason for further substitution at C-2 is evident from consideration of the canonical forms (266) and (267). It can be seen that the pyridine ring substituents are able to facilitate attack at C-2; no such activation is possible for attack at C-3.

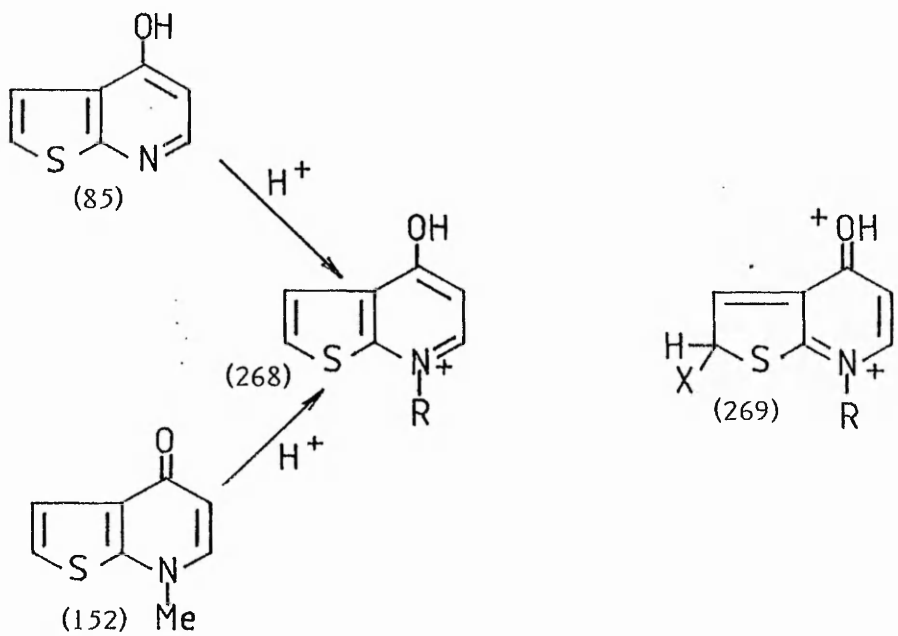


(266)

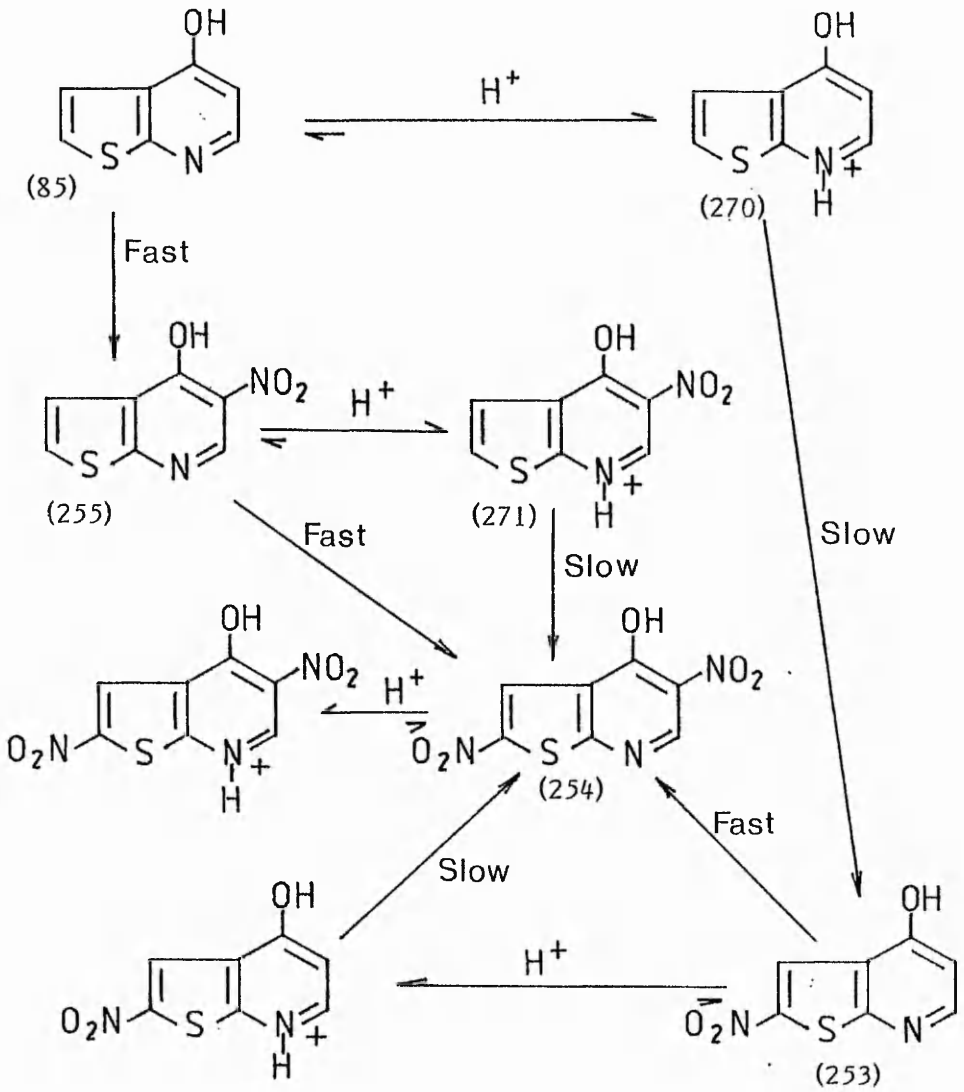


(267)

The change in preferred site of mononitration (from pyridine ring to thiophene ring) in moving from the [3,2-b] to the [2,3-b] system is less easy to explain. The hydroxy compound (85) is protonated on nitrogen and the N-methyl compound (152) is protonated on oxygen, giving similar conjugate acids [(268) R=H,Me, respectively] both of which are able to stabilise attack at C-2, as in (269).



A rationale for the nitration of these systems is given in Scheme 77. In the acid medium an equilibrium exists in which almost all the free base (85) is protonated, giving (270). The free base undergoes rapid reaction at C-5, giving (255), which also is in equilibrium with its conjugate acid (271). The protonated species undergo slow reaction at C-2 (it is assumed that when protonated the pyridine ring is not reactive). Since protonated forms predominate, the reaction in the thiophene ring will be significant, but slow. Further reaction of both (253) and (255) then affords (254). The rate of the overall reaction and the relative amounts of the products will depend on the position of the equilibria and on the rates of each individual process. In different reaction conditions (for example mixed acid or nitric acid alone) the positions of the equilibria and the rates of the processes will be different and different amounts of the products will be formed.



Scheme 77

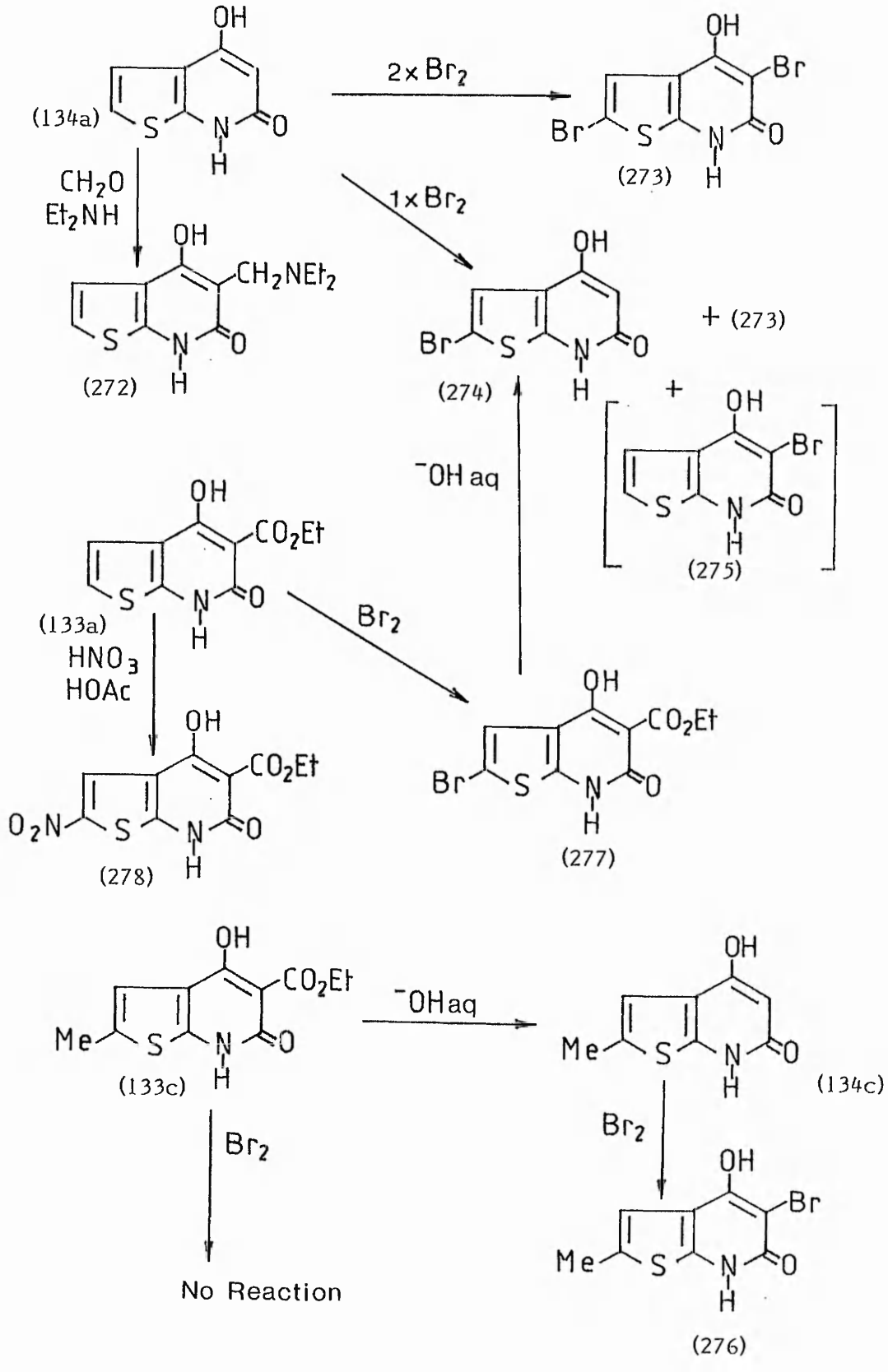
The same arguments will apply to the nitration of 7-methylthieno[2,3-b]pyridin-4-one (152), and a similar reaction scheme could be envisaged.

For the thieno[3,2-b]pyridine system a similar approach can be taken. In this case the substituent does not activate the thiophene ring at C-2 and hence reaction in the thiophene ring will be much slower, and will occur at C-3. This explains the preferred site for mononitration being the pyridine ring in thieno[3,2-b]pyridines and the thiophene ring in thieno[2,3-b]pyridines.

4-Hydroxythieno[2,3-b]pyridin-6-one (134a) proved to be less stable than its thieno[3,2-b]pyridine counterpart. Thus nitric acid in acetic or sulphuric acids, and a variety of Friedel-Crafts acylation catalysts all caused decomposition. The Mannich reaction proceeded smoothly in the pyridine ring but treatment with 4-diethylaminobutanone/methyl iodide in aqueous potassium hydroxide, successful in the quinoline and thieno[3,2-b]pyridine cases, gave a complex mixture with (134a). A change in orientation of substitution from the pyridine ring to the thiophene ring was noted when (134a) was brominated with bromine in acetic acid. With two equivalents of bromine a dibromo derivative (273) was formed readily whilst with one equivalent (274) was the somewhat impure product. The i.r. spectrum of (274) was identical to that of pure material (see later) and mixed m.p. gave no depression. However, close inspection of the ^{1}H n.m.r. spectrum of (274) indicated the presence of small amounts of impurities, tentatively identified as the the dibromo compound (274) and the product of pyridine ring bromination (275), although these minor components were not isolated. That substitution had taken place at C-2 was deduced from the fact that in a compound with the 2-position blocked (134c) bromination occurred in the pyridine ring affording (276). The ester (133a) was also readily brominated, giving (277) which was hydrolysed and decarboxylated to a product identical to (274). Further evidence for substitution at C-2 was given by the fact that the 2-methyl compound (133c) did not react with bromine in acetic acid, even at reflux temperature.

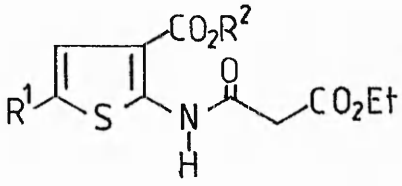
It has previously been noted that (134a) was decomposed by nitric acid in acetic acid. The related ester (133a) however, did give a nitration product under these conditions. By analogy with the results discussed above the nitro group was presumed to have entered at C-2 although this was not proved by chemical transformation. Attempts to hydrolyse (278) under basic conditions failed, highly coloured complex mixtures being produced. In recognition of the possibility that the change in the site of reaction from the pyridine ring under Mannich conditions to the thiophene ring upon bromination might be due to the reaction proceeding <u>via</u> the anion in the former case, (134a) was treated with pyridinium hydrobromide perbromide, and with bromine under basic conditions,

but in both cases the substrate was decomposed. The reactions just described are depicted in Scheme 78.



Scheme 78

Initially some difficulty was experienced in establishing the location of the bromine atom in the thiophene ring in (274). Attempts to prepare an authentic 2-bromo compound by a ring closure of the malonamide (279) failed at the cyclisation stage; various bases either induced decomposition or gave non-cyclised products. The related 5-nitrothiophene (280) behaved similarly. Thermolysis of the t-butyl ester (135) gave modest yields of the cyclised product (134a) (see Chapter 2) and it was hoped that (281) would do the same. However, bromination of (135) was accompanied by loss of the t-butyl group, forming the acid (282). This acid was decomposed on heating in diphenyl ether, in ethyl polyphosphate and alone under vacuum. A correlation was finally established between the monobrominated product of (134a) [(274)] and a compound in which the position of the derived group was certain was established by the reaction sequence outline in Scheme 79. Conversion of the bromo compound (283) into its lithio derivative followed by treatment with methyl iodide afforded material (285) identical to that derived from an authentic 2-methyl compound (134c).



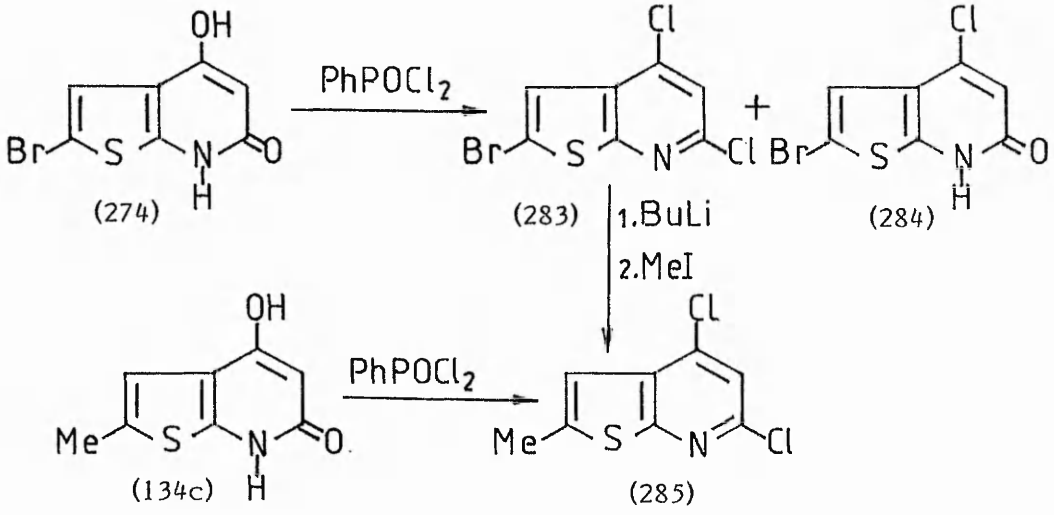
(282) R^1 = Br R^2 = H

(279) R^1 = Br R^2 = Et

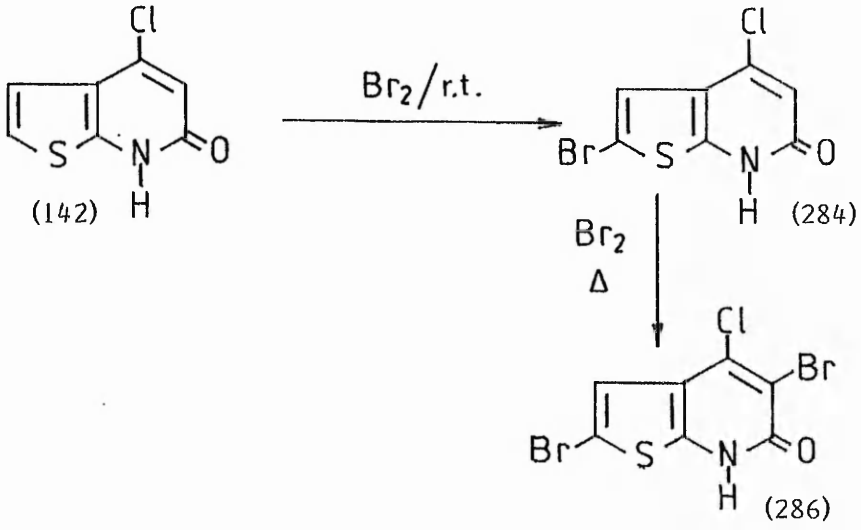
(280) R^1 = NO_2 R^2 = Et

(135) R^1 = H R^2 = Bu^t

(281) R^1 = Br R^2 = Bu^t

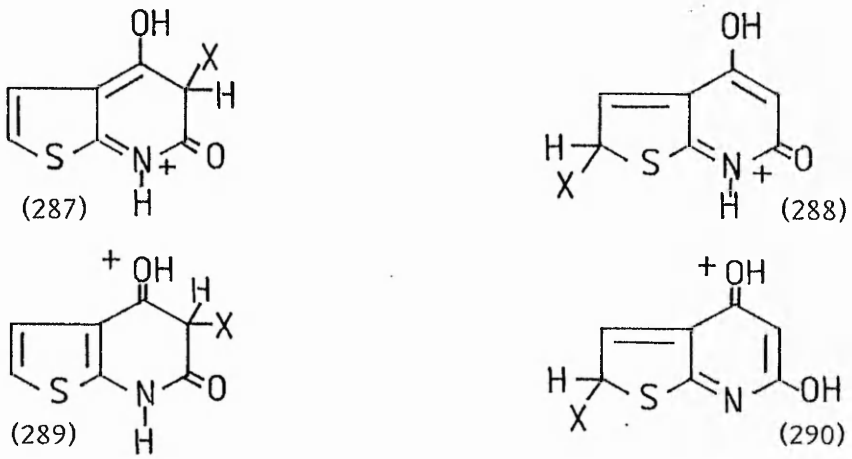


Replacement of the hydroxyl group in (134a) by chlorine [as in (142)] had no great effect on the pattern of behaviour. Monobromination (by bromine in acetic acid at room temperature) occurred at C-2 [giving (284), identical to the by-product formed in the chlorination of (274) (see Scheme 79)]. The selectivity of reaction in (142) appeared more pronounced than in (134a), no other product being observed under these conditions. The dibrominated product (286) was formed, however, when (284) was treated with bromine in acetic acid at reflux. (Scheme 80)



Scheme 80

The reactions just described may be explained in a manner similar to the other thienopyridines discussed. Thus the 6-pyridone function can activate positions C-2 and C-5 [structures (287) and (288)] and the 4-hydroxy function can activate C-5 (289). If a different tautomeric form is considered, activation by the 4-hydroxy group at C-2 can be postulated (290).



It has been observed that positions C-2 and C-5 in (134a) are of the same order of reactivity towards bromine, there being a preference for reaction at C-2. When the 4-hydroxy group is replaced by chlorine [as in (142)] the strong activating effect of the hydroxy group at C-5 is lost and the main directive influence is by the 6-pyridone function. Since (142) shows a marked preference for bromination at C-2 it is clear that this group tends to activate C-2 more than C-5.

5.3 Summary

The work just described reveals that several electrophilic substitution reactions are possible in both thieno[2,3-b] and [3,2-b]pyridines but that the site and degree of reactivity of analogous compounds are not always the same. The effect of substituents in the six-membered ring may be summarised by reference to Figure 9; a pyridine ring is regarded as an aza-substituent.

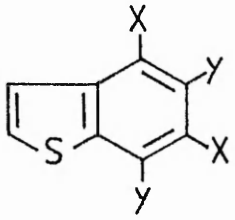


Figure 9

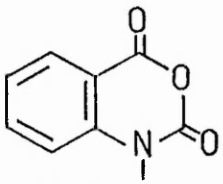
Substituents, either +M or -M at positions Y have no effect on the vacant sites in the thiophene ring. Substituents at positions X interact with C-2, +M substituents increasing the reactivity, -M substituents decreasing it.

CHAPTER SIX

ANALOGUES OF ISATOIC ANHYDRIDES AND 2-ARYL-4-QUINOLONE ALKALOIDS

ANALOGUES OF ISATOIC ANHYDRIDES AND 2-ARYL-4-QUINOLONE ALKALOIDS

Derivatives of isatoic anhydride (291) have found wide use in organic synthesis[202]; of particular relevance here is their use in the preparation of quinolone alkaloids.[130,139,203]

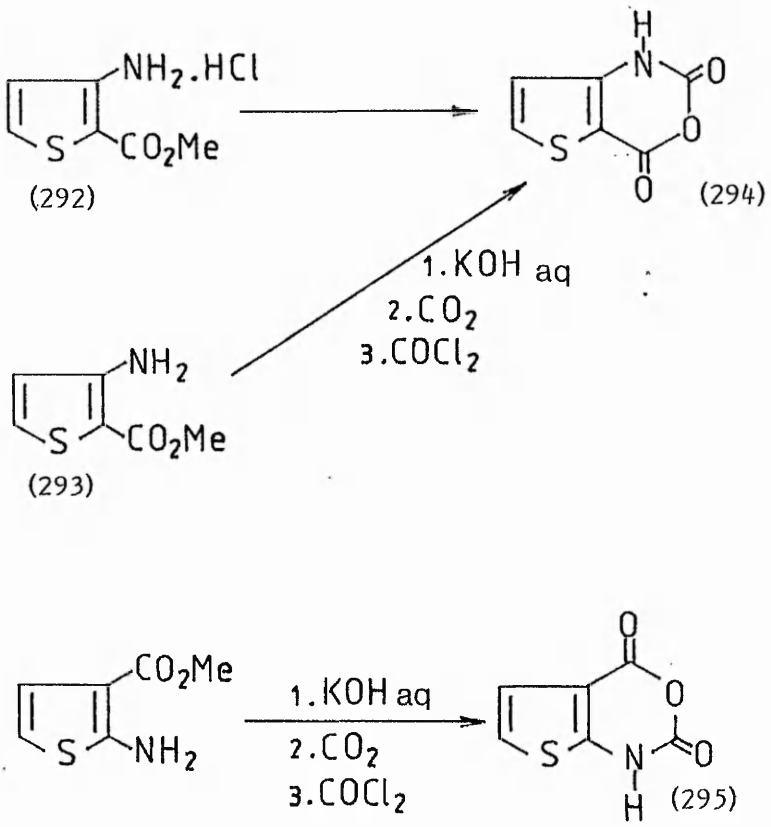


(291)

A few analogues of (291) in which the benzene ring has been replaced by pyridine[204-6], furan[207], and thiophene[208] have recently been reported. It was hoped that the use of thiophene analogues of (291) in procedures described in the literature for the preparation of quinoline alkaloids would be attractive routes for the preparation of the desired thienopyridines.

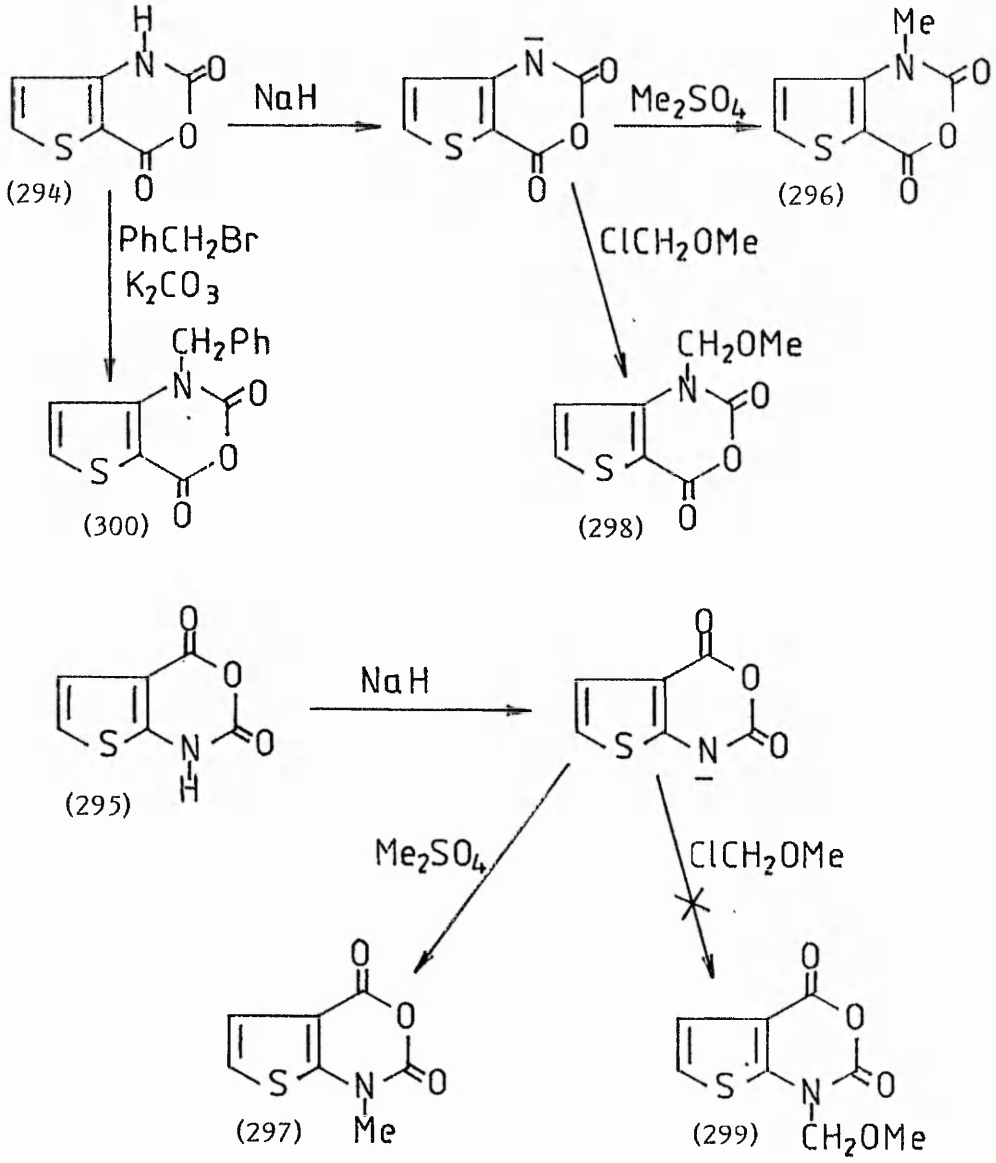
5H-Thieno[3,2-d][1,3](1H)oxazin-5,7(4H)-dione (294) has been prepared by reaction of the sodium salt of 3-aminothiophene-2-carboxylic acid (prepared in situ by hydrolysis of methyl 3-aminothiophene-2-carboxylate hydrochloride(292)) with gaseous phosgene.[208] Material required for the present work was prepared by a similar procedure. The ester (292) was hydrolysed by aqueous potassium hydroxide and the resulting alkaline solution was buffered by the addition of solid carbon dioxide. A solution of an excess of phosgene in toluene was added with vigorous stirring, yielding (294) which was collected by filtration, washed with water and dried. This crude material could be recrystallised from ethanol, ethyl acetate or acetic acid, the latter being the solvent of choice. Although (294) is decomposed by hot water, it appears to be stable to water at room temperature, and to storage in a sealed container.

The analogous compound (295), derived from methyl 2-aminothiophene-3-carboxylate was prepared in a similar manner; although no satisfactory recrystallisation solvent for (295) could be found material of analytical purity was produced by slurrying the crude product with ethanol. (Scheme 81)



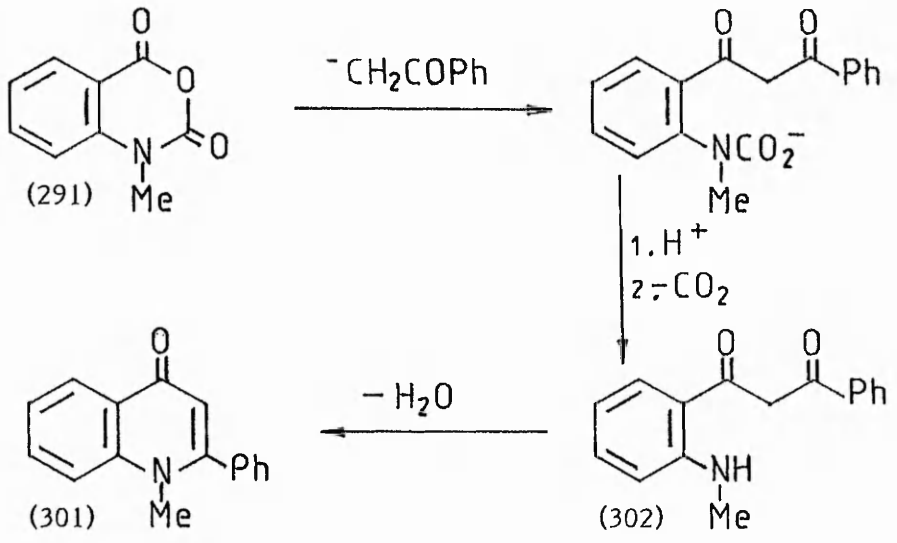
Scheme 81

N-Alkyl derivatives of isatoic anhydrides have been prepared by formation of the anion (usually by sodium hydride) followed by addition of a suitable alkylating agent[209], and this method was successfully applied to the thiophene analogues (294) and (295). Treatment of both (294) and (295) with sodium hydride in dimethylacetamide (DMA) furnished the respective anions; addition of dimethyl sulphate then yielded the N-methyl derivatives [(296) and (297)], respectively. Chloromethyl methyl ether with the anion of (294) afforded the N-methoxymethyl compound (298), however use of this reagent with the anion of (295) gave only high melting polymeric material, none of the desired (299) could be isolated. The N-benzyl compound (300) was prepared from (294) and benzyl bromide; in this case potassium carbonate was used as base. (Scheme 82)



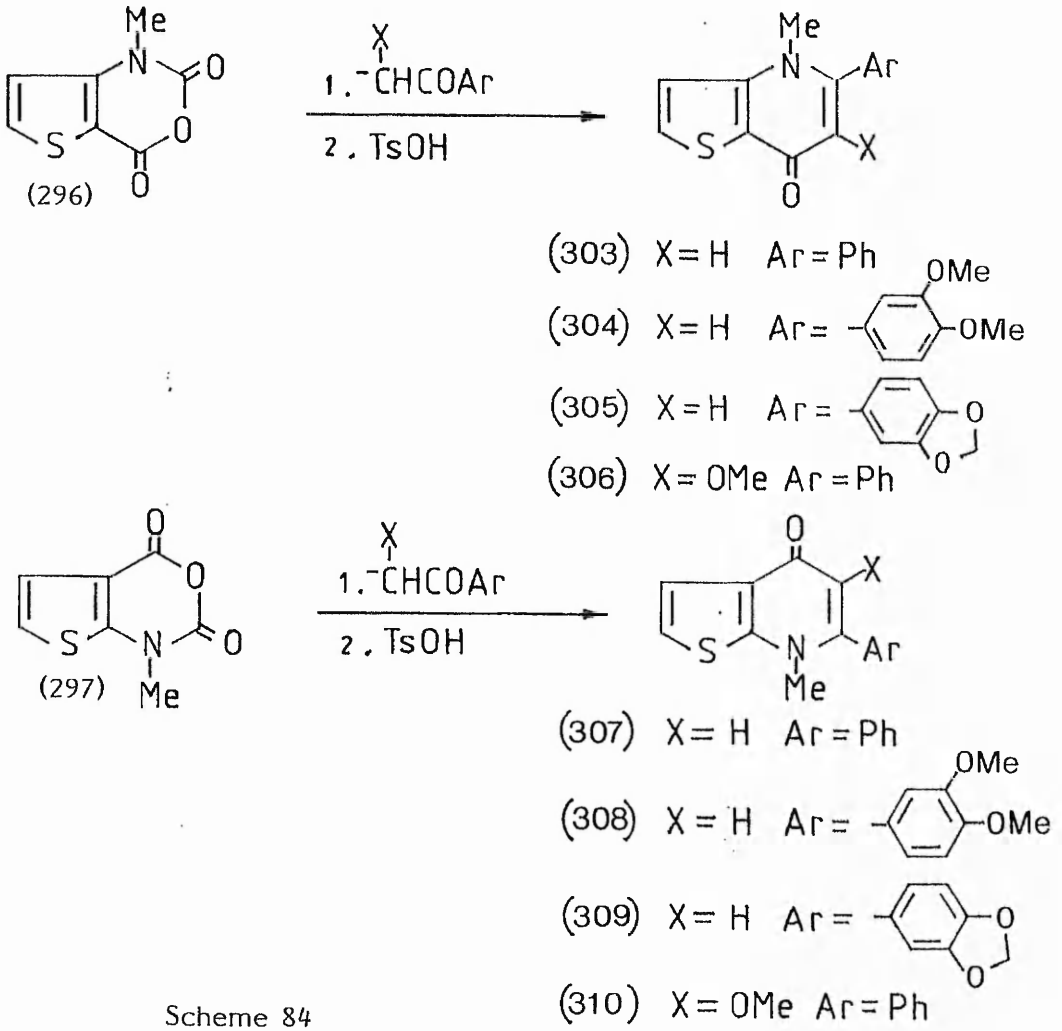
Scheme 82

The preparation of 2-aryl-4-quinolone alkaloids from N-methyl isatoic anhydrides and acetophenones has recently been reported.[139] The synthesis of 1-methyl-2-phenyl-4-quinolone (301) outlined in Scheme 83 is an example of such a preparation. Attack of the acetophenone enolate at the carbonyl group attached to the benzene ring yielded the o-aminoketone (302) which spontaneously cyclised to the desired quinolone.



Scheme 83

This procedure was applied to the synthesis of thieno[2,3-b]pyridines [from (297)] and thieno[3,2-b]pyridines [from (296)] by reaction with the enolate of the appropriate acetophenone (generated from the ketone and lithium diisopropylamide). Scheme 84 shows the various thienopyridines formed in this way; the yields in all cases were low, the [2,3-b] compounds being formed in particularly poor yield. The presence of the o-aminoketones in the crude reaction mixtures was evident by the yellow colours formed (typical of such compounds[130]). Cyclisation of these products did not proceed spontaneously (as in the quinoline series) but was achieved by heating the crude products in toluene containing a catalytic amount of p-toluenesulphonic acid (TsOH). When α-methoxyacetophenone was used [in attempts to prepare (306) and (310)] this procedure was ineffective and no cyclised products were formed.



Scheme 84

These thienopyridines are analogues of the quinoline alkaloids 1-methyl-2-phenyl-4-quinolone (301), graveoline (117), folimidine (311) and japonine (118), depicted in Figure 10. (See also Section 1.2.3)

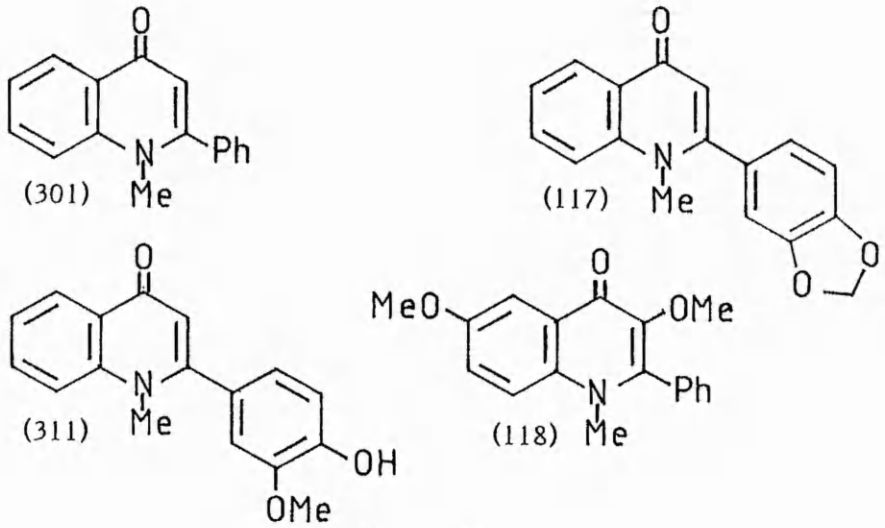
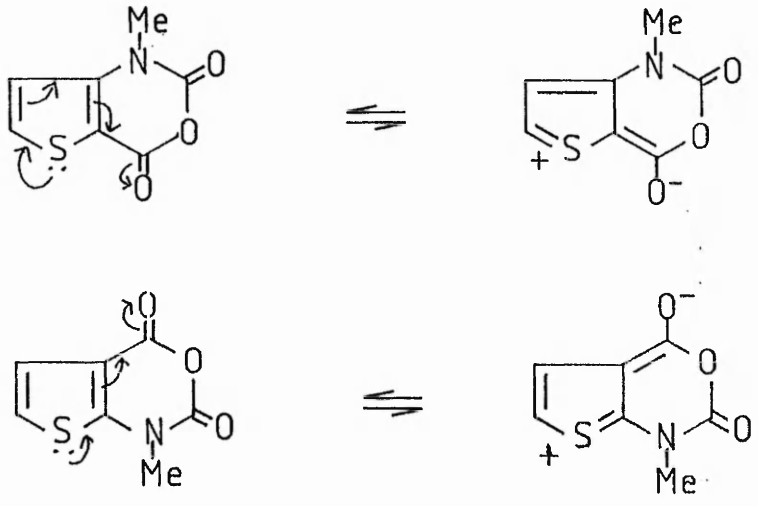


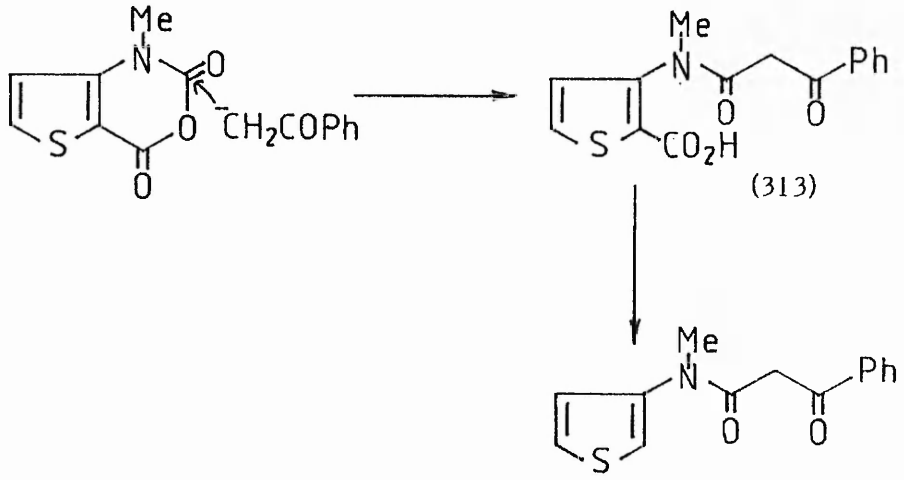
Figure 10

The low yields observed in the preparation of these thienopyridines may be due to attach by the anion at the amide carbonyl group instead of the carbonyl group attached to the thiophene ring. In both (296) and (297) electron release from the sulphur atom is possible, increasing the electron density at the thenoyl carbon thus lowering its reactivity towards nucleophiles. Indeed in the furan compound (312), where a similar possibility exists, reaction occurs solely at the amide carbonyl group.[207]



(312)

If reaction were to occur at the amide carbonyl group an acid, for example (313), which could not cyclise to a thienopyridine would be produced. Such an acid could decarboxylate and then undergo further transformations which may explain the presence of several unidentified products observed in the reaction mixtures. (Scheme 85)



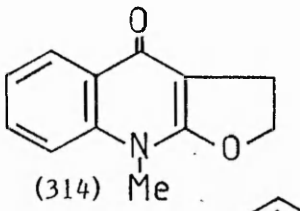
Scheme 85

CHAPTER SEVEN

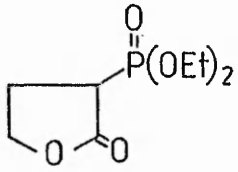
ATTEMPTS TO PREPARE LINEAR FUROTHIENOPYRIDINES

ATTEMPTS TO PREPARE LINEAR FUROTHIENOPYRIDINES

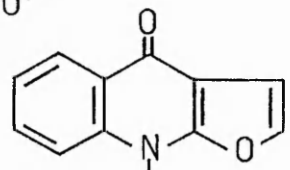
The final part of the work was concerned with attempts to prepare analogues of furoquinoline alkaloids. It was decided to attempt to adapt syntheses of furoquinolines that have been described in the literature to the production of furothienopyridines. A recent report[210] describes the preparation of the dihydrofuroquinoline (314) by reaction of N-methylisatoic anhydride with the lactone (315). Dehydrogenation of (314) should be possible, giving the alkaloid isodictamnine (123).



(314)

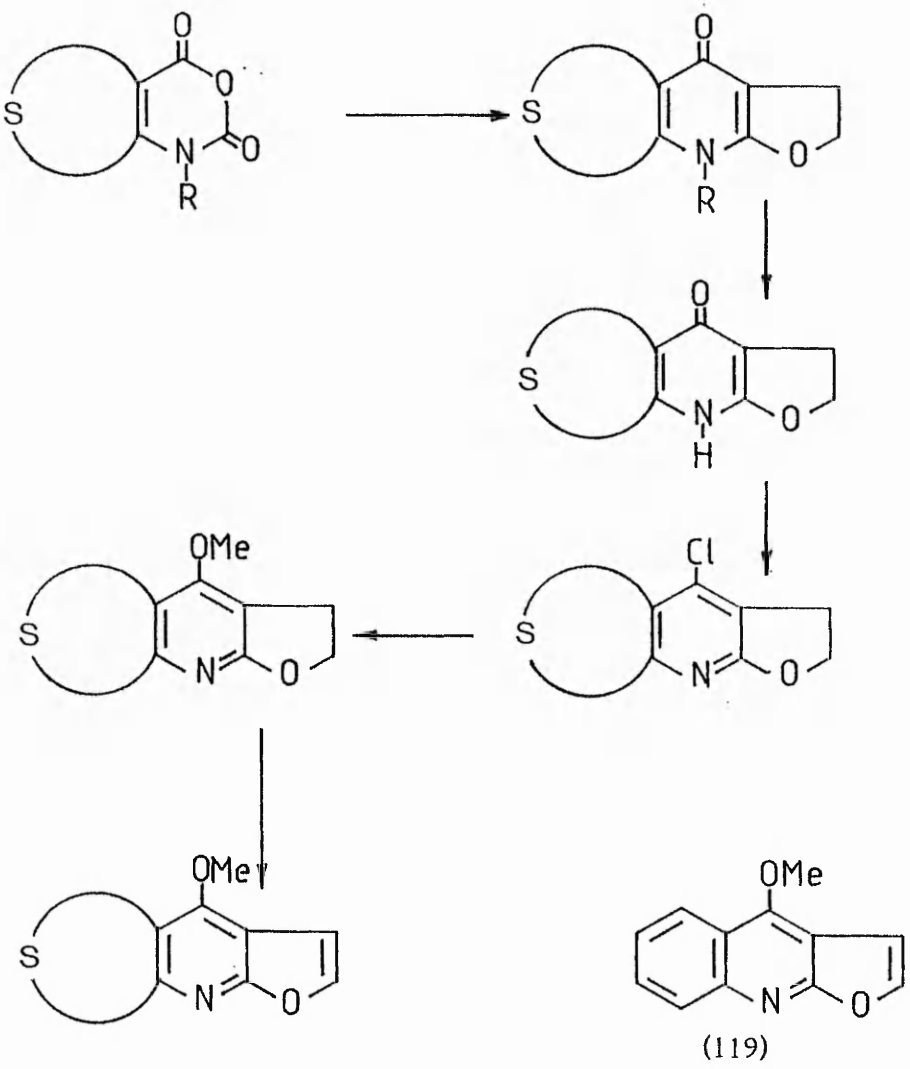


(315)



(123)

It was hoped that the preparation of thienopyridine analogues of isodictamnine could be achieved by applying this procedure to the thiophene analogues of isatoic anhydride [(296) and (297)], described in Chapter Six. Also, by choice of a suitable protecting group, the application of this reaction to the preparation of analogues of dictamnine (119) in the manner outlined in Scheme 86 was considered.

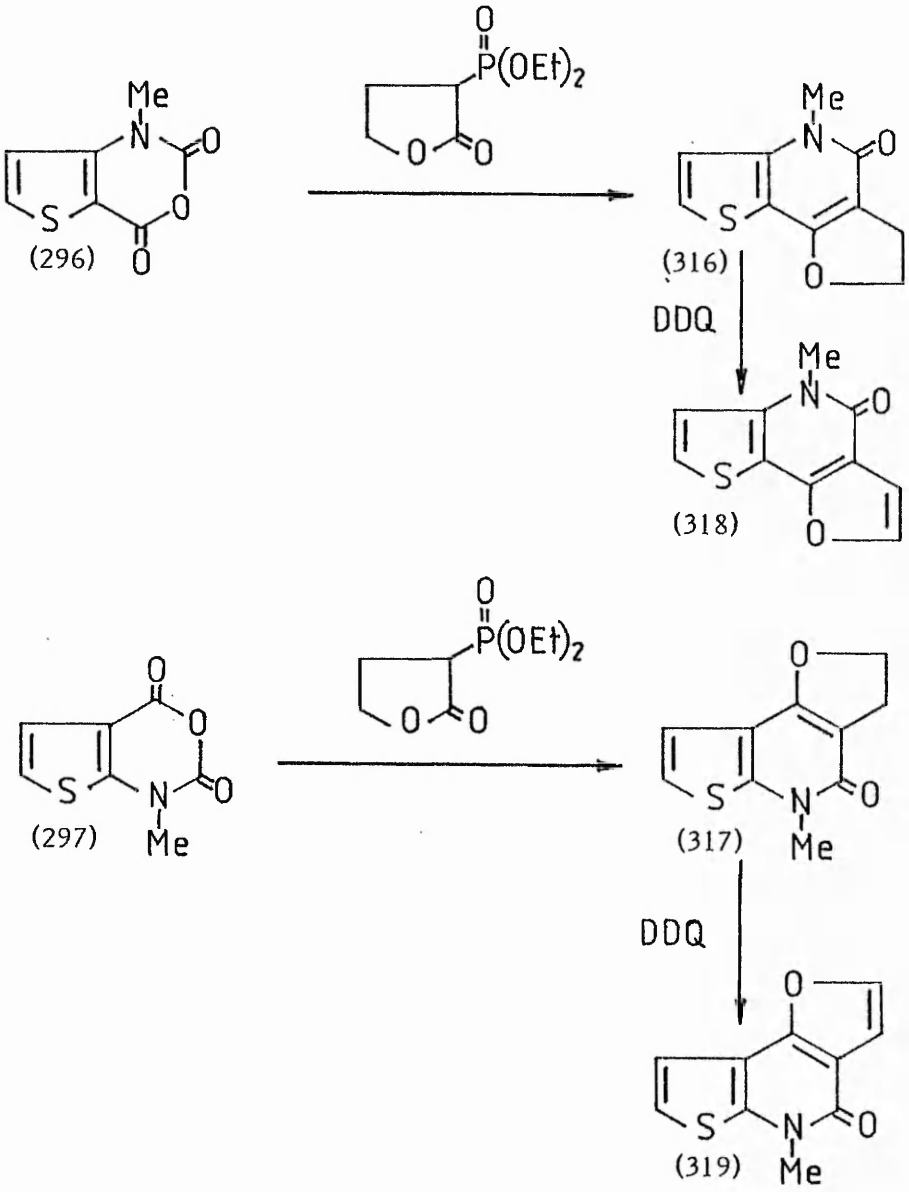


(119)

Scheme 86

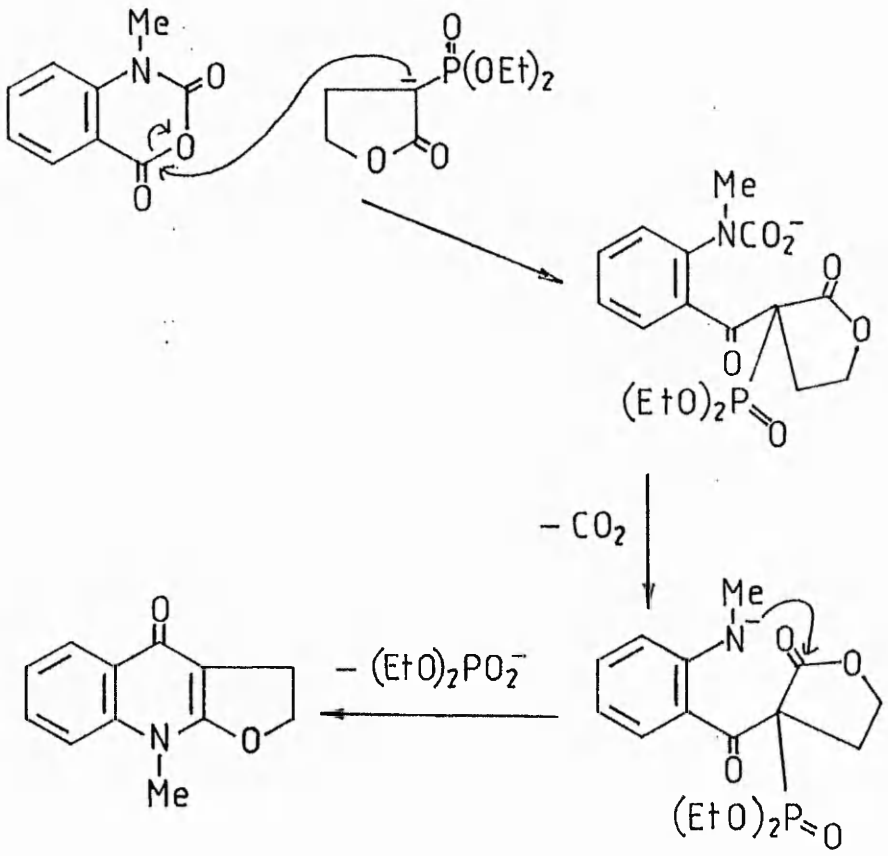
However, when the thiophene compounds [(296) and (297)] were used, the products were different from those reported for the quinoline (314). Dihydrofurothienopyridones were produced; each was then dehydrogenated by boiling under reflux with an excess of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in 1,4-dioxan. Inspection of the ^{13}C n.m.r. and i.r. spectra of these furothienopyridines suggested that they had the angular mode of fusion rather than the expected linear structures, ie were (316) - (319). The carbonyl peaks in the i.r. spectra were located in the region 1650 - 1640cm^{-1} which is more characteristic of a 2-quinolone than a 4-quinolone[126] (in 4-quinolones the carbonyl peak is generally found in the region 1620 - 1610cm^{-1}). The signals for the carbonyl carbon atoms in the ^{13}C n.m.r. spectra were found in the

region 159 - 162ppm, which is again characteristic of 2-quinolones rather than 4-quinolones.[211] In 4-quinolones the signal due to the carbonyl carbon is found at ≏ 175ppm, but in none of the present cases was a signal in this region observed. The syntheses of these angular tricycles are presented in Scheme 87.



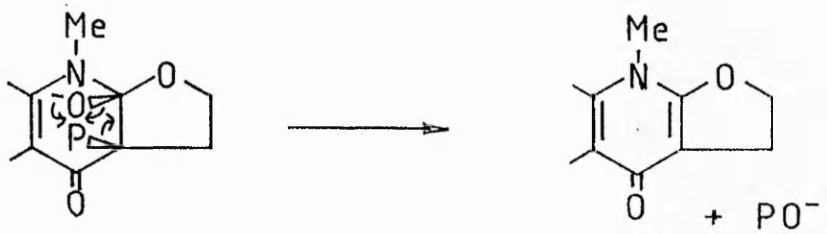
Scheme 87

In view of the unexpected nature of results it was decided to investigate the linear furoquinoline reported in the literature.[210] In the author's hands the reaction of N-methylisatoic anhydride with (315) gave a complex mixture, and no furoquinoline could be isolated. However the carbonyl peak in the i.r. spectrum reported by the previous workers (1660cm^{-1}) suggests that the compound isolated was, in fact, the angular tricycle. The mechanism outlined in Scheme 88 was proposed for the formation of the linear system.



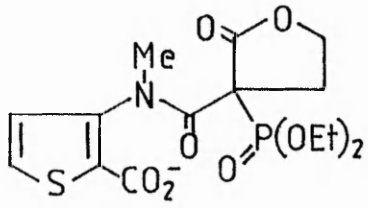
Scheme 88

Evidently it is assumed that elimination of the phosphorus group occurs via a 4-membered transition state (as depicted in Equation 39). Such eliminations are well known in, for example, the Wittig reaction.

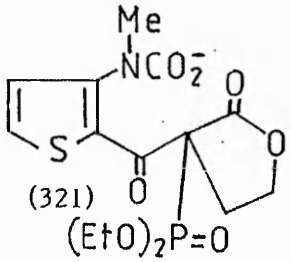


Equation 39

The way in which angular compounds are formed is not particularly obvious, a number of mechanisms being possible. One possibility is attack of the anion at the amide carbonyl group. However, this is not likely under the reaction conditions since it would involve elimination of carbon dioxide from a carboxylate group attached to an aromatic ring [as in (320)], rather than to a nitrogen atom [as in (321)].

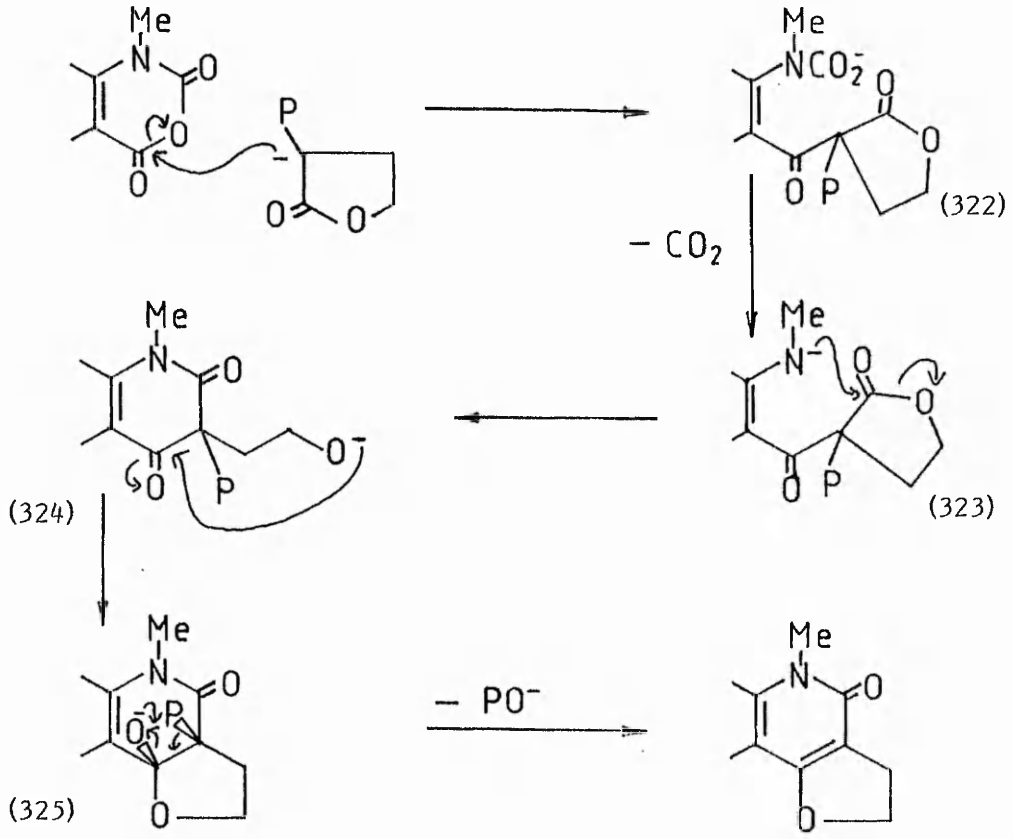


(320)



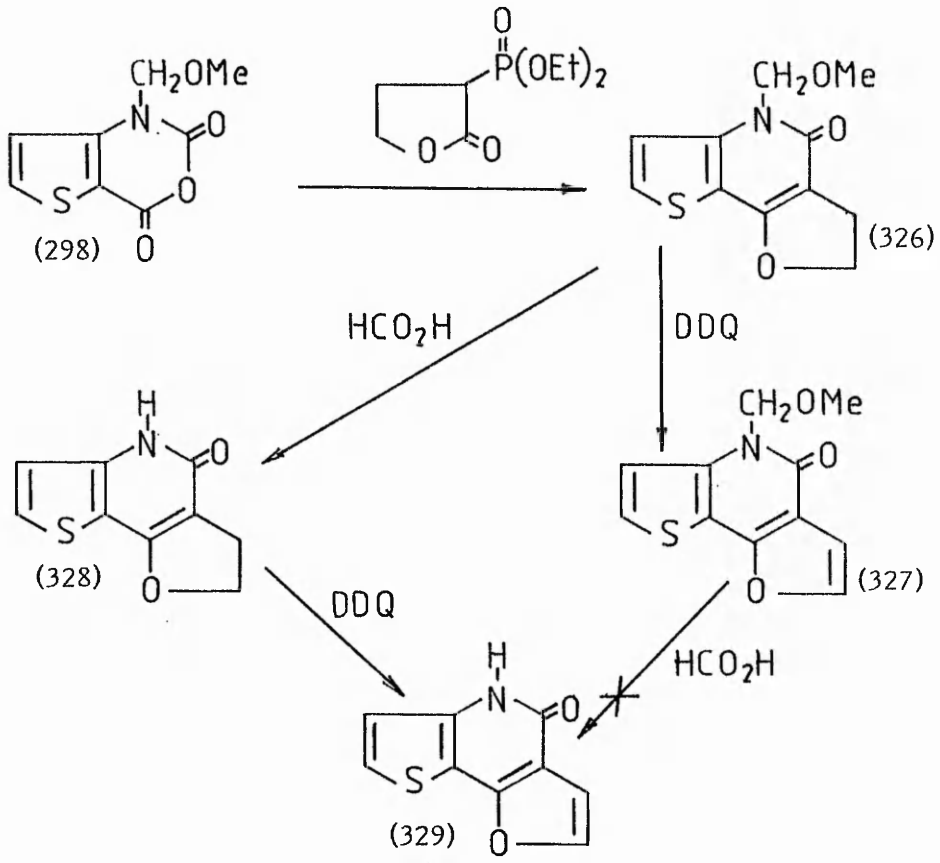
(321)

Given that the attack is most likely to occur at the aroyl carbon atom, an alternative route to the angular system is isomerisation of the linear compound, but again, at the temperature used in this reaction (110 - 120°) this is unlikely. An alternative mechanism which also involves initial attack at the aroyl carbonyl group is outlined in Scheme 89. The first intermediate (322) decarboxylates to give (323); attack of the nitrogen atom at the lactone carbonyl group then results in ring opening, leading to (324). The latter then cyclises to (325), which loses the phosphorus group, via a 4-membered transition state, to form the angular compound.



Scheme 89

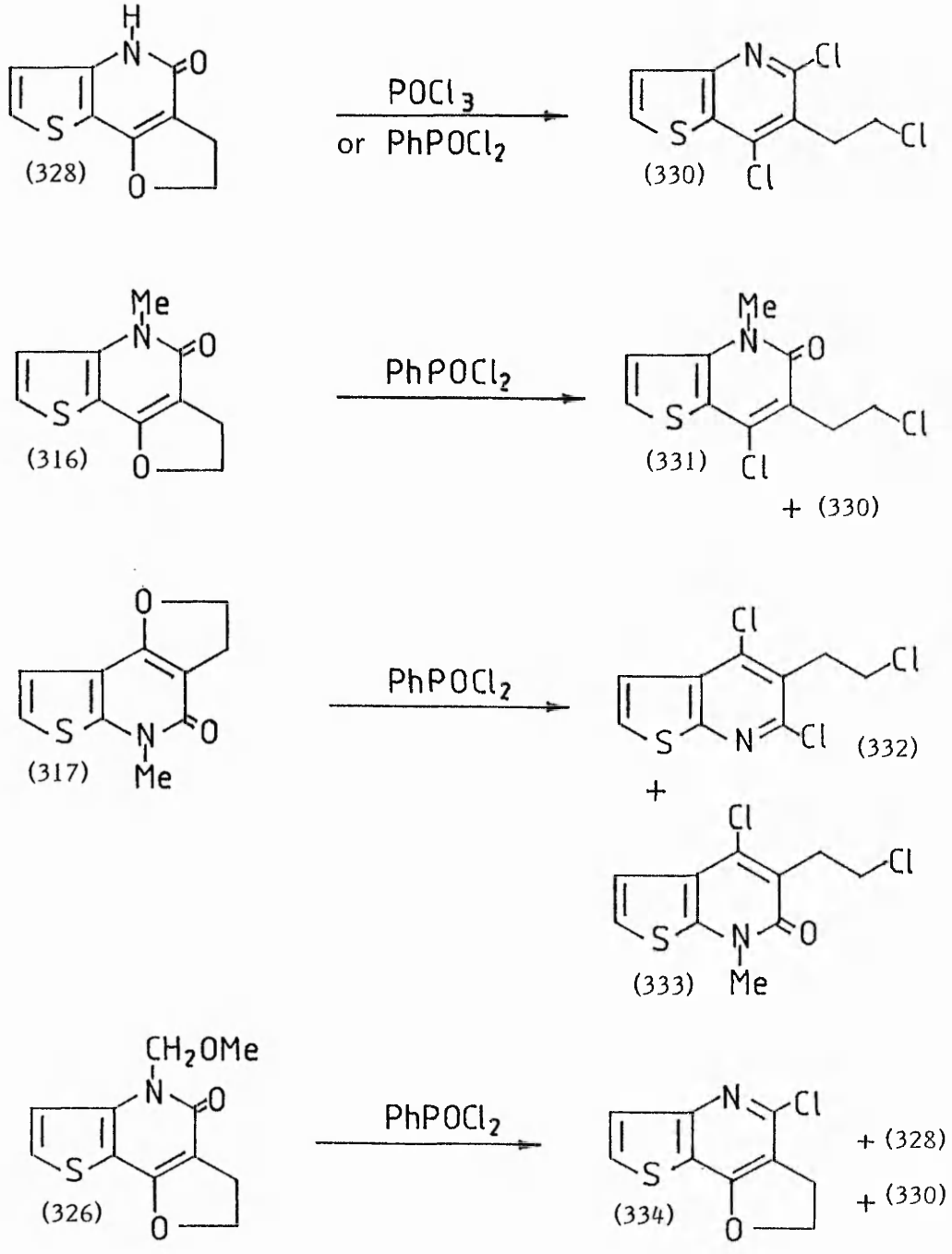
Although the hoped-for linear furothienopyridines were not obtained from the thiophene isatoic anhydride analogues, a further study of the latter and the angular furothienopyridines derived from them was made. Firstly the use of methoxymethyl as a protecting group was investigated. It was found that from (298) an angular furothienopyridine (326) was again formed; this was dehydrogenated by DDQ to (327). Deprotection proved to be more difficult than expected, the reagents previously described[212] for the removal of the methoxymethyl group being ineffective; eventually it was found that boiling (326) in formic acid resulted in deprotection, affording (328). However, this reagent was ineffective with (327), the product being high melting, highly insoluble material which was not identified. Treatment of (328) with DDQ, however, afforded the desired deprotected material (329). (Scheme 90)



Scheme 90

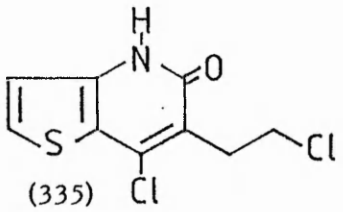
Next, a study of the reaction of the tricycles with chlorinating agents was undertaken. Reaction of the -NH compound (328) with phosphoryl chloride was slow, but the trichloro compound (330) was eventually formed; (330) was also formed, more rapidly, from (328) and phenyl phosphonic dichloride. When the N-methyl compound (316) was heated with phenyl phosphonic dichloride two products were formed; one was the previously described (330), the other was the N-methylthieno[3,2-b]pyridine-5-one (331). Reaction of this chlorinating

with the isomeric N-methyfurothieno[2,3-b]pyridine (317) gave a similar result, the products being (332) and (333). When the N-methyxymethyl derivative (326) was boiled under reflux with phosphoryl chloride a mixture was obtained. The major product was deprotected material (328). Some trichloro compound (330) and a third product, identified as the furan (334), were also isolated. An attempt to dechlorinate (334) using zinc in acetic acid failed, a complex mixture being formed. These reactions are presented in Scheme 91.

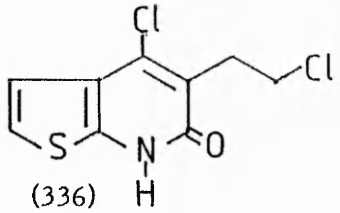


Scheme 91

The isolation of trichloro compounds [(330) and (332)] suggested that it might be possible to prepare the desired linear furothienopyridines by the method described by Grundon and McCorkindale[143] (presented in Section 1.2.4, Scheme 50). The next step in this scheme would involve acid hydrolysis of (330) and (332), yielding (335) and (336), respectively. However, when (330) and (332) were subjected to the conditions described[143] for this transformation, no reaction occurred.



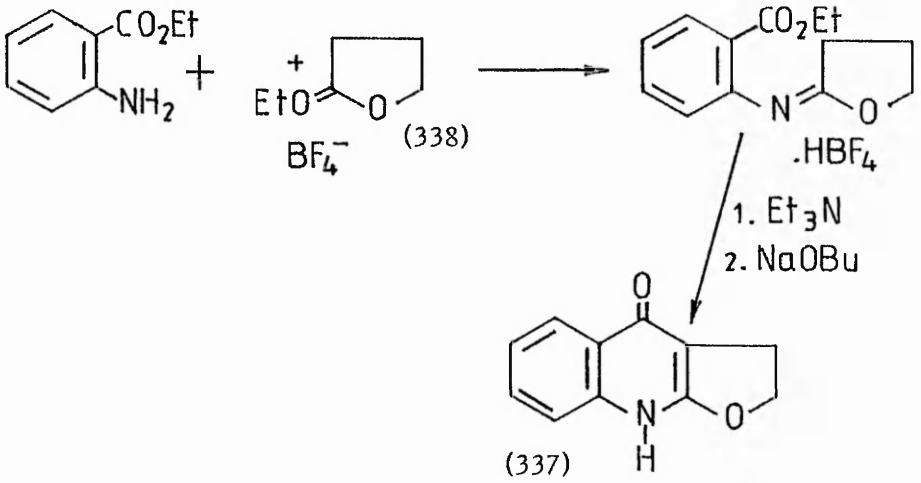
(335)



(336)

In view of the lack of success with this approach, other potential routes to linear furothienopyridines were investigated.

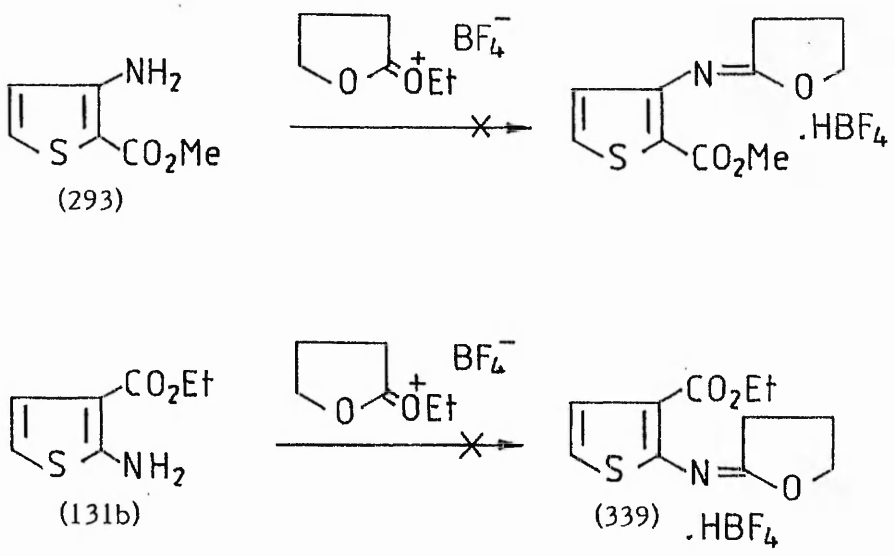
Russian workers[213] have described the preparation of the dihydro compound (337) in the manner outlined in Scheme 92.



(337)

Scheme 92

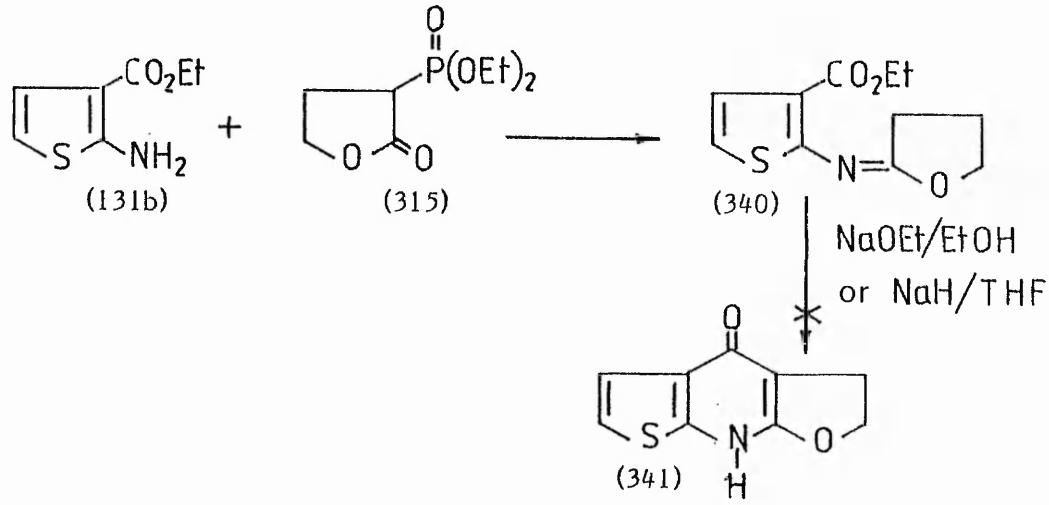
This sequence was applied to the aminothiophenes (293) and (131b). No reaction of the desired kind occurred between (293) and the oxonium salt (338); only the hexafluoroborate salt of (293) was isolated. When ethyl 2-amino-thiophene-3-carboxylate (131b) was used a brown tarry material was formed from which the desired (339) could not be isolated. (Scheme 93)



Scheme 93

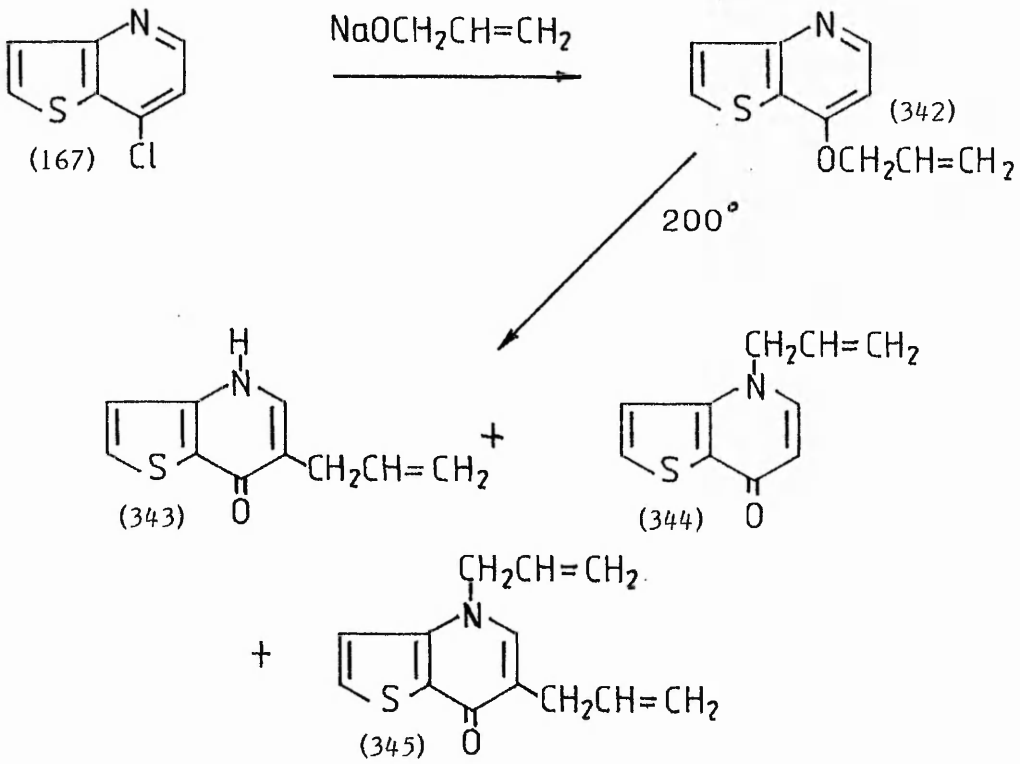
Reaction of the amines [(293) and (131b)] with the phosphorylated lactone (315) was then investigated. Under the conditions successful for the anhydrides [(296) and (297)] methyl 3-aminothiophene-2-carboxylate (293) gave a complex mixture.

Ethyl 2-aminothiophene-3-carboxylate (131b), on the other hand, gave an oil having spectroscopic properties compatible with the desired (340). Attempts to cyclise this material using sodium ethoxide in ethanol or sodium hydride in tetrahydrofuran were unsuccessful, in both cases decomposition occurred and none of the cyclised product (341) could be isolated. (Scheme 94)



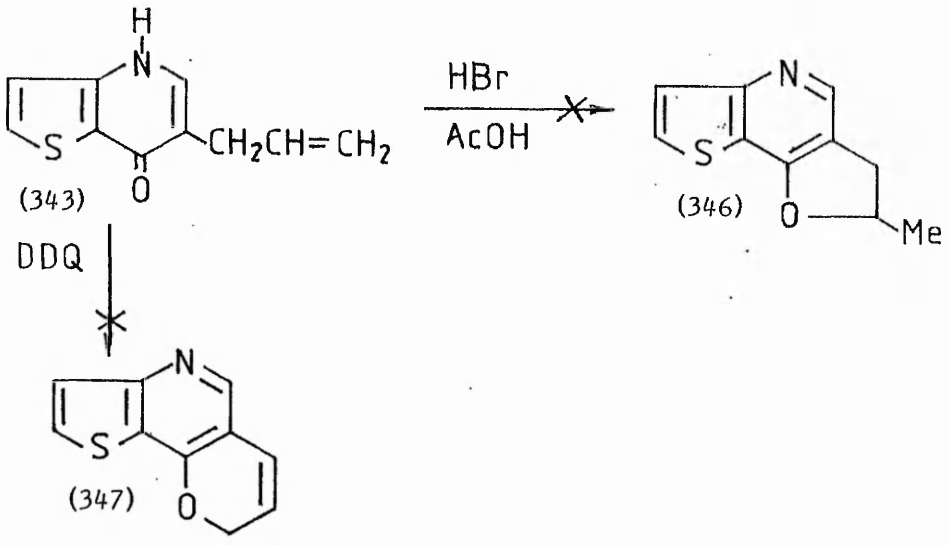
Scheme 94

In the final part of the work the use of the Claisen rearrangement as a route to furothienopyridines was investigated. 7-Chlorothieno[3,2-b]pyridine (167) reacted with the sodium salt of allyl alcohol to yield the 7-allyloxy derivative (342). When (342) was heated alone at 200° (successful for the corresponding quinoline[214]) a mixture of products was formed, the major being identified as the 6-allyl compound (343). The two minor components were identified as the 4-allyl compound (344) and the 4,6-bisallyl derivative (345). The isolation of the latter product suggests that the reaction is not totally intramolecular and that some intermolecular reaction takes place. (Scheme 95)



Scheme 95

A few attempts to cyclise the 6-allyl compound (343) were made. Standing (343) in a solution of hydrogen bromide in acetic acid gave a mixture of several components, the major being unreacted starting material; none of the desired furan (346) could isolated. An attempt to perform an oxidative ring closure by use of DDQ [giving (347)] resulted in decomposition and a complex mixture was produced. (Scheme 96)



Scheme 96

Due to lack of time it was not possible to continue these studies but it was shown that the Claisen rearrangement is possible in thienopyridines.

CHAPTER EIGHT

EXPERIMENTAL

EXPERIMENTAL

I.r. spectra were for KBr discs unless otherwise stated and were recorded on a Perkin Elmer 157G spectrometer. For n.m.r. spectra the internal standard was tetramethylsilane; ^{13}C spectra were recorded (with proton decoupling) on a JEOL FX60Q instrument, and ^{1}H on a Hitachi Perkin Elmer R-24B. Melting points were uncorrected. Ether and dichloromethane solutions were dried over $MgSO_4$ and were evaporated under reduced pressure. The stationary phase for flash-column chromatography was Merck Kieselgel 60, 230-400 mesh. Light petroleum, unless otherwise stated, refers to the fraction b.p. 40-60° and nitric acid to the concentrated acid of density 1.42. The zinc used for reductive dechlorinations was first activated with 10% hydrochloric acid, as described by Vogel.[215] The ^{13}C n.m.r. spectra of the compounds prepared in this work (apart from those discussed in more detail in Chapter 4) are presented in Tables 10-13 at the end of the Experimental Section.

8.1 Work Described in Chapter Two

2-Methoxycarbonyl-N-(3-methoxycarbonyl-2-thienyl)acetamide (132a)-

Methyl 2-aminothiophene-3-carboxylate (25g) and dimethyl malonate (100ml) were boiled together under reflux beneath an air condenser for 2h. The excess of dimethyl malonate was removed under vacuum, and the residue (which solidified upon cooling) was recrystallised twice from methylated spirits to provide the title amide (27.9g, 68%), m.p. 113-5° (Found: C, 46.9; H, 4.4; N, 5.3. $C_{10}H_{11}NO_5S$ requires C, 46.7; H, 4.3; N, 5.5%), δ ($CDCl_3$) 7.15 (1H, d, J=6Hz, 5-H), 6.20 (1H, d, J=6Hz, 4-H), 3.89 (3H, s, $CH_2CO_2\underline{Me}$), 3.81 (3H, s, $ArCO_2\underline{Me}$), and 3.60 (2H, s, $COC\underline{H}_2CO$), ν_{max} 3200, 1740, 1700, 1660, and 1550cm^{-1}.

2-Ethoxycarbonyl-N-(3-ethoxycarbonyl-2-thienyl)acetamide (132b) and the Bisamide (138) -

Ethyl 2-aminothiophene-3-carboxylate (240g) and diethyl malonate (1 1) were boiled together under reflux beneath an air condenser for 2h. The excess of diethyl malonate was removed under vacuum, and the residue was repeatedly extracted with boiling light petroleum. A small quantity of insoluble material was crystallised from DMF-methanol to give N,N'-bis-(3-ethoxycarbonyl-2-thienyl)propan-1,3-diamide (138) (12.1g, 4%), m.p. 162-164° (Found: C, 49.6; H, 4.4; N, 6.5. $C_{17}H_{18}N_2O_6S_2$ requires C, 49.8; H, 4.4; N, 6.8%), δ ($[CD_3]_2SO$) 7.24 (2H, d, J=6Hz, thiophene5-H), 7.05 (2H, d, J=6Hz, thiophene4-H), 4.37 (4H, q, J=7Hz, $OC\underline{H}_2$), 4.19 (2H, s, $COCH_2CO$), and 1.39 (6H, t, J=7Hz, $C\underline{H}_3$), ν_{max} 3140-3260, 1670, and 1540 cm^{-1}. Evaporation of the combined light petroleum extracts gave the title amide (273g, 68%), pure enough for use in the next stage. A portion was crystallised from ether-light petroleum and had

m.p. 58-59° (Found: C, 50.5; H, 5.3; N, 4.4. $C_{12}H_{15}NO_5S$ requires C, 50.5; H, 5.3; N, 4.9%), δ ($CDCl_3$) 7.23 (1H, d, J=6Hz, 5-H), 6.74 (1H, d, J=6Hz, 4-H), 4.11-4.56 (4H, m, 2xCH_2CH_3), 3.59 (2H, s, $COCH_2CO$), and 1.19-1.47 (6H, m, 2xCH_2CH_3), ν_{max} 3210, 1720, 1680, and 1550 cm^{-1}.

2-Ethoxycarbonyl-N-(3-ethoxycarbonyl-5-ethyl-2-thienyl)acetamide (132c) -

This was prepared as described above for (132b), from 2-amino-3-ethoxycarbonyl-5-ethylthiophene (50g) and diethyl malonate (250ml). Cooling of the light petroleum extracts in a dry ice/acetone bath afforded the pure amide (48g, 61%) as an off-white solid, m.p. 35-7° (Found: C, 53.7; H, 6.1; N, 4.3. $C_{14}H_{19}NO_5S$ requires C, 53.7; H, 6.1; N, 4.5%), δ ($CDCl_3$) 6.81 (1H, s, 4-H), 4.23 (4H, m, 2x$CO_2CH_2CH_3$), 3.50 (2H, s, $COCH_2CO$), 2.69 (2H, q, J=7Hz, $ArCH_2CH_3$), and 1.31 (9H, m, 3xCH_2CH_3), ν_{max} 3400, 1730, 1670, and 1560 cm^{-1}.

2-Ethoxycarbonyl-N-(3-ethoxycarbonyl-5-methyl-2-thienyl)acetamide (132d) -

This was obtained in the manner described for (132b) from 2-amino-3-ethoxycarbonyl-5-methylthiophene (100g) and diethyl malonate (400ml). The crude amide (128g, 79%) thus prepared had m.p. 40-44°C. The analytical sample was purified by flash-column chromatography, using ethyl acetate (1 part) - light petroleum (9 parts) as eluent, and had m.p. 46-8° (Found: C, 52.3; H, 5.8; N, 4.3. $C_{13}H_{17}NO_5S$ requires C, 52.2; H, 5.7; N, 4.7%), δ ($CDCl_3$) 6.96 (1H, q, J=2Hz, H-4), 4.36 (4H, m, 2x$CO_2CH_2CH_3$), 3.55 (2H, s, $COCH_2CO$), 2.35 (3H, d, J=2Hz, Ar-Me), and 1.35 (6H, m, 2xCH_2CH_3), ν_{max} 3280, 1740, 1680, 1570, and 1540 cm^{-1}.

5-Ethoxycarbonyl-4-hydroxythieno[2,3-b]pyridin-6(7H)-one (133a) -

The amide (132b) (51.1g, 0.179mol) in THF (200ml) was added to a stirred suspension of sodium hydride (8.6g, 0.358mol) in THF (400ml) over a period of 15 minutes. The mixture was then boiled under reflux, with stirring, for 3 h, then cooled and treated cautiously with ethanol (10ml); stirring was continued for a further 30 minutes. Evaporation of the solvent left a solid, which was dissolved in water; acidification (concentrated hydrochloric acid) yielded a precipitate. The washed (water) and dried precipitate was crystallised from methylated spirits to provide the title thieno[2,3-b]pyridin-6(7H)-one (133a) (31.5g, 73%) as a white solid, m.p. 218-221° (Found: C, 50.1; H, 3.7; N, 5.7. $C_{10}H_9NO_4S$ requires C, 50.2; H, 3.8; N, 509%), δ ($[CD_3]_2SO$) 7.24 (2H, s, 2-H and 3-H), 4.35 (2H, q, J=7Hz, CH_2), and 1.31 (3H, t, J=7Hz, CH_3), ν_{max} 2500-3100 and 1640 cm^{-1}. The yields in this cyclisation were variable; in three other runs 42, 48, and 64% were obtained.

5-Ethoxycarbonyl-2-ethyl-4-hydroxythieno[2,3-b]pyridin-6(7H)-one (133b) -

This was prepared from the amide (132c) (12.5g, 0.04mol) and sodium hydride (1.9g, 0.08mol) in the manner just described for (133a). The crude product was recrystallised from ethyl acetate giving the thieno[2,3-b]pyridine (133b) (3.6g, 31%) as its hydrate having m.p. 196° (decomp.) (Found: C, 50.1; H, 5.3; N, 5.2. $C_{12}H_{13}NO_4S$. H_2O requires C, 50.5; H, 5.3; N, 4.9%), δ ($[CD_3]_2SO$) 7.03 (1H, s, 3-H), 4.29 (2H,q, J=7Hz, $CO_2CH_2CH_3$), 2.82 (2H, q, J=7Hz, $ArCH_2CH_3$), and 1.33 (6H, m, $2xCH_2CH_3$), ν_{max} 3000-2500, 1640 cm^{-1}.

5-Ethoxycarbonyl-4-hydroxy-2-methylthieno[2,3-b]pyridin-6(7H)-one (133c) -

This was obtained from the amide (132d) (15.0g, 0.05mol) and sodium hydride (2.4g, 0.1mol) as described for (132a). After recrystallisation from methylated spirits the thieno[3,2-b]pyridin-6(7H)-one (133c) (3.0g, 24%) had m.p. 218° (decomp.) (Found: C, 52.5; H, 4.2; N, 5.0. $C_{11}H_{11}NO_4S$ requires C, 52.2; H, 4.4; N, 5.5%), δ ($[CD_3]_2SO$) 6.87 (1H, q, J=1.2Hz, 3-H), 4.30 (2H, q, J=7Hz, $CO_2CH_2CH_3$), 2.38 (3H, d, J=1.2Hz, Ar-Me), and 1.28 (3H, t, J=7Hz, $CO_2CH_2CH_3$), ν_{max} 3000-2500, and 1650 cm^{-1}.

Attempted cyclisation of 2-Methoxycarbonyl-N-(3-methoxycarbonyl-2-thienyl)-acetamide (132a) -

The bis-methyl ester (132a) (2.57g, 0.01mol) was treated with sodium hydride (0.48g, 0.02mol) in the usual manner. However, acidification of the aqueous solution gave a brown gum which was shown by t.l.c. to consist of several components, none of whose Rf corresponded to that expected for the required thieno[2,3-b]pyridine.

2-Ethoxycarbonyl-N-(3-t-butoxycarbonyl-2-thienyl)acetamide (135) -

When t-butyl 2-amino-3-carboxylate (thiophene) and diethyl malonate were boiled together for 15 minutes a mixture of products was formed, the title amide being obtained in low yield. In a much improved synthesis the thiophene amino ester (30g) and diethyl malonate (120ml) were dissolved in toluene (600ml) and the whole was boiled under reflux in a Dean and Stark apparatus for 3h. Periodically the distillate was removed and an equal volume of fresh toluene added to the reaction mixture. The excess of diethyl malonate and the toluene were removed in vacuo. and the solid residue was crystallised from ether - light petroleum (with a final chilling in an ice - salt mixture) to give the amide (135) (34g, 72%), m.p. 63-65°. The analytical sample had m.p. 65-67° (from light petroleum) (Found: C, 54.2; H, 6.3; N, 4.6. $C_{14}H_{19}N=_5S$ requires C, 53.7; H, 6.1; N, 4.5%), δ ($CDCl_3$) 7.21 (1H, d, J=6Hz, 5-H), 6.76 (1H, d, J=6Hz, 4-H), 4.31 (2H, q, J=7Hz, OCH_2CH_3), 3.63 (2H, s, $COCH_2CO$), 1.59 (9H, s, $C(CH_3)_3$), and 1.32 (3H, t, J=7Hz, OCH_2CH_3), ν_{max} 3200, 1730, 1690, 1670, and 1550 cm^{-1}.

4-Hydroxythieno[2,3-b]pyridin-6(7H)-one (134a) -

a. **From ethyl ester (133a)** - The ester (46.2g) was boiled under reflux for 2h with an excess of 2M-sodium hydroxide. The precipitate obtained on acidification (concentrated hydrochloric acid) of the solution was filtered off, washed with water, and dried, to give 4-hydroxythieno[2,3-b]pyridin-6(7H)-one (134a) (30.2g, 93%), m.p. 317-320°. The analytical sample (from glacial acetic acid) had m.p. 320-322° (Found: C, 49.8; H, 3.0; N, 8.1. $C_7H_5NO_2S$ requires C, 50.3; H, 3.0; N, 8.4%), δ ($CDCl_3$-$(CD_3)_2SO$) 7.15 (1H, d, J=6Hz, 2-H), 7.02 (1H, d, J=6Hz, 3-H), and 5.68 (1H, s, 5-H), ν_{max} 2000-3500, 3370, 1690, 1610, and 1560 cm^{-1}.

b. **From the t-butyl ester (135)** - The ester (1g) was added to boiling diphenyl ether (10ml); after 10 minutes the solution was cooled and diluted with light petroleum (10ml). The solid was filtered off and recrystallised from glacial acetic acid, when it had m.p. 322-325°, undepressed on admixture with material prepared from (133a) (yield 0.35g, 66%).

2-Ethyl-4-hydroxythieno[2,3-b]pyridin-6(7H)-one (134b) -

This was prepared from the ester (133b) (1.34g, 0.005mol) in the manner described for (134a). The thieno[2,3-b]pyridin-6(7H)-one (134b) (0.71g, 71%) was recrystallised from glacial acetic acid to give the analytical sample having m.p. >300° (Found: C, 55.2; H, 4.6; N,7.1. $C_9H_9NO_2S$ requires C, 55.4; H, 4.6; N, 7.2%), δ ($[CD_3]_2SO$) 6.92 (1H, s, 3-H), 5.78 (1H, s, 5-H), 2.80 (2H, q, J=7Hz, $C\underline{H}_2CH_3$), 1.31 (3H, t, J=7Hz, $CH_2C\underline{H}_3$), ν_{max} 3300-2100, and 1640-1550 cm^{-1}.

4-Hydroxythieno-2-methylthieno[2,3-b]pyridin-6(7H)-one (134c) -

This was prepared by hydrolysis of the ester (133c) (11.3g, 0.045mol), as previously described for (134a). The crude 4-hydroxythieno[2,3-b]pyridin-6(7H)-one (134c) (7.8g, 96%), after recrystallisation from glacial acetic acid, had m.p. >300° (Found: C, 52.8; H, 3.8; N, 7.5. $C_8H_7NO_2S$ requires C, 53.0; H, 3.9; N, 7.7%), δ ($[CD_3]_2SO$) 6.94 (1H, q, J=1.2Hz, 3-H), 5.80 (1H, s, 5-H), 2.44 (3H, d, J=1.2Hz, Ar-Me), ν_{max} 3200-2100, and 1650-1600 cm^{-1}.

5-Ethoxycarbonyl-4-hydroxy-7-methylthieno[2,3-b]pyridin-6(7H9-one (136) -

A mixture of hydroxy-oxo ester (133a) (2.39g, 10mol), dimethyl sulphate (1.4g, 11mol), anhydrous potassium carbonate (1.7g, 15mol), and butanone (40ml) was boiled under reflux for 5h. When cool the suspension was added to water; a small quantity of precipitate (0.15g), identified as starting material, was filtered off then the filtrate was neutralised with concentrated hydrochloric acid. Extraction with dichloromethane gave a sticky semi-solid, which was purified by flash-column chromatography (ethyl acetate) to give the title

N-methyl thieno[2,3-b]pyridone (136) (0.9g, 36%), m.p. 105-108° (Found: C, 52.8; H, 4.4; N, 5.1. $C_{11}H_{11}NO_4S$ requires C, 52.2; H, 4.4; N, 5.5%), δ ($CDCl_3$) 7.25 (1H, d, J=6Hz, 2-H), 6.85 (1H, d, J=6Hz, 3-H), 4.47 (2H, q, J=7Hz, $OC\underline{H}_2$), 3.54 (3H, s, N-$C\underline{H}_3$), and 1.47 (3H, t, J=7Hz, $OCH_2C\underline{H}_3$), ν_{max} 2300-2800, 1620-1700, 1590, and 1540 cm^{-1}.

4-Hydroxy-7-methylthieno[2,3-b]pyridin-6(7H)-one (137) -

4-Hydroxythieno[2,3-b]pyridin-6(7H)-one (134a) (0.7g) was dissolved in 4M-sodium hydroxide (6ml), dimethyl sulphate (1.4ml) was added, and the mixture was shaken for 15 minutes. Water (20ml) was added, the solution was acidified (concentrated hydrochloric acid) and the precipitate was filtered off, washed with water, and dried. The product was freed from several minor impurities by flash-column chromatography (methylated spirits [1 part]-dichloromethane [9 parts]) to give the title N-methylthieno[2,3-b]pyridone (137) (0.35g, 46%) as a solid, m.p. 250-252° (Found: C, 52.7; H, 3.9; N, 7.8. C_8H_7NOS requires C, 53.0; H, 3.9; N, 7.7%), δ ($CDCl_3$-$(CD_3)_2SO$) 7.24 (1H, d, J=6Hz, 2-H), 7.09 (1H, d, J=6Hz, 3-H), 5.72 (1H, s, 5-H), and 3.48 (3H, s, $NC\underline{H}_3$), ν_{max} 2200-3150, 1600, and 1510 cm^{-1}.

Reaction of 4-Hydroxythieno[2,3-b]pyridin-6(7H)-one (134a) with Phenyl Phosphonic Dichloride -

The thienopyridine (15g) and the reagent (40ml) were heated together at 160-170°C for 1h, then the solution was cooled and added to water. After neutralisation (sodium hydrogen carbonate) the whole was extracted with dichloromethane (3x), the dried extracts were evaporated, and the resulting semi-solid was treated with boiling light petroleum to give soluble and insoluble fractions. The soluble material was recovered from the solvent and was purified by flash-column chromatography (ethyl acetate [1 part] - light petroleum [9 parts], then crystallisation from light petroleum, to give 4,6-dichlorothieno[2,3-b]pyridine (141) (7.0g, 38%), m.p. 79-81° (Found: C, 41.1; H, 1.4; N, 6.5. $C_7H_3Cl_2NS$ requires C, 41.2; h, 1.5; N, 6.9%), δ ($CDCl_3$) 7.47 (1H, d, J=6Hz, 2-H), 7.26 (1H, d, J=6Hz, 3-H), and 7.24 (1H, s, 5-H), ν_{max} 1560, and 1530 cm^{-1}. The insoluble material was crystallised from methylated spirits, giving 4-chlorothieno[2,3-b]pyridin-6(7H)-one (142) (1.2g, 7%), m.p. 245-247° (Found: C,45.6; H, 2.1; N, 7.6. C_7H_4ClNOS requires C, 45.3; H, 2.2; N. 7.6%), δ ($CDCl_3$-$(CD_3)_2SO$) 7.27 (1H, d, J=6Hz, 2-H), 7.14 (1H, d, J=6Hz, 3-H), and 6.59 (1H, s, 5-H), ν_{max} 2500-3150, 1650, and 1530 cm^{-1}.

Ethyl 4,6-Dichlorothieno[2,3-b]pyridine-5-carboxylate (143) -

A mixture of the ester (133a) (10g) and phenyl phosphonic dichloride (20ml) was heated at 160-170° for 1h. The cooled solution was added to water and stirred for 30 minutes, then neutralised with sodium hydrogen carbonate.

Extraction with dichloromethane (3x) yielded an oil, shown by t.l.c. to be a mixture of two major and several minor components. The product was subjected to flash-column chromatography, using ethyl acetate (1 part) - light petroleum (9 parts) as eluant. First of the major components to be eluted was 4,6-dichlorothieno[2,3-b]pyridine-5-carbonyl chloride (144); it was purified by a further flash column treatment (using ethyl acetate- light petroleum 1:19), after which the acid chloride (0.85g, 8%) had m.p. 92-94° (Found: C, 36.6; H, 0.9; N, 5.3. $C_8H_2Cl_3NOS$ requires C, 36.0; H, 0.75; N, 5.25%), δ ($CDCl_3$) 7.74 (1H, d, J=6Hz, 2-H) and 7.45 (1H, d, J=6Hz, 3-H), ν_{max} 1780, 1560, and 1510 cm^{-1}. The second major product, ethyl 4,6-dichlorothieno[2,3-b]pyridine-5-carboxylate (143), was obtained from the column as a white solid (2.4g, 20%), m.p. 75-77° (Found: C, 43.4; H, 2.5; N, 4.7. $C_{10}H_7Cl_2NO_2S$ requires C, 43.5; H, 2.5; N, 5.1%), δ ($CDCl_3$) 7.65 (1H, d, J=6Hz, 2-H), 7.39 (1H, d, J=6Hz, 3-H), 4.51 (2H, q, J=7Hz, $C\underline{H}_2$), and 1.43 (3H, t, J=7Hz, $C\underline{H}_3$), ν_{max} 1730, 1570, and 1510 cm^{-1}.

Reductive Dechlorination of 4,6-Dichlorothieno[2,3-b]pyridine

a. The dichloro-compound (1g), glacial acetic acid (20ml), and zinc powder (1g) were stirred together at room temperature for 48h. The zinc was filtered off and washed with glacial acetic acid, the filtrate and washings were combined, made basic with 4M-sodium hydroxide, and the organic product was isolated by extraction into dichloromethane. The product was purified by flash-column chromatography (ethyl acetate [1 part] - light petroleum [4 parts], giving 6-chlorothieno[2,3-b]pyridine (145) (0.27g, 32%) as a solid. m.p. 48-50°, unchanged by distillation (b.p. 100°/0.05mmHg), (Klemm and Hartling[102] give 56.5-58.5°, and Meth-Cohn[97] 57° as the m.p. of this compound), δ ($CDCl_3$) 7.98 (1H, d, J=8Hz, 4-H), 7.51 (1H, d, J=6Hz, 2-H), 7.28 (1H, d, J=8Hz, 5-H), and 7.23 (1H, d, J=6Hz, 3-H), ν_{max} 1580, and 1550 cm^{-1}.

b. The chloro-compound (2.5g) was reacted with zinc powder (2.5g) in glacial acetic acid (50ml) for 24h. at room temperature, followed by 3h. at 30°C. The organic product was isolated as just described to give, after flash-column chromatography (ethyl acetate [1 part] - light petroleum [9 parts]), 6-chlorothieno[2,3-b]pyridine (0.23g, 11%), m.p. 46-49°, and thieno[2,3-b]-pyridine (1.09g, 66%), b.p. 120°/4mmHg.

c. When the chloro-compound (1.36g) was boiled under reflux for 1h. in glacial acetic acid (30ml) with a greater excess of zinc (2.7g) the sole product of the reaction, isolated as just described, was thieno[2,3-b]pyridine (0.71g, 79%).

Ethyl Thieno[2,3-b]pyridine-5-carboxylate (150) -

Chloro compound (149) (2g) was stirred in acetic acid (15ml) with zinc powder

(2g) for 1h. after the initial exothermic reaction was complete. The mixture was filtered, the solids were washed with acetic acid, combined filtrate and washings were made basic with 2M-sodium hydroxide and the dechlorinated material was isolated by extraction into dichloromethane. The solid product was crystallised from light petroleum to give the ester (150) (0.72g, 42%), m.p. 57-59° (Found: C, 57.7; H, 4.4; N, 6.9. $C_{10}H_9NO_2S$ requires C, 58.0; H, 4.4; N, 6.8%), δ ($CDCl_3$) 9.13 (1H, d, J=1.5Hz, 4-H), 7.56 (1H, d, J=6Hz, 2-H), 7.28 (1H, d,J=6Hz, 3-H), 4.41 (2H, q, J=7Hz, OCH_2), and 7.40 (3H, t, J=7Hz, OCH_2CH_3), ν_{max} 1710, 1590, and 1540cm^{-1}.

Thieno[2,3-b]pyridine-5-carboxylic acid (151) -

The ester (150) (1.4g) was stirred with a solution of sodium hydroxide (1g) in water (30ml) for 6h. The solid formed upon acidification of the resulting solution with glacial acetic acid was collected by filtration, washed with water, and dried giving the title acid (151) (0.83g, 93%). The analytical sample was recrystallised from methylated spirits and had m.p. 298° (decomp.) (Found: C, 53.7; H, 2.7 ; N, 7.7%), δ ($[CD_3]_2SO$) 9.00 (1H, d, J=2Hz, 6-H), 8.76 (1H, d, J=2Hz, 4-H), 7.97 (1H, d, J=6Hz, 2-H), 7.57 (1H, d, J=6Hz, 3-H), ν_{max} 3000-2800, 2700-2300, 1820-1810, 1710, 1590, and 1550 cm^{-1}.

7-Methylthieno[2,3-b]pyridin-4(7H)-one (152)-

a From (85) - 4-Hydroxythieno[2,3-b]pyridine (85) (3.02g, 20mmol) was dissolved in a solution of potassium hydroxide (1.12g, 20mmol) in water (50ml), dimethyl sulphate (2.52g, 20mmol) was added, and the mixture was stirred. After 1h. t.l.c. indicated that reaction was incomplete. More potassium hydroxide (0.56g, 10mmol) and dimethyl sulphate (1.26g, 10mmol) were added, and after one further hour the starting material had been consumed. The solution was saturated with sodium chloride and extracted with dichloromethane (10x). From the combined extracts a solid was obtained: it was crystallised from ethyl acetate to give 7-methylthieno[2,3-b]pyridin-4(7H)-one (152) (2.62g, 79%), m.p. 126-128° (Found: C, 56.3; H, 4.5; N, 7.8%. C_8H_7NOS requires C, 56.3; H, 4.5; N, 8.2%), δ ($CDCl_3$) 7.54 (1H, d, J=6Hz, 2-H), 7.39 (1H, d, J=7.5Hz, 6-H), 7.02 (1H, d, J=6Hz, 3-H), 6.24 (1H, d, J=7.5Hz, 5-H), and 3.77 (3H, s, NCH_3), ν_{max} 1610, 1550, and 1520 cm^{-1}.

b From (154) - 4-Methoxythieno[2,3-b]pyridine (154) (3.0g) was heated on the steam-bath with dimethyl sulphate (10ml) for 3h; the cooled solution was triturated with ether to give a hygroscopic semi-solid. The material was dissolved in a small volume of water, 4M-sodium hydroxide (20ml) was added, the solution was heated briefly then set aside at room temperature for 18h. Extraction with dichloromethane (6x) gave a solid (2.1g, 70%), m.p. 115-118°, which, in crystallisation from ethyl acetate, afforded the thienopyridone (152)

(1.8g, 60%), m.p. 126-128°, undepressed by the substance prepared from (85).

4-Methoxythieno[2,3-b]pyridine (154) -

4-Chlorothieno[2,3-b]pyridine (153) (4.8g, m.p. 38-40°C, lit.[27] 31-32°C) was boiled under reflux with sodium methoxide (from 1.3g sodium) in methanol (80ml) for 30h. The cooled solution was diluted with water and the organic product extracted into dichloromethane. Flash-column chromatography (ethyl acetate [1 part] - light petroleum [4 parts]) of the extracted material gave the methoxy-compound (4.0g, 85%) as an oil b.p. 88-89°/0.05mmHg (Found: C, 57.6; H, 4.2; N, 8.1. C_8H_7NOS requires C, 58.2; H, 4.2; N, 8.5%), δ ($CDCl_3$) 8.37 (1H, d, J=6Hz, 6-H), 7.31 (2H, s, 2-H and 3-H), 6.61 (1H, d, J=6Hz, 5-H), and 3.90 (3H, s, OCH_3), ν_{max} (film) 1580, and 1550 cm^{-1}.

8.2 Work described in Chapter Three

N.B. In all the thieno[3,2-b]pyridines described in this section H-2 and H-3 were doublets, J_{23}=5.5Hz.

Ethyl 5-Chloro-7-ethoxythieno[3,2-b]pyridine-6-carboxylate (155) -

Ethyl 5,7-dichlorothieno[3,2-b]pyridine-6-carboxylate (72) (4.95g, 17.9mmol) was boiled under reflux with sodium ethoxide (19.5mmol, from 0.45g sodium) in ethanol (50ml) for 1h. When cool the mixture was added to water (500ml) and the product was isolated with dichloromethane (3x) to give an oil which, on trituration with light petroleum, afforded the pure title ester (155) (3.7g, 72%), m.p. 45-47° (unchanged on crystallisation from ethyl acetate - light petroleum [b.p. 60-80°]) (Found: C, 50.4; H, 4.3; N, 4.9. $C_{12}H_{12}ClNO_3S$ requires C, 50.4; H, 4.2; N, 4.9%), δ ($CDCl_3$) 7.80 (H-2), 7.44 (H-3), 4.5 (2 x q, CO_2CH_2 and $ArOCH_2$), and 1.50 (2 x t, $CO_2CH_2CH_3$ and $ArOCH_2CH_3$), ν_{max} (film) 1730, 1570, and 1530 cm^{-1}.

Reductive Dechlorination of Ethyl 5-Chloro-7-ethoxythieno[3,2-b]pyridine-6-carboxylate -

The thienopyridine derivative (155) (1.5g), zinc powder (3g), and glacial acetic acid (30ml) were stirred together at room temperature for 24h. The zinc was filtered off and washed with acetic acid, the combined solutions were made basic (4M-sodium hydroxide) and the liberated oil (1.27g) was isolated with dichloromethane. Flash-column chromatography (EtOAc [1 part] - light petroleum [9 parts] gave unreacted (155) (0.71g) and an oil (0.29g). The latter had infra-red and ^1H n.m.r spectra identical with those of ethyl 7-ethoxy-thieno[3,2-b]pyridine-6-carboxylate (157), prepared by an unambiguous route (see later).

Ethyl 7-Ethoxythieno[3,2-b]pyridine-6-carboxylate (157) -

Sodium (0.2g, 9mg-atom) was dissolved in ethanol (20ml) and ethyl

7-chlorothieno[3,2-b]pyridine-6-carboxylate[99] (158) (1.81g, 7.5mmol) was added. The mixture was stirred at room temperature overnight, added to ice and water and the product was isolated with ether. Crystallisation at low temperature of the product from light petroleum provided the ethoxyethyl ester (157) (0.86g, 46%), m.p. 34-36° (Found: C, 57.1; H, 5.2; N, 5.6. $C_{12}H_{13}NO_3S$ requires C, 57.3; H, 5.2; N, 5.5%) δ ($CDCl_3$) 9.03 (s, H-5), 7.83 (H-2), 7.55 (H-3), 4.47 (2 x q; $ArOC\underline{H}_2$ + $CO_2C\underline{H}_2$), and 1.46 (2 x t; $ArOCH_2C\underline{H}_3$ + $CO_2CH_2C\underline{H}_3$) ν_{max} (film) 1720, 1580, and 1530 cm^{-1}.

Ethyl 5,7-Diethoxythieno[3,2-b]pyridine-6-carboxylate (159) -

The dichloro- ester (72) (1g, 3.5mmol) was added to a solution of sodium ethoxide (37mmol, from 0.85g sodium) in ethanol (20ml). The whole was boiled under reflux for 2h, cooled, and added to water (500ml). The organic product was isolated with dichloromethane and purified by flash-column chromatography (ethyl acetate [1 part] - light petroleum [9 parts]) yielding the 5,7-diethoxy compound (159) (0.31g, 30%) as an oil. It was distilled, when it had b.p. 150°/0.4mmHg (Kugelrohr) (Found: C, 56.9; H, 5.8; N, 5.8. $C_{14}H_{17}NO_4S$ requires C, 56.95; H, 5.8; N, 4.75%), δ ($CDCl_3$) 7.65 (H-2), 7.32 (H-3), 4.43 (3 x q, 2 x $ArCOH_2$ and $CO_2C\underline{H}_2$), and 1.40 (3 x t, 2 x $ArOCH_2C\underline{H}_3$ and $CO_2CH_2C\underline{H}_3$), ν_{max} (film) 1725, 1580, and 1540 cm^{-1}.

5-Chloro-4,7-dihydro-7-oxothieno[3,2-b]pyridin-6-carboxylic Acid (156) -

The ethyl ester (72) (4.9g, 17.8mmol) was boiled under reflux in a mixture of methylated spirits (50ml) and 4M-aqueous sodium hydroxide (50ml) for 3h. A further portion of 4M-alkali (50ml) was added, and the whole was boiled for a further 5h. The solution was cooled and acidified with concentrated hydrochloric acid, the precipitate was collected, washed with water, and dried. After crystallisation from ethanol containing a little 2M-hydrochloric acid the title acid (2.9g, 71%) had m.p. 200-202° (decomp.). (Found: C, 41.8; H, 1.7; N, 6.4. $C_8H_4ClNO_3S$ requires C, 41.8; H, 1.7; N, 6.1%), δ [$(CD_3)_2SO$] 8.30 (H-2), and 7.42 (H-3), ν_{max} 2000-3300, 1695, and 1600 cm^{-1}.

5-Chloro-7-ethoxythieno[3,2-b]pyridine-6-carboxylic acid (160) -

The ester (155) (2g, 7mmol) was boiled under reflux with a solution of sodium hydroxide (0.28g, 7mmol) in water (25ml) for 2h. The cooled solution was washed with ether, acidified (concentrated hydrochloric acid) and the resulting solid was collected and recrystallised from methylated spirits giving the acid (0.9g, 49%), m.p. 193-4° (Found: C, 46.5; H, 3.2; N, 5.3. $C_{10}H_8ClNO_3S$ requires C, 46.6; H, 3.1; N, 5.4%), δ ($CDCl_3$-[CD_3]$_2$SO) 7.92 (H-2), 7.44 (H-3), 4.61 (2H, q, J=7Hz, $OC\underline{H}_2CH_3$), and 1.46 (3H, t, J=7Hz, $OCH_2C\underline{H}_3$), ν_{max} 2500, 1950, 1720, and 1550 cm^{-1}.

Ethyl 5-Chloro-7-ethylthiothieno[3,2-b]pyridine-6-carboxylate (161) -

Sodium (0.21g, 9mg-atom) was dissolved in ethanol (50ml) and, at 0°C, ethanethiol (0.85g, 13.5mmol) was added. The solution was allowed to warm to room temperature then (72) (2.07g, 7.5mmol) was added. After being stirred at room temperature overnight, the mixture was heated at 80° for 30 minutes, cooled, and added to water. The resulting oil (1.8g) was extracted with ether then subjected to flash-column chromatography (EtOAc [1 part] - light petroleum [4 parts]), whereupon 1.3g of material running as a single spot on t.l.c. was obtained. Distillation (Kugelrohr) yielded ethyl 5-chloro-7-ethylthiothieno[3,2-b]pyridine-6-carboxylate (161) (1.0g, 44%) as an oil, b.p. 180°/0.3mmHg (Found: C, 47.0; H, 3.7; N, 4.1. $C_{12}H_{12}ClNO_2S_2$ requires C, 47.7; H, 4.0; N, 4.6%), δ ($CDCl_3$) 7.89 (H-2), 7.53 (H-3), 4.51 (q, $OC\underline{H}_2$, J=7Hz), 3.11 (q, $SC\underline{H}_2$, J=7Hz), 1.45 (t, $OCH_2C\underline{H}_3$, J=7Hz), and 1.25 (t, $SCH_2C\underline{H}_3$, J=7Hz), ν_{max} (film) 1735, 1550, 1520 cm^{-1}.

Ethyl 5-Chloro-7-diethylaminothieno[3,2-b]pyridine-6-carboxylate (162) -

A mixture of ethyl 5,7-dichlorothieno[3,2-b]pyridine-6-carboxylate (72) (1g, 3.6mmol) and diethylamine (20ml) was stirred overnight at room temperature, then boiled under reflux for 3h. Water (200ml) was added to the cooled solution, and the liberated oil was extracted into ether, giving an oil (0.8g). Thin layer chromatography (CH_2Cl_2) showed that two components were present. Separation was achieved by flash-column chromatography (CH_2Cl_2), the component of high R_F being (72) and than of lower R_F the desired product. Distillation (Kugelrohr) gave ethyl 5-chloro-7-diethylaminothieno[3,2-b]pyridine-6-carboxylate (162) as an oil, b.p. 140°/0.02mmHg (Found: C, 52.8; H, 5.2; N, 7.8. $C_{14}H_{17}ClN_2O_2S$ requires C, 53.8; H, 5.4; N, 9.0%), δ ($CDCl_3$) 7.65 (H-2), 7.34 (H-3), 4.35 (q, $OC\underline{H}_2$ J=7Hz), 3.34 (2 x q, 2 x $NC\underline{H}_2$, J=7Hz), 1.38 (t, $OCH_2C\underline{H}_3$, J=7Hz), and 1.05 (2 x t, 2 x $NCH_2C\underline{H}_3$, J=7Hz) ν_{max} (film) 1725, 1550, and 1525 cm^{-1}.

Reaction of 5,7-Dichlorothieno[3,2-b]pyridine with one equivalent of sodium alkoxide -

Reaction of dichloro compound (73) with one equivalent of sodium methoxide or ethoxide in the appropriate alcohol gave 5-chloro-7-methoxy- (163) or 5-chloro-7-ethoxythieno[3,2-b]pyridine (164), respectively, and not (as previously reported[46]) the 5-alkoxy-7-chloro compounds. The ^{13}C n.m.r. data for (163) and (164) are recorded in Table 3, and the values are compared with predicted ones in Chapter 4; the ^{1}H n.m.r spectra were as previously recorded. The melting points of (163) and (164) prepared in the present work were taken on a hot stage apparatus, and were 101-103° and 71-73°, respectively (lit.[46] in capillary tubes 97-98° and 63-65°).

Reductive Dechlorination of 5-Chloro-7-methoxythieno[3,2-b]pyridine -

The title compound (163) (1.37g) was stirred at room temperature overnight in glacial acetic acid (20ml) with zinc powder (2.8g), then boiled under reflux for 2h. The cooled mixture was filtered, the residue was washed with acetic acid and the combined filtrate and washings were made basic with 4M-aqueous sodium hydroxide. The liberated oil was isolated with ether and distilled, to give 7-methoxythieno[3,2-b]pyridine (165) (0.89g, 78%), b.p. 135°/0.2mmHg, δ ($CDCl_3$) 8.55 (d, H-5, J=6Hz), 7.66 (H-2), 7.48 (H-3), 6.66 (d, H-6, J=6Hz), and 3.99 (s, OCH_3), ν_{max} (film) 1580, 1550, and 1510 cm^{-1}. The substance was identical in all respects to a sample prepared by an unambiguous route from (167) (see later).

Reductive Dechlorination of 5-Chloro-7-ethoxythieno[3,2-b]pyridine -

Reduction of (164) (1.46g) with zinc powder (3.0g) in acetic acid (20ml) by the method just described for (163) gave, from the ether extract, a solid. This was crystallised from pentane to yield 7-ethoxythieno[3,2-b]pyridine (166) (0.95g, 78%), m.p. 50-52° (Found: C, 60.0; H, 5.0, N, 7.9. C_9H_9NOS requires C, 60.3; H, 5.0; N, 7.8%), δ ($CDCl_3$) 8.52 (d, H-5, J=6Hz), 7.66 (H-2), 7.48 (H-3), 6.62(d, H-6, J=6Hz), 4.23 (q, OCH_2, J=7.5Hz), and 1.49 (t, OCH_2CH_3, J=7.5Hz), ν_{max} 1580, 1550, and 1510 cm^{-1}. This, too, was identical to material prepared from (167) (see later).

Decarboxylation of 5-Chloro-7-ethoxythieno[3,2-b]pyridine-6-carboxylic acid (160) -

The acid (2g) was heated in an oil bath held at 190° for 15 minutes, by which time effervescence had ceased. The semi-solid residue was taken into dichloromethane, washed with sodium bicarbonate solution, dried, and evaporated. Flash-column chromatography gave 5-chloro-7-ethoxythieno[3,2-b]-pyridine (164) (0.85g, 51%) m.p. 71-3°. This material had infra-red and ^1H n.m.r. spectra identical to those of material prepared from 5,7-dichlorthieno-[3,2-b]pyridine.

7-Alkoxythieno[3,2-b]pyridines (165) and (166) -

7-Methoxythieno[3,2-b]pyridine (165) was obtained from (167) by the method previously described[32]. Similarly (167) (1.5g) and sodium ethoxide (from 0.4g sodium) in ethanol (30ml) gave (after being boiled under reflux for 20h. and work-up of ref.[32]) 7-ethoxythieno[3,2-b]pyridine (166) (1.21g, 76%), b.p. 120°/0.6mmHg, m.p. 50-52°. The 7-methoxy- and -ethoxy derivatives prepared here were identical in all respects to the dechlorination products of (163) and (164), respectively.

Reaction of 5,7-Dichlorothieno[3,2-b]pyridine with sodium hydroxide

i. In aqueous ethanol - The dichlorothienopyridine (2g) was boiled under reflux in a mixture of 4M-aqueous sodium hydroxide (30ml) and methylated spirits (20ml) for 10h. Water (100ml) was added and the product was extracted into dichloromethane. Recrystallisation from light petroleum gave a material of m.p. 60-64° (2g), raised to 65-68° on admixture with5-chloro-7-ethoxy-thieno[3,2-b]pyridine (164). Thin layer chromatography and ^{1}H n.m.r. spectroscopy confirmed that the material was (164), containing a small proportion of (73).

ii. In aqueous dimethylsulphoxide - The dichloro compound (73) (1g) was boiled with a mixture of 4M-aqueous sodium hydroxide (20ml) and dimethyl-sulphoxide (20ml) for 10 minutes. The cooled solution was diluted with water (60ml), acidified (concentrated hydrochloric acid) and extracted with dichloromethane; the small amount of oil obtained from the latter was discarded. The aqueous phase was saturated with sodium chloride and cooled in ice. Crystallisation of the resulting precipitate from methanol gave 5-chloro-7-hydroxythieno[3,2-b]pyridine (168) identified via its infra-red spectrum and by its mixed m.p. (212-214°) with material prepared by decarboxylation of the acid (156) (see below).

Decarboxylation of 5-Chloro-4.7-dihydro-7-oxothieno[3,2-b]pyridine-6-carboxylic Acid -

The acid (156) (1.0g) was added in portions over 5 minutes to diphenyl ether (20ml) at 210°, then the temperature was held at 210-220° for a further 5 minutes. When cool the ether was decanted from a small quantity of dark material, then diluted with light petroleum (50ml). The precipitate was filtered off, washed with more light petroleum, dried, and crystallised from ethyl acetate-light petroleum to give 5-chloro-7-hydroxythieno[3,2-b]pyridine (168), m.p. 202-204°. The analytical sample (from methanol) had m.p. 212-214° (Found: C, 45.0; H, 2.2; N, 7.5. C_7H_4ClNOS requires C, 45.3; H, 2.2; N, 7.5%), δ [$(CD_3)_2SO$] 8.16 (H-2), 7.60 (H-3), and 6.80 (s, H-6), ν_{max} 2300-3100, 1600, and 1540 cm^{-1}.

Decarboxylation of 7-Chloro-4,5-dihydro-5-oxothieno[3,2-b]pyridine-6-carboxylic Acid -

The acid (170) (2.6g) was added in portions to diphenyl ether (100ml) at 230°, the internal temperature was held at 230-235° until effervescence was finished (15 minutes), then the mixture was cooled. It was diluted with light petroleum (300ml) and the solid was filtered off and washed with more light petroleum. The crude product was digested with boiling methanol, the insoluble solid was discarded and the methanol was evaporated to give the thienopyridone (1.5g,

71%). After two crystallisations from methylated spirits the product, 7-chlorothieno[3,2-b]pyridin-5(4H)-one (169) had m.p. 252-254 (lit.[46] 258-260°).

7-Chloro-5-ethoxythieno[3,2-b]pyridine (171) -

A solution of 7-chlorothieno[3,2-b]pyridin-5(4H)-one (169) (1g) in dichloromethane (20ml) was stirred while triethyloxonium tetrafluoroborate in the same solvent (8ml of a 1M solution; 1.5 equivalents) was added. After 1h. the solution was washed with sodium bicarbonate solution, dried and evaporated. The oil so produced was subjected to flash-column chromatography (EtOAC [1 part] - light petroleum [4 parts]) giving 7-chloro-5-ethoxythieno[3,2-b]pyridine ((0.15g, 13%) as a solid, m.p. 59-62° (depressed to 43-48° by (164) (Found: C, 50.3; H, 4.0; N, 6.6. C_9H_8ClNOS requires C, 50.6; H, 3.75; N, 6.6%), δ ($CDCl_3$) 7.61 (H-2), 7.30 (H-3), 6.73 (s, H-6), 4.38 (q, $OC\underline{H}_2$, J=7.5Hz), and 1.39 (t, $OCH_2C\underline{H}_3$, J=7.5Hz), ν_{max} 1580, and 1540 cm^{-1}.

Reductive Dechlorination of 5,7-Dichlorothieno[3,2-b]pyridine -

The dichloro compound (5g) was stirred overnight at toom temperature with zinc powder (5g) in glacial acetic acid (50ml). The residue was filtered off and washed with acetic acid; the united acid solutions were made basic (4M-sodium hydroxide) and the oil was isolated with dichloromethane. Thin layer chromatography indicated that the product was a mixture of two substances; flash-column chromatography (EtOAC [1 part] - light petroleum [10 parts]) effected separation. The material of higher R_F, a solid, was crystallised from pentane to give 5-chlorothieno[3,2-b]pyridine (172) (0.9g, 22%), m.p. 70-72° (lit.[42] m.p. 63-64°) (Found: C, 49.2; H, 2.3; N, 8.0. Calculated for C_7H_4ClNS C, 49.6; H, 2.4; N, 8.3%), δ ($CDCl_3$) 8.01 (d, H-7, J=8.4Hz), 7.72 (H-2), 7.39 (H-3), and 7.16 (d, H-6, J=8.4Hz), ν_{max} 1560 and 1535 cm^{-1}. The material of lower R_F was combined with that obtained from the zinc residues: the residues were dissolved in 4M-hydrochloric acid, the solution was basified with 4M-sodium hydroxide and the oil was isolated with dichloromethane. distillation of the combined oils afforded thieno[3,2-b]pyridine (2) (2.4g, 73%), b.p. 120°/5mmHg (lit.[53] 129-131°/16mmHg and 107-107°/10mmHg) ν_{max} (film) 1550 cm^{-1}.

Reductive Dechlorination of 7-Chlorothieno[3,2-b]pyridine -

Treatment of (167) (2.4g) with zinc powder (4.8g) in acetic acid (50ml) for 5h at room temperature, followed by basification (4M-sodium hydroxide), isolation with ether and distillation gave 1.52g (76%) of thieno[3,2-b]pyridine.

5-Methoxythieno[3,2-b]pyridine (173) -

5-Chlorothieno[3,2-b]pyridine (0.9g) was boiled under reflux with a solution of

sodium methoxide (10 equivalents, from 1.2g sodium) in methanol. After 10h. thin layer chromatography revealed that very little reaction had occurred. A further portion of sodium methoxide (40 equivalents, from 4.8g sodium) in methanol (60ml; total volume 100ml) was added, and the solution was boiled under reflux for a further 30h. The solvent was removed, water was added, and the crude product was isolated with ether. Flash-column chromatography (EtOAC [1 part] - light petroleum [19 parts]) gave an oil that ran as a single spot on thin layer chromatography (EtOAc/light petroleum). Distillation gave 5-methoxythieno[3,2-b]pyridine (173) (0.51g, 58%) as an oil, b.p. 110°/0.5mmHg (Found: C, 58.1; H, 4.3; N, 8.0. C_8H_7NOS requires C, 58.2; H, 4.2; N, 8.5%), δ ($CDCl_3$) 7.97 (d, H-7, J=8.4Hz), 7.65 (H-2), 7.37 (H-3), 6.77 (d, H-6, J=8.4Hz), and 3.97 (s, OCH_3), ν_{max} (film) 1580, and 1550 cm^{-1}.

5,7-Dichloro-6-cyanothieno[3,2-b]pyridine (174) -

6-Cyano-7-hydroxythieno[3,2-b]pyridin-5(4H)-one[46] (12.8g) and phosphoryl chloride (75ml) were heated together on the steam bath for 2h, then boiled gently under reflux for 3h. The excess of reagent was removed by vacuum distillation, and the residue was added to ice and water. The solid obtained by extraction with dichloromethane was treated in a Soxhlet apparatus with light petroleum (b.p. 80-100°) to give soluble and insoluble fractions. The insoluble material was intractable, but from the light petroleum solution was obtained 5,7-dichloro-6-cyanothieno[3,2-b]pyridine (174) (9.2g, 61%). The analytical sample (from light petroleum [b.p. 80-100°]) had m.p. 186-188° (Found: C, 42.0; H, 1.4; N, 12.0. $C_8H_2Cl_2N_2S$ requires C, 42.0; H, 0.9; N, 12.0%), δ ($CDCl_3$) 8.15 ((H-2), and 7.60 (H-3), ν_{max} 2240, 1565, and 1510 cm^{-1}.

5-Chloro-6-cyano-7-methoxythieno[3,2-b]pyridine (175) -

The dichloronitrile (174) (2.48g, 10.8mmol) was boiled under reflux with sodium methoxide (10.9mmol, from 0.25g sodium) in methanol (50ml) for 2.5h. The mixture was allowed to stand at room temperature for 48h, then evaporated to dryness. The residue was stirred with acetone; crystallisation of the acetone-soluble material from methanol gave chloromethoxy compound (175) (1.55g, 64%), m.p. 182-184° (Found: C, 48.2; H, 2.3; N, 12.0. $C_9H_5ClN_2OS$ requires C, 48.1; H, 2.2; N, 12.4%), δ ($CDCl_3$) 8.45 (H-2), 7.55 (H-3), and 4.50 (s, OCH_3), ν_{max} 2220, 1565, and 1510 cm^{-1}.

Hydrolysis of 5-Chloro-6-cyano-7-methoxythieno[3,2-b]pyridine -

The nitrile (175) was heated under reflux for 8h. with 4M-aqueous sodium hydroxide (20ml). When cool the solution was acidified with concentrated hydrochloric acid, the precipitate was collected by filtration, washed with water, and dried. Thus was obtained 5-chloro-4,7-dihydro-7-oxothieno[3,2-b]-pyridine-6-carboxylic acid (156) (0.22g, 73%), m.p. 202-204° (decomp.),

undepressed on admixture with an authentic sample.

Methyl 6-Amino-5-chlorodithieno[3,2-b:2',3'-d]pyridine-7-carboxylate (176) -

i. From 5,7-Dichloro-6-cyanothieno[3,2-b]pyridine -

Methyl thioglycolate (0.54g, 5mmol) was added to a solution of sodium methoxide (4.6mmol, from 0.11g sodium) in methanol (30ml). The nitrile (174) (0.5g, 2.2 mmol) in hot methanol (10ml) was added, and the whole set aside at room temperature overnight. The precipitate was filtered off, washed with a little methanol, and recrystallised from glacial acetic acid to yield the title dithienopyridine derivative (176) (0.6g, 90%), m.p. 236-8° (Found: C, 44.1; H, 2.3; N, 9.2. $C_{11}H_7ClNO_2S_2$ requires C, 44.2; H, 2.35; N, 9.4%), δ (CF_3CO_2H) 8.37 (H-2), 7.81 (H-3), and 4.14 (s, CO_2CH_3), ν_{max} 3500, 3370, 1690, 1610, and 1530 cm^{-1}.

ii. From 5-Chloro-6-cyano-7-methoxythieno[3,2-b]pyridine -

Treatment of the methoxychloronitrile (175) (0.57g, 5.7mmol) with the anion of methyl thioglycolate (from the ester [0.61g, 5.7mmol] and sodium methoxide [5.2mmol] in the manner described for the preceding experiment gave methyl 6-amino-5-chlorodithieno[3,2-b:2',3'-d]pyridine-7-carboxylate (176) (0.41g, 57%), m.p. and mixed m.p. with the material prepared from (174) 236-238°.

6-Cyano-5,7-dimethoxythieno[3,2-b]pyridine (177) -

Dichloro compound (174) (0.5g, 2.2mmol) was boiled under reflux for 5h with sodium methoxide (6.6mmol, from 0.15g sodium) in methanol (50ml). The solution was chilled, the precipitate was filtered off, washed with methanol and dried to give 0.37g (77%) of 6-cyano-5,7-dimethoxythieno[3,2-b]pyridine (177), m.p. 177-178° (Found: C, 54.5; H, 3.4; N, 12.8. $C_{10}H_8N_2O_2S$ requires C, 54.5; H, 3.6; N, 12.7%), δ ($CDCl_3$) 7.75 (H-2), 7.28 (H-3), 4.40 (s, C-7, OCH_3), and 4.03 (s, C-5, OCH_3), ν_{max} 2220, 1575, and 1535 cm^{-1}.

ii From 5-Chloro-6-cyano-7-methoxythieno[3,2-b]pyridine -

Reaction of the chloromethoxy compound (175) (0.67g, 3mmol) with sodium methoxide (6mmol) in methanol (40ml) in the manner just described afforded 0.41g (62%) of (177), m.p. 176-178°.

Attempted reaction of Ethyl 5-Chloro-7-ethoxythieno[3,2-b]pyridine- -carboxylate (155) with ethyl thioglycolate -

Ethyl thioglycolate(1.2g, 10mmol) was dissolved in a solution of sodium ethoxide (10mmol, from 0.23g sodium) in ethanol (25ml) and ethyl 5-chloro-7-ethoxythieno[3,2-b]pyridine-6-carboxylate (1.4g, 5mmol) was added. After stirring at room temperature overnight thin layer chromatography indicated that no reaction had occurred. The mixture was boiled under reflux for a further 6 hours, but again no reaction was observed.

Ethyl 6-Chloro-4-ethoxythieno[2,3-b]pyridine-5-carboxylate (180) -

The dichloro-ester (143) (0.55g, 2mmol) was added to a solution of sodium ethoxide (from (0.046g, 2mg-atom, sodium) in ethanol (30ml), and the whole was boiled under reflux for 1 hour. The cooled solution was added to water and the organic product was extracted into dichloromethane. After flash-column chromatography (ethyl acetate [1 part] - light petroleum [9 parts]), and distillation, ethyl 6-chloro-4-ethoxythieno[2,3-b]pyridine-5-carboxylate (180) (0.33g, 58%) was obtained as an oil b.p. 160°/0.05mmHg (Found: C, 50.3; H, 4.1; N, 5.1. $C_{12}H_{12}ClNO_3S$ requires C, 50.4; H, 4.2; N, 4.9%), δ ($CDCl_3$), 7.42 (2H, s, 2-H and 3-H), 4.42 (4H, q, J=7Hz, 2xCH_2), and 1.28-1.58 (6H, m, 2xCH_3), ν_{max} (film) 1730, 1570, and 1530 cm^{-1}.

Ethyl 4-Ethoxythieno[2,3-b]pyridine-5-carboxylate (181) -

To a solution of sodium ethoxide (from 0.35g, 15mg-atom, sodium) in ethanol (20ml) was added ethyl 4-chlorothieno[2,3-b]pyridine-5-carboxylate (149) (1.2g, 5mmol). The mixture was set aside at room temperature for 2h then added to water. The precipitate was filtered off, washed with water, dried, and crystallised from light petroleum to give ethyl 4-ethoxythieno[2,3-b]pyridine-5-carboxylate (181) (0.7g, 56%), m.p. 70-72° (Found: C, 57.5; H, 5.1; N, 5.8. $C_{12}H_{13}NO_3S$ requires C, 57.4; H, 5.2; N, 5.6%), δ ($CDCl_3$) 8.87 (1H, s, 6-H), 7.41 (2H, s, 2-H and 3-H) 4.20-4.61 (4H, m, 2xCH_2), ν_{max} 1700, 1580, and 1530 cm^{-1}.

Dechlorination of Ethyl 6-Chloro-4-ethoxythieno[2,3-b]pyridine-5-carboxylate -

The chloroethoxy-ester (180) (1g) was heated on the steam-bath for 24h with zinc (2g) in glacial acetic acid (20ml); more zinc (2g) was then added and heating was continued for a further 24h. The mixture was filtered, the residue was washed with acetic acid, and the combined filtrate and washings were made basic with 4M-sodium hydroxide. Thin layer chromatography of the dichloromethane extract of the mixture revealed that reaction was still not complete. The crude product (an oil) was subjected to flash-column chromatography (ethyl acetate [1 part] - light petroleum [19 parts]) gave firstly a mixture (0.51g) of the dechlorinated material and (180), then ethyl 4-ethoxythieno[2,3-b]pyridine-5-carboxylate, m.p. 70-72° alone and when mixed with the product of the preceding experiment. The i.r. and ^1H n.m.r. spectra of the substances from both sources were identical.

Methyl 7-Chloro-6-hydroxydithieno[2,3-b:2',3'-d]pyridine-5-carboxylate (182) -

Sodium (0.276g, 12mg-atom) was dissolved in methanol (60ml). Methyl thioglycolate (1.59g, 15mmol) was added followed, after 5 minutes, by a solution of ethyl 4,6-dichlorothieno[2,3-b]pyridine-5-carboxylate (143) (1.65gm,

6mmol) in methanol (30ml). The whole was stirred at toom temperature for 2h; the solid was filtered off, washed with methanol, and crystallised from glacial acetic acid, furnishing the title dithieno[2,3-b:2',3'-d]pyridine derivative (1.57g, 87%), m.p. 225-227° (decomp.) (Found: C, 44.0; H, 1.8; N, 4.2. $C_{11}H_6ClNO_3S$ requires C, 44.1; H, 2.0; N, 4.7%), δ ([CD_3]$_2$SO) 8.15 1H, d, J=6Hz, 2-H), 7.80 (1H, d, J=6Hz, 3-H), and 3.98 (3H, s, CH_3), ν_{max} 1660, and 1570 cm^{-1}.

Methyl 6-Hydroxydithieno[2,3-b:2',3'-d]pyridine-5-carboxylate (183) -

The anion of methyl thioglycolate was prepared as just described from the thiol ester (5.1g, 50mmol) and sodium methoxide (from 0.92g, 40mg-atom, sodium) in methanol (50ml). To it was added ethyl 4-chlorothieno[2,3-b]-pyridine-5-carboxylate (4.82g, 20mmol) in methanol (20ml). After 3h at room temperature the mixture was poured into water, the precipitate was collected, washed with water, dried, and crystallised from glacial acetic acid to give the title tricyclic ester (183) (3.35g, 63%), m.p. 228-230° (decomp.) (Found: C, 49.5; H, 2.5; N, 5.2. $C_{11}H_7NO_3S_2$ requires C, 49.8; H, 2.6; N, 5.3%), δ ([CD_3]$_2$SO) 9.11 (1H, s, 7-H), 8.14 (1H, d, J=6Hz, 2-H), 7.79 (1H, d, J=6Hz, 3-H), and 3.91 (3H, s, CH_3), ν_{max} 3280, 1680, 1580, and 1570 cm^{-1}.

Dechlorination of Methyl 7-Chloro-6-hydroxydithieno[2,3-b;2',3'-d]pyridine-5-carboxylate -

The chloro-compound (182) (0.7g) was dissolved in glacial acetic acid (20ml), zinc powder (1.4g) was added, and the whole was boiled under reflux for 4h. The solids were filtered off and washed with acetic acid the combined filtrate and washings were added to water and the solution was extracted with dichloromethane (3x). The extracts were washed free of acid with sodium hydrogen carbonate solution, then with water, dried, and evaporated. Trituration of the residue with a mixture of dichloromethane and light petroleum gave a buff solid (0.35g) which, after crystallisation from acetic acid, had m.p. 224-226°, undepressed by (183). The pure material (0.21g, 34%) had an i.r. spectrum identical to that of (183).

Ethyl 4,6-Diethoxythieno[2,3-b]pyridine-5-carboxylate (184) -

When boiled under reflux with a solution of sodium ethoxide in ethanol ethyl 4,6-dichlorothieno[2,3-b]pyridine-5-carboxylate afforded a material which rapidly blackened on exposure to air. For this reason the dichloro-ester (1.1g, 4mmol) and sodium ethoxide (from 0.46g, 20mg-atom, sodium) were allowed to stand together in ethanol (30ml) at room temperature for 10 days. Thin layer chromatography revealed that the starting material had been consumed and that a mixture of (180) and a second component was present. Separation by flash-column chromatography (ethyl acetate [1 part] - light petroleum [9

parts]) of the products (obtained by addition of the reaction mixture to water and extraction into dichloromethane) yielded the 6-chloro-4-ethoxy ester (180) (0.3g) and ethyl 4,6-diethoxythieno[2,3-b]pyridine-5-carboxylate (184) (0.29g, 25%), b.p. 150°/0.05mmHg (Found: C, 56.8; H, 5.9; N, 4.7. $C_{14}H_{17}NO_3S$ requires C, 57.0; H, 5.8; N, 4.8%), δ ($CDCl_3$) 7.28 (1H, d, J=6Hz, 2-H), 7.12 (1H, d, J=6Hz, 3-H), 4.20-4.68 (6H, m, 3xCH_2), and 1.26-1.58 (9H, m, 3xCH_3), ν_{max} (film) 1730, 1590, and 1540 cm^{-1}.

6-Chloro-4-methoxythieno[2,3-b]pyridine (185) -

The dichloro-compound (141) (2.04g, 10mmol) was boiled under reflux for 6h with a solution of sodium methoxide (from 0.23g, 10mg-atom, sodium) in methanol (25ml). The cooled solution was diluted with water and the organic product was extracted into dichloromethane. Flash-column chromatography (ethyl acetate [1 part] - light petroleum [9 parts]) of the extracted material gave pure 6-chloro-4-methoxythieno[2,3-b]pyridine (185) (1.41g, 71%) as a white solid, m.p. 78-80° (Found: C, 48.0; H, 3.0; N, 6.8. C_8H_6ClNOS requires C, 48.1; H, 3.0; N, 7.0%), δ ($CDCl_3$) 7.31 (2H, s, 2-H and 3-H), 6.71 (1H, s, 5-H), and 3.98 (3H, s, OCH_3), ν_{max} 1580, and 1550 cm^{-1}.

Dechlorination of 6-Chloro-4-methoxythieno[2,3-b]pyridine -

The chloro-compound (1.2g) and zinc powder (2.4g) were boiled together in glacial acetic acid (30ml) for 5h; reaction was not complete, so a further quantity (2.4g) of zinc was added and the mixture was refluxed for a further 5h. The mixture was filtered, the solid was washed with acetic acid, the washings and filtrate were combined, basified (4M-sodium hydroxide) and extracted with dichloromethane. The extract yielded an oil which was purified by flash-column chromatography (ethyl acetate [1 part] - light petroleum [4 parts]) giving 4-methoxythieno[2,3-b]pyridine (154) (0.72g, 73%) having identical ^1H, ^{13}C and i.r. spectra to those of the authentic material.

6-Chloro-4-ethoxythieno[2,3-b]pyridine (186) -

Reaction of 4,6-dichlorothieno[2,3-b]pyridine (0.82g, 4mmol) with sodium ethoxide (from 0.115g, 5mg-atom, sodium) in ethanol (30ml), and isolation and purification of the product in the manner just described for (185) gave 6-chloro-4-ethoxythieno[2,3-b]pyridine (186) (0.52g, 49%), m.p. 70-82° (Found: C, 50.8; H, 3.8; N, 6.6. C_9H_8ClNOS requires C, 50.6; H, 3.7; N, 6.6%), δ ($CDCl_3$) 7.34 (2H, s, 2-H and 3-H), 6.69 (1H, s, 5-H), 4.69 (2H, q, J=7Hz, OCH_2CH_3), and 1.50 (3H, t, J=7Hz, OCH_2CH_3), ν_{max} 1580, and 1550 cm^{-1}.

4,6-Dimethoxythieno[2,3-b]pyridine (187) -

Dichloro-compound (141) (1.02g, 4mmol) was boiled under reflux in methanol (30ml) for 12h with sodium methoxide (from 0.92, 40mg-atom sodium); t.l.c.

then showed that very little reaction had taken place, so more methoxide (from 3.68g, 160mg-atom sodium) in methanol (30ml) was added and reaction was continued at reflux for a further 12h. The solution was cooled and added to water, the resulting precipitate was filtered off, washed with water, dried, and crystallised from light petroleum. Thus was obtained 4,6-dimethoxythieno-[2,3-b]pyridine (187) (0.56g, 57%), m.p. 50-52° (Found: C, 55.0; H, 4.6; N, 6.6. $C_9H_9NO_2S$ requires C, 55.4; H, 4.6; N, 7.2%), δ ($CDCl_3$) 7.28 (1H, d, J=6Hz, 2-H), 7.08 (1H, d, J=6Hz, 3-H), 6.12 (1H, s, 5-H), 3.98 (3H,s, OCH_3), and 3.89 (3H, s, OCH_3), ν_{max} 1590, and 1580 cm^{-1}.

Reaction of 4,6-Dichlorothieno[2,3-b]pyridine with Sodium Hydroxide in Dimethyl Sulphoxide-Water -

Thedichloro-compound (141) (1g) was heated on the steam-bath for 1h with a mixture of 4M-aqueous sodium hydroxide (20ml) and dimethyl sulphoxide (20ml). Water (110ml) was added, the whole was acidified (concentrated hydrochloric acid) and extracted with dichloromethane (3x). From the extracts was obtained an oil which, on trituration with water gave a solid. The latter was dissolved in the minimum volume of acetone and applied to a flash chromatography column; elution with ether (1 part)-light petroleum (4 parts) furnished two fractions. That of lower R_F (0.04g, 4%) had m.p. 234-238°, and was identified (i.r. spectrum, and mixed m.p.) as 4- chlorothieno[2,3-b]pyridin-6(7H)-one (142). The component of higher R_F was 6-chloro-4-hydroxythieno-[2,3-b]pyridine (188) (0.44g, 46%), m.p. 231-233° (decomp.) (Found: C, 45.0; H, 2.2; N, 7.0. C_7H_4ClNOS requires C, 45.3; H, 2.2; N, 7.5%), δ ($CDCl_3$-$(CD_3)_2$-SO) 7.43 (2H, s, 2-H and 3-H), and 6.78 (1H, s, 5-H), ν_{max} 2300-3200, 1600, 1570, and 1540 cm^{-1}.

Reaction of 4-Chlorothieno[2,3-b]pyridin-6(7H)-one with Triethyloxonium Tetrafluoroborate -

The title pyridone (1.06g, 5.7mmol) was stirred with dichloromethane (20ml) while triethyloxonium tetrafluoroborate (8ml of a 1M solution in dichloromethane) was added. After 2h at room temperature the mixture was treated with a further portion (4ml) of the reagent solution; stirring was continued for a further 48h. Evaporation of the washed (sodium hydrogen carbonate) and dried solution yielded an oil, shown by t.l.c. to consist of two components. The mixture was separated by flash-column chromatography; ethyl acetate (1 part)-light petroleum (4 parts) eluted the component of higher R_F, which was 4-chloro-6-ethoxythieno[2,3-b]pyridine (190) (0.07g, 6%), b.p. 120°/0.05mmHg, m.p. 65-67° (Found: C, 50.8, H, 3.8; N, 6.2. C_9H_8ClNOS requires C, 50.6; H, 3.8; N, 6.6%), δ ($CDCl_3$) 7.30 (2H, s, 2-H and 3-H), 6.83 (1H, s, 5-H), 4.47

(2H, q, J=7Hz, $OC\underline{H}_2CH_3$), and 1.42 (3H, t, J=7Hz, $OCH_2C\underline{H}_3$), ν_{max} 1580, and 1550 cm^{-1}. Elution of the column with ethyl acetate gave the major component, 4-chloro-7-ethylthieno[2,3-b]pyridine-6(7H)-one (189) (0.59g, 48%), m.p. 91-93° (from light petroleum) (Found: C, 50.2; H, 3.7; N, 6.3. C_9H_8ClNOS requires C, 50.6; H, 3.8; N,6.6%), δ ($CDCl_3$) 7.21 (1H, d, J=6Hz, 2-H), 7.00 (1H, d, J=6Hz, 3-H), 6.59 (1H, s, 5-H), 4.16 (2H, q, J=7Hz, $NC\underline{H}_2CH_3$), and 1.41 (3H, t, J=7Hz, $NCH_2C\underline{H}_3$), ν_{max} 1640, and 1530 cm^{-1}.

6-Methoxythieno[2,3-b]pyridine (191) -

6-Chlorothieno[2,3-b]pyridine (0.3g, 1.8mmol) was boiled under reflux with sodium methoxide (from 1.6g, 72mg-atom sodium) in methanol (60ml) for 20h. The product was isolated in the manner described for the preparation of (185); after the flash-column chromatography stage 6-methoxythieno[2,3-b]pyridine (191) (0.21g, 72%) was obtained as an oil, b.p. 100°/0.2mmHg, (Found: C, 55.6; H, 4.3; N, 8.3. C_8H_7NOS requires C, 58.2; H, 4.2; N, 8.5%), δ ($CDCl_3$) 7.86 (1H, d, J=8Hz, 4-H), 7.22 (1H, d, J=6Hz, 2-H), 7.09 (1H, d, J=6Hz, 3-H), 6.71 (1H, d, J=8Hz, 5-H), and 3.98 (3H, s, $OC\underline{H}_3$), ν_{max} (film) 1590, and 1560 cm^{-1}.

Ethyl 2,4-Dichloroquinoline-3-carboxylate (193) -

This compound was prepared by the method described by Grundon, McCorkindale and Roger[149] and had m.p. 101-103° (lit.[149] 104°), δ_C($CDCl_3$) 145.6 (C-2), 127.4 (C-3), 141.3 (C-4), 147.3 (C-9), 124.5 (C-10), 124.5, 128.6, 129.0, and 132.2 (C-5 - C-8).

Reaction of (193) with Sodium Ethoxide in Ethanol -

Sodium (0.46g, 0.02g-atom) was dissoved in ethanol and the solution was added to ethyl 2,4-dichloroquinoline-3-carboxylate (5.4g, 0.02mol) in ethanol (100ml). The mixture was set aside at toom temperature for 3 days, then added to water; the products were isolated by extraction into dichloromethane. Flash-column chromatography of the resulting oil, using ethyl acetate (1 part)-light petroleum (19 parts) as eluant, afforded three fractions. First to be eluted was slightly impure ethyl 4-chloro-2-ethoxyquinoline-3-carboxylate (195) (0.28g, 5%), as an oil, b.p. 150°/0.05mmHg, (Found: C, 61.3; H, 5.4; N, 4.4. $C_{14}H_{14}ClNO_3$ requires C, 60.1; H, 5.4; N, 4.4%), δ_H($CDCl_3$ 7.29-8.27 (4H, m, 5-H - 8H), 4.36-4.78 (4H, m, $2xOC\underline{H}_2CH_3$), and 1.30-1.55 (6H, m, $2xOCH_2C\underline{H}_3$); δ_C($CDCl_3$) 157.8 (C-2), 122.3 (C-3), 140.5 (C-4), 146.5 (C-9), 124.5, 125.2, 127.6, and 131.1 (C-5 - C-8) [no C-10 signal observed], ν_{max} (film) 1740, 1610, 1600, and 1560 cm^{-1}. This was followed by a very small quantity of unreacted (193), then by ethyl 2-chloro-4-ethoxyquinoline-3-carboxylate (194) (4.0g, 72%) as a solid, m.p. 55-57° (Found: C, 60.5; H, 5.2; N,

4.9. $C_{14}H_{14}ClNO_3$ requires C, 60.1; H, 5.0; N, 5.0%), $\delta_H(CDCl_3)$ 7.30-8.19 (4H, m, 5-H-8-H), 4.18-4.65 (4H, m, 2x$OC\underline{H}_2CH_3$), and 1.31-1.61 (6H, m, $OCH_2C\underline{H}_3$); $\delta_C(CDCl_3)$ 148.0 (C-2), 122.0 (C-3), 165.5 (C-4), 147.3 (C-9), 116.5 (C-10), 122.9, 126.9, 128.4, and 131.5 (C-5-C-8), ν_{max} 1730, 1610, and 1570 cm^{-1}.

2-Chloro-4(1H)-oxoquinoline-3-carboxylic Acid (196) -

The 2-chloro-4-ethoxyquinoline ester (194) (1.5g) was heated on the steam-bath for 30 minutes with a mixture of 4M-aqueous sodium hydroxide (30ml) and methylated spirits (30ml). The ethanol was removed by distillation and the remaining aqueous solution was kept on the steam-bath for a further 1h. When cool the solution was acidified with concentrated hydrochloric acid, the precipitate was filtered off, washed with water, and dried, to give the title acid (0.95g, 79%), m.p. 192-194° (decomp.), raised to 193-194° after crystallisation from methanol (lit.[149] 194-195°).

4-(1H)-Oxoquinoline-3-carboxylic Acid (198) -

The foregoing chloro-compound was converted into 2-hydrazino-4(1H)-oxoquinoline-3-carboxylic acid (197), m.p. 220-221° (decomp.) [lit.[149] 224° (decomp.)] and thence to the title oxo-acid (198), m.p. 262-264° (decomp.) [lit.[149] 264-266° (decomp.)] by methods described in the literature [149]. The proton n.m.r. and i.r. spectra of the product were identical to those of a sample of 4(1H)-oxoquinoline-3-carboxylic acid, m.p. 264-266° (decomp.) prepared by an alternative method from the literature[159] and there was no depression of m.p. when materials from the two sources were mixed.

4-Chloro-2(1H)-oxoquinoline-3-carboxylic Acid (200) -

Ethyl 2,4-dichloroquinoline 3-carboxylate (4g) was heated on the steam-bath for 3h with a mixture of 6M-aqueous hydrochloric acid (120ml) and dioxan (100ml), then the cooled solution was diluted with water. The precipitated solid was collected by filtration, washed with water, and dried, to provide ethyl 4-chloro-3-ethoxycarbonylquinolin-2(1H)-one (1.3g, 35%), m.p. 200-203° (lit.[149] 202-203°C). The oxo-ester was saponified by heating it on the steam-bath for 3h. with 2M-sodium hydroxide (30ml); acidification (concentrated hydrochloric acid) of the chilled solution yielded 4-chloro-2(1H)-oxoquinoline-3-carboxylic acid (200) (0.8g, 69%), m.p. 248-250°. The analytical sample (from methylated spirits) had m.p. 250-252° (decomp.) (Found: C, 53.7; H, 2.7; N, 6.6. $C_{10}H_6ClNO_3$ requires C, 53.7; H, 2.7; N, 6.3%), δ (D_2O-NaOD) 8.10-7.06 (m, 5-H-8-H), ν_{max} 3200-2500, 1740, 1630, 1590, and 1550 cm^{-1}.

Competitive Methoxydechlorination Reactions of 4-Chloroquinoline, 4-Chlorothieno[2,3-b]pyridine, and 7-Chlorothieno[3,2-b]pyridine (with G Bryant)

Equimolar amounts of pairs of the title compounds in methanol (total concentration 8% w/v) were boiled under reflux with one equivalent of sodium methoxide for 70h. The cooled solution was added to water and the organic material was extracted (4x) into dichloromethane. The extracts were washed with water, dried, and evaporated. The product composition was examined by ^{1}H n.m.r. (using the integrals of the methoxy protons to assess the relative proportions of the substitution products), and by g.l.c. (15% Carbowax 20M on 60-80 mesh Chromosorb W, 2m column, operated at 160°C). For the g.l.c. analysis the peaks due to the methoxylated products were weighed, allowance being made for the different response of the detector to the individuals. The results are presented in Table 9, in which the following symbols are employed:

A = 4-Chloroquinoline
B = 4-Chlorothieno[2,3-b]pyridine
C = 7-Chlorothieno[3,2-b]pyridine
D = 4-Methoxyquinoline
E = 4-Methoxythieno[2,3-b]pyridine
F = 7-Methoxythieno[3,2-b]pyridine

Table 9

Competitive Methoxydechlorinations of 4-Chloroquinoline and its Thieno[2,3-b]- and -[3,2-b]pyridine Analogues

Competing Pair	Ratio of Methoxylated Products	g.l.c.	^{1}H n.m.r.[a]
A + B	D:E	1.9:1	1.5:1
A + C	D:F	4.1:1	b
B + C	E:F	1.5:1	1.25:1

Notes: a, run in $CDCl_3$
b, OCH_3 peaks coincident

8.3 Work Described in Chapter Five

6-Bromothieno[3,2-b]pyridin-7(4H)-one (225) -

A solution of thieno[3,2-b]pyridin-7(4H)-one (212) (0.76g, 5mmol) in glacial acetic acid (20ml) at 40°C was treated, over 10 minutes, with bromine (1g, 6mmol) in the same solvent (10ml). After a further 10 minutes the solution was added to water, the precipitate (0.85g, 74%) was filtered off, washed with water, dried and crystallised from DMF-ethanol to provide the title bromocompound (0.46g), m.p. >300°C (Found: C, 36.2; H, 1.7; N, 5.7. C_7H_4BrNOS requires C, 36.5; H, 1.7; N, 6.1%), ν_{max} 3200, 3100-2300, 1610, 1590, and 1570-1480 cm^{-1}, δ [$(CD_3)_2SO$] 8.35 (1H, s, 5-H), 7.94 (1H, d, J=5.5Hz, 2-H), and 7.26 (1H, d, J=5.5Hz, 3-H).

3,6-Dibromothieno[3,2-b]pyridin-7(4H)-one (226) -

Thienopyridone (212) (0.76g, 5mmol) in glacial acetic acid (20ml) was treated under reflux with a solution of bromine (2g, 12.5mmol) in the same solvent (10ml), over 10 minutes. The mixture was boiled for a further 10 minutes, then water (30ml) was added. After 3 days the precipitate was collected by filtration, washed with water, and dried. The product (0.87g) was shown by t.l.c. (CH_2Cl_2-EtOH, 9:1) to consist of a major component of higher R_F, and a minor component. It was crystallised from methanol to yield 3,6-dibromothieno[3,2-b]pyridin-7(4H)-one (226) (0.32g, 20%), decomp. >270°C (Found: C, 26.9; H, 1.0; N, 4.4. $C_7H_3Br_2NOS$ requires C, 27.2; H, 1.0; N, 4.5%), ν_{max} 2100-2500, 1580, and 1540 cm^{-1}, δ [$(CD_3)_2SO$] 8.27 (1H, s, 5-H), and 8.22 (1H, s, 2-H). When this reaction was carried out in the presence of sodium acetate the product, after 2h under reflux, was a mixture of approximately equal amounts of the mono- (225) and dibromocompound (226).

6-Nitrothieno[3,2-b]pyridin-7(4H)-one (227) -

Compound (212) (1g) and nitric acid (15ml) were heated together on the steam-bath for 30 minutes. The cooled solution was added to ice water, the precipitate (0.46g) was collected, washed with water, dried, and crystallised from DMF, giving 6-nitrothieno[3,2-b]pyridin-7(4H)-one (227) (0.36g, 28%), m.p. >300°C (Found: C, 43.1; H, 1.9; N, 14.3. $C_7H_4N_2O_3S$ requires C, 42.9; H, 2.0; N, 14.3%), ν_{max} 3100-2300, 1600, and 1550 cm^{-1}, δ [$(CD_3)_2SO$] 9.12 (1H, s, 5-H), 8.20 (1H, d, J=5.5Hz, 2-H), and 7.41 (1H, d, J=5.5Hz, 3-H).

Nitrate Salt of Thieno[3,2-b]pyridin-7(4H)-one -

The thienopyridone (1.5g, 10mmol) was boiled under reflux for 30 minutes with a solution of nitric acid (2ml) in glacial acetic acid (20ml). On cooling a solid (1.7g) crystallised out; it was recrystallised from the same solvent to furnish

the title salt (1.4g, 65%), m.p. 182°C (decomp.) (Found: C, 39.5; H, 2.7; N, 13.4. $C_7H_6N_2O_4S$ requires C, 39.2; H, 2.8; N, 13.1%), ν_{max} 3300-2100, 1620, and 1510 cm^{-1}, δ [$(CD_3)_2SO$] 8.63 (1H, d, J=7.5Hz, 5-H), 8.46 (1H, d, J=5.5Hz, 2-H), 7.59 (1H, d, J=5.5Hz, 3-H), and 7.05 (1H, d, J=7.5Hz, 6-H).

3,6-Dinitrothieno[3,2-b]pyridin-7(4H)-one (228) -

A solution of nitric acid (6ml) in concentrated sulphuric acid (15ml) was cooled, and to it was added the thienopyridone (212) (1g), in portions, over 15 minutes, the temperature being maintained at 0.5°C. The cooled solution was stirred fora further 15 minutes, then set aside for 3 days at room temperature. It was added to water, the solid was collected by filtration, washed with water and dried giving the title dinitrocompound (228) (1.14g, 71%), m.p. >300°C after crystallisation from glacial acetic acid (Found: C, 34.9; H, 1.2; N, 17.3. $C_7H_3N_3O_5S$ requires C, 34.9; H, 1.2; N, 17.4%), ν_{max} 3300-2500, 1620, 1590, and 1550 cm^{-1}, δ [$(CD_3)_2SO$] 9.40 (1H, s, 5-H), and 8.83(1H, s, 2-H).

6-Diethylaminomethylthieno[3,2-b]pyridin-(4H)-one (229) -

A mixture of (212) (1.51g, 10mmol), aqueous formaldehyde (40%, 1ml, 13mmol), diethylamine (1.6g, 22mmol), and ethanol (100ml) was boiled under reflux for 6h; more formaldehyde solution (0.5ml) and diethylamine (0.8g) were added, and boiling was continued for a further 4h. The solution was evaporated to dryness and the residue was chromatographed on alumina; elution with dichloromethane-methanol (9:1) gave a sticky yellow solid (1.1g, 47%) which, on trituration with ether afforded the title base (229), m.p. 127-129°C (Found: C, 60.8; H, 6.6; N, 11.6. $C_{12}H_{16}N_2OS$ requires C, 61.0; H, 6.8; N, 11.9%), ν_{max} 3100-2300, 1600, and 1500 cm^{-1}, δ ($CDCl_3$) 8.12 (1H, s, 5-H), 7.62 (1H, d, J=5.5Hz, 2-H), 7.36 (1H, d, J=5.5Hz, 3-H), 3.89 (2H, s, $ArCH_2$), 2.72 (4H, q, J=7.5Hz, $2xCH_2CH_3$), and 1.14 (6H, t, J=7.5Hz, $2xCH_3$). A solution of the product (1g) in ethanol (10ml) was treated with oxalic acid (1g) in the same solvent. The precipitate was filtered off, washed with ethanol, and dried to give (229) oxalate having m.p. 164-166°C (decomp.) (from ethanol) (Found: C, 49.9; H, 5.4; N, 8.2. $C_{12}H_{16}N_2OS.C_2H_2O_4$ requires C, 51.5; H, 5.5; N, 8.6%), ν_{max} 3300-2500, 1720, 1620, 1580, and 1540 cm^{-1}, δ [$(CD_3)_2SO$] 8.22 (1H, s, 5-H), 8.05 (1H, d, J=5.5Hz, 2-H), 7.37 (1H, d, J=5.5Hz, 3-H), 4.19 (2H, s, $ArCH_2$), 3.12 (4H,q, J=7Hz, $2xCH_2CH_3$), and 1.28 (6H, t, J=7Hz, $2xCH_3$).

6-Bromo-4-methylthieno[3,2-b]pyridin-7(4H)-one (231) -

The N-methylthieno[3,2-b]pyridone (230) (0.66g, 4mmol) in glacial acetic acid (20ml) containing sodium acetate (0.33g, 4mmol) was treated at room temperature with a solution of bromine (0.64g, 4mmol) in glacial acetic acid (10ml). After 30 minutes the solution was diluted with water, made basic (4M-sodium hydroxide), and extracted with dichloromethane (x3). From the washed

(water) and dried extracts was obtained a solid which, on crystallisation from acetone-light petroleum, gave the title bromocompound (0.66g, 68%), m.p. 187-89°C (Found: C, 39.0; H, 2.4; N, 5.7. C_8H_6BrNOS requires C, 39.3; H, 2.5; N, 5.7%), ν_{max} 1610, 1570, and 1510 cm^{-1}, δ [$(CD_3)_2SO$-$CDCl_3$] 8.18 (1H, s, 5-H), 7.84 (1H, d, J=5.5Hz, 2-H), 7.29 ((1H, d, J=5.5Hz 3-H), and 3.93 (3H, s, CH_3). The same product was obtained when the reaction was repeated with a two-fold excess of bromine.

4-Methyl-6-nitrothieno[3,2-b]pyridin-7(4H)-one (232) -

Reaction of compound (230) (1g) with nitric acid (20ml) on the steam-bath for 2.5h, followed by addition to ice water yielded a solid (0.7g) which, after being washed with water, and dried, was crystallised from glacial acetic acid to give 4-methyl-6-nitrothieno[3,2-b]pyridin-7(4H)-one (232) (0.6g, 47%), m.p. 256-258°C (Found: C, 45.9; H, 2.7; N, 12.8. $C_8H_6N_2O_3S$ requires C, 45.7; H, 2.9; N, 13.3%), ν_{max} 1630, 1620, 1590, and 1520 cm^{-1}, δ [$(CD_3)_2SO$] 9.12 (1H, s, 5-H), 8.15 (1H, d, J=5.5Hz, 2-H), 7.48 (1H, d, J=5.5Hz, 3-H), and 3.98 (3H, s, CH_3).

4-Methyl-3,6-dinitrothieno[3,2-b]pyridin-7(4H)-one (233) -

Treatment of (230) 0.66g, 4mmol) with nitric acid (6ml) in sulphuric acid (15ml) in the manner described for the dinitration of (212) gave a solid (0.56g, 55%), m.p. 250°C (decomp.). After crystallisation from glacial acetic acid the dinitrocompound (233) had m.p. 252-254°C (decomp.) (Found: C, 37.4; H, 1.8; N, 16.2. $C_8H_5N_3O_5S$ requires C, 37.6; H, 2.0; N, 16.5%), ν_{max} 1630, 1540, and 1510 cm^{-1}, δ [$(CD_3)_2SO$] 9.33 (1H, s, 2-H), 9.20 (1H, s, 5-H), and 4.00 (3H, s, CH_3).

6-Diethylaminomethyl-7-hydroxythieno[3,2-b]pyridin-5(4H)-one (238) -

7-Hydroxythieno[3,2-b]pyridin-5(4H)-one (234) (1.67g, 10mmol) in ethanol (50ml) was added to a cold (-5°C) mixture of aqueous formaldehyde (40% w/v; 1.0ml, 13mmol), diethylamine (1.6g, 22mmol), and ethanol (10ml). The whole was set aside at -5°C for 40h, the solvent was removed in vacuo giving the title base (238) (2.1g, 83%), m.p. >300°C (Found: C, 57.0; H, 6.4; N, 11.1. $C_{12}H_{16}N_2O_2S$ requires C, 57.1; H, 6.3; N, 11.1%), ν_{max} 3100-2500, 1610, and 1570 cm^{-1}, δ (D_2O-NaOD) 7.58 (1H, d, J=5.5Hz, 2-H), 7.03 (1H, d, J=5.5Hz, 3-H), 3.82 (2H, s, $ArCH_2$), 2.74 (4H, q, J=7Hz, $2xCH_2CH_3$), and 1.14 (6H, t, J=7Hz, $2xCH_3$).

3,4-Dihydro-2-hydroxy-2-methylthieno[3,2-b]-2H-pyrano[2,3-d]pyridin-5(6H)-one (239) -

A solution of iodomethane (2.85g, 20mmol) and 4-dimethylaminobutan-2-one (2.85g, 20mmol) in ethanol (10ml) was added at room temperature over 30

minutes to a mixture of the thieno[3,2-b]pyridone (234) (1.67g, 10mmol) and potassium hydroxide (1.1g, 20mmol) in ethanol (25ml). The whole was boiled under reflux for 30 minutes, then cooled, and diluted with water (30ml). After neutralisation (concentrated hydrochloric acid) the mixture was further diluted with water (500ml) to yield a solid (1.4g, 59%) which was filtered off, washed with water, and dried. Thus was obtained the tricyclic substance (239), m.p. 210-213°C (decomp.). The analytical sample (from aqueous methanol) had m.p. 213-215°C (decomp.) (Found: C, 55.5; H, 4.7; N, 5.5. $C_{11}H_{11}NO_3S$ requires C, 55.7; H, 4.6; N, 5.9%), ν_{max} 3300-2500, 1630, and 1570 cm^{-1}. In trifluoroacetic acid the pyran ring in (239) is opened, and in this solvent the spectrum is that of 7-hydroxy-6-(2-oxobutan-4-yl)thieno[3,2-b]pyridin-5(4H)-one δ_H 7.97 (1H, d, J=5.5Hz, 2-H), 7.35 (1H, d, J=5.5Hz, 3-H), 3.09 (4H, br s, Ar $C\underline{H}_2C\underline{H}_2$) and 2.30 (3H, br s, $COCH_3$); δ_C 165.1 (CO), 162.3 (5-C), 159.8 (7-C), 142.1 (9-C), 136.5 (2-C), 120.0 (6-C), 117.2 (3-C), 27.7 ($\underline{C}H_2CO$ and $CO\underline{C}H_3$), and 15.7 ($Ar\underline{C}H_2$).

7-Hydroxy-3,6-dinitrothieno[3,2-b]pyridin-5(4H)-one (240) -

7-Hydroxythieno[3,2-b]pyridin-5(4H)-one (1.67g, 10mmol) was added over 15 minutes to a mixture of nitric (6ml) and concentrated sulphuric acid (15ml), at 0-5°C. The mixture was stirred at room temperature overnight, then added to water; the solid [1.7g, 66%; m.p. 180°C (decomp.)] was filtered off, washed with water, dried, and crystallised from glacial acetic acid to give the title dinitrocompound (240), m.p. 188°C (decomp.) (Found: C, 32.7; H, 1.1; N, 15.9. $C_7H_3N_3O_6S$ requires C, 32.7; H, 1.2; N, 16.3%), ν_{max} 3310, 1680, and 1510 cm^{-1}, δ [$(CD_3)_2SO$] 9.14 (s, 2-H).

6-Ethoxycarbonyl-7-hydroxy-3-nitrothieno[3,2-b]pyridin-5(4H)-one (241) -

Ester (237) (1.5g) was reacted with mixed acid (nitric, 6ml; sulphuric, 15ml) in the manner just described. The crude product (1.44g, 81%) was crystallised from aqueous acetic acid to yield the title nitrocompound (241), m.p. 205°C (decomp.) (Found: C, 42.0; H, 2.8; N, 9.7. $C_{10}H_8N_2O_6S$ requires C, 42.2; H, 2.8; N, 9.9%), ν_{max} 3320, 3120, 1660, 1600, and 1560 cm^{-1}, δ (CF_3CO_2H) 9.38 (1H, s, 2-H), 4.89 (2H, q, J=7Hz, CH_2), and 1.61 (3H, t, J=7Hz, CH_3).

Attempted Fries rearrangement of 7-Acetoxythieno[3,2-b]pyridin-5(4H)-one (242) -

The acetate (1.05g, 5mmol) and aluminium chloride (0.67g, 5mmol) were heated in nitrobenzene (10ml) on the steam-bath for 4h. The mixture was added to ice/4M hydrochloric acid and the whole distilled until the nitrobenzene had been removed. However, extraction of the resulting solution failed to yield any characterisable material.

6-Bromo-7-chlorothieno[3,2-b]pyridin-5(4H)-one (244) -

A boiling solution of 7-chlorothieno[3,2-b]pyridin-5(4H)-one (0.93g, 5mmol) in glacial acetic acid (50ml) was treated over 15 minutes, under reflux, with a solution of bromine (0.8g, 5mmol) in the same solvent (10ml). After a further 15 minutes at the boil the solution was cooled and poured into water. The washed (H_2O) and dried precipitate (1.1g, 83%) was crystallised from DMF-methanol to provide 6-bromo-7-chlorothieno[3,2-b]pyridin-5(4H)-one (0.98g), m.p. 290-292°C (decomp.) (Found: C, 31.5; H, 1.1; N, 5.1. $C_7H_3BrClNOS$ requires C, 31.8; H, 1.1; N, 5.3%), ν_{max} 3200-2300, and 1640 cm^{-1}, δ[$(CD_3)_2SO$-$CDCl_3$] 7.88 (1H, d, J=5.4Hz, 2-H), and 7.00 (1H, d, J=5.4Hz, 3-H).

6-Bromo-5,7-dimethoxythieno[3,2-b]pyridine (245) -

Bromine (0.4g, 2.5mmol) in glacial acetic acid (10ml) was added to a solution of 5,7-dimethoxythieno[3,2-b]pyridine (0.49g, 2.5mmol) in glacial acetic acid (10ml). The solution was stirred at room temperature for 48h, then added to sodium metabisulphite solution. The organic material was isolated by extraction into dichloromethane; it was an oil, and was shown by t.l.c. (EtOAc-light petroleum, 1:4) to consist of a mixture of the starting material and a product of higher R_F. By use of the same solvent mixture the compounds were separated by flash-column chromatography, which gave unreacted (243) (0.21g) and the title bromodimethoxycompound (245) (0.15g, 22%), m.p. 79-81°C (Found: C, 39.7; H, 2.9; N, 5.0. $C_9H_8BrNO_2S$ requires C, 39.4; H, 2.9; N, 5.1%), ν_{max} 1560, and 1540 cm^{-1}, δ ($CDCl_3$) 7.63 (1H, d, J=5.5Hz, 2-H), 7.35 (1H, d, J=5.5Hz, 3-H), 4.25 and 4.07 (6H, 2 x s, 2xCH_3).

6-Bromo-5-chloro-7-hydroxythieno[3,2-b]pyridine (246) -

Thienopyridine derivative (168) (0.56g, 3mmol) in glacial acetic acid (20ml) was treated with bromine (0.48g, 3mmol) in the same solvent (10ml) in the presence of sodium acetate (0.25g, 3mmol), at room temperature. The solid present after 10 minutes was filtered off, washed with water, dried, and crystallised from glacial acetic acid to afford the title bromocompound (0.7g, 88%), m.p. 297°C (decomp.) (Found: C, 31.4; H, 1.1; N, 5.1. $C_7H_3ClBrNOS$ requires C, 31.8; H, 1.1; N, 5.3%), ν_{max} 3000-2300, and 1580-1500 cm^{-1}, δ [$(CD_3)_2SO$] 8.20 (1H, d, J=5.5Hz, 2-H), and 7.46 (1H, d, J=5.5Hz, 3-H).

5-Bromo-4-hydroxythieno[2,3-b]pyridine (247) -

A solution of bromine (0.8g, 5mmol) in glacial acetic acid (10ml) was added to a solution of 4-hydroxythieno[2,3-b]pyridine (0.76g, 5mmol) and sodium acetate (0.41g, 5mmol) in the same solvent (20ml). The mixture was stirred at room temperature overnight, the solids were collected by filtration, washed with water, and dried to give 5-bromo-4-hydroxythieno[2,3-b]pyridine (247) (0.82g,

71%), m.p. 273°C. The analytical sample (from glacial acetic acid) had m.p. 276-278°C (Found: C, 36.3; H, 1.8; N, 6.1. C_7H_4BrNOS requires C, 36.5; H, 1.7; N, 6.1%), ν_{max} 3000-2300, 1590, and 1520 cm^{-1}, δ [$(CD_3)_2SO$] 8.41 (1H, s, 6-H), and 7.45 (2H, s, 2-H and 3-H).

5-Diethylaminomethyl-4-hydroxythieno[2,3-b]pyridine (248) -

4-Hydroxythieno[2,3-b]pyridine (1.51g, 10mmol) was added to a solution in ethanol (50ml) of aqueous formaldehyde (40%, 1ml, 13mmol) and diethylamine (1.6g, 22mol). After being kept 10 days at room temperature the solution was evaporated to dryness at room temperature (the product was decomposed when this evaporation was carried out at 60°C). The oil so obtained was subjected to flash-column chromatography (CH_2Cl_2-MeOH, 9:1) to give 5-diethylaminomethyl-4-hydroxythieno[2,3-b]pyridine (248) (1.8g, 76%), as a pale yellow oil, ν_{max} (film) 3100-2500, 1610, and 1550 cm^{-1}, δ ($CDCl_3$) 8.05 (1H, s, 6-H), 7.38 (1H, d, J=6Hz, 2-H), 7.28 (1H, d, J=6Hz, 3-H), 3.92 (2H, s, $ArC\underline{H}_2$), 2.71 (4H, q, J=7Hz, $2xC\underline{H}_2CH_3$), and 1.16 (6H, t, J=7Hz, $2xCH_3$). A solution of the product (1g) in ethanol (10ml) was treated with oxalic acid (1g) in the same solvent (10ml). The precipitate was filtered off, washed with ethanol, and dried at room temperature to give (248)oxalate (1.4g), m.p. 150-152°C (Found: C, 48.6; H, 5.2; N, 7.7. $C_{12}H_{16}N_2OS.1.5\ C_2H_2O_4$ requires C, 48.5; H, 5.1; N, 7.55%); ν_{max} 3200-2300, 1720, and 1610 cm^{-1}, δ [$(CD_3)_2SO$] 8.30 (1H, s, 6-H), 7.43 (2H, s, 2-H and 3-H), 4.21 (2H, s, $ArC\underline{H}_2$), 3.12 (4H, q, J=7Hz, $C\underline{H}_2$-CH_3), and 1.28 (6H, t, J=7Hz, $2xCH_3$).

2,5-Dibromo-4-hydroxythieno[2,3-b]pyridine (252) -

Bromine (1.6g, 10mmol) in glacial acetic acid (10ml) was added to a boiling solution of 4-hydroxythieno[2,3-b]pyridine (0.76g, 5mmol) and sodium acetate (0.82g, 10mmol) in glacial acetic acid (20ml). The whole was boiled under reflux for 10 minutes, then cooled and filtered. The residue was washed with water, and dried, to give the title dibromocompound (1.3g, 84%); a portion was crystallised from glacial acetic acid, when it had m.p. >300°C (Found: C, 27.3; H, 1.0; N, 4.4. $C_7H_3Br_2NOS$ requires C, 27.2; H, 1.0; N, 4.5%); ν_{max} 3100-2300, 1590, and 1520 cm^{-1}, δ [$(CD_3)_2SO$] 8.51 (1H, s, 6-H), and 7.71 (1H, s, 3-H).

2-Bromo-4-hydroxythieno[2,3-b]pyridine (251) -

2-Bromo-4-hydroxythieno[2,3-b]pyridine-5-carboxylic acid[201] (2g) was added over 10 minutes to boiling diphenyl ether (20ml), the solution was boiled under reflux for a further 10 minutes, then cooled and diluted with light petroleum (50ml). The precipitate was collected by filtration, washed with light petroleum, and dried, to give 2-bromo-4-hydroxythieno[2,3-b]pyridine (1.4g, 84%), m.p. 208-211°C. The analytical sample (from methanol-water) had m.p. 211-

213°C (Found: C, 36.2; H, 1.6; N, 6.1. C_7H_4BrNOS requires C, 36.5; H, 1.7; N, 6.1%), ν_{max} 3100-2100, δ [$(CD_3)_2SO$] 8.20 (1H, d, J=5.5Hz, 6-H), 7.53 (1H, s, 3-H), and 6.71 (1H, d, J=5.5Hz, 5-H).

Bromination of 2-Bromo-4-hydroxythieno[2,3-b]pyridine -

The foregoing bromocompound (0.46g, 2mmol) and sodium acetate (0.17g, 2mmol) were dissolved in glacial acetic acid and a solution of bromine (0.32g, 2mmol) in the same solvent (5ml) was added, over 10 minutes, at room temperature. The solution was stirred for a short time, then poured into water; the washed and dried precipitate of 2,5-dibromo-4-hydroxythieno[2,3-b]pyridine (0.5g, 81%) had m.p. 315°C (decomp.) and was identical to the product obtained by dibromination of (85).

Reaction of 4-Hydroxythieno[2,3-b]pyridine with Nitric Acid -

The hydroxycompound (1g) was heated with nitric acid (10ml) on the steam-bath for 10 minutes. The cooled solution was added to ice-water, the precipitate was filtered off, washed with water, and dried to give a solid (0.8g) which was shown by t.l.c. (SiO_2 : CH_2Cl_2-MeOH, 9:1) to be a mixture of two compounds. The products were separated by column chromatography (SiO_2 : CH_2Cl_2-MeOH, 9:1). The material of lower R_F (0.14g) was identical with 4-hydroxy-2,5-dinitrothieno[2,3-b]pyridine (254) (see below), and that of higher R_F was 4-hydroxy-2-nitrothieno[2,3-b]pyridine (253) (0.57g, 44%), m.p. 286°C (decomp.) (Found: C, 41.9; H, 2.4; N, 13.8. $C_7H_4N_2O_3S.0.25H_2O$ requires C, 41.9; H, 2.3; N, 14.0%); ν_{max} 3200-2200, 1630, and 1560-1520 cm^{-1}, δ [$(CD_3)_2$ SO] 8.26 (1H, d, J=5.5Hz, 6-H), 8.28 (1H, s, 3-H), and 6.68 (1H, d, J=5.5Hz, 5-H).

4-Hydroxy-2,5-dinitrothieno[2,3-b]pyridine (254) -

A solution of nitric acid (6ml) in concentrated sulphuric acid (15ml) was cooled, and to it was added 4-hydroxythieno[2,3-b]pyridine (1g), in portions, over 15 minutes, the temperature being maintained at 0-5°C. The cooled solution was stirred for a further 15 minutes, then set aside overnight at room temperature. It was added to water, the solid [0.46g, 29%, m.p. ca 290°C (decomp.)] was collected by filtration, washed with water, dried, and crystallised from glacial acetic acid to give the dinitrocompound, m.p. 299°C (decomp.) (Found: C, 34.4; H, 1.1; N, 16.9. $C_7H_3N_3O_5S$ requires C, 34.8; H, 1.2; N, 17.4%); ν_{max} 3200-2500, 1620, 1580, and 1540 cm^{-1}, δ [$(CD_3)_2SO$] 9.15 (1H, s, 6-H), and 8.25 (1H, s, 3-H).

4-Chloro-2-nitro-(257), 4-Chloro-5-nitro-(259), and 4-Chloro-2,5-dinitro-thieno-[2,3-b]pyridine (258) -

4-Hydroxythieno[2,3-b]pyridine (5g) was reacted with nitric acid (50ml) as

described above, but on this occasion the aqueous quench was neutralised by the addition of sodium hydrogen carbonate. The pH was then adjusted to 4 by the addition of acetic acid; the solid was filtered off, washed with water, dried, and crystallised from glacial acetic acid to give a mixture (3.6g) consisting of one major and two minor components. Three grams of the mixture was boiled under reflux for 3h with phosphoryl chloride (60ml), the excess of reagent was removed in vacuo, and the residue was added to water. The crude product (2.5g), isolated by extraction into dichloromethane, was dissolved in THF (30ml), the solution was diluted with light petroleum (200ml), and set aside in the refrigerator for 12h. The solid (1.6g) was filtered off and purified by flash-column chromatography (CH_2Cl_2) to give pure 4-chloro-2-nitrothieno[2,3-b]pyridine (257) (1.3g), m.p. 131-133°C (Found: C, 38.9; H, 1.1; N, 13.1. $C_7H_3ClN_2O_2S$ requires C, 39.2; H, 1.4; N, 13.05%); ν_{max} 1570, 1540, and 1510 cm^{-1}, δ ($CDCl_3$) 8.65 (1H, d, J=5Hz, 6-H), 8.26 (1H, s, 3-H), and 7.47 (1H, d, J=5Hz, 5-H). The original filtrate and the dichloromethane fractions from the purification of (257) were combined, evaporated to dryness, and subjected to flash-column chromatography (CH_2Cl_2). The earlier fractions contained (257) and the minor component of higher R_F; these fractions were evaporated to dryness and the residue was crystallised from THF-light petroleum as before to give further quantity (0.7g) of (257). The later fractions and the mother liquor from the crystallisation just described were combined and evaporated to dryness. Flash-column chromatography (CH_2Cl_2) of the resulting solid led to pure samples of the minor components. That with the greater R_F (110mg) was 4-chloro-5-nitrothieno[2,3-b]pyridine (259), m.p. 111-113°C (Found: C, 39.3; H, 1.4; N, 13.1. $C_7H_3ClN_2O_2S$ requires C, 39.2; H, 1.4; N, 13.05%); ν_{max} 1550, and 1510 cm^{-1}, δ ($CDCl_3$) 9.08 (1H, s, 6-H), 7.83 (1H, d, J=6Hz, 2-H), and 7.58 (1H, d, J=6Hz, 3-H). The product with the lower R_F (90mg) was 4-chloro-2,5-dinitrothieno[2,3-b]pyridine (258), m.p. 108-110°C, ν_{max} 1550 cm^{-1}, δ ($CDCl_3$) 8.83 (1H, s, 6-H), and 8.33 (1H, s, 3-H). A small proportion of persistent impurity led to poor microanalytical results for (258).

2-Acetylamino-4-chlorothieno[2,3-b]pyridine (260) -

4-Chloro-2-nitrothieno[2,3-b]pyridine (0.5g), reduced iron (1g), glacial acetic acid (20ml) and acetic anhydride (5ml) were heated together at 60-70°C for 0.5h. The cooled mixture was added to ice-water, the solid was filtered off, washed with water, and crystallised from aqueous ethanol to provide 2-acetylamino-4-chlorothieno[2,3-b]pyridine (0.38g, 72%), m.p. 244-246°C (decomp.) (Found: C, 47.2; H, 2.9; N, 12.1. $C_9H_7ClN_2OS$ requires C, 47.7; H, 3.1; N, 12.4%); ν_{max} 3250-2800, 1710, 1590, 1560, and 1530 cm^{-1}, δ [$(CD_3)_2SO$] 8.30 (1H, J=5Hz, 6-H), 7.43 (1H, d, J=5Hz, 5-H), 6.80 (1H, s, 3-H), and 2.19 (3H, s, CH_3).

2-Acetylaminothieno[2,3-b]pyridine (256) -

The foregoing chlorocompound (0.7g) was boiled under reflux with zinc powder (1.4g) in glacial acetic acid (50ml) for 4 days. The solids were filtered off, washed with glacial acetic acid, then dissolved in 4M-hydrochloric acid. Both acidic solutions were made basic with 4M-sodium hydroxide, and extracted with dichloromethane (x3); the combined extracts were dried and evaporated. Flash-column chromatography (EtOAc) of the residue yielded the title amide, m.p. 227-230°C (lit.[79] 235-236°C; lit.[107] 3-acetylaminothieno[2,3-b]pyridine 156-157°C), ν_{max} 3200-2800, 1690, 1590, 1570, and 1550, δ [$(CD_3)_2SO$-$CDCl_3$] 8.43 (1H, dd, J_{56}=4.5Hz, J_{46}=1.5Hz, 6-H), 8.03 (1H, dd, J_{45}=8Hz, J_{46}=1.5Hz, 4-H), 7.32 (1H, dd, J_{45}=8Hz, J_{56}=4.5Hz, 5-H), 6.91 (1H, s, 3-H), and 2.19 (3H, s, CH_3) (lit.[107] 6-H, 8.40; 4-H, 8.01; 5-H, 7.30; 3-H, 6.90; J_{45}=8Hz; J_{46}=1.5Hz).

5-Bromo-7-methylthieno[2,3-b]pyridin-4(7H)-one (262) -

Bromine (0.8g, 5mmol) in glacial acetic acid (20ml) was added to a solution of 7-methylthieno[2,3-b]pyridin-4(7H)-one (1.65g, 10mmol) and sodium acetate (0.42g, 5mmol) in acetic acid (30ml) at room temperature. Next day the mixture was added to water, the whole was made basic with 4M-sodium hydroxide and the products were isolated by extraction into dichloromethane (x3). Flash-column chromatography (CH_2Cl_2 - MeOH, 9:1) gave a solid (160mg), later identified as the dibromocompound (261), and 5-bromo-7-methylthieno-[2,3-b]pyridin-4(7H)-one (252) (0.72g, 59%), m.p. 224-226°C (from ethyl acetate) (Found: C, 39.3; H, 2.4; N, 5.7. C_8H_6BrNOS requires C, 39.3; H, 2.5; N, 5.7%), ν_{max} 1600, 1570, and 1510 cm^{-1}, δ [$(CD_3)_2SO$-$CDCl_3$] 8.28 (1H, s, 6-H), 7.40 (1H, d, J=6Hz, 2-H), 7.24 (1H, d, J=6Hz, 3-H), and 3.87 (3H, s, CH_3).

2,5-Dibromo-7-methylthieno[2,3-b]pyridin-4(7H)-one (261) -

A mixture of the thienopyridone (152) (0.66g, 4mmol), bromine (1.28g, 8mmol), sodium acetate (0.66g, 8mmol), and glacial acetic acid (30ml) was boiled under reflux for 15 minutes. The cooled solution was added to water, the precipitate was filtered off, washed with water, and dried to give the title dibromocompound (261) (1.1g, 85%), m.p. 266-269°C. The analytical sample (from methanol) had m.p. 268-270°C (Found: C, 29.9; H, 1.5; N, 4.3. $C_8H_5Br_2NOS$ requires C, 29.7; H, 1.6; N, 4.3%), ν_{max} 1600, 1580, and 1520 cm^{-1}, δ (CF_3CO_2H) 8.80 (1H, s, 6-H), 7.91 (1H, s, 3-H), and 4.41 (3H, s, CH_3).

7-Methyl-2-nitrothieno[2,3-b]pyridin-4(7H)-one (265) -

Compound (152) (1g) and nitric acid (20ml) were heated together on the steam-bath for 1.5h, then the cooled solution was added to ice-water. The mixture was neutralised (2M-sodium hydroxide) and extracted with dichloromethane (x3); the combined extracts were dried and evaporated to yield a solid which was shown by t.l.c. (SiO_2 : CH_2Cl_2-MeOH, 9:1) to contain one major, and

several minor components. The mixture was applied to a column of silica; elution firstly with ethyl acetate, then ethyl acetate-methanol (19:1) removed the minor components. 7-Methyl-2-nitrothieno[2,3-b]pyridin-4(7H)-one (265) (0.57g, 45%), m.p. 215-218°C was obtained by elution with dichloromethane-methanol (9:1) (Found: C, 45.6; H, 2.7; N, 13.3. $C_8H_6N_2O_3S$ requires C, 45.7; H, 2.9; N, 13.3%), ν_{max} 1620, 1590, and 1520 cm^{-1}, δ [$(CD_3)_2SO$] 8.23 (1H, s, 3-H), 7.98 (1H, d, J=7.5Hz, 6-H), 6.27 (1H, d, J=7.5Hz, 5-H), and 3.85 (3H, s, CH_3).

7-Methyl-2,5-dinitrothieno[2,3-b]pyridin-4(7H)-one (264) -

Compound (152) (1g) was added, over 10 minutes, to a cooled (0-5°C) stirred solution of nitric acid (6ml) in concentrated sulphuric acid (15ml). The solution was set aside at room temperature overnight, then added to water; the solid (0.56g) was collected by filtration, washed with water, dried, and crystallised from glacial acetic acid to yield the title dinitrocompound (0.42g, 27%), m.p. 289°C (decomp.) (Found: C, 38.0; H, 1.9; N, 16.3. $C_8H_5N_3O_5S$ requires C, 37.6; H, 2.0; N, 16.5%), ν_{max} 1640, 1530, and 1490 cm^{-1}, δ [$(CD_3)_2SO$] 9.36 (1H, s, 6-H), 8.37 (1H, s, 3-H), and 3.98 (3H, s, CH_3).

Conversion of (252) into (261) -

2,5-Dibromo-4-hydroxythieno[2,3-b]pyridine (252) (0.31g, 1mmol) was dissolved in a solution of potassium hydroxide (0.06g, 1mmol) in water (5ml), dimethyl sulphate (0.13g, 1mmol) was added and the whole was stirred for 1h. Further portions of alkali (0.06g) and dimethyl sulphate (0.13g) were added, and the mixture was stirred for 1h more. The precipitate was filtered off, washed with water, and dried, to give the N-methylthieno[2,3-b]pyridone (261) (0.3g, 93%), m.p. and mixed m.p. with the product of dibromination of (152) 267-269°C.

Conversion of (253) into (265) -

4-Hydroxy-2-nitrothieno[2,3-b]pyridine (253) (0.59g, 3mmol), dimethyl sulphate (0.4g, 3.3mmol), and potassium carbonate (0.62g, 4.5mmol) were stirred and heated under reflux in butanone (150ml) for 4h. The solvent was removed by distillation and the residue added to water and stirred for 0.5h. Extraction with dichloromethane (3x) and evaporation of the dried extracts yielded a semi-solid which was purified by column chromatography (alumina), eluting with chloroform. Thus was obtained the N-methylthieno[2,3-b]pyridone (265) (0.3g, 48%) having m.p. 205-210°C, undepressed by admixture with the product of nitration of (152).

5-Diethylaminomethyl-4-hydroxythieno[2,3-b]pyridin-6(7H)-one (272) -

4-Hydroxythieno[2,3-b]pyridin-6(7H)-one (0.83g, 5mmol) in ethanol (25ml) was added to a cold (-5°C) mixture of aqueous formaldehyde (40% w/v; 0.5ml,

6.5mmol), diethylamine (0.8g, 11mmol), and ethanol (5ml). The whole was set aside at -5°C for 40h, the solvent was removed in vacuo at room temperature and the base (1.1g, 92%) was crystallised from ethanol, when it had m.p. >350°C (Found: C, 56.6; H, 6.5; N, 11.0. $C_{12}H_{16}N_2O_2S$ requires C, 57.1; H, 6.35; N, 11.1%), ν_{max} 3300-2100, 1600, 1480, 1450, and 1425 cm^{-1}, δ (D_2O, internal standard $Me_3SiCH_2CH_2SO_3Na$) 7.23 (1H, d, J=6.5Hz, 2-H), 6.92 (1H, d, J=6.5Hz, 3-H), 4.22 (2H, s, $ArCH_2$), 3.21 (4H, q, J=7.7Hz, $2xCH_2CH_3$), and 1.36 (6H, t, J=7.7Hz, $2xCH_3$).

Bromination of 4-Hydroxythieno[2,3-b]pyridin-6(7H)-one with one Equivalent of Bromine -

Bromine (0.72g, 4.5mmol) in glacial acetic acid (20ml) was added, over 30 minutes, to a boiling solution of the thienopyridine derivative (134a) (0.83g, 5mmol) in acetic acid (80ml), under reflux; after a short time the solution was cooled and added to water. The solid so obtained was filtered off, washed with water, dried, and crystallised from aqueous DMF to yield a product (0.6g), m.p. 235°C (decomp.), mixed m.p. with pure 2-bromo-4-hydroxythieno[2,3-b]-pyridin-6(7H)-one [(274) see later] 240°C (decomp.). The ^1H n.m.r. spectrum of the product indicated that small amounts of the dibromocompound [(273), see below] and unreacted (134a) were present.

2,5-Dibromo4-hydroxythieno[2,3-b]pyridin-6(7H)-one (273) -

Thienopyridone (134a) (0.83g, 5mmol) in glacial acetic acid (60ml) was reacted as just described with bromine (1.6g, 10mmol) in acetic acid (10ml) to give the title dibromocompound (273) (0.9g, 56%), m.p. 230°C (decomp.) (from aqueous DMF) (Found: C, 25.8; H, 0.9; N, 4.3. $C_7H_3Br_2NO_2S$ requires C, 25.85; H, 0.9; N, 4.3%), ν_{max} 3000-2300, 1620, 1580, and 1560 cm^{-1}, δ [$(CD_3)_2SO$] 7.59 (s, 3-H).

5-Bromo-4-hydroxy-2-methylthieno[2,3-b]pyridin-6(7H)-one (276) -

A suspension of 4-hydroxy-2-methylthieno[2,3-b]pyridin-6(7H)-one (143c) (0.91g, 5mmol) in glacial acetic acid (20ml) was stirred at room temperature while bromine (0.8g, 5mmol) in the same solvent (10ml) was added over 5 minutes. The colourless mixture was added to water, the solid was filtered off, washed with water, and dried to give 1.15g (88%) of the essentially pure 5-bromo-4-hydroxythieno[2,3-b]pyridin-6(7H)-one (276). After crystallisation from glacial acetic acid the product (0.85g) had m.p. 238°C (decomp.) (Found: C, 36.7; H, 2.2; N, 5.4. $C_8H_6BrNO_2S$ requires C, 36.9; H, 2.3; N, 5.4%), ν_{max} 3300-2500, 1650, and 1510 cm^{-1}, δ [$(CD_3)_2SO$] 7.03 (1H, q, J=1.2Hz, 3-H), and 2.42 (3H, d, J=1.2Hz, CH_3).

2-Bromo-5-ethoxycarbonyl-4-hydroxythieno[2,3-b]pyridin-6(7H)-one (277) -

Treatment of the ester (133a) (1.2g, 5mmol) in hot acetic acid (50ml) with bromine (0.8g, 5mmol) in acetic acid (10ml), followed, after 2h, by addition to water gave a precipitate of the title bromocompound (1.4g). After crystallisation from aqueous acetic acid the substance (1.0g, 63%) had m.p. 234-236°C (decomp.) (Found: C, 37.9; H, 2.5; N, 4.2. $C_{10}H_8BrNO_4S$ requires C, 37.7; H, 2.5; N, 4.4%), ν_{max} 3000-2300, 1660-1610, 1430, and 1230 cm^{-1}, δ [$(CD_3)_2SO$] 7.46 (1H, s, 3-H), 4.36 (2H, q, J=7Hz, CH_2), and 1.31 (3H, t, J=7Hz, CH_3).

2-Bromo-4-hydroxythieno[2,3-b]pyridin-6(7H)-one (274) -

The bromo ester (277) (2g) was saponified in the manner described earlier for the preparation of (134a) from (133a). The solid product obtained on acidification was crystallised from aqueous DMF to give the title bromothieno[2,3-b]pyridone (0.92g, 59%), m.p. 248-250°C (decomp.) (Found: C, 34.5; H, 1.6; N, 5.8. $C_7H_4BrNO_2S$ requires C, 34.2; H, 1.6; N, 5.7%), ν_{max} 3100-2500, 1660-1610, 1560, and 1440 cm^{-1}, δ [$(CD_3)_2SO$] 7.25 (1H, s, 3-H), and 5.81 (1H, s, 5-H); the latter signal disappeared on the addition of D_2O.

5-Ethoxycarbonyl-4-hydroxy-2-nitrothieno[2,3-b]pyridin-6(7H)-one (278) -

Ester (133a) (1.2g, 5mmol) in hot glacial acetic acid (30ml) was treated, in one lot, with nitric acid (0.5ml, 8mmol). The mixture was stirred and heated for a further 5 minutes, then cooled; the precipitate (1.2g) was filtered off, washed with light petroleum, then crystallised from DMSO-ethanol to afford the nitrocompound (278) (0.9g, 63%), m.p. 245°C (decomp.) (Found: C, 42.5; H, 2.9; N, 10.1. $C_{10}H_8N_2O_6S$ requires C, 42.3; H, 2.8; N, 9.9%), ν_{max} 3000-2300, 1650, 1580, and 1560 cm^{-1}, δ (CF_3CO_2H) 8.13 (1H, s, 3-H), 8.48 (2H, q, J=7Hz, CH_2), and 1.30 (3H, t, J=7Hz, CH_3).

2-Ethoxycarbonyl-N-(5-bromo-3-ethoxycarbonyl-2-thienyl)acetamide (279) -

Bromine (8.7g, 54mmol) in glacial acetic acid (20ml) was added over 15 minutes at room temperature to a stirred solution of 2-ethoxycarbonyl-N-(3-ethoxycarbonyl-2-thienyl)acetamide (15.5g, 54mmol) in glacial acetic acid (70ml). Next day the mixture was added water, the solid was filtered off and dissolved in dichloromethane; the solution was washed with sodium hydrogen carbonate solution, then dried and concentrated to small volume. On the addition of light petroleum a solid was obtained which, on crystallisation from methylated spirits, gave the title bromocompound (7.2g, 37%), m.p. 105-107°C (Found: C, 37.5; H, 3.8; N, 3.8. $C_{12}H_{14}BrNO_5S$ requires C, 39.6; H, 3.9; N, 3.8%), ν_{max} 3190, 1720, 1690, 1670, and 1540 cm^{-1}, δ ($CDCl_3$) 7.24 (1H, s,

ArH), 4.38 (4H, m, 2xOCH$_2$), 3.58 (2H, s, COCH$_2$CO), and 1.37 (6H, m, 2xCH$_3$).

2-Ethoxycarbonyl-N-(3-ethoxycarbonyl-5-nitro-2-thienyl)acetamide (280) -

2-Ethoxycarbonyl-N-(3-ethoxycarbonyl-2-thienyl)acetamide (2.85g, 10mmol) was dissolved in concentrated sulphuric acid (20ml) and a mixture of fuming nitric acid (0.45ml, 10.2mmol) and concentrated sulphuric acid (2ml) was added to the cooled (0-5°C) solution over 15 minutes. After a further 10 minutes at 0-5°C the mixture was added to ice water, the solid was filtered off and dissolved in dichloromethane. After being washed successively with water, sodium hydrogen carbonate solution, and water the solution was evaporated; trituration of the residue with ether gave the nitrocompound (2g, 61%). When crystallised from ethanol it (1.3g) had m.p. 126-128°C (Found: C, 43.4; H, 4.3; N, 8.5. $C_{12}H_{14}N_2O_7S$ requires C, 43.6; H, 4.2; N, 8.5), ν_{max} 3190, 1720, 1690, and 1550 cm^{-1}, δ ($CDCl_3$) 8.11 (1H, s, ArH), 4.40 (4H, m, 2xOCH$_2$), 3.66 (2H, s, COCH$_2$CO), and 1.36 (6H, m, 2xCH$_3$).

2-Ethoxycarbonyl-N-(5-bromo-3-carboxy-2-thienyl)acetamide (282) -

2-Ethoxycarbonyl-N-(3-t-butyloxycarbonyl-2-thienyl)acetamide (135) (15.5g, 50mmol) in glacial acetic acid (100ml) was reacted at room temperature with bromine (8.0g, 50mmol) in the same solvent (30ml). After 1h the solution was added to water, the precipitate was collected by filtration, washed with light petroleum, and recrystallised from ethanol to give the title acetamide (6g, 36%), m.p. 164-166°C (Found: C, 35.7; H, 2.9; N, 4.2. $C_{10}H_{10}BrNO_5S$ requires C, 35.7; H, 3.0; N, 4.2%), ν_{max} 3200, 3100-2700, 1730, 1670, and 1530 cm^{-1}, δ [$(CD_3)_2SO$] 7.32 (1H, s, ArH), 4.22 (2H, q, J=7Hz, OCH$_2$), 3.85 (2H, s, COCH$_2$CO), and 1.26 (3H, t, J=7Hz, CH$_3$).

4,6-Dichloro-2-methylthieno[2,3-b]pyridine (285) -

A mixture of the hydroxythieno[2,3-b]pyridone (134c) (2g) and phenylphosphonic dichloride (6ml) was heated at 170-180°C for 1h, then cooled and poured into water. After being stirred for 30 minutes the whole was extracted with dichloromethane (x3); removal of solvent from the combined, dried extracts afforded a solid which was digested with boiling light petroleum. Flash-column chromatography (EtOAc-light petroleum, 1:9) of the light petroleum soluble material gave 4,6-dichloro-2-methylthieno[2,3-b]pyridine (0.5g, 21%), m.p. 74-76°C (from light petroleum) (Found: C, 44.5; H, 2.3; N, 6.3. $C_8H_5Cl_2NS$ requires C, 44.0; H, 2.3; N, 6.4%), ν_{max} 1560 and 1510 cm^{-1}, δ ($CDCl_3$) 7.31 (1H, s, 5-H), 7.08 (1H, q, J=1.2Hz, 3-H), and 2.62 (3H, d, J=1.2Hz, CH$_3$).

Reaction of 2-Bromo-4-hydroxythieno[2,3-b]pyridin-6(7H)-one (274) with Phenylphosphonic Dichloride -

Compound (274) (6g) and the reagent (18ml) were heated together at 160-170°C

for 45 minutes; the mixture was cooled, added to water, and the aqueous phase was extracted with dichloromethane (x3). The combined extracts were washed with sodium hydrogen carbonate solution, dried, and evaporated. The solid residue was digested with a mixture of ethyl acetate (1 part) and light petroleum (9 parts), to give soluble and insoluble fractions. The soluble material was purified by column chromatography on alumina (EtOAc-light petroleum, 1:9), followed by crystallisation from light petroleum, to give 2-bromo-4,6-dichlorothieno[2,3-b]pyridine (283) (2.2g, 32%), m.p. 101-103°C (Found: C, 29.7; H, 0.8; N, 5.0. $C_7H_2BrCl_2NS$ requires C, 29.7; H, 0.7; N, 5.0%), ν_{max} 1560 and 1540 cm^{-1}, δ ($CDCl_3$) 7.47 (1H, s, 3-H), and 7.37 (2H, s, 5-H). The insoluble portion was crystallised from methanol, to yield 2-bromo-4-chlorothieno[2,3-b]pyridin-6(7H)-one (284) (0.68g, 10%), m.p. 247-249°C (decomp.) (Found: C, 31.9; H, 1.2; N, 5.3. $C_7H_3BrClNOS$ requires C, 31.8; H, 1.1; N, 5.3%), ν_{max} 3200-2500, 1650, 1590, and 1560 cm^{-1}, δ [$(CD_3)_2SO$] 7.42 (1H, s, 3-H), and 6.78 (1H, s, 5-H).

Reaction of 2-Bromo-4,6-dichlorothieno[2,3-b]pyridine with n-Butyllithium-Iodomethane -

A solution of (283) (0.85g, 3mmol) in ether (20ml)-THF (20ml) was stirred at -70°C under nitrogen while a solution of n-butyllithium (1.55M in hexane; 2ml, 3.1mmol) was added. After 15 minutes iodomethane (0.51g, 3.6mmol) in THF (10ml) was added (over 5 minutes), then the mixture was allowed to warm to room temperature (2h). Water was added, the aqueous phase was saturated with sodium choride, and the organic products were isolated by extraction into ether. Initial purification was by flash-column chromatography (EtOAc-light petroleum, 1:9), then the two compounds that were eluted were separated by column chromatography on alumina (light petroleum-THF, 49:1). The product of higher R_F (0.26g, 40%) was identical to the 4,6-dichloro-2-methylthieno[2,3-b]pyridine (285) that had been prepared via (134c). The second substance (0.19g, 31%) was shown by mixed m.p. to be 4,6-dichlorothieno[2,3-b]pyridine.

Bromination of 4-Chlorothieno[2,3-b]pyridin-6(7H)-one -

The title chlorocompound (1.23g, 6.6mmol) in glacial acetic acid (30ml) was treated with bromine (1.06g, 6.6mmol) in the same solvent (10ml) at room temperature. After a short time the precipitate (1.4g, 80%) was collected by filtration then recrystallised from glacial acetic acid to give 2-bromo-4-chlorothieno[2,3-b]pyridin-6(7H)-one (284) (1.2g), m.p. 247-249°C, identical in all respects with the by-product from the chlorination of (274) (qv).

2,5-Dibromo-4-chlorothieno[2,3-b]pyridin-6(7H)-one (286) -

Bromothienopyridone (284) (1.2g, 4.5mmol), bromine (0.73g, 4.5mmol) and glacial acetic acid (30ml) were boiled together under reflux for 35 minutes,

then the mixture was cooled. The precipitate was filtered off, washed with water, and dried, providing the title dibromocompound (286) (1.13g, 72%), m.p. 290-293°C (decomp.). The analytical sample (from glacial acetic acid) had m.p. 294-296°C (decomp.) (Found: C, 24.3; H, 0.5; N, 4.0. $C_7H_2Br_2ClNOS$ requires C, 24.4; H, 0.6; N, 4.1%), ν_{max} 3200-2500, 1650, and 1540 cm^{-1}, δ [$(CD_3)_2SO$] 7.44 (s, 3-H).

8.4 Work Described in Chapter Six

5H-Thieno[3,2-d][1,3]oxazin-5,7(4H)-dione (292) -

Methyl 3-aminothiophene-2-carboxylate (31.4g, 0.2mmol) was boiled under reflux in a solution of potassium hydroxide (21.4g, 0.4mol) for 1h. The cooled solution was treated with solid carbon dioxide until it had pH9. A solution of phosgene in toluene (20%, 119ml, 0.24mol) was added with vigorous stirring at 15-20° over 1h and stirring continued for 0.5h. The precipitate was collected by filtration, washed with water then light petroleum, and dried under vacuum at room temperature. Recrystallisation from glacial acetic acid afforded the title thienooxazine derivative (23.4g, 69%) having m.p. 218°C (decomp.) (lit.[208] m.p. 220-221°C), (Found: C, 42.7; H, 1.8; N, 8.5. Calculated for $C_6H_3NO_3S$ C, 42.6; H, 1.8; N, 8.3%), δ [$(CD_3)_2SO$] 8.28 (1H, d, J=5.5Hz, 2-H), and 7.00 (1H, d, J=5.5Hz, 3-H), ν_{max} 3300-2800, 1800-1700, 1570, and 1530 cm^{-1}.

6H-Thieno[2,3-d][1,3]oxazin-4,6(7H)-dione (295) -

This was prepared in the manner described for (294) from methyl 2-aminothiophene-3-carboxylate (31.4g, 0.2mol). The crude material (which was coloured brown) was purified by slurrying with ethanol (200ml) followed by drying at room temperature under vacuum. Thus was produced the title oxazine derivative (19.9g, 59%) as an off-white solid having m.p. 215°C (decomp.) (Found: C, 42.5; H, 1.9; N, 8.2. $C_6H_3NO_3S$ requires C, 42.6; H, 1.8; N, 8.3%), δ [$(CD_3)_2SO$] 7.24 (2H, s, 2-H and 3-H), ν_{max} 3300-2500, 1770, 1710, 1550, and 1530 cm^{-1}.

5H-4-Methylthieno[3,2-d][1,3]oxazin-5,7-dione (296) -

Sodium hydride (2.64g, 0.11mol) was suspended in dimethyl acetamide (DMA, 40ml) under a nitrogen atmosphere and a solution of (294) (16.9g, 0.1mol) in DMA (100ml) was added at 5-10°C over 15 minutes then stirred for a further 0.5h. A solution of dimethyl sulphate (15.1g, 0.12mol) was added at 5-10°C over 0.5h and the mixture stired at room temperature overnight. It was then added to ice-water and the precipitated solid was collected, washed with water, and dissolved in dichloromethane. The residue obtained on evaporation of the dried solution was recrystallised from ethyl acetate giving the title N-Methyl compound (11.5g, 62%) as a white solid m.p. 188°C (decomp.) (Found:

C, 46.2; H, 2.8; N, 7.9. $C_7H_5NO_3S$ requires C, 45.9; H, 2.7; N, 7.6%), δ [$(C\underline{D}_3)_2SO$] 8.25 (1H, d, J=5.5Hz, 2-H), 7.26 (1H, d, J=5.5Hz, 3-H), and 3.52 (3H, s, N-C$\underline{H}_3$), ν_{max} 1770, 1720, and 1570 cm^{-1}.

6H-7-Methylthieno[2,3-d][1,3]oxazin-4,6-dione (297) -

This was prepared from (295) (16.9g, 0.1mol) in the manner previously described for (296). The (dark brown) crude product was purified by firstly slurrying with ethyl acetate then recrystallisation from ethyl acetate giving the title N-methyl derivative (5.9g, 32%) as a white solid having m.p. 180°C (decomp.) (Found: C, 46.0; H, 2.7; N, 7.9. $C_7H_5NO_3S$ requires C, 45.9; H, 2.7; N, 7.7%), δ [$(CD_3)_2SO$] 7.22 (2H, s, 2-H and 3-H), and 3.42 (3H, s, N-C$\underline{H}_3$), ν_{max} 1780, 1730, 1550, and 1510 cm^{-1}.

5H-4-Methoxymethylthieno[3,2-d][1,3]oxazin-5,7-dione (298) -

Sodium hydride (5.3g, 0.22mol) was suspended in DMA (50ml) under a nitrogen atmosphere and a solution of (294) (33.8g, 0.2mol) in DMA (250ml) was added at 5-10°C over 15 minutes and stirring continued for a further 0.5h. A solution of chloromethyl methyl ether (19.3g, 0.24mol) in DMA (50ml) was added at 5-10°C over 15 minutes and the whole stirred at room temperature under nitrogen overnight. The mixture was poured into ice-water (2l) and the precipitate collected, washed with water, and dissolved in dichloromethane. The residue obtained upon evaporation of the dried solution was recrystallised from ethyl acetate giving the N-methoxymethyl compound (30.1g, 70%) having m.p. 128-130°C (Found: C, 44.6; H, 3.1; N, 6.5. $C_8H_7NO_4S$ requires C, 45.1; H, 3.3; N, 6.6%), δ ($CDCl_3$) 7.98 (1H, d, J=5.5Hz, 2-H), 7.17 (1H, d, J=5.5Hz, 3-H), 5.45 (2H, s, N-C$\underline{H}_2$O-), and 3.46 (3H, s, $CH_2OC\underline{H}_3$), ν_{max} 1770, 1720, and 1560 cm^{-1}.

Attempted preparation of 6H-7-Methoxymethylthieno[2,3-d][1,3]oxazin-4,6-dione (299) -

The preparation of this material was attempted in the manner described for (298) from (295) (33.8g). However, the product obtained on adding the reaction mixture to water was mostly insoluble in dichloromethane, the soluble material recovered upon evaporation of the solvent was a black tar. Since no product having the properties expected for the required material could be isolated the reaction was abandoned.

5H-4-Benzylthieno[3,2-d][1,3]oxazin-5,7-dione (300) -

Benzyl bromide (5.6g, 0.033mol), (294) (5.1g, 0.03mol), and potassium carbonate (6.2g, 0.045mol) were stirred in DMA (80ml) for 24h then the mixture was added to water (1l). The precipitated solid was collected, washed with water, and dissolved in dichloromethane. The residue obtained upon evaporation of

the dried solution was washed with light petroleum then recrystallised from ethyl acetate afforded the N-benzyl derivative (4.7g, 60%) m.p. 159-161°C (Found: C, 60.5; H, 3.4; N, 5.5. $C_{13}H_9NO_3S$ requires C, 60.2; H, 3.5; N, 5.4%), δ [$(CD_3)_2SO$] 8.28 (1H, d, J=5.5Hz, 2-H), 7.36 (5H, s, CH_2Ph), 7.25 (1H, d, J=5.5Hz, 3-H), and 5.24 (2H, s, CH_2Ph), ν_{max} 1770, 1720, and 1560 cm^{-1}.

Preparation of thienopyridine analogues of 2-Aryl-1-methyl-4-quinolone alkaloids (303) - (310)

General Procedure -

To a solution of diisopropylamine (2.02g, 0.02mol) in tetrahydrofuran (THF, 50ml) under a nitrogen atmosphere was added n-butyllithium (2.5M in hexane, 8ml, 0.02mol) at -30°C. After cooling to -65°C a solution of the acetophenone (0.02mol) in THF (20ml) was added dropwise over 15 minutes and the mixture stirred at -65°C for 1h. Then a suspension of the oxazin-dione [(296) or (297), 0.01mol] in THF (50mol) was added over 10 minutes and the mixture allowed to warm to 0° and held at that temperature for 1h. The mixture was quenched with saturated ammonium chloride solution (1l) and extracted with dichloromethane (3x). The oil remaining after evaporation of the combined, dried, extracts was dissolved in toluene (50ml) and boiled under reflux with p-toluene sulphonic acid (0.1g) for 0.5h. After removal of the solvent the residue was subjected flash-column chromatography (ethyl acetate[19 parts] - methanol [1 part]) giving the desired thienopyridone. The analytical samples were further purified by recrystallisation from ethyl acetate. In this manner the following thienopyridones were produced:

4-Methyl-5-phenylthieno[3,2-b]pyridin-7-one (303) -

From (296) and acetophenone was produced the title thienopyridone (303) (0.74g, 31%) having m.p. 181-183°C (Found: C, 68.6; H, 4.6; N, 5.7. $C_{14}H_{11}NOS.0.25H_2O$ requires C, 68.4; H, 4.6; N, 5.7%), δ ($CDCl_3$) 7.73 (1H, d, J=5.5Hz, 2-H), 7.46 (5H, s, Ar-Ph), 7.19 (1H, d, J=5.5Hz, 3-H), 6.29 (1H,s, 6-H), and 3.62 (3H, s, N-CH_3), ν_{max} 1610 cm^{-1}.

7-Methyl-6-phenylthieno[2,3-b]pyridin-4-one (307) -

From (297) and acetophenone was produced the title thieno[2,3-b]pyridine (307) (0.31g, 13%), having m.p. 138-141°C (Found: C, 68.8; H, 4.7; N, 5.9. $C_{14}H_{11}NOS.0.25H_2O$ requires C, 68.4; H, 4.7; N, 5.9%), δ ($CDCl_3$) 7.70 (1H, d, J=6Hz, 2-H), 7.45 (5H, m, Ar-Ph), 7.02 (1H, d, J=6Hz, 3-H), 6.31 (1H, s, 5-H), and 3.69 (3H, s, N-CH_3), ν_{max} 1610cm^{-1}.

4-Methyl-5-(3,4-methylenedioxyphenyl)thieno[3,2-b]pyridin-7-one (305) -

From (296) and 3',4'-methylenedioxyacetophenone was obtained the title

methylenedioxyphenyl derivative (305) (0.85g, 30%) having m.p. 246-248°C (Found: C, 63.1; H, 3.8; N, 4.8. $C_{15}H_{11}NO_3S$ requires C, 63.2; H, 3.9; N, 4.9%), δ [$(CD_3)_2SO$] 8.15 (1H, d, J=5.5Hz, 2-H), 7.60 (1H, d, J=5.5Hz, 3-H), 7.20 (1H, s, 1xAr-H), 7.10 (2H, s, 2xAr-H), 6.17 (2H, s, -OCH_2O-), 6.01 (1H, s, 6-H), and 3.66 (3H, s, N-CH_3), ν_{max} 1600, 1590, and 1550 cm^{-1}.

7-Methyl-6-(3,4-methylenedioxyphenyl)thieno[2,3-b]pyridin-4-one (309) -

From (297) and 3',4'-methylenedioxyacetophenone was obtained the title 3,4-methylenedioxyphenyl derivative (0.42g, 15%) having m.p. 175-177°C (Found: C, 63.5; H, 3.9; N, 4.9. $C_{15}H_{11}NO_3S$ requires C, 63.2; H, 3.9; N, 4.9%), δ [$(CD_3)_2SO$] 7.33 (2H, s, 3-H and 2-H), 7.13 (1H, s, 1xAr-H), 7.02 (2H, s, 2xAr-H), 6.11 (2H, s, -OCH_2O-), 5.98 (1H, s, 5-H), and 3.55 (3H, s, N-CH_3), ν_{max} 1610, 1550, and 1500 cm^{-1}.

5-(3,4-Dimethoxyphenyl)-4-methylthieno[3,2-b]pyridin-7-one (304) -

From (296) and 3',4'-dimethoxyacetophenone was obtained the title 3,4-dimethoxyphenyl derivative (304) (0.81g, 28%) having m.p. 254-256°C (Found: C, 64.2; H, 4.9; N, 4.8. $C_{16}H_{15}NO_3S$ requires C, 63.8; H, 5.0; N, 4.7%), δ ($CDCl_3$) 7.80 (1H, d, J=5.5Hz, 2-H), 7.27 (1H, d, J=5.5Hz, 3-H), 7.04 (3H, s, 3xAr-H), 6.34 (1H, s, 6-H), 3.98 (3H, s, 1xOMe), 3.94 (3H, s, 1xOMe), and 3.70 (3H, s, N-CH_3), ν_{max} 1600, 1560, 1530, and 1510 cm^{-1}.

6-(3,4-Dimethoxyphenyl)-7-methylthieno[2,3-b]pyridin-4-one (308) -

From (297) and 3',4'-dimethoxyacetophenone was obtained the title 3,4-dimethoxyphenyl derivative (308) (0.37g, 12%) having m.p. 202-204°C (Found: C, 63.6; H, 5.1; N, 5.0. $C_{16}H_{15}NO_3S$ requires C, 63.8; H, 5.0; N, 4.7%), δ [$(CD_3)_2SO$] 7.44 (2H, s, 2-H and 3-H), 7.17 (3H, s, 3xAr-H), 6.10 (1H, s, 5-H), 3.89 (6H, s, 2xOMe), and 3.63 (3H, s, N-CH_3), ν_{max} 1600, 1560, and 1510 cm^{-1}.

Attempted preparation of 6-Methoxy-4-methyl-5-phenylthieno[3,2-b]pyridin-7-one (306) -

When (296) and 2-methoxyacetophenone were used in the above general procedure none of the required (306) could be isolated. Thin layer chromatography of the reaction mixture showed the absence of starting material (296) and the yellow colour indicated the presence of an o-aminoketone. However, when subjected to the cyclisation conditions a very dark solution was obtained which showed only the 2-methoxyacetophenone and dark baseline material upon thin layer chromatography, no spot corresponding to the required product (306) was observed.

Attempted preparation of 5-Methoxy-7-methyl-6-phenylthieno[2,3-b]-pyridin-4-one (310)

When (297) and 2-methoxyacetophenone were subjected to the above general procedure a similar result to that observed in the attempted preparation of (306) was observed.

8.5 Work Described in Chapter Seven

6,7-Dihydro-4-methylfuro[2,3-d]thieno[3,2-b]pyridin-5-one (316) -

A solution of α-(O,O-diethylphosphono)-γ-butyrolactone (315) (2.22g, 0.01mol) in DMF (20ml) was added under nitrogen to a suspension of sodium hydride (0.24g, 0.01mol) in DMF (10ml) over 10 minutes then stirred at 40°C for a further 10 minutes. To the resulting solution was added a solution of 5H-4-methylthieno[3,2-d][1,3]oxazin-5,7-dione (296) (1.83g, 0.01mol) in DMF (10ml) and the whole was stirred at 110-120° for 1h. The DMF was distilled off under vacuum and the residue added to water (100ml) and extracted with dichloromethane (x3). Evaporation of the dried solution furnished a solid which upon recrystallisation from ethyl acetate gave the title furothienopyridine (1.4g, 68%) having m.p. 248-250°C (decomp). (Found: C, 58.3; H, 4.3; N, 6.4. $C_{10}H_9NO_2S$ requires C, 58.0; H, 4.4; N, 6.8%), δ ($CDCl_3$) 7.57 (1H, d, J=5.5Hz, 2-H), 7.07 (1H, d, J=5.5Hz, 3-H), 4.82 (2H, t, J=9Hz, $-OCH_2CH_2$), 3.59 (3H, s, N-Me), and 3.24 (2H, t, J=9Hz, $-OCH_2CH_2$), ν_{max} 1630, and 1530 cm^{-1}.

5,6-Dihydro-8-methylfuro[2,3-d]thieno[2,3-b]pyridin-7-one (317) -

This was prepared as described in the previous experiment from the thienooxazine (297) (1.83g, 0.01mol) and the lactone (315) (2.22g, 0.01mol). Thus was produced the title furothienopyridine (317) (1.84g, 78%) having m.p. 201-203°C (from ethyl acetate) (Found: C, 58.1; H, 4.4; N, 6.9. $C_{10}H_9NO_2S$ requires C, 58.0; H, 4.4; N, 6.8%), δ ($CDCl_3$) 7.14 (1H, d, J=6Hz, 2-H), 6.96 (1H, d, J=6Hz, 3-H), 4.78 (2H, t, J=9Hz, OCH_2CH_2), 3.64 (3H, s, N-Me), and 3.16 (2H, t, J=9Hz, OCH_2CH_2), ν_{max} 1630, and 1550 cm^{-1}.

4-Methylfuro[2,3-d]thieno[3,2-b]pyridin-5-one (318) -

The dihydro compound (316) (1.86g, 9mmol) and DDQ (2.45g, 11mmol) were refluxed in 1,4-dioxan (150ml) for 1.5h. The solution was evaporated to dryness and the residue dissolved in dichloromethane, washed with sodium bicarbonate solution, dried and evaporated to dryness. Column chromatography (alumina) of the residue (eluting with ethyl acetate) afforded the title furo-[2,3-d]thieno[3,2-b]pyridine (318) (1.52g, 82%) having m.p. 227-229°C (Found: C, 58.9; H, 3.3; N, 6.9. $C_{10}H_7NO_2S$ requires C, 58.5; H, 3.4; N, 6.8%),

δ [$(CD_3)_2SO$] 8.08 (1H, d, J=1.5Hz, 7-H), 8.07 (1H, d, J=5Hz, 2-H), 7.57 (1H, d, J=5Hz, 3-H), 7.18 (1H, d, J=1.5Hz, 6-H), and 3.77 (3H, s, N-Me), ν_{max} 1640, and 1550 cm^{-1}.

8-Methylfuro[2,3-d]thieno[2,3-b]pyridin-7-one (319) -

This was prepared from the dihydro compound (317) (2.07g, 0.01mol) and DDQ (2.72g, 0.012mol) as described in the previous experiment. Thus was produced the title furo[2,3-d]thieno[2,3-b]pyridine (319) (1.18g, 58%) having m.p. 184-186°C (Found: C, 58.4; H, 3.4; N, 6.9. $C_{10}H_7NO_2S$ requires C, 58.5; H, 3.4; N, 6.8%), δ ($CDCl_3$) 7.57 (1H, d, J=1.5Hz, 5-H), 7.40 (1H, d, J=6Hz, 2-H), 7.10 (1H, d, J=6Hz, 3-H), 7.09 (1H, d, J=1.5Hz, 6-H), and 3.75 (3H, s, N-Me), ν_{max} 1640, 1550, and 1520 cm^{-1}.

4-Methoxymethyl-6,7-dihydrofuro[2,3-d]thieno[3,2-b]pyridin-5-one (326) -

This was prepared from the N-methoxymethythienooxazine (298) (2.13g, 0.01mol) and the lactone (315) (2.22g, 0.01mol) in the manner describedfrom the N-methyl compound (316). This gave the title N-methoxymethyl compound (326) (1.84g, 78%) having m.p. 159-161°C (from ethyl acetate/light petroleum) (Found: C, 55.5; H, 4.7; N, 5.9. $C_{11}H_{11}NO_3S$ requires C, 55.7; H, 4.6; N, 5.9%), δ ($CDCl_3$) 7.54 (1H, d, J=5.5Hz, 2-H), 7.20 (1H, d, J=5.5Hz, 3-H), 5.62 (2H, s, CH_2OMe), 4.83 (2H, t, J=9Hz, OCH_2CH_2), 3.38 (3H, s, CH_2OMe), and (2H, t, J=9Hz, OCH_2CH_2), ν_{max} 1630, and 1540 cm^{-1}.

4-Methoxymethylfuro[2,3-d]thieno[3,2-b]pyridin-5-one (327) -

The dihydro compound (326) (2.37g, 0.01mol) was dehydrogenated using DDQ (2.72g, 0.012mol) in the manner described for the N-methyl compound. Thus was produced the title furo[2,3-d]thieno[3,2-b]pyridine (327) (1.7g, 72%) having m.p. 124-126°C (Found: C, 55.7; H, 3.4; N, 6.0. $C_{11}H_9NO_3S$ requires C, 56.2; H, 3.8; N, 6.0%), δ ($CDCl_3$) 7.49 (1H, d, J=5.5Hz, 2-H), 7.51 (1H, d, J=2Hz, 7-H), 7.25 (1H, d, J=5.5Hz, 3-H), 7.06 (1H, d, J=2Hz, 6-H), 5.71 (2H, s, NCH_2O), and 3.41 (3H, s, CH_2OMe), ν_{max} 1670, and 1550 cm^{-1}.

6,7-Dihydrofuro[2,3-d]thieno[3,2-b]pyridin-5(4H)-one (328) -

The N-methoxymethyl compound (326) (4.75g, 0.02mol) was boiled under reflux in 90% formic acid (100ml) for 4h. The formic acid was distilled off under vacuum and the residue washed with water, dried, and recrystallised from aqueous acetic acid giving the N-H compound (328) (3.1g, 80%) having m.p. 299°C (decomp.) (Found: C, 55.7; H, 3.7; N, 7.2. $C_9H_7NO_2S$ requires C, 56.0; H, 3.6; N, 7.2%), δ (DMSO) 8.06 (1H, d, J=5.5Hz, 2-H), 7.29 (1H, d, J=5.5Hz, 3-H), 4.97 (2H, t, J=8Hz, OCH_2CH_2), and 3.13 (2H, t, J=8Hz, OCH_2-CH_2), ν_{max} 1650, and 1550 cm^{-1}.

Furo[2,3-d]thieno[3,2-b]pyridin-5(4H)-one (329) -

This was prepared from the dihydro compound (328) (0.58g, 3mmol) and DDQ in the usual manner. The crude product was purified by column chromatography (alumina) eluting with a mixture of dichloromethane (8 parts) and methanol (2 parts). Thus was obtained the title furothienopyridine (329) (0.32g, 56%) having m.p. 304°C (decomp.) (Found: C, 56.5; H, 2.5; N, 7.2. $C_9H_5NO_2S$ requires C, 56.6; H, 2.6; N, 7.3%), δ (CF_3CO_2H) 8.00 (1H, d, J=5.5Hz, 2-H), 7.92 (1H, d, J=2Hz, 7-H), 7.56 (1H, d, J=5.5Hz, 3-H), and 7.37 (1H, d, J=2Hz, 6-H), ν_{max} 1670 cm^{-1}.

Preparation of 5,7-Dichloro-6-(2-chloroethyl)thieno[3,2-b]pyridine (330) by reaction of 6,7-Dihydrofuro[2,3-d]thieno[3,2-b]pyridin-5(4H)-one (328) -

a **With Phenylphosphonic dichloride** -

The tricycle (328) (0.5g) and phenylphosphonic dichloride (2ml) were heated at 160-170°C for 1h. The reaction mixture was cooled and added to water and stirred for 0.5h. Extraction with dichloromethane (3x), washing the combined extracts with sodium bicarbonate and evaporation of the dried solution gave an oil. This was dissolved in boiling light petroleum, treated with charcoal, filtered and cooled in ice-salt. Thus was obtained the thieno[3,2-b]pyridine (330) (0.47g, 72%) having m.p. 96-98°C (Found: C, 40.8; H, 2.1; N, 4.9. $C_9H_6Cl_3NS$ requires C, 40.7; H, 2.3; N, 5.3%), δ ($CDCl_3$) 7.79 (1H, d, J=5.5Hz, 2-H), 7.50 (1H, d, J=5.5Hz, 3-H), and 4.0-3.3 (4H, m, 2xCH_2), ν_{max} 1570 and 1520 cm^{-1}.

b **With Phosphoryl chloride** -

The tricycle (328) (0.5g) was boiled under reflux in phosphoryl chloride (10ml) for 18h. The excess of the reagent was distilled under vacuum and the residue added to ice-water. Extraction with dichloromethane, washing with sodium bicarbonate solution and evaporation of the dried extract afforded a solid which was shown by t.l.c. to be a mixture of starting material (mainly), and the trichloro compound (330).

Reaction of 4-Methyl-6,7-dihydrofuro[2,3-d]thieno[3,2-b]pyridin-5-one (316) with Phenylphosphonic dichloride

The tricycle (316) (1g) and phenylphosphonic dichloride (4ml) were heated at 160-170°C for 1h. The mixture was allowed to cool, poured into water and stirred for 0.5h. This was extracted with dichloromethane (3x) and the combined extracts washed with sodium bicarbonate solution, dried, and evaporated giving a solid. Extraction with boiling light petroleum afforded soluble and insoluble fractions. Flash-column chromatography of the soluble material furnished the previously mentioned 5,7-dichloro-6-(2-chloroethyl)-

thieno[3,2-b]pyridine (330) (0.52g, 40%), identified by its i.r. spectrum and by mixed m.p. with authentic material. The insoluble fraction was recrystallised from ethyl acetate, furnishing 7-chloro-6-(2-chloroethyl)-4-methylthieno[3,2-b]-pyridin-5-one (331) (0.32g, 25%), having m.p. 194-196°C (Found: C, 45.7; H, 3.4; N, 5.3. $C_{10}H_9Cl_2NOS$ requires C, 45.8; H, 3.4; N, 5.3%), δ [$(CD_3)_2SO$/$CDCl_3$] 7.91 (1H, d, J=5.5Hz, 2-H), 7.36 (1H, d, J=5.5Hz, 3-H), 3.80 (2H, t, J=8Hz, $C\underline{H}_2Cl$), 3.74 (3H, s, N-Me), and 3.24 (2H, t, J=8Hz, $ArC\underline{H}_2CH_2$), ν_{max} 1620 and 1540 cm^{-1}.

Reaction of 6,7-Dihydro-8-methylfuro[2,3-d]thieno[2,3-b]pyridin-7-one (317) with Phenylphosphonic dichloride -

The tricycle (317) (1g) and phenylphosphonic dichloride (3ml) were heated at 110-120°C for 1h. The cooled mixture was added to water, stirred for 0.5h, then extracted with dichloromethane (3x). The combined extracts were dried and evaporated giving a solid. Column chromatography (silica) eluting with dichloromethane yielded 4,6-dichloro-5-(2-chloroethyl)thieno[2,3-b]pyridine (332) (0.48g, 37%) as a white solid having m.p. 74-76°C (from light petroleum) (Found: C, 40.6; H, 2.2; N, 5.2. $C_9H_6Cl_3NS$ requires C, 40.5; H, 2.2; N, 5.2%), δ ($CDCl_3$) 7.62 (1H, d, J=6Hz, 2-H), 7.41 (1H, d, J=6Hz, 3-H), and 4.0-3.3 (4H, m, 2x$C\underline{H}_2$), ν_{max} 1570, and 1520 cm^{-1}. Elution of the column with ethyl acetate (1 part) - dichloromethane (1 part) then furnished 4-chloro-5-(2-chloroethyl)-7-methylthieno[2,3-b]pyridin-6-one (333) (0.14g, 11%) having m.p. 172-174°C (from ethyl acetate) (Found: C, 45.7; H, 3.3; N, 5.2. $C_{10}H_9Cl_2NOS$ requires C, 45.8; H, 3.4; N, 5.3%), δ [$(CD_3)_2SO$] 7.44 (1H, d, J=6Hz, H-2), 7.30 (1H, d, J=6Hz, H-3), 3.81 (2H, t, J= 8Hz, $C\underline{H}_2Cl$), 3.16 (2H, t, J=8Hz, $ArC\underline{H}_2$), and 3.62 (3H, s, N-Me), ν_{max} 1630 and 1540 cm^{-1}. Further elution with ethyl acetate then gave 0.21g of starting material.

Reaction of 4-Methoxymethylfuro[2,3-d]thieno[3,2-b]pyridin-5-one (326) with Phosphoryl chloride -

The N-methoxymethyl compound (326) (1g) was boiled under reflux with phosphoryl chloride (10ml) for 6h. The excess reagent was removed by distillation under vacuum and the residue added to water. This was extracted with dichloromethane (3x) and the combined extracts washed with sodium bicarbonate solution, dried, and evaporated giving an oil. Thin layer chromatography indicated three components, the one having lowest R_F was the deprotected material (328). The two components of higher R_F were separated by flash-column chromatography (dichloromethane). First to be eluted was the trichlorocompound (330) (0.13g) then was isolated 5-chloro-6,7-dihydrofuro-[2,3-d]thieno]3,2-b]pyridine (334) (0.18g, 20%) having m.p. 154-156°C (Found:

C, ; H, ; N, . C_9H_6ClNOS requires C, ; H, ; N, %), δ ($CDCl_3$) 7.72 (1H, d, J=5.5Hz, H-2), 7.47 (1H, d, J=5.5Hz, H-3), 4.89 (2H, t, J=9Hz, $C\underline{H}_2O$), and 3.37 (2H, d, J=9Hz, $ArC\underline{H}_2$), ν_{max} 1610, 1550, and 1540 cm^{-1}.

Attempted dechlorination of 5-Chloro-6,7-dihydrofuro[2,3-d]thieno[3,2-b]-pyridine (334) -

The chloro compound (334) (0.3g) and zinc (0.3g) were stirred in acetic acid (20ml). After 18h at room temperature little reaction had occurred. The mixture was then boiled under reflux for 2h. Thin layer chromatography then indicated that the major component was starting material together with small amounts of several other compounds.

Attempted acidic hydrolysis of the trichloro compounds (330) and (332) -

When 0.5g samples of the thieno[2,3-b]- and -[3,2-b]pyridines, [(330) and 332)], respectively, were boiled under reflux in a mixture of 1,4-dioxan (20ml) and 6M hydrochloric acid (20ml) for 3h thin layer chromatography indicated that in neither case had reaction occurred.

Ethyl 2-(Tetrahydrofuran-2-ylideneamino)thiophene-3-carboxylate (340) -

A solution of α-(0,0-diethylphosphono)-γ-butyrolactone (315) (6.66g, 0.03mol) in DMF (60ml) was added under nitrogen to a suspension of sodium hydride (0.72g, 0.03mol) in DMF (30ml) then stirred at 40°C for a further 10 minutes. To the resulting solution was added a solution of ethyl 2-aminothiophene-3-carboxylate (131b) (5.1g, 0.03mol) and the whole was stirred at 110-120°C for 3h. The DMF was distilled under vacuum and the residue added to water (200ml) and extracted with dichloromethane (3x). Evaporation of the dried extracts yielded an oil which was purified by flash-column chromatography (ethyl acetate) and distilled giving the title thiophene (340) (2.8g, 39%) having b.p. 122-124°C/0.05mmHg (Found: C, ; H, ; N, . $C_{11}H_{13}NO_3S$ requires C, ; H, ; N, %), δ ($CDCl_3$) 7.34 (1H, d, J=6Hz, 2-H), 7.09 (1H, d, J=6Hz), 4.5-3.7 (4H, m, 2x$OC\underline{H}_2$), 2.9-2.0 (4H, m, $NC\underline{H}_2$-$C\underline{H}_2$), and 1.5-1.1 (3H, m, $OCH_2C\underline{H}_3$), ν_{max}

Attempts to cyclise the imino compound (340) -

a **Sodium Ethoxide in ethanol** -

When the imino compound (340) (0.48g, 2mmol) was boiled under reflux with a solution of sodium ethoxide (from 0.14g sodium, 6mg-atom) in ethanol (10ml) the solution rapidly became dark brown and thin layer chromatography indicated a complex mixture.

b **Sodium hydride in THF** -

When the imino compound (340) (0.48g, 2mmol) was boiled under reflux with sodium hydride (0.1g, 4mmol) in THF (20ml) for 4h, thin layer chromatography indicated that the starting material had been consumed. On exposure to air the reaction mixture rapidly darkened and no one component could be isolated from the resulting complex mixture.

7-Allyloxythieno[3,2-b]pyridine (342) -

Sodium (0.7g, 30mg-atom) was dissolved in allyl alcohol (30ml) and 7-chlorothieno[3,2-b]pyridine (167) (1.7g, 10mmol) added and boiled under reflux for 18h. The solution was poured into water and extracted with dichloromethane (3x). The combined extracts were dried and evaporated and the residue distilled giving 7-allyloxythieno[3,2-b]pyridine (342) (1.4g, 74%) having b.p. 107-109°C/0.1mmHg. δ ($CDCl_3$) 8.53 (1H, d, J=5.5Hz, 5-H), 7.66 (1H, d, J=5.5Hz, 2-H), 7.49 (1H, d, J=5.5Hz, 3-H), 6.66 (1H, d, J=5.5Hz, 6-H), 6.50-5.20 (3H, m, $C\underline{H}=C\underline{H}_2$), and 4.65 (2H, m, $OC\underline{H}_2CH=CH_2$), ν_{max} 1570, and 1550 cm^{-1}. The picrate was prepared for analysis and had m.p. 175-177°C (from methanol) (Found: C, 45.6; H, 2.6; N, 13.2. $C_{16}H_{12}N_4O_8S$ requires C, 45.7; H, 2.9; N, 13.3%).

Claisen Rearrangement of 7-Allyloxythieno[3,2-b]pyridine -

The allyl ether (342) (4.8g) was heated at 200°C for 2h. The resulting semi-solid which formed on cooling was partitioned between dichloromethane and 2M aqueous sodium hydroxide. The aqueous solution was acidified with hydrochloric acid and the resulting precipitate washed with water and dried. Recrystallisation from ethyl acetate afforded 6-allylthieno[3,2-b]pyridin-7(4H)-one (343) (1.6g, 33%) having m.p. 188-190°C (decomp.) (Found: C, 63.1; H, 4.9; N, 7.4. $C_{10}H_9NOS$ requires C, 62.8; H, 4.7; N, 7.3%), δ ($CDCl_3[CD_3]_2$-SO) 7.75 (1H, d, J=6Hz, 2-H), 7.60 (1H, s, 5-H), 7.18 (1H, d, J=6Hz, 3-H), 6.40-4.90 (3H, m, $C\underline{H}=C\underline{H}_2$), and 3.28 (2H, m, $C\underline{H}_2CH=CH_2$), ν_{max} 2950-2400, 1610, 1580, and 1510 cm^{-1}. The dichloromethane solution was dried and evaporated. The resulting oil was subjected to flash-column chromatography (ethyl acetate [9 parts] - methanol [1 part]). First to be eluted was 4,6-diallythieno[3,2-b]pyridin-7-one (345) (0.26g, 5%) (Found: C, ; H, ; N, . $C_{13}H_{13}NOS$ requires C, 67.5; H, 5.7; N, 6.1%), δ ($CDCl_3$) 7.58 (1H, d, J=5.5Hz, 2-H), 7.25 (1H, s, 5-H), 7.01 (1H, d, J=5.5Hz, 3-H), 6.3-5.6 (2H, m, 2x$C\underline{H}=CH_2$), 5.4-5.0 (4H, m, 2xCH=$C\underline{H}_2$), 4.70 (2H, m, N-$C\underline{H}_2$), and 3.31 (2H, m, Ar$C\underline{H}_2$), ν_{max} 1610, and 1520 cm^{-1}. Next to be eluted was 4-allylthieno-[3,2-b]pyridin-7-one (344) (0.5g, 10%) having m.p. 90-92°C (Found: C, 62.7; H, 4.6; N, 7.4. $C_{10}H_9NOS$ requires C, 62.8; H, 4.7; N, 7.3%), δ ($CDCl_3$) 7.66 (1H,

d, J=5.5Hz, 2-H), 7.43 (1H, d, J=7.5Hz, 5-H), 7.08 (1H, d, J=5.5Hz, 3-H), 6.21 (1H, d, J=7.5Hz, 6-H), 6.11-5.69 (1H, m, $CH_2\underline{CH}=CH_2$), 5.42-5.00 (2H, m, $CH_2CH=\underline{CH_2}$), and 4.86-4.71 (2H, m, $NC\underline{H_2}CH=CH_2$), ν_{max} 1610, 1560, and 1510 cm^{-1}.

Attempted cyclisations of 6-Allylthieno[3,2-b]pyridin-7(4H)-one (343)

a **With HBr in acetic acid** -

The allyl compound (1.0g) was dissolved in a solution of HBr in acetic acid (33%, 20ml) and set aside at room temperature for 7days. Poured into water (100ml) and the mixture neutralised with sodium bicarbonate. The whole was then extracted with dichloromethane; t.l.c. of the extract showed several minor components but mainly unreacted starting material.

b **With DDQ in toluene** -

The allyl compound (343) (0.57g, 3mmol) and DDQ (0.82g, 3.6mmol) were heated at 100°C in toluene (80ml) for 4h. Some black tar was precipitated but t.l.c. of the solution indicated a complex mixture.

Table 10

^{13}C NMR Spectra of Thieno[2,3-b]pyridines described in Chapter 5

Compound	Solvent[a]	Chemical Shift (ppm) C-2	C-3	C-4	C-5	C-6	C-8	C-9	Other
247	P + Q	121.7	120.7	163.5	106.6	142.0	153.7	126.8	
248	P	123.5	118.3	161.8	111.5	146.3	162.9	123.2	CH_2, 54.3, 46.3; CH_3, 10.9
248 oxalate	P + Q	121.1	119.9	163.3	111.5	140.7	150.6	128.8	CO, 172.3; CH_2, 49.2, 46.3; CH_3, 8.6
252	P + Q	110.2	123.0	159.8	105.9	144.3	156.0	126.0	
249	P + R	108.0	122.8	155.4	119.3	142.8	167.3	128.1	CO, 168.0; CH_2, 65.4; CH_3, 13.8
250	P + R	108.1	123.5	156.4	120.2	143.9	168.1	128.9	CO, 171.2
251	P + Q	110.7	121.9	159.9	107.1	146.9	162.0	124.1	
253	P + Q	145.7	122.6	166.2	109.1	148.8	159.2	123.4	
254	P + Q	145.6	124.8	151.9	134.4	143.2	164.1	130.2	
257	P + Q	151.6	121.8[b]	141.7	121.2[b]	151.6	160.8	129.8	
259	P	131.4	121.0	131.4	142.6	142.6	164.4	132.0	
258	P	139.3	120.8	130.7	137.3	150.9	c	128.8	
260	P + Q	141.5	100.7	135.2	119.7	144.5	158.1	129.9	CO, 167.9; CH_3, 22.9
256	P + Q	140.5	103.1	128.6	119.6	144.3	157.5	131.2	CO, 167.8; CH_3, 23.0
262	P + Q	123.1	119.1	176.7	108.6	141.2	150.5	128.1	CH_3, 42.3
261	P + Q	106.2	125.8	166.3	108.7	141.5	150.4	128.1	CH_3, 43.5
265	P + R	150.2	122.5	169.7	111.2	148.5	154.7	125.1	CH_3, 45.6
264	P + R	148.8	125.1	153.6	134.1	146.5	c	131.6	CH_3, 45.1
274	P + Q	103.8	121.9	163.8	93.8	160.8	153.4	116.8	

continued/

Table 10 (continued)

Compound	Solvent[a]	Chemical Shift (ppm) C-2	C-3	C-4	C-5	C-6	C-8	C-9	Other
276	P + Q	130.3	117.1	159.9	93.2	158.1	145.8	115.4	CH_3, 15.3
273	P + Q	103.9	122.5	159.7	93.2	157.4	148.8	116.0	
277	P + Q	104.2	122.4	166.9	96.3	159.5	153.2	114.3	CO, 171.0; CH_2, 61.2; CH_3, 14.0
278	P + Q	142.1	123.6	169.7	97.6	159.9	154.2	112.5	CO, 171.1; CH_2, 61.7; CH_3, 14.0
284	P + Q	108.7	110.2	138.8	122.3	161.9	156.0	123.8	
133c	P + Q	130.8	117.0	169.3	95.1	160.5	151.5	114.1	CO, 172.6; CH_2, 61.4; CH_3, 15.2, 14.2
134c	P + Q	129.8	116.7	164.0	94.1	161.5	149.3	116.2	CH_3, 15.3
285	P	143.1	116.9	138.0	119.7	146.5	160.8	131.5	CH_3, 16.7
283	P	117.9	122.1	138.3	120.6	147.9	161.5	131.2	

Key: a: P = $CDCl_3$, Q = $(CD_3)_2SO$, R = CF_3CO_2H

b: assignments may be interchanged

c: no signal observed

Table 11

^{13}C NMR Spectra of Thieno[3,2-b]pyridines described in Chapter 5

Compound	Solvent[a]	Chemical Shift (ppm) C-2	C-3	C-5	C-6	C-7	C-8	C-9	Other
212 nitrate	P + Q	131.7	118.4	137.3	109.3	173.4	127.8	144.3	
225	P + Q	132.5	118.2	137.6	106.2	c	126.9	143.8	
229	P	130.0	123.3	144.5	112.8	165.3	131.5	154.2	CH_2, 53.2, 46.6; CH_3, 11.1
229 oxalate	P + Q	127.3	118.6	140.1	110.2	163.8	133.0	144.7	CO, 172.6; CH_2, 49.0, 46.3; CH_3, 8.6
227	P + R	141.0	120.1	145.7	127.2	162.2	c	149.3	
228	P + Q	141.5	136.4	138.4	134.5	163.5	133.2[b]	133.0[b]	
226	P + Q	130.1	106.7	138.5	99.7	167.6	126.0	141.4	
230	P	132.0	116.3	140.8	110.9	173.9	129.5	144.9	CH_3, 41.1
231	P + Q	132.8	116.9	141.7	106.3	167.7	127.5	144.7	CH_3, 41.2
232	P + R	144.3	118.4	146.2	128.0	161.7	c	150.0	CH_3, 45.8
233	P + Q	147.6	139.3	136.9	134.5	162.6	c	131.9	CH_3, 44.0
238	S	133.0	120.0	168.4	98.0	c	c	144.0	
240	P + Q	136.4	133.8	157.8	125.7	156.6	115.2	135.2	
241	R	144.0	137.5	166.4	96.4	170.0	120.1	144.7	CO, 171.7; CH_2, 68.9; CH_3, 14.5
242	P + Q	130.8	117.3	163.5	106.9	154.5	112.1	144.0	CO, 166.9; CH_3, 20.8
245	P	130.0	124.7	159.4	94.9	160.3	118.2	153.9	CH_3, 59.7, 54.8

Key: a: P = $CDCl_3$, Q = $(CD_3)_2SO$, R = CF_3CO_2H, S = D_2O

b: assignments may be interchanged

c: no signal observed

Table 12

^{13}C NMR Spectra[a] of Thienopyridine Analogues of 2-Aryl-4-Quinolone Alkaloids

No.	Chemical Shift																			
	C-2	(C-1′)	C-3	(C-2′)	C-4	(C-3′)	C-5	(C-4′)	C-6	(C-5′)	C-7	(C-6′)	C-8	(Other)	C-9	$N\text{-}CH_3$
303	132.0	(129.5)	117.0	(128.8)	[N-CH_3]	(128.8)	146.0	(128.8)	111.3	(128.8)	173.4	(128.8)	b		152.2	38.4
304	131.9	(127.1)	117.1	(111.2[c])	[N-CH_3]	(149.1[d])	146.0	(150.1[d])	112.2	(113.4[c])	173.4	(121.7)	129.3	(2 x OCH_3, 56.1)	152.2	38.4
305	132.0	(125.0)	118.3	(108.3[e])	[N-CH_3]	(146.1[f])	147.5	(148.4[f])	112.3	(109.1[e])	172.2	(122.8)	b	(OCH_2O, 101.5)	151.9	38.4
307	124.1	(130.2)	117.4	(128.8)	174.3	(128.8)	115.8	(129.7)	151.5	(128.8)	[N-CH_3]	(128.8)	152.7		134.2	40.1
308	124.1	(126.7)	117.4	(113.3[g])	174.4	(149.2[h])	115.9	(150.3[h])	151.5	(112.2[g])	[N-CH_3]	(121.8)	152.7	(2 x CH_3, 56.1)	130.2	40.1
309	124.0	(127.7)	117.5	(108.6[i])	174.3	(148.0[j])	115.8	(148.9[j])	151.3	(109.2[i])	[N-CH_3]	(123.0)	152.7	(OCH_2O, 101.7)	130.2	40.0

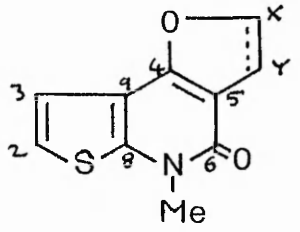
Key: a: run in $CDCl_3$

b: no signal observed

cc-jj: assignments interchangeable

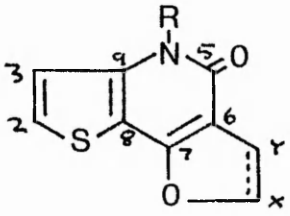
Table 13

^{13}C NMR Spectra of Furothienopyridones



(317)[a] 120.1 (C-2), 116.2 (C-3), 160.8 (C-4), 150.4 (C-5), 162.2 (C-6), c (C-8), 110.9 (C-9), 73.9 (x), and 27.3 (Y).

(319)[a] 119.5 (C-2), 117.1 (C-3), 154.5 (C-4), 113.0 (C-5), 159.0 (C-6), 146.4 (C-8), 111.4 (C-9), 142.4 (x), and 108.5 (Y).



(316)[b] 130.9 (C-2), 124.6 (C-3), 145.4 (C-5), 115.6 (C-6), 162.6 (C-7), 114.9 (C-8), 157.6 (C-9), 73.2 (x), and 28.4 (Y).

(318)[b] 127.6 (C-2), 117.8 (C-3), c (C-5), c (C-6), c (C-7), c (C-8), 141.1 (C-9), 143.5 (x), and 108.0 (Y).

(326)[a] 129.2 (C-2), 117.5 (C-3), 162.1 (C-5), 105.2 (C-6), 161.5 (C-7), 107.5 (C-8), 145.1 (C-9), 74.4 (x), and 27.5 (Y).

(327)[a] 126.9 (C-2), 118.0 (C-3), 159.7 (C-5), c (C-6), c (C-7), c (C-8), 143.0 (x), and 108.6 (Y).

(329)[b] 127.8 (C-2), 117.5 (C-3), 158.9 (C-5), 112.9 (C-6), c (C-7), c (C-8), 114.1 (C-9), 143.6 (x), and 107.7 (Y).

Notes
- a: run in $CDCl_3$
- b: run in $CDCl_3$-$(CD_3)_2SO$
- c: No signal observed
- d: Compound (328) was not sufficiently soluble in these solvents for a spectrum to be observed.

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Thienopyridines. Part 6.[1] Synthesis and Nucleophilic Substitution of Some Chlorothieno[2,3-*b*]pyridine Derivatives, and Comparisons with the Analogous Quinoline Compounds

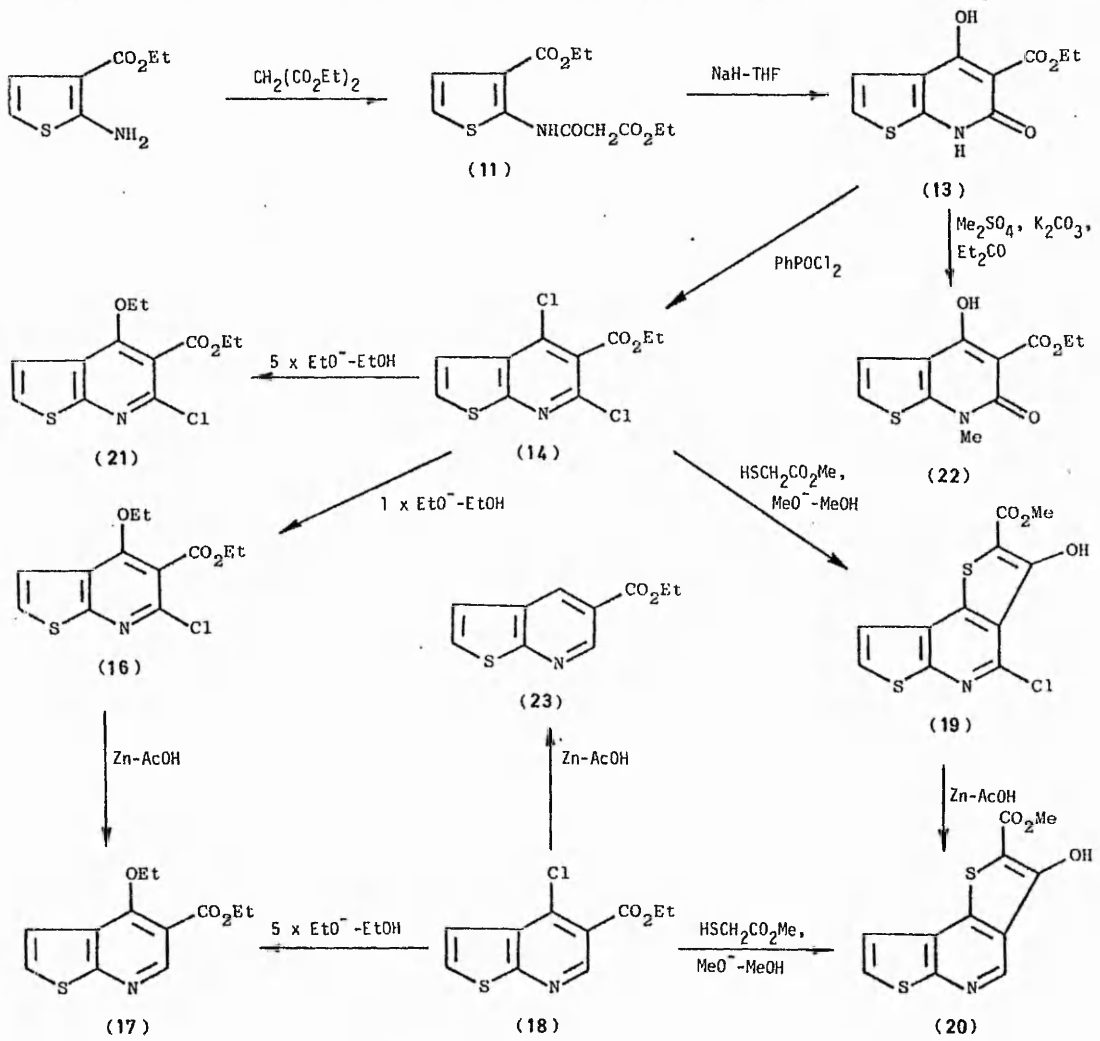
J. Chem. Research (S), 1985, 214–215
J. Chem. Research (M), 1985, 2501–2523

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A number of thieno[2,3-*b*]pyridine derivatives, containing various substituents in the pyridine ring, have been synthesised; in 4,6-dichlorinated compounds the chlorine atom at C-4 is preferentially replaced by nucleophiles.

In previous reports[1,9] we have recorded that, in 5,7-dichlorothieno[3,2-*b*]pyridine derivatives (both with and without an ester group at C-6), the chlorine atom γ- to the nitrogen (*i.e.* at C-7) is much more readily replaced than that α- to it (at C-5). We now report that the same pattern of behaviour is exhibited by the thieno[2,3-*b*]pyridine analogues of these compounds.

pyridines the chlorine atoms of 2,4-dichloroquinoline are of approximately equal reactivity towards ethoxide ions,[2] and, although the halogen at C-4 is preferentially displaced by methoxide, replacement at C-2 still takes place to a significant extent.[3,4] We have examined the reaction of ethyl 2,4-dichloroquinoline-3-carboxylate with one equivalent of sodium ethoxide in ethanol. The products were ethyl 2-chloro-4-ethoxy- (72%) and ethyl 4-chloro-2-ethoxy-quinoline-3-carboxylate (5%). We ascribe the greater reactivity of the chlorine atom at C-4 to the ability of the ester group in that case to delocalise the negative charge in the sigma complex without dis-



Scheme A

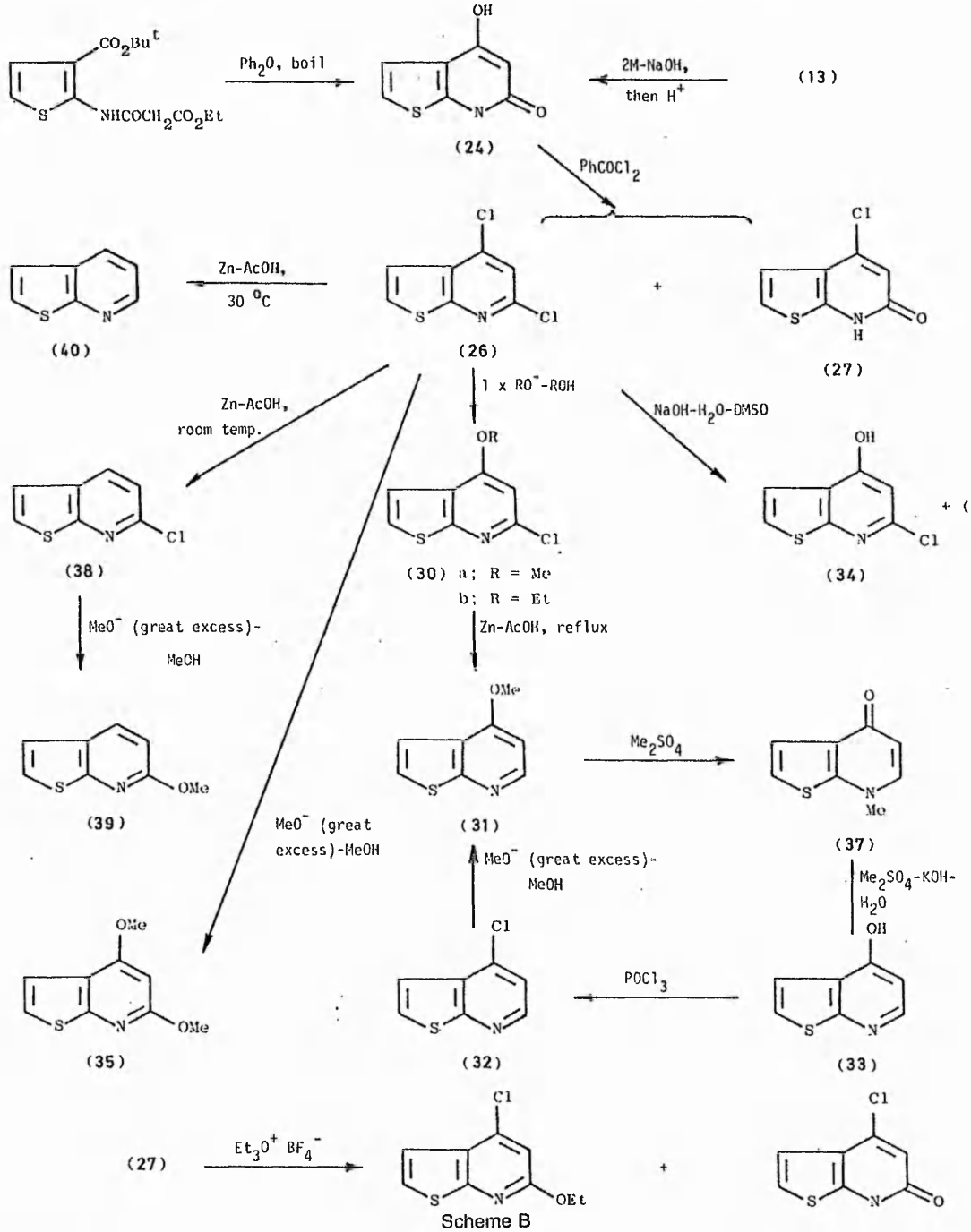
The synthesis and some reactions of the substances studied are presented in Schemes A and B. The identities of the various products were established, where necessary, by unambiguous preparations from compounds of unarguable structure, and from spectroscopic data; carbon-13 n.m.r. spectra in particular provide firm evidence of constitution in the series.

In contrast to the related α,γ-dichlorinated thieno[*b*]-

ruption of the benzene ring (structure X); the comparable structure (Y) for substitution at C-2 requires a quinoid arrangement.

Competitive experiments indicate that the order of reactivity towards methoxide of chlorine atoms at γ-positions in thieno[*b*]pyridines and their quinoline isotere is 4-chloroquinoline > 4-chlorothieno[2,3-*b*]-pyridine > 7-chlorothieno[3,2-*b*]pyridine. Chlorine atoms α- to the nitrogen in the two thienopyridines are (in contrast to that in 2-chloroquinoline) very resistant

*To receive any correspondence.

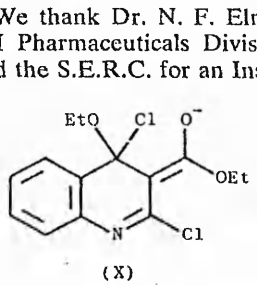


Scheme B

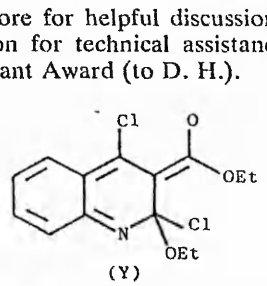
to replacement by methoxide.

A further point of difference between related compounds in the three groups concerns the tautomeric preferences in substances carrying an oxygen atom γ to the pyridine ring nitrogen. In both the quinoline and thieno[3,2-*b*]pyridine series the preferred form is the (NH)-quinolone, whereas the thieno[2,3-*b*]pyridine counterpart exists as the hydroxy tautomer (**33**).

We thank Dr. N. F. Elmore for helpful discussions, ICI Pharmaceuticals Division for technical assistance, and the S.E.R.C. for an Instant Award (to D. H.).



(X)



(Y)

Techniques used: N.m.r. (^{1}H and ^{13}C), i.r., g.l.c.

References: 15

Table 1: ^{13}C N.m.r. spectra of thieno[2,3-*b*]pyridines

Table 2: ^{13}C N.m.r. spectra of thieno[2,3-*b*]pyridin-6

Paper: E/033/85 Received: 8th Februa

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Thienopyridines. Part 5.[1] Carbon-13 N.m.r. Spectra of Some Thieno[3,2-*b*]pyridines, and Some Further Transformations in the Series

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Thienopyridines. Part 5.[1] Carbon-13 N.m.r. Spectra of Some Thieno[3,2-*b*]pyridines, and Some Further Transformations in the Series

J. Chem. Research (S), 1984, 84–85
J. Chem. Research (M), 1984, 0771–0795

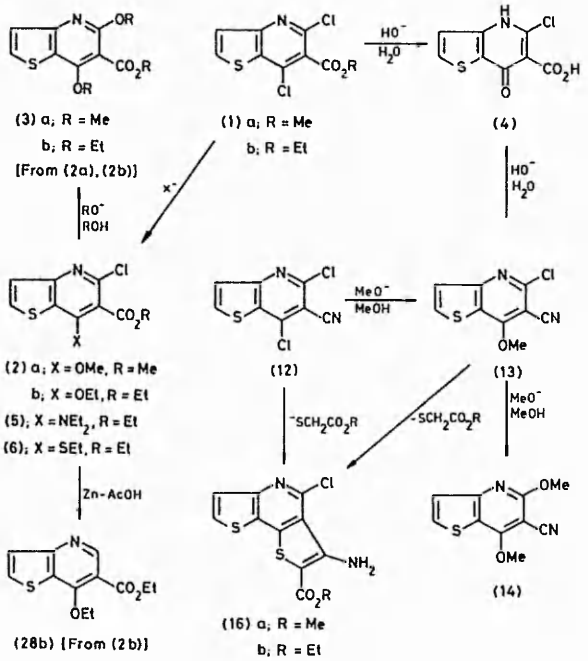
JOHN M. BARKER,[a,*] PATRICK R. HUDDLESTON,[a] DAVID HOLMES,[a] GUY J. KEENAN,[a] and (in part) BRIAN WRIGHT[b]

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The ^{13}C n.m.r. spectra of more than forty thieno[3,2-*b*]pyridine derivatives have been recorded, and assignments of the resonances made; the products of mono-nucleophilic substitution of some 5,7-dichlorothieno[3,2-*b*]pyridines have been shown by ^{13}C n.m.r. spectroscopy and by chemical correlations to be the 7-substituted 5-chloro derivatives.

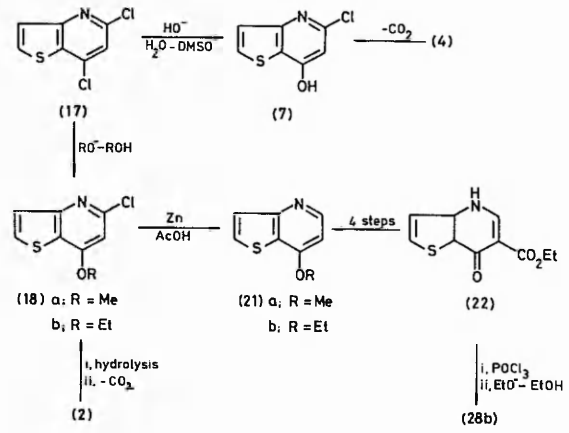
By making allowance for substituent effects, derived from the effect that the same substituent has upon the chemical shift of a comparable carbon atom in a reference system, it was possible to assign the resonances due to the pyridine ring carbon atoms in a number of thieno[3,2-*b*]pyridine compounds. It was also possible to deduce the shifts induced at the thiophene ring atoms (C-2 and C-3) by substituents in the pyridine ring. Of particular interest in this context is that the C-3 resonance (which normally occurs in the range 124–126 ppm) was observed at 116.5–118.5 in thieno[3,2-*b*]-pyridin-5(4*H*)- and -7(4*H*)-ones, thus permitting a ready distinction to be made between keto and enol tautomers.

Some nucleophilic substitution reactions of alkyl 5,7-dichlorothieno[3,2-*b*]pyridine-6-carboxylates (1a and b) were examined, and in each case it was found that the chlorine atom at C-7 was replaced, the remaining chlorine being very resistant to nucleophilic displacement. Similarly the related 6-cyano compound (12) was attacked at C-7 by methoxide; further nucleophilic attack upon the product (13) involved loss of the methoxy group rather than the chlorine atom at C-5. The identities of the various products were established by ^{13}C n.m.r. spectroscopy and by chemical correlations with the ester (28b) of known structure. Some of the reactions of the 6-substituted 5,7-dichloro compounds are shown in Scheme A.



Scheme A

The greater reactivity of C-7 towards nucleophiles in these compounds caused us to question our earlier report[10] that 5,7-dichlorothieno[3,2-*b*]pyridine (17) gave 5-alkoxy-7-chloro derivatives when treated with alkoxide. We have re-examined this earlier work (and extended it), and have found the original conclusion to have been erroneous. As is the case with (1a), (1b), and (12), (17) undergoes preferential substitution at C-7. The orientation is clear from the ^{13}C n.m.r. spectra of the products and from their relationship to a substance of known form (22).[9] Scheme B gives an outline of this



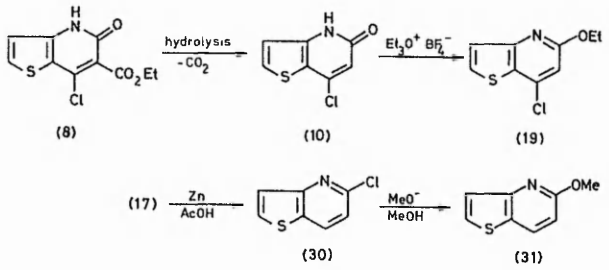
Scheme B

part of the work, and illustrates direct chemical connection between the nucleophilic substitution products of (1) [(2a and b)] and of both (1) and (12) [(4)] with those of (17).

For comparison with (18b) and (21a) samples of 7-chloro-5-ethoxy- (19) and 5-methoxy-thieno[3,2-*b*]-pyridine (31) were prepared (Scheme C), *via* (10) and (30), respectively. It is of interest that the i.r. and ^{13}C n.m.r. spectra of (10) indicate the keto tautomer, whereas the isomeric 5-chloro-7-oxygenated derivative (7) exists as the 7-ol.

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*To receive any correspondence.



Scheme C

Techniques used: N.m.r. (^{1}H and ^{13}C), i.r.

References: 13.

Schemes: 6

Table I: Chemical shift increments used in the assignment of thieno[3,2-*b*]pyridine ^{13}C spectra

Table II: ^{13}C N.m.r. spectra of thieno[3,2-*b*]pyridines

Table III: ^{13}C N.m.r. spectra of thieno[3,2-*b*]pyridin-7(4*H*)-ones

Table IV: ^{13}C N.m.r. spectra of thieno[3,2-*b*]pyridin-5(4*H*)-ones

Table V: Shifts produced at C-2 and C-3 by substituents in the pyridine ring of thieno[3,2-*b*]pyridines

Table VI: Chemical shifts from thieno[3,2-*b*]pyridine values produced by Cl and O-Alkyl

Table VII: Observed and predicted chemical shifts of 5,7- and 7,5-alkoxychlorothieno[3,2-*b*]pyridines

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