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in collaboration with

SHELL RESEARCH CENTRE, SITTINGBOURNE

STUDIES OF THIENO(3,4-b)PYRIDINES

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

DOCTOR OF PHILOSOPHY

by

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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 November 1985 and September 1988. 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.

During this work, the author has attended a post-graduate lecture course on n.m.r. spectroscopy at Trent Polytechnic. In addition, many academic lectures were attended at Nottingham and Keele Universities, at Leicester Polytechnic and at Fisons Pharmaceuticals, Loughborough. The author presented a poster at the Thiophene Symposium (1987) at the University of Salford and also delivered a lecture at the Tenth East Midland Regional Symposium (Perkin Division) (1988) at Loughborough University.

The author wishes to express his gratitude to Dr. J.M. Barker for his supervision in the work covered in Part 1 of this thesis and to Dr. E. Jackson for his supervision in Part 2 of this thesis. Many thanks are also due to Dr. P.R. Huddleston for his helpful advice.

Thanks are also extended to the technical staff at Trent Polytechnic over this period for their support, in particular to Miss E. Woodland, Mr. F. Karpowicz, Mr. A. Richards, Mrs. M. Richards and Mr. M.L. Wood.

Part of this work has been submitted for publication to the Journal of Chemical Research.

ABSTRACT

D Heath: STUDIES OF THIENO(3,4-b)PYRIDINES

The preparations of 2,3- and 3,2-fused thieno(b)pyridines developed at Trent Polytechnic were applied to the production of 2,4-dioxygenated and 4-oxygenated thieno(3,4-b)-pyridine analogues, from which chloro compounds were made.

The nucleophilic substitution reactions of some chlorothieno(3,4-b)pyridine compounds were found either to be similar to the quinoline analogues or to be anomalous to both the quinoline and 2,3-fused thieno(b)pyridine series. The methoxydechlorination of 2,4-dichlorothieno(3,4-b)pyridine with one-mol equivalent of methoxide, gave both the α- and γ-monosubstituted products under mild conditions. Under identical conditions, 2,4-dichloro-3-methoxycarbonylthieno-(3,4-b)pyridine, gave a mixture of the dimethoxy product and starting material.

The electrophilic substitution reactions of four 2,4-dioxygenated and 4-oxygenated thieno(3,4-b)pyridine compounds were studied. Of these only one reacted smoothly to give a single (bromination) product. The 2,3-fused thieno(b)-pyridine and quinoline analogues of these compounds all react smoothly to give single substitution products.

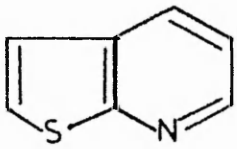
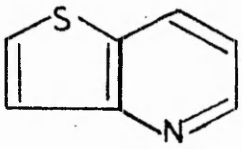
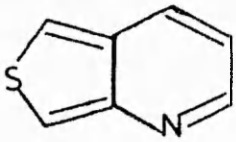
The ^{13}C n.m.r. spectra of a number of thieno(3,4-b)pyridine compounds were recorded and in most cases resonances were assigned. The information helped in structure determination and preferred keto-enol tautomeric forms were determined. The 2,4-dioxygenated thieno(3,4-b)pyridines prepared exist as the γ-enol, α-keto forms, in line with the other thieno(b)pyridine and quinoline analogues.

Some thieno(3,4-b)pyridine analogues of stable 2,3-fused thieno(b)pyridine and quinoline compounds were found to be unstable. The lack of stability in the thieno(3,4-b)pyridine series is probably due to the higher energy quinonoid structure in the pyridine ring, compared to the Kekule form found in the other three systems.

The rates of nucleophilic displacement of α- and γ-chlorine atoms in the monochlorinated quinoline and thieno(b)-pyridine compounds were determined. A solvent system was developed which allowed the rates to be determined conveniently and comparisons of the rate constants within each of the systems were made. The activation energy and activation entropy for a few reactions have been calculated.

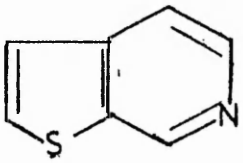
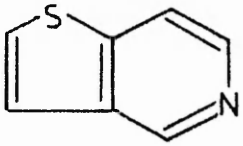
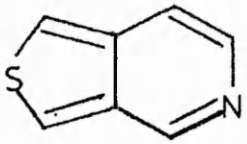
1.1. INTRODUCTION

The six possible thienopyridine ring systems fall into two classes, the thieno(b)pyridines, which are regarded as thienyl analogues of quinoline i.e.

[2,3-b] (1) [3,2-b] (2) [3,4-b] (3)

and thieno(c)pyridines, regarded as thienyl analogues of isoquinoline.

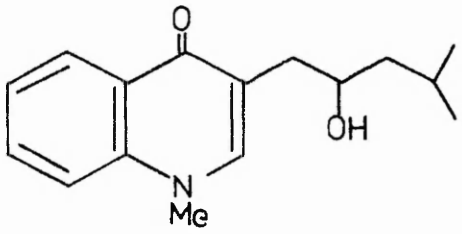
[2,3-c] [3,2-c] [3,4-c]

The present work is concerned with the thieno(b)pyridine series and this introduction will concentrate primarily on them.

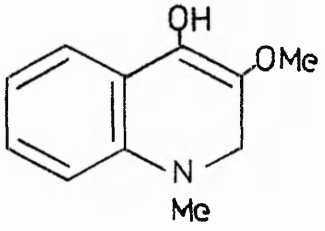
Of the thieno(b)pyridines, only members of the (3,2-b)- and (2,3-b)- series are found naturally (in shale oils)[1,2] but the chemistry of both of these fused thieno(b)-pyridines is well established, with most of the work being published during the last three decades. Thienopyridine chemistry has been reviewed by Barker[3] and by Schneller[4]. In contrast, very little is known about the thieno(3,4-b)pyridine series. The aim of this project was

to prepare novel thieno(3,4-b)pyridine analogues of compounds known in the other series, to study their chemical behaviour and to make the appropriate comparisons.

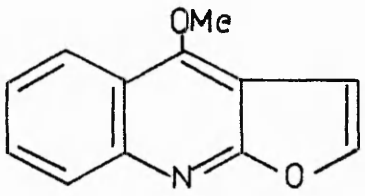
The chemistry of thienopyridines is of interest for two particular reasons. In the first, thieno(b)pyridines are regarded as thienyl analogues of the quinolines, which form the nucleus of many alkaloids and other biologically active compounds. The structures of a few examples of quinoline based alkaloids are given below;



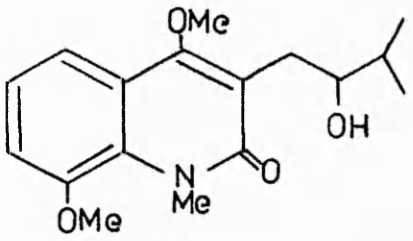
Pilokeanine



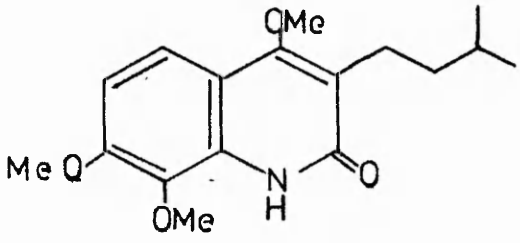
Echinine



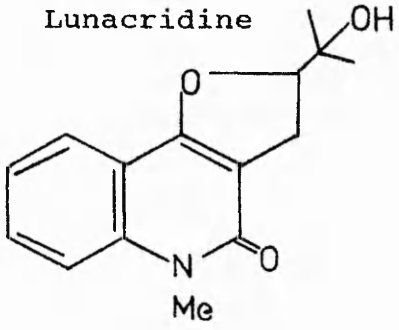
Dictamnine



Lunacridine



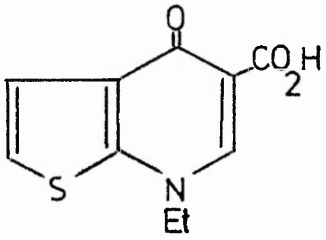
Preskimmianine



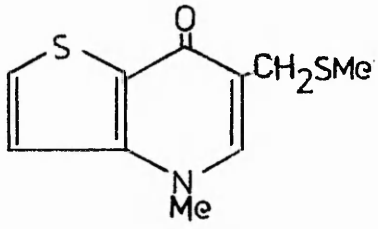
Araliopsine

Some work[5,6] in the past has centred around the

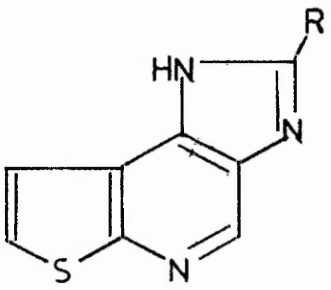
syntheses of thieno(b)pyridine isosteres of the alkaloids, to discover the effect that substitution of the benzene ring by thiophene has on biological activity. Generally, it has been found that thieno(b)pyridine analogues are of lower activity than their quinoline isosteres; they may even be completely inactive. However, some thieno(2,3-b)- and -(3,2-b)pyridine analogues act as anxiolytic, antidepressant or cardiovascular agents; some examples of such compounds are given below;



antibacterial agent[7]

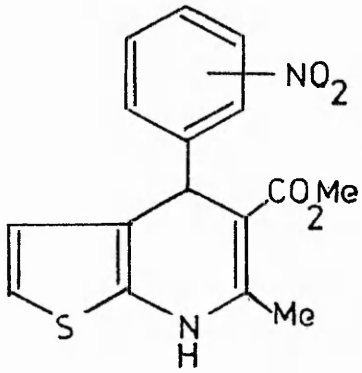


antihypertensive agent[8]



R = aryl, heteroaryl

antidepressant and anxiolytic agents[9]



cardiovascular agent[10]

The second broad area of interest arises from the fact that thienopyridines possess a pi-electron rich thiophene ring fused to a pi-electron deficient pyridine ring.

Interest here has centred on how electronic interactions between these two fused rings modify their chemical properties with respect to the quinoline and separate pyridine and thiophene series. This matter will be discussed in more detail later.

The introduction will be presented in three parts;

(i) a general review of the syntheses and chemical properties of thieno(2,3-b)- and -(3,2-b)pyridines, in relation to their quinoline analogues,

(ii) a review of the syntheses, properties and theoretical studies of thieno(3,4-b)pyridines,

(iii) comparison of the resonance energies of the Kekule and quinonoid forms of heterocycles and their application to assess the relative stabilities of thieno(3,4-b)pyridine analogues with the other thieno(b)pyridines.

A detailed review of the nucleophilic substitution reactions of chlorinated thieno(b)pyridines and their quinoline analogues will be given in Part II in this Thesis.

1.2.1. THIENO(2,3-b)-AND-(3,2-b)PYRIDINES AND QUINOLINE

Syntheses

Many of the established synthetic routes to quinolines (such as the Skraup synthesis and cyclisation of amides, enamines and Schiff bases) have been applied to the syntheses of thieno(2,3-b)- and -(3,2-b)pyridines, usually with success. Syntheses on a preparative scale of the parent ring systems (1)[11] and (2)[11,12] have been reported; the former is stable indefinitely under normal conditions, but its (3,2) isomer is unstable. However, it can be kept indefinitely at $0^{o}C$, especially in a nitrogen atmosphere.

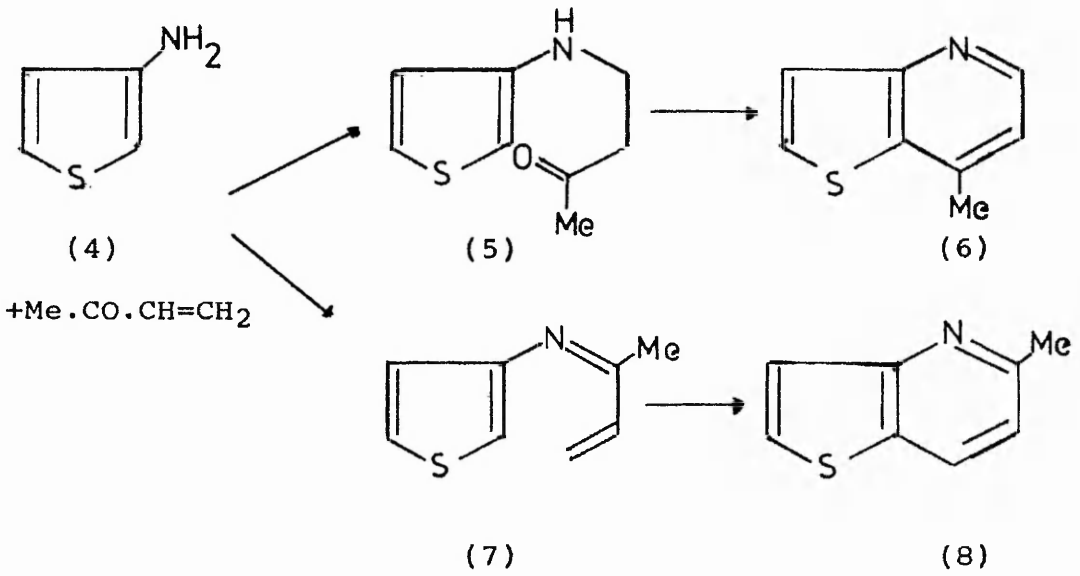
Syntheses of the (2,3-b)- and (3,2-b)- fused thieno-pyridines may be classified into two different groups, according to which heterocyclic ring is constructed.

Synthesis by pyridine ring construction.

(a) The Skraup Synthesis.

This well-known route to quinoline analogues by condensation of substituted anilines with α,β- unsaturated carbonyl compounds has been applied successfully to the syntheses of thieno(b)pyridine analogues by various workers. Steinkopf[13,14] prepared thieno(2,3-b)pyridine (1) from the intermediate acrolein and the tin double-salt of 2-aminothiophene $(C_4H_3\text{-}NH_3^+)_2SnCl_6^{2-}$ (9), the free amine being too unstable to use directly. Other α,β-unsaturated carbonyl compounds were later applied by Russian workers[15] and then by Klemm[11] to prepare 5-methylthieno(3,2-b)pyridine (8) (major product) and 7-methylthieno(3,2-b)pyridine (6) via cyclisation of the Schiffs base (7) and Michael adduct (5) respectively

(Scheme 1);

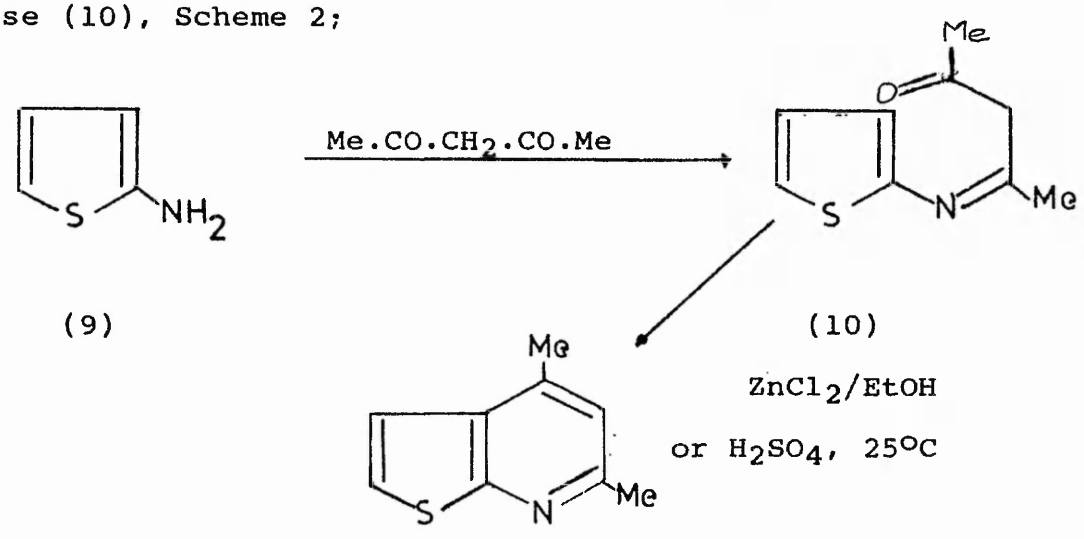


Scheme 1.

The thieno(2,3-b)pyridine analogues were similarly prepared, from the 2-aminothiophene tin-double salt (9).

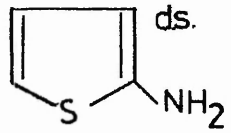
(b) Reactions of aminothiophenes and 1,3-dicarbonyl compounds.

Emerson, Holly and Klemm[16] prepared 4,6-dimethyl-thieno(2,3-b)pyridine (11) by cyclisation of the Schiffs base (10), Scheme 2;



Scheme 2

Other 1,3-dicarbonyl compounds usually led to tar formation, but their acetal and ketal derivatives sometimes proved effective. Klemm[11] prepared the parent systems (1) and (2) by condensation-cyclisation of malondialdehyde tetraethylacetal (MTA) with the 2- and 3-aminothiophene tin double-salts (9) and (4), respectively, (Eq. 1),



$$\xrightarrow[CH_2(CH(CO_2Et)_2)_2]{ZnCl_2/EtOH} \quad (1),\ 41\% \qquad (1)$$

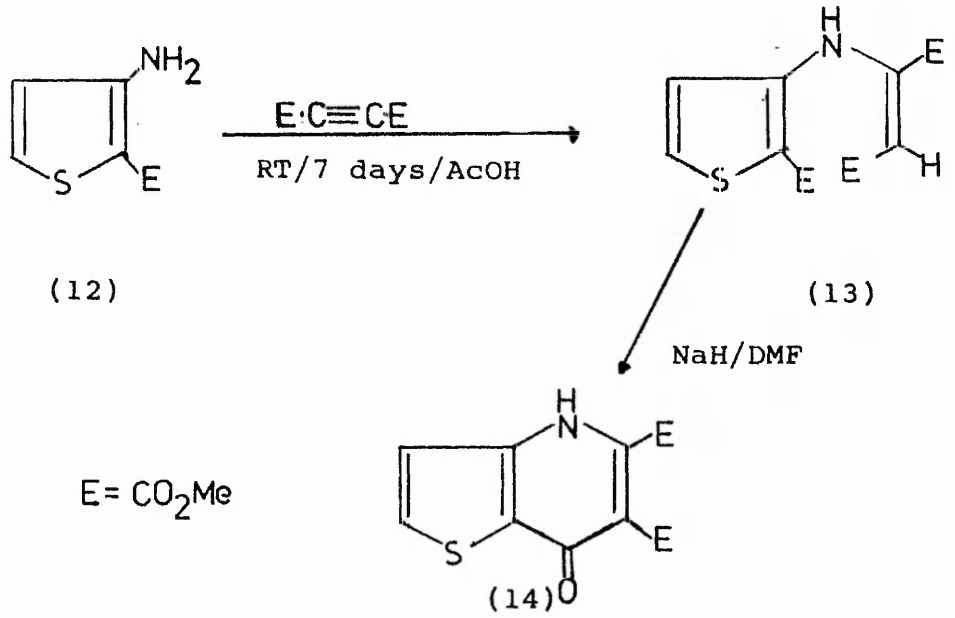
(9) d.s. = double salt of $SnCl_6^{2-}$

(c) Cyclisation of thiophene-enamines.

The stabilities of 2- and 3- aminothiophenes are greatly enhanced by introducing electron-withdrawing groups either into the thiophene ring (e.g. ester) or onto nitrogen, as in enamines, amides or Schiffs bases. Thus esters of 3-aminothiophene-2-carboxylate are stable, as are the acetamide (23) and Schiffs base (10).

Cyclisation of ethoxymethylene malonate condensation products and dimethyl acetylenedicarboxylate (DMAD) adducts of (15) and (12) have led to convenient syntheses of substituted thieno(2,3-b)- and -(3,2-b)pyridines, some of this work being performed at Trent Polytechnic.

(i) Barker[5] prepared the substituted thieno(3,2-b)-pyridin-4(7H)-one (14) by base-catalysed cyclisation of the Michael adduct (13), (Scheme 3) an application of the Conrad-Limpach[18-24] route to quinolines.

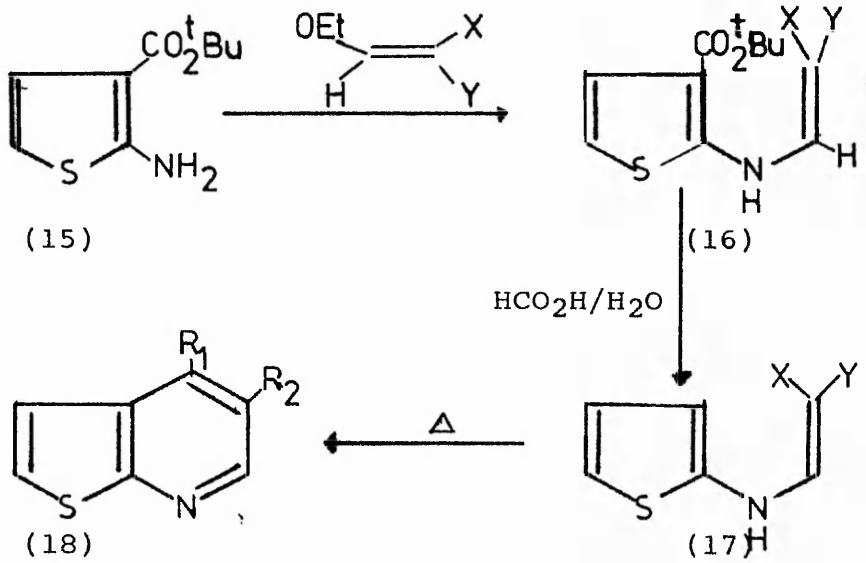


Scheme 3

Similarly, the thieno(2,3-b)pyridine[24] isomer of the thienopyridione (14) was prepared, although in much lower overall yields; the Michael addition of DMAD to the related Methyl 2-aminothiophene-3-carboxylate gave complex mixtures from which only low yields of the Michael adduct were isolated.

(ii) The Gould-Jacobs reaction.

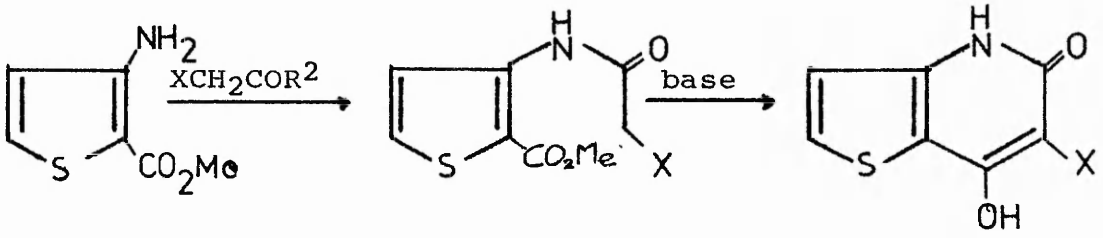
A modification of the Conrad-Limpach reaction for the synthesis of quinolines, this involves the thermal cyclisation of vinylamines derived from the condensation reactions of arylamines and ethoxymethylene malonate derivatives, (Scheme 4). Various thieno(3,2-b)- and -(2,3-b)pyridines have been prepared in this way [25-28].



X	Y	R_1	R_2	ref.	
CN	CO_2Et	OH	CN	25	
CN	CN	NH_2	CN	29	(2-Me
MeCO	CO_2Et	OH	COMe	25	or Ph)
MeCO	MeCO	Me	COMe	25	

Scheme 4

(d) Various 5,7-dioxygenated thieno(3,2-b)-[30] and -(2,3-b)[31] pyridines have been prepared, respectively, by base induced cyclisation of amides derived from the amino esters (12) and (15) and acetic acid derivatives. Scheme 5 illustrates the formation of thieno(3,2-b)pyridines by this method.

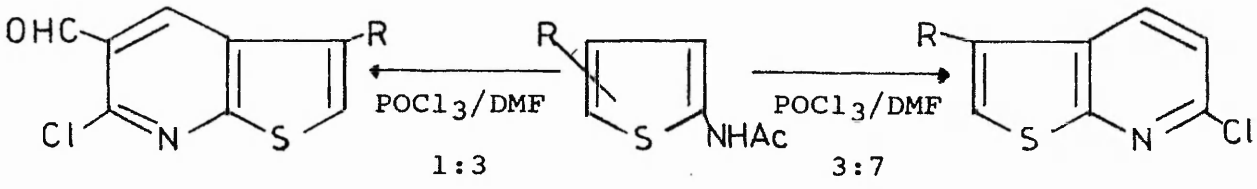


(12) (19) (20)

X= CO2Et, COMe, CN

Scheme 5

(e) By modification of the Vilsmeier reaction, Meth-Cohn[32,33] prepared various 6-chlorothieno(2,3-b)-pyridines (21) and (22) from 5-substituted-2-acetamido-thiophenes, and 5-chlorothieno(3,2-b)pyridines (24) from 3-acetamidothiophene (23) (Scheme 6);



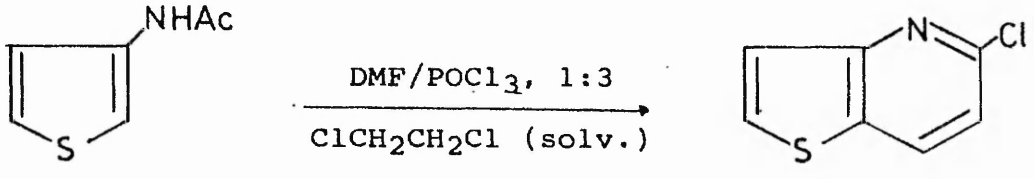
(21) (22)

R= 2,3-Me_2

2,3-$(CH_2)_4$-

2-Me

2-Br



(23) (24)

Scheme 6

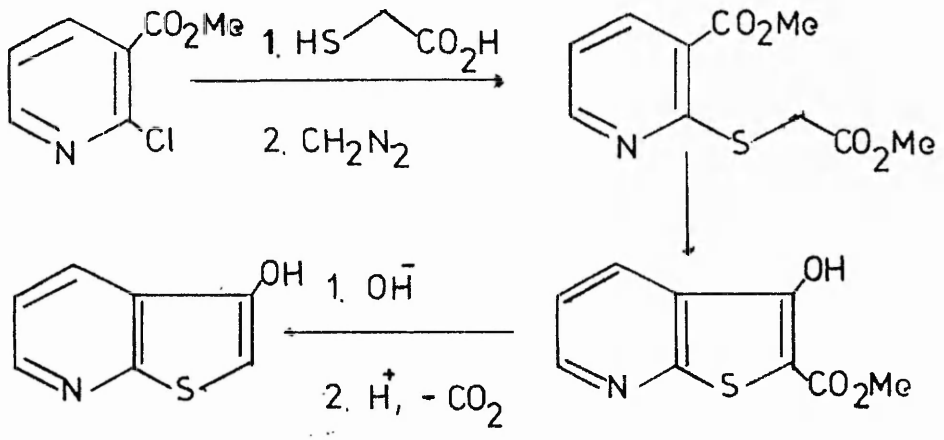
This provided very convenient routes to such chlorinated thieno(b)pyridines and also to valuable chemical intermediates for further study.

Synthesis By Construction Of The Thiophene Ring

This mode of synthesis of thieno(b)pyridines has been much less widely applied than the construction of the pyridine ring, and is limited mainly to the preparations of thieno(2,3-b)pyridines.

(a) From pyridinecarboxylic acid derivatives.

Chichibabin and Vorozhtov[34] prepared 3-hydroxy-thieno(2,3-b)pyridine (25), by the route depicted in Scheme 7;

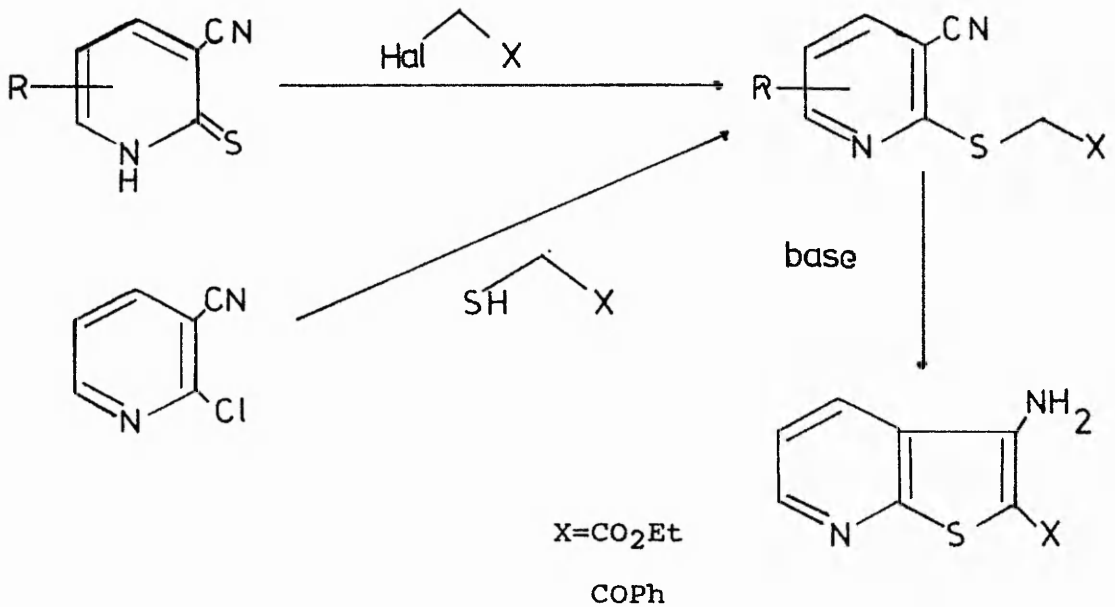


(25)

Scheme 7

Thieno(3,2-b)pyridines were also be similarly produced.

(b) Base cyclisation of 2-alkylthio-3-cyanopyridines has provided a successful route to thieno-(2,3-b)pyridines (26)[35-40]; the general approach is outlined in Scheme 8;



X=CO_2Et

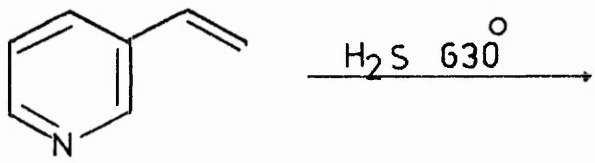
COPh

CN (26)

Scheme 8

(c) High Temperature Cyclisation Methods

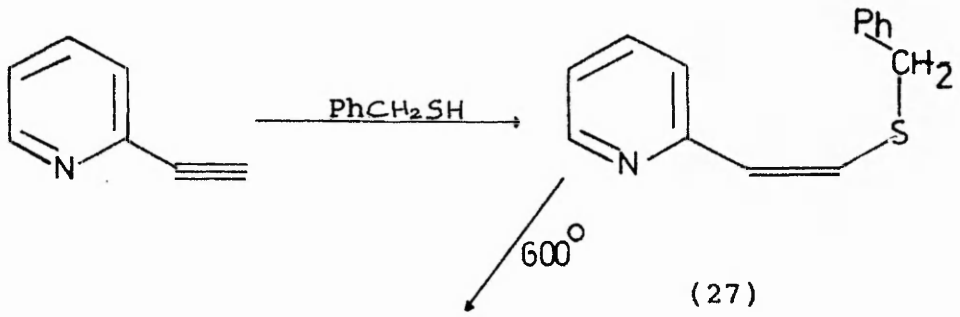
Klemm and co-workers prepared thienopyridines by employing high temperature catalytic processes, which generally gave only low yields of product. Thieno(2,3-b)-pyridine was prepared[41] by heating 3-vinylpyridine with hydrogen sulphide over an iron(II)sulphide-alumina catalyst at 630°C, (Eq. 2)



(1) + (5) (2)

Under identical conditions[42], 2-vinylpyridine gave (2) in low yield (1.6%). Improved returns[43] of (2) were attained by reacting the 2-vinylpyridine with benzylmercaptan to give benzylpyridiylethylsulphide , which on pyrolysis gave a much improved yield (28%). A

considerably better synthesis of (2)[44] is shown in Scheme 9.



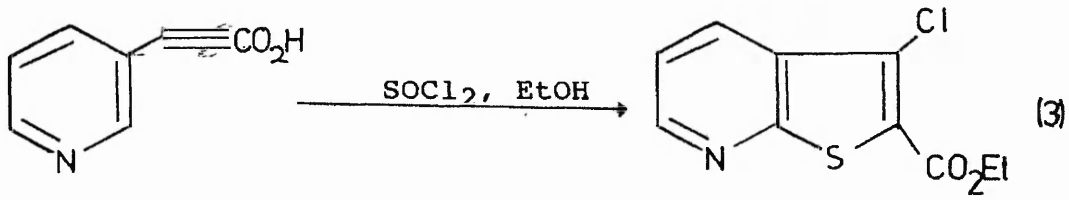
(27)

(2)

Scheme 9

MISCELLANEOUS.

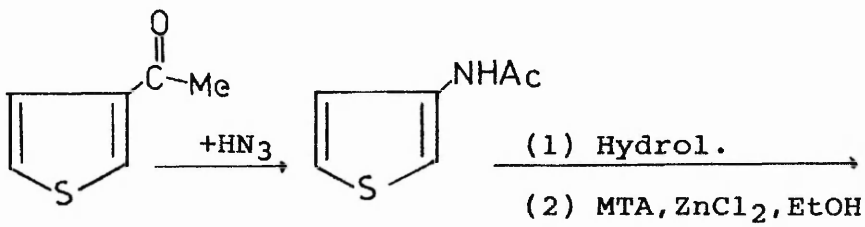
A low yield of the thieno(2,3-b)pyridine (28) was obtained by heating pyridin-3-ylpropiolic acid in refluxing thionyl chloride[45] (Eq. 3);



(3)

(28)

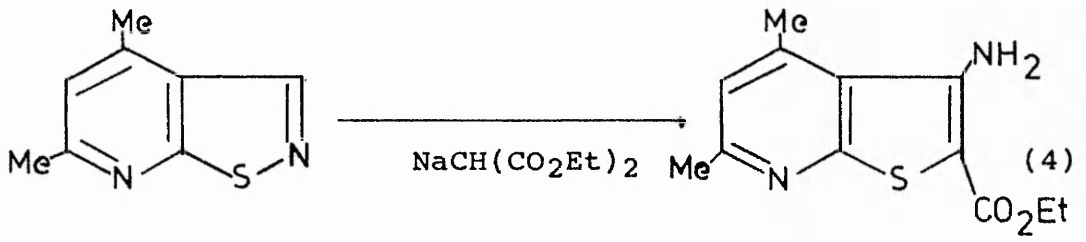
Thieno(3,2-b)pyridine has been prepared in high yield via a Schmidt reaction by Outurquin[46], Ah Kow and Paulmier (Scheme 10). Although, Meth-Cohn had prepared (2) earlier from the 3-aminothiophene tin double-salt, the Schmidt reaction provided an excellent route to the amide (23) and so to the free amine of (4).



(23) Scheme 10

MTA = Malondialdehyde Tetraethyl Acetal

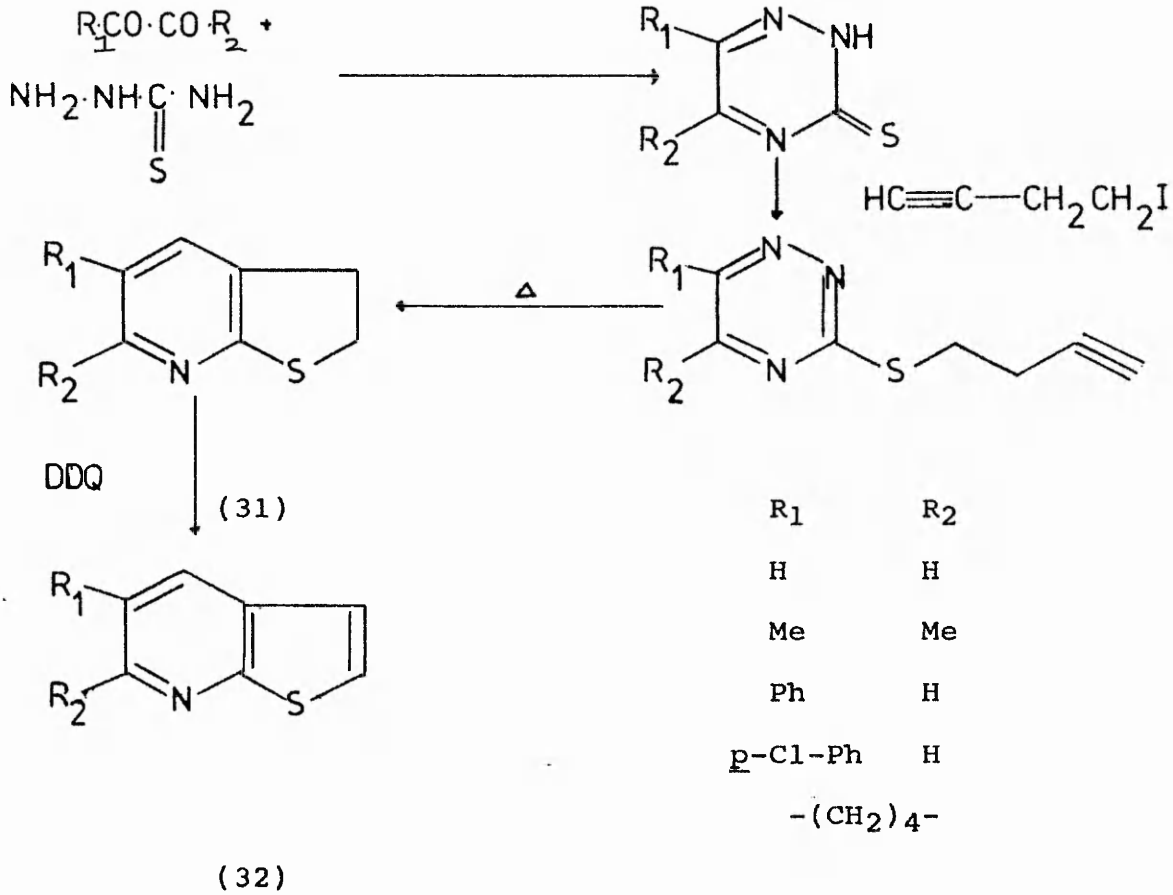
The more complex thieno(2,3-b)pyridine (30) has been synthesised from isothiazolopyridine (29) by the route[35] shown in Eq. (4);



(4)

(29) (30)

Taylor[47] has recently prepared thieno(2,3-b)pyridines (32) (and 2,3-dihydrothieno(2,3-b)pyridines (31)) by intra-molecular Diels-Alder reactions of 1,2,4-triazines (Scheme 11)



R_1	R_2
H	H
Me	Me
Ph	H
p-Cl-Ph	H
	$-(CH_2)_4-$

(32)

Scheme 11

1.2.2. PROPERTIES AND REACTIONS.

Theoretical studies.

In thienopyridines, a pi-electron deficient pyridine ring, characterised by its resistance to electrophilic substitution, but undergoing facile nucleophilic substitution is fused to a pi-electron rich thiophene ring which, in isolation, exhibits the opposite behaviour. Comparisons of the electrophilic and nucleophilic substitution reactions of the thienopyridines with their quinoline and separate thiophene and pyridine analogues would give some insight into the mutual electronic effects between the two fused rings. The conclusions drawn can then be interpreted in the light of the observed bond lengths and calculated bond orders and electron densities on the three parent thieno(b)pyridine isomers and quinoline to see if their chemical properties can be readily explained using these parameters.

Bond lengths

The bond lengths in quinoline[48] have been determined absolutely (x-ray crystallography), but those for the thienopyridines and benzothiophenes have only been estimated[49] by calculations based on the values for known compounds. The results (bond lengths in Angstroms) are collected in fig. 1.

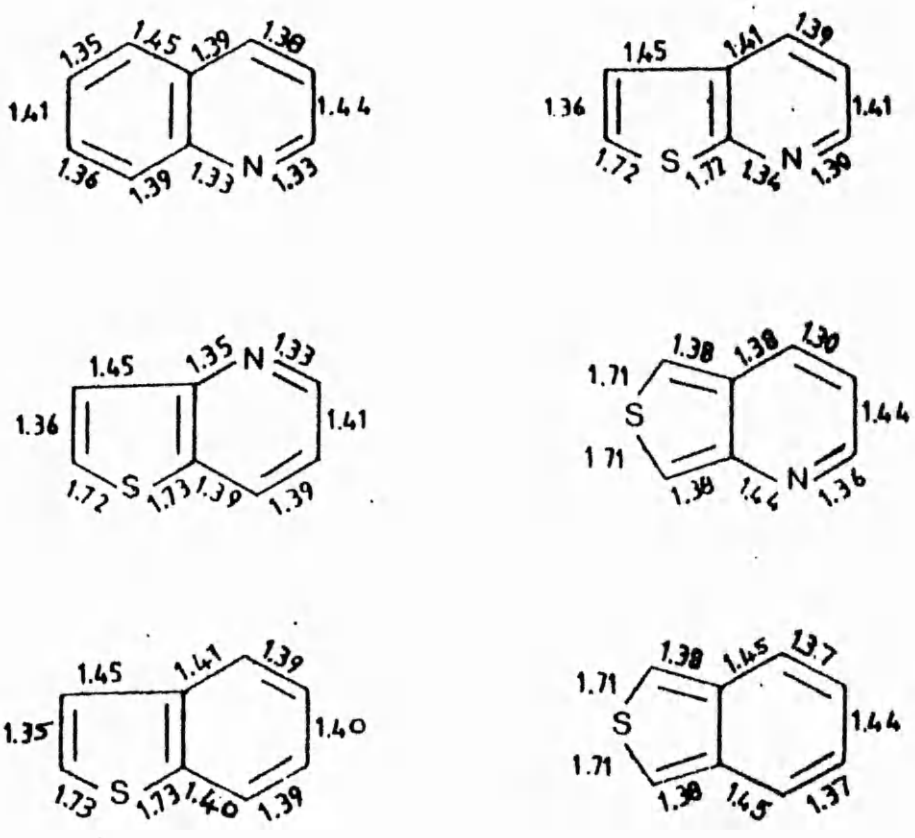


Figure 1

Bond lengths (Å) in [b]-fused pyridines and in benzothiophenes.

It appears that replacement of a benzene ring by a thiophene ring i.e. in the change from quinoline to a thieno(b)pyridine has no pronounced effect on bond lengths in the neighbouring pyridine ring, the geometry of the latter remaining essentially unchanged. Likewise, the geometry of the thiophene ring remains essentially the same on replacement of the pyridine ring by benzene, i.e. in the change from a thieno(b)pyridine to a benzothiophene.

Electron densities.

Quinoline has been the subject of a number of studies[50]. Theoretical studies using the Hückel Molecular Orbital Method (H.M.O.) of the thieno(b)pyridines[11,51,52]

and of quinoline have given the pi-electron densities at each ring position shown in Figure 2

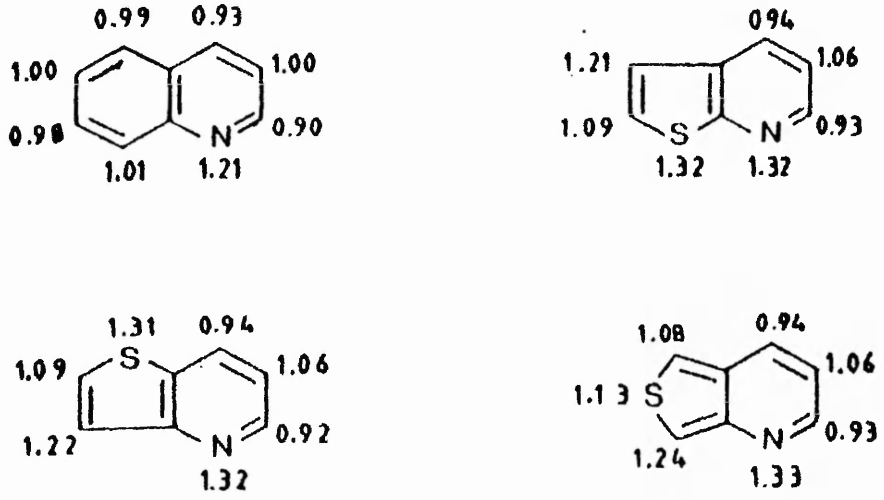


Figure 2

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

It is evident that there is an increase in electron density in the pyridine ring on replacement of benzene by thiophene, i.e. in the change from quinoline to a thieno(b)pyridine. This would be expected since 10 pi-electrons are now distributed among nine ring atoms instead of ten. However, the relative order of electron densities in the α, β, and γ-positions of the pyridine ring is the same as in quinoline and so the normal mesomeric effect of nitrogen on this ring is apparent. This correlation would suggest that the order of rates of nucleophilic attack on these positions be the same, but slower than in quinoline.

Base Strengths.

The pKa values for thieno(2,3-b)- and -(3,2-b)pyridine and quinoline have been determined in water at 25°C[53] and are as follows;

Compound	pKa
Thieno(2,3-b)pyridine	2.75
Thieno(3,2-b)pyridine	4.35
Quinoline	4.87

This order is explained in terms of the electron-withdrawing (inductive) effect of the sulphur atom on the nitrogen. As expected, the systems become less basic (i.e. pKa increases), as the distance between the sulphur and nitrogen atoms decreases.

1.2.3. REACTIONS.

Electrophilic Substitution.

Studies of the electrophilic substitution reactions of quinoline have led to the following conclusions;

(i) Electrophiles (particularly H^+) co-ordinate with the nitrogen atom, inhibiting the pyridine ring to electrophilic attack.

(ii) In strong acid conditions, where the nitrogen atom is protonated substitution almost invariably occurs in the benzene ring, the rate being slower than in naphthalene but faster than in benzene. In weak acid conditions, where protonation at nitrogen is not so profound, electrophilic substitution also occurs readily at C-3, i.e. in the pyridine ring.

(iii) 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.

(iv) A 4-oxygenated function in a quinoline derivative activates the neighbouring C-3 position (if vacant) towards electrophilic attack, so that substitution into the pyridine ring now becomes preferred.

Klemm and Barker have carried out much of the work on electrophilic substitution reactions of thieno(2,3-b)- and -(3,2-b)pyridines; nitration, deuteration and halogenation have been studied to the greatest extent.

Deuteration.

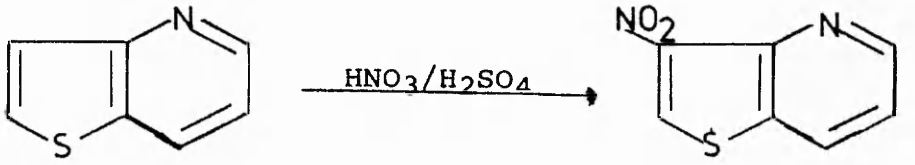
Clementi[54] and Gronowitz[55] employed proton n.m.r. to study the rates of deuteriodeprotonation of thieno(2,3-b)-pyridine and thieno(3,2-b)pyridine in D_2SO_4 at 100°C. The 3-position was the most readily substituted, and attack at C-2 took place only after prolonged heating in more concentrated acid. Attack took place on the protonated species and the rate was considerably faster than in both quinoline and benzene, but slower than in thiophene. Qualitatively, these results are as expected, with the rates decreasing as electron density in the thiophene ring decreases. The (2,3-b)- system was found to be slightly more reactive than the (3,2-b)-.

Nitration.

The nitration of thieno(2,3-b)pyridine has also been studied[54] kinetically (spectrophotometrically) and results similar to those observed in the deuteration experiments were obtained.

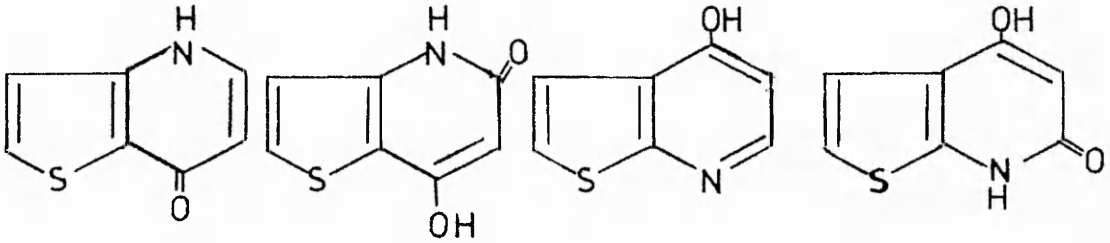
Preparative nitrations have also been carried out on (1) and (2)[52] in nitric-sulphuric acid mixtures to give

the 3-substituted products in each case, (Eq. 5)



(5)

Barker[56] discovered that the oxygenated thieno(3,2-b)-pyridines (33) and (34)



(33) (34) (35) (36)

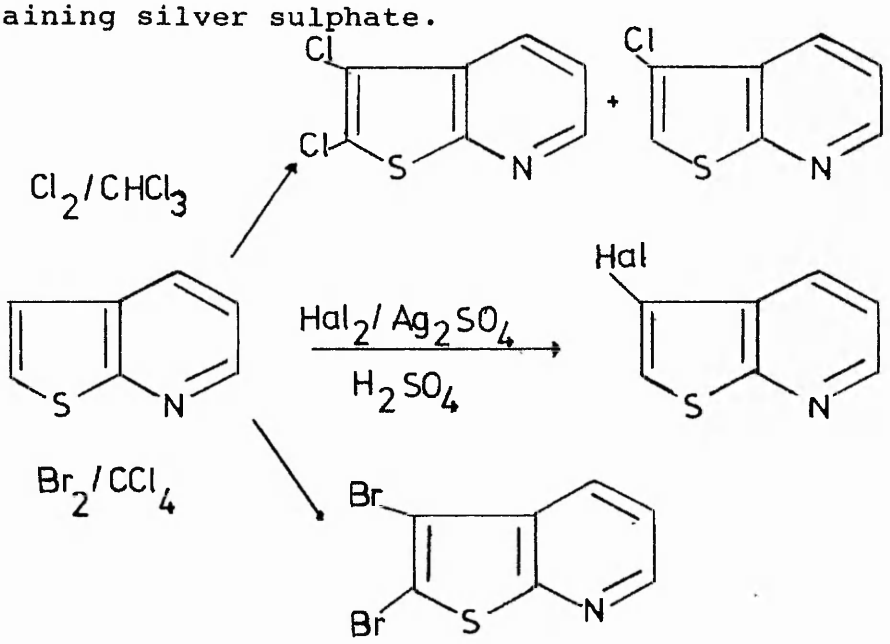
were similar to their quinoline isosteres in that the γ-oxygenated function activated its adjacent β-position towards electrophilic attack (Table 1). However, of the compounds in the (2,3-b)- series (35) (which exists as the enol tautomer) was anomalous in that substitution occurred in the thiophene ring at C-2 and (36) gave an unstable product. In a mixture of sulphuric/nitric acids, (33) and (34) were dinitrated at the 3- and 6-positions; (35) and (36) returned the 2,5-dinitro products. These results are summarised in Table 1.

Table 1. Major products in the nitration reactions of some thienopyridines

	SUBSTRATE			
reagent	(33)	(34)	(35)	(36)
HNO_3 or HNO_3/AcOH	6-NO_2	6-NO_2	2-NO_2	dec.
HNO_3-H_2SO_4	3,6-di-NO_2	3,6-di-NO_2	2,5-di-NO_2	dec.

Halogenation.

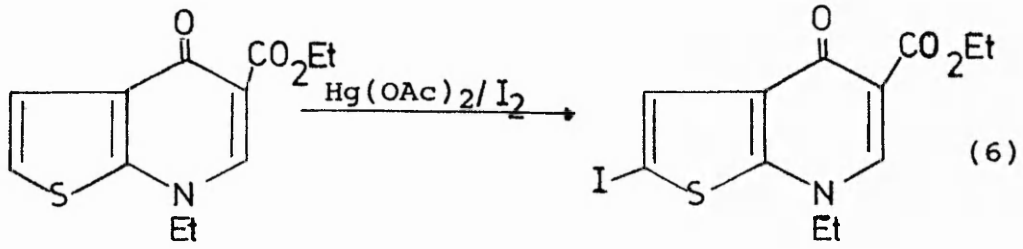
Substitution by halogen was found to be more complex than nitration and deuteriodeprotonation, the reactions being in competition with oxidation and addition[57,58]. Although nitric acid is also an oxidant, no such side reactions were found in the thieno(b)pyridine series. Treatment of thieno(2,3-b)pyridine with excess of bromine in carbon tetrachloride-water gave a low yield of the 2,3-disubstituted product (37)[16], (Scheme 12). Under similar conditions chlorination gave a mixture of 3-chloro and 2,3-dichlorothieno(2,3-b)pyridines[57]. Moderate yields of the 3-halo derivatives[55] were obtained by treating (1) with elemental halogen in warm concentrated sulphuric acid containing silver sulphate.



(37)

Scheme 12

A few iodination reactions[59] have been successful, using iodine/mercury(II) acetate solutions or iodine monochloride, (Eq. 6)



(6)

Bromination[56] (like nitration) of the thieno(3,2-b)-pyridones (33) and (34) occurred in the β-position of the pyridine ring (Table 2). Bromination, in contrast to nitration (see Table 1), of the (2,3-b)- analogue (35) occurred at the β- position in the pyridine ring. Bromination also occurred at the β-position in (36), to give a stable compound.

Table 2. Major products in the bromination reactions of some thienopyridines

	SUBSTRATE			
reagent	(33)	(34)	(35)	(36)
1 mol eq. Br_2-AcOH	6-Br	6-Br	5-Br	2-Br
xs. Br_2-AcOH	6-Br+3,6-di-Br	6-Br	2,5-di-Br	2,5-di-Br

If the β-positions in (34) and (36) are blocked substitution then occurs in the thiophene ring at C-2 in the (2,3-b) compound and at C-3 in the isomeric (3,2-b) compound.

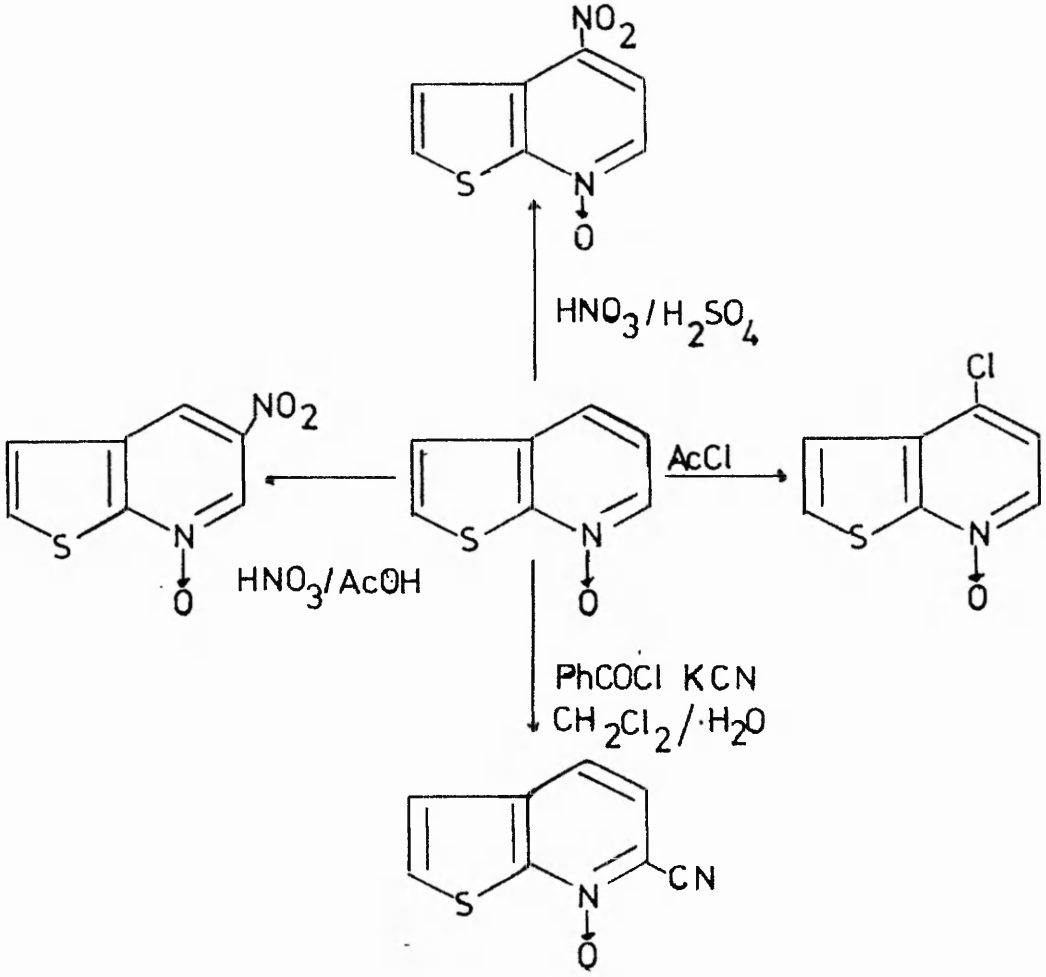
Mannich Reaction.

Work by Barker[56] and co-workers has shown that each of the thieno(b)pyridones (33), (34), (35) and (36) is

attacked by the weaker electrophile involved in the Mannich reaction; in all cases the β-substituted products were isolated.

N-oxides.

The N-oxides of (1)[60] and (2)[61] are formed in high yield by their reaction with hydrogen peroxide/acetic acid or m-chloroperoxybenzoic acid. Their chemical properties[60,62,63], some of which are shown in Scheme 13, are very similar to those of their quinoline counterparts.



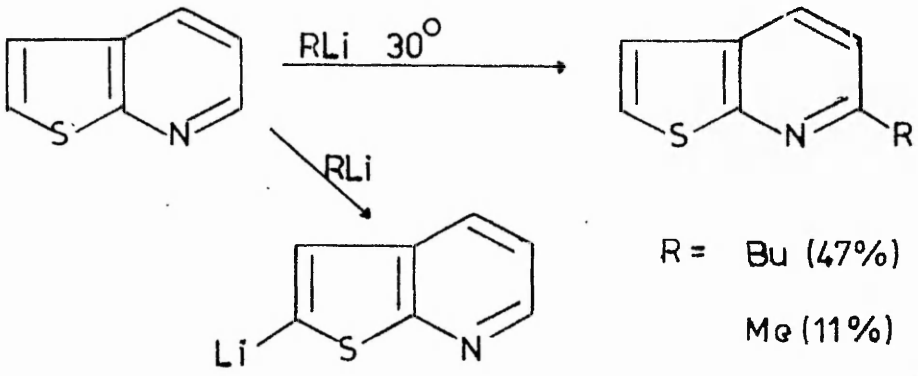
Scheme 13

Nucleophilic Substitution

A brief precis will be given here. For a more detailed survey, see "PART II: KINETICS". Studies of aromatic nucleophilic substitution in thieno(b)pyridines have involved a variety of nucleophiles, but only two different leaving groups, hydride and halide.

Hydride.

Only one example has been reported in thieno(b)pyridines, by Klemm[11] et al, involving reaction of thieno(2,3-b)pyridine with n-butyllithium (Scheme 14);



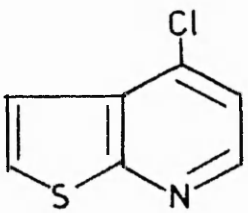
Scheme 14

Halide.

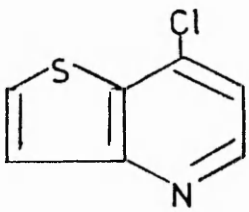
The nucleophilic substitution reactions of 2- and 4-haloquinolines have been studied in depth, both qualitatively and quantitatively. A variety of solvents and nucleophiles (piperidine[64], ethoxide[64] and methoxide[65,66]) have been used, under a wide range of temperatures. Generally, under identical conditions, 2- and 4- chloroquinoline undergo nucleophilic attack at very similar rates. Studies[68] of competitive reactions on 2,4-dichloroquinoline (ethanolic potassium hydroxide) also

showed the similarity in reactivity of the two positions, the two isomeric chlorohydroxyquinolines being isolated in almost equal proportions. With sodium methoxide[66,69] in methanol, 2-chloro-4-methoxyquinoline was the major product by a factor of almost 2:1, but generally the activities of the α- and γ- chlorine atoms are very similar.

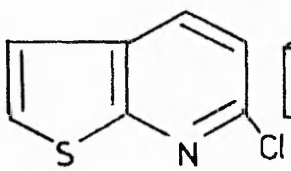
Barker[6,31,69,70] has studied the nucleophilic substitution reactions of a variety of α- and γ-chlorinated thieno(2,3-b)- and -(3,2-b)pyridines. In both of the 2,3- and 3,2- fused thieno(b)pyridine series the γ-position was found to be much more reactive than the α-position. Table 3 illustrates the reaction conditions applied in the methoxydechlorination reactions of (38) to (41) with methanol employed as solvent in each case.



(38)



(39)



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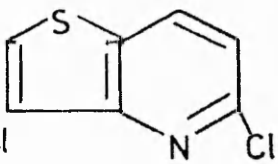


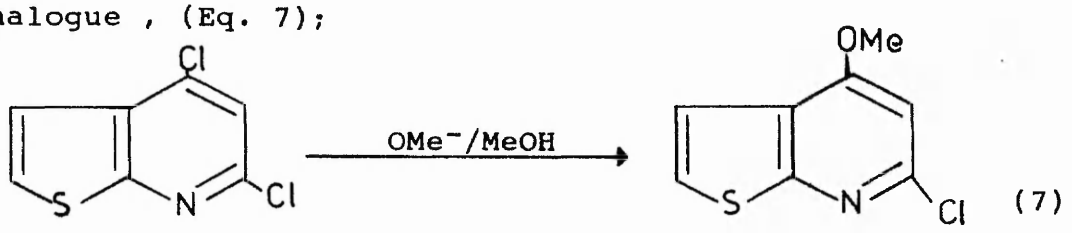
(41)

Table 3. Conditions required in the nucleophilic substitution reactions of some thieno(b)pyridines.

	mol. equivalent			
No.	substrate	OMe	reflux time (hrs.)	yield (%)
38	1	2	30	85
39	1	1.5	6	73
40	1	39	20	72
41	1	50	30	58

Table 3

Similar results were found in the α-, γ- dichloro thieno(2,3-b)pyridine[31] (42), and also its (3,2-b)-[69,70] analogue , (Eq. 7);

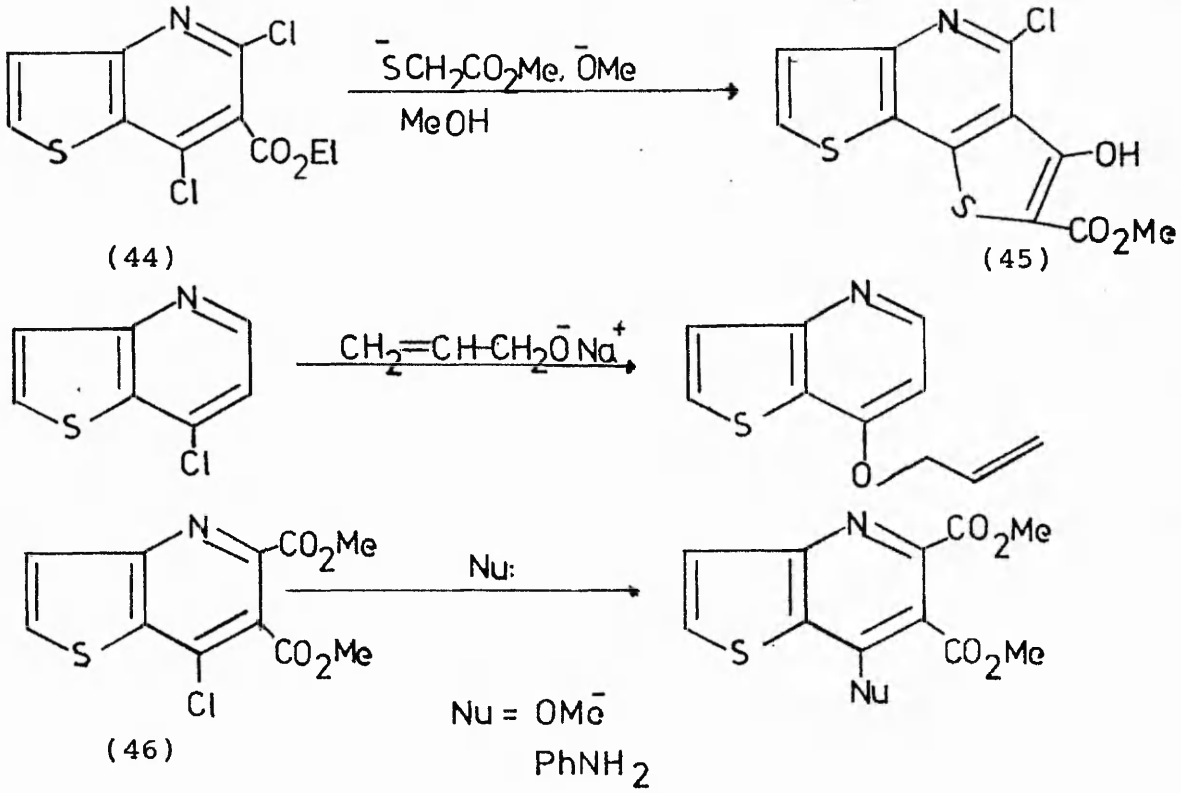


(7)

(42) (43)

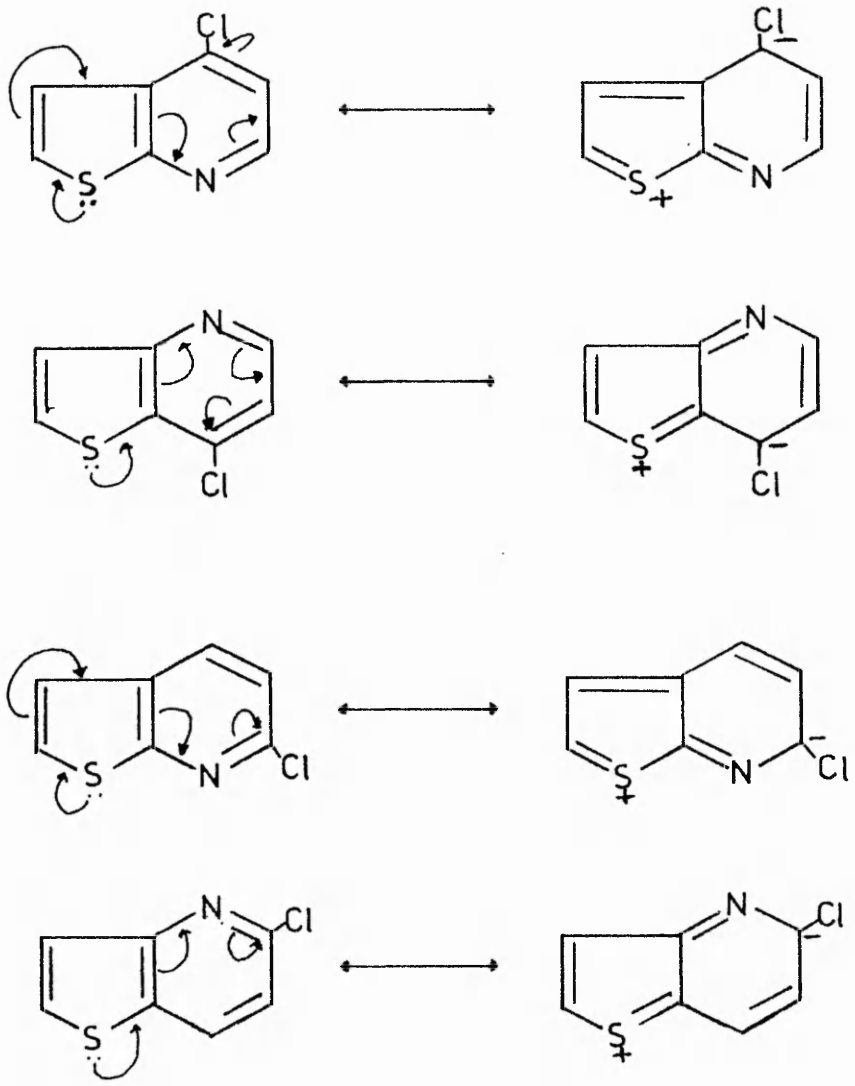
Further, the presence of a carboxylate group at the β-position in each case has no effect on the relative reactivities of the α- and γ- chlorine atoms.

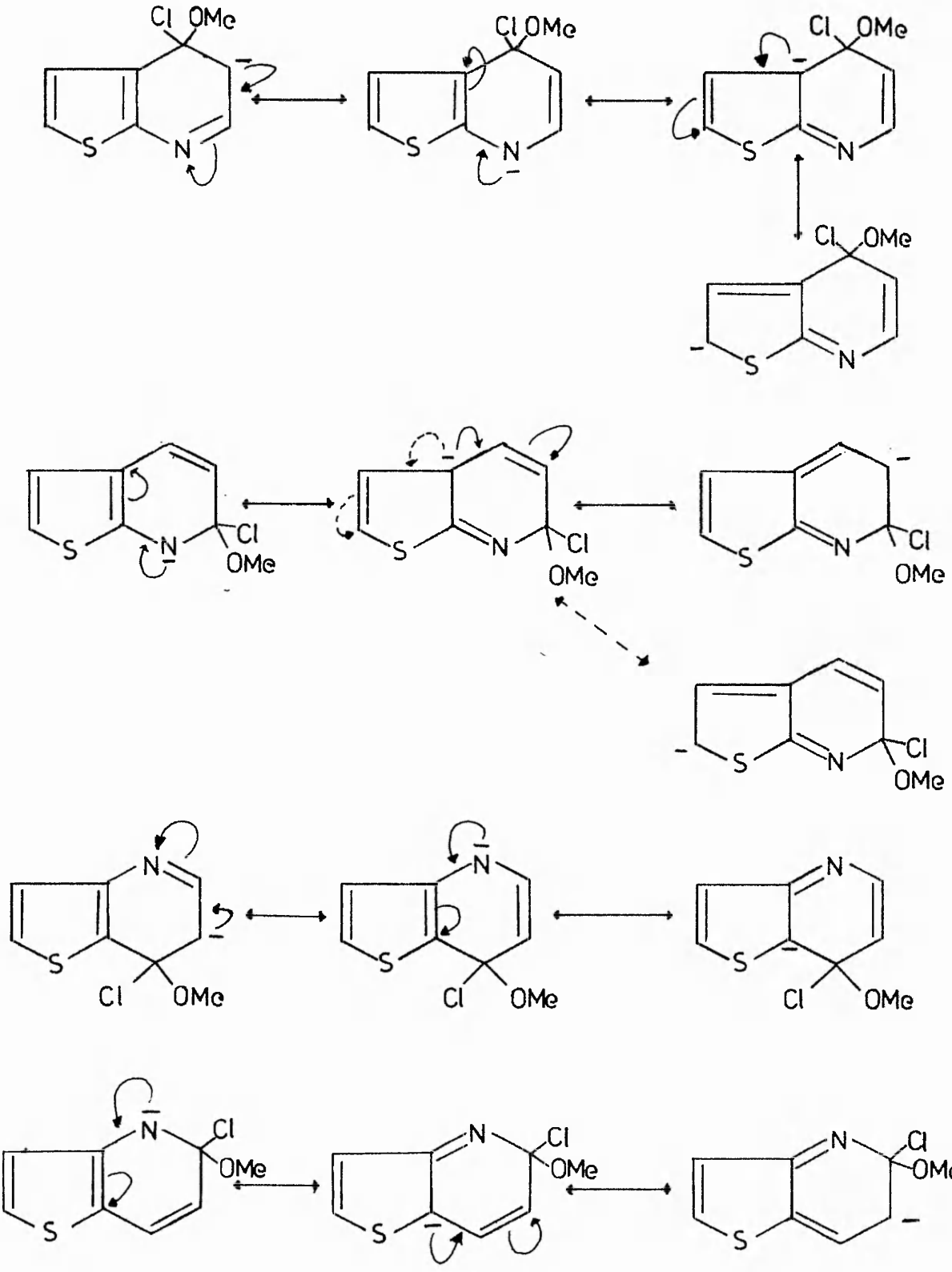
More elaborate nucleophiles were also studied by Barker. A series of reactions is illustrated in Scheme 15 for the thieno(2,3-b)pyridine series;



Scheme 15

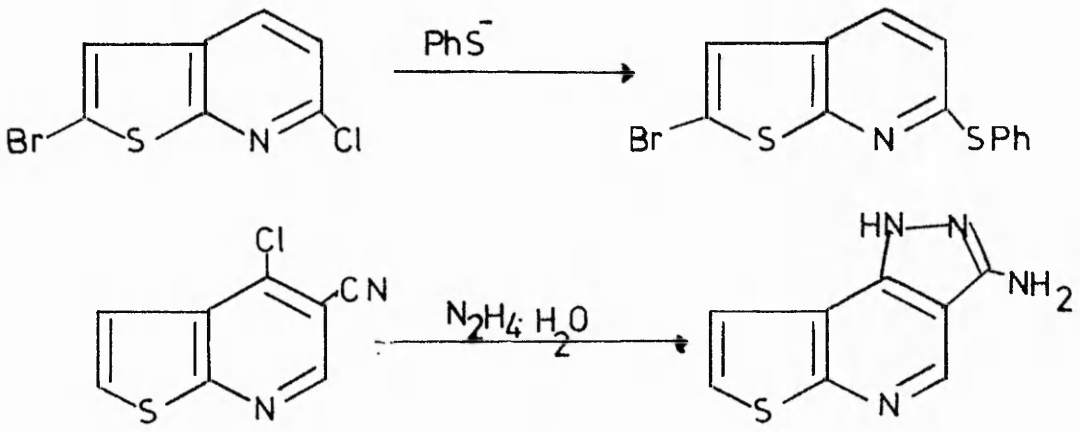
Such a drastic difference in reactivity between the α- and γ- positions is not readily explained. The canonical forms of the substrate (mesomeric effect of sulphur on the ring) and of the intermediate σ-complex do not indicate any obvious factors for either lability at the γ-position or almost inert character at the α- position (Scheme 16);





Scheme 16

Meth-Cohn[71] and Khan[72] used the thiophenoxide anion and hydrazine respectively as nucleophilic agents for the nucleophilic substitution reactions shown in Scheme 17;



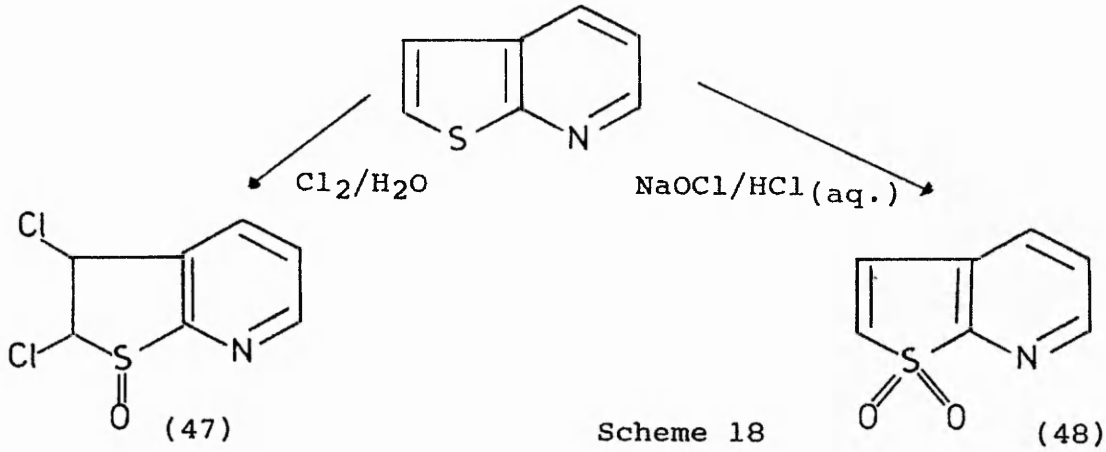
Scheme 17

Both the thiophene ring protons and the β-position of the pyridine ring are much less reactive sites for nucleophilic attack than the α- and γ- positions, as would be expected. Consequently, more forcing conditions were required. Thus, 3-bromo[57] and 5-bromothieno(2,3-b)-pyridines[73] form the corresponding nitriles with copper(I) cyanide in refluxing DMF (b.p. 153°). Also, iodine has been replaced from the 2-position in both thieno(2,3-b)-[59] and -(3,2-b)pyridine[44] using copper(I)cyanide in DMF and sodium methoxide-copper(I)oxide in methanol, respectively.

OXIDATION.

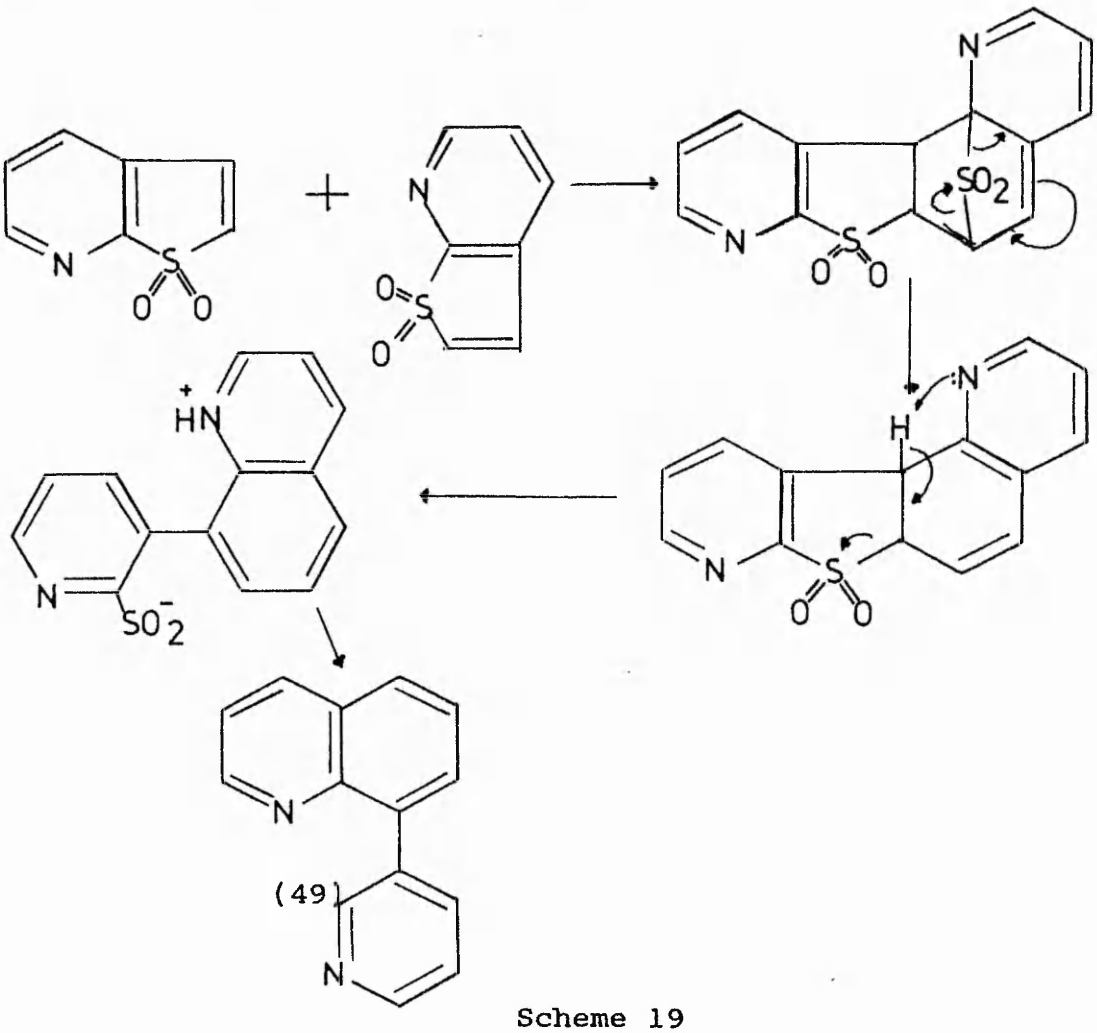
Thieno(b)pyridines have been oxidised at both sulphur (giving the sulphoxide or sulphone) and nitrogen (giving the N-oxide). The action of per-acids on thieno(2,3-b)-[60] and -(3,2-b)pyridines[61] leads to their respective N-oxides, some properties of which have been desribed

earlier (P. 23). Oxidation at sulphur is more complicated. Reaction of thieno(2,3-b)pyridine with chlorine water gave the 2,3-dihydro compound [60] (47), and with sodium hypochlorite and dilute hydrochloric acid the sulphone[58] (48) was formed (Scheme 18).



(47) Scheme 18 (48)

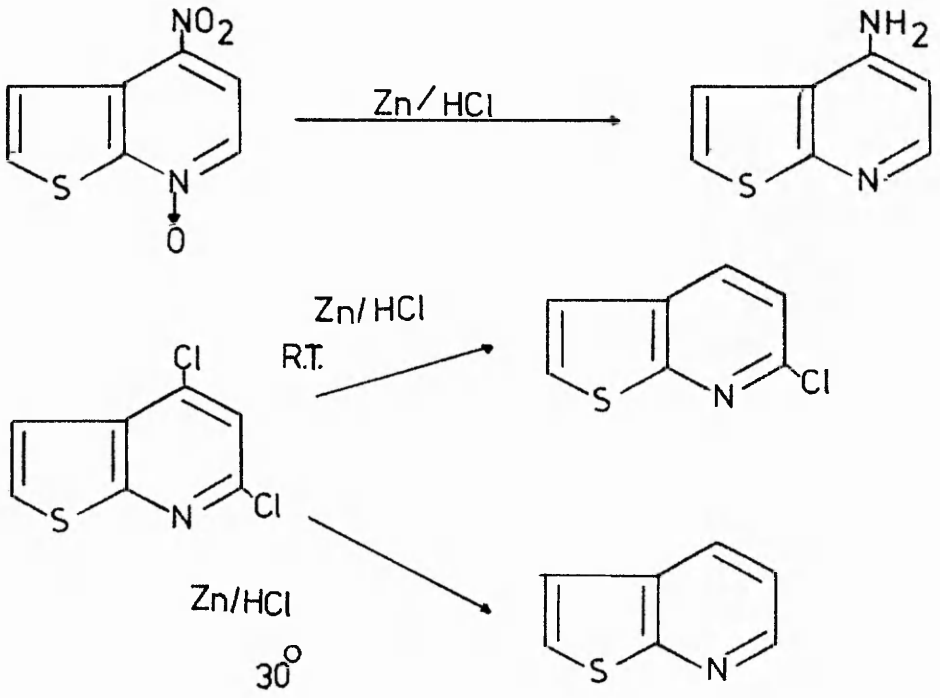
Thieno(3,2-b)pyridine is oxidised in the same way. The sulphone (47) is unstable, acting as a dienophile in Diels-Alder reactions and forming adducts with anthracene, with furan and with naphthacene. On heating, (48) condensed with itself in a Diels-Alder fashion; sulphur dioxide was then eliminated from the adduct to give the quinoline (49), as illustrated in Scheme 19



Scheme 19

Reduction.

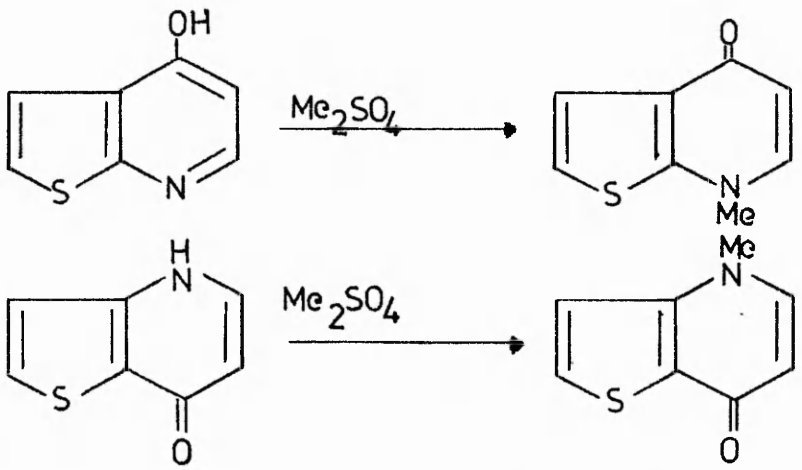
The only reported reduction of a thieno(b)pyridine system concerned the use of Raney Nickel[3], to give ethyl pyridines. In tin/hydrochloric acid[61] and iron/acetic acid[60,74] the ring systems are stable, but any nitro substituents are reduced to the corresponding amines and any halogens replaced by nascent hydrogen (scheme 20);



Scheme 20

Methylation.

All reactions with dimethyl sulphate of oxygenated (2,3-b) and (3,2-b) fused thieno(b)pyridines, (in which either the nitrogen or oxygen functions can be methylated) return the N-methylated product (Scheme 21). This preferred position of methylation is also found in the quinoline analogues.



ref. 30

ref. 31

Scheme 21

1.2.4. KETO-ENOL TAUTOMERISM

Of major interest in oxygenated thienopyridines and quinolines is the extent to which they exist in their pyridin-ol/pyridin-one tautomers. Carbon-13 n.m.r.[70] has been invaluable in determining the preferred form, which can be deduced from the chemical shift of the carbon atom bonded to the oxygenated function. In the O-oxygenated quinoline and thieno(2,3-b)- and -(3,2-b)pyridine systems a phenolic carbon atom exhibits a lower chemical shift than a ketonic one (Fig. 3).

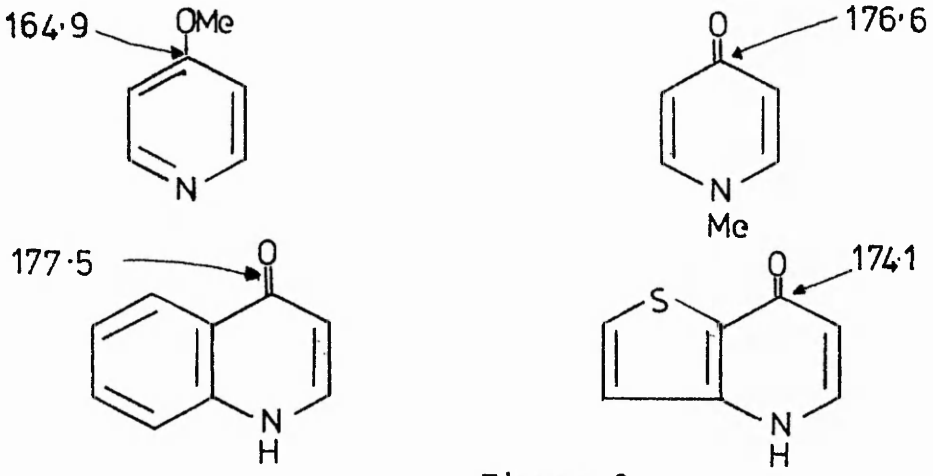
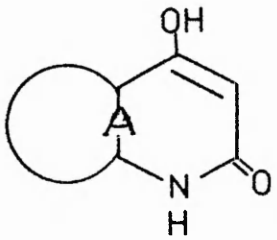


Figure 3.

In 2,4-dioxygenated systems, the γ-hydroxy-α-pyridone state is preferred for quinoline and the 2,3- fused thieno(b)pyridines



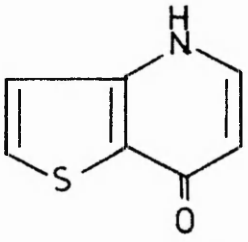
A= thieno(2,3-b)pyridine

A= thieno(3,2-b)pyridine

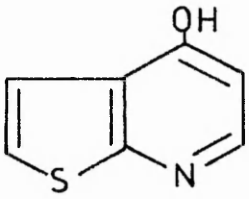
A= quinoline

An ester group at C-3 in each case has little, if any effect on these tautomeric preferences.

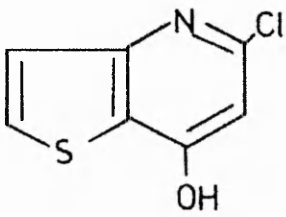
In the case of γ-oxygenated systems, no set behaviour is found and the predominant tautomeric state is dependent on the specific system and its substituents;



(33)



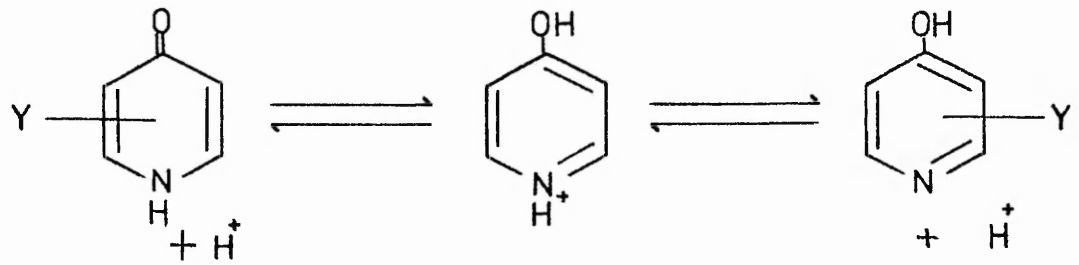
(35)



(50)

Generally, such quinolines and thieno(3,2-b)pyridines exist mainly in the pyridone states except that the presence of electron withdrawing groups at the β-position tend to cause reversion to the enol form, for example as in as in (50).

It is thought[75] that the position of tautomeric equilibrium is determined by the relative acidities of the O-H and N-H functions in the conjugate acid (51), (Scheme 22).



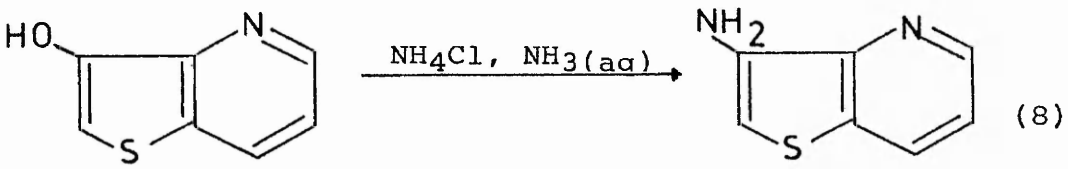
(51)

Scheme 22

If the O-H proton is more acidic than the N-H, then the keto form will predominate. Generally, this is the case but any electron-withdrawing group at the β- position

is bound to weaken the N-H bond, so enhancing its acidity. This may explain why (50) exists mainly in the enol form. In the case of 4-hydroxythieno(2,3-b)pyridine (35), the proximity of the sulphur atom may weaken the N-H bond (in comparison to its (3,2-b)analogue), this difference being sufficient to alter the predominant tautomer[51].

2-Oxygenated functions in the thiophene ring of thienopyridines are unknown, and only a few examples of 3-oxygenated derivatives have been reported. Spectroscopic evidence[76] suggests that in the latter the hydroxy tautomer is prevalent, although (52) reacts with ammonia/ammonium chloride[77,78] to give the corresponding amine (53); (Eqn. 8)



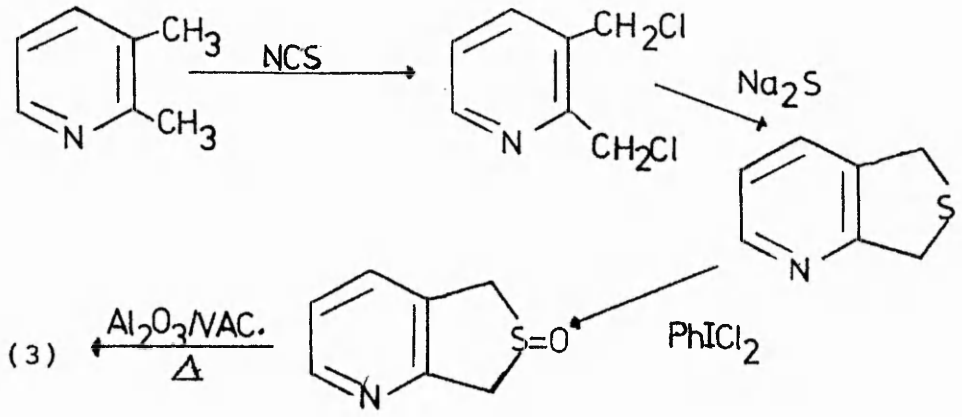
(8)

(52) (53)

THIENO(3,4-b)PYRIDINES.

1.3.1. Preparation.

(i) The parent system was prepared by Klemm,[51,79,80] by construction of the thiophene ring in the manner shown in Scheme 23 below;

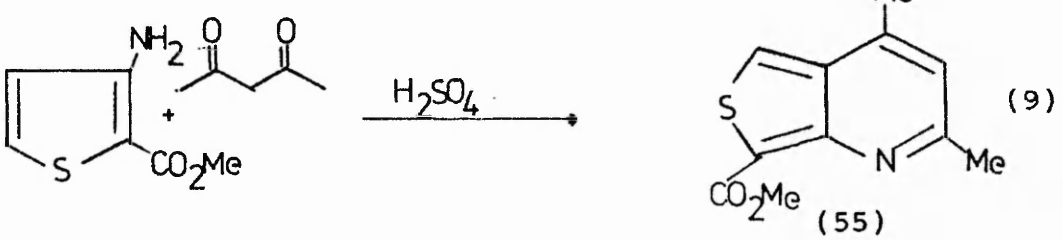


(54)

Scheme 23

In contrast to the stable thieno(2,3-b)-[11] and -(3,2-b)pyridine[82] , the (3,4-b)- isomer (3) was an unstable yellow oil, darkening after a few hours under normal conditions and eventually resinifying. However, it could be kept as its more stable picrate salt. Several preparations of substituted thieno(3,4-b)pyridines have been reported.

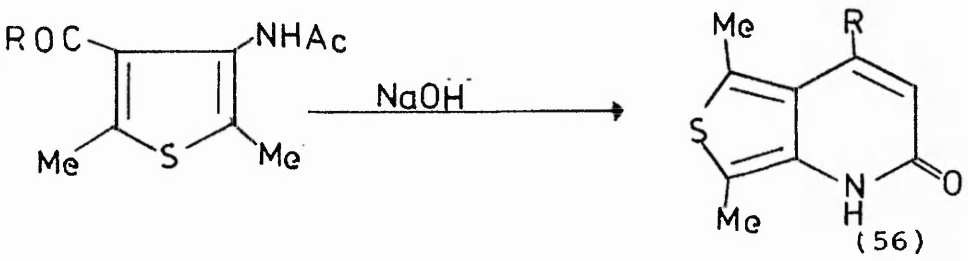
Reaction[82] of the free amine (12) with pentan-2,4-dione in concentrated sulphuric acid led to the thieno(3,4-b)-pyridine (55) in low yields, (Eq. 9)



(9)

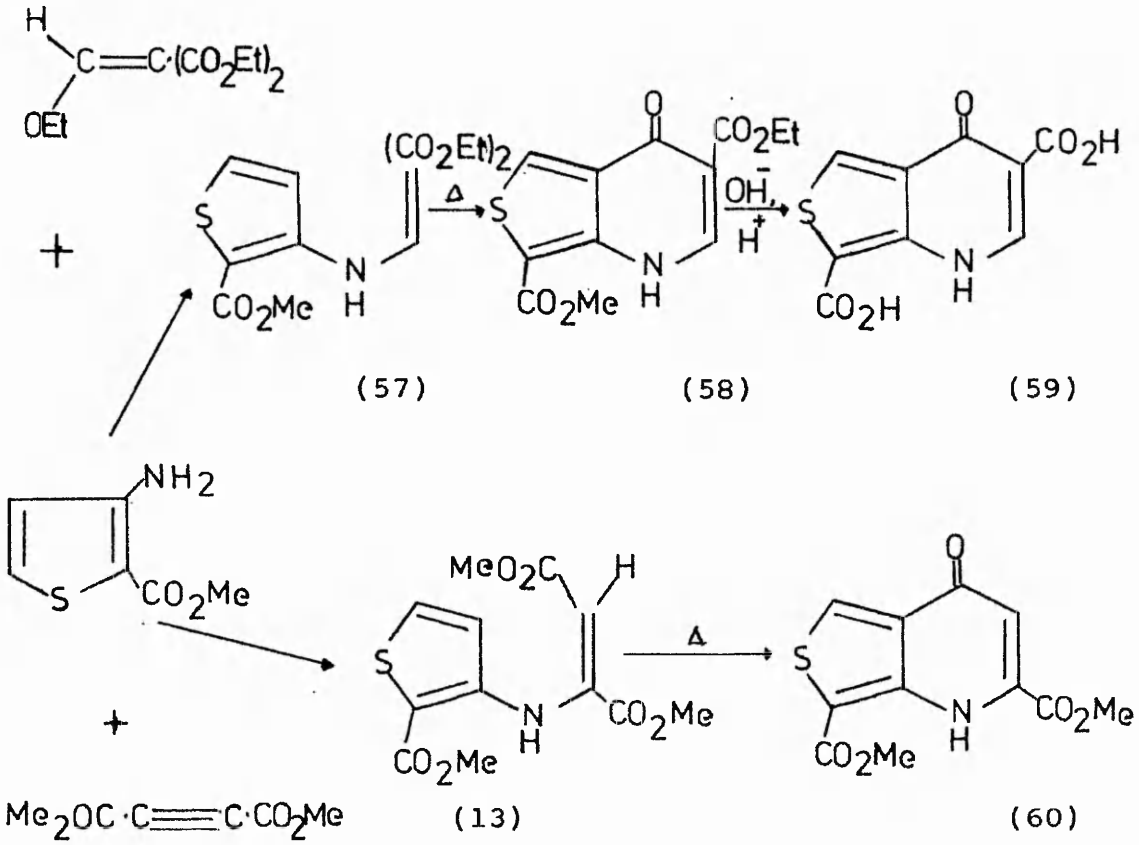
(55)

Various 5,7-dimethylthieno(3,4-b)pyridines[83,84] of the type (56) have been prepared by based catalysed cyclisation of acetamidothiophenes (Eq. 10);



(56) (10)

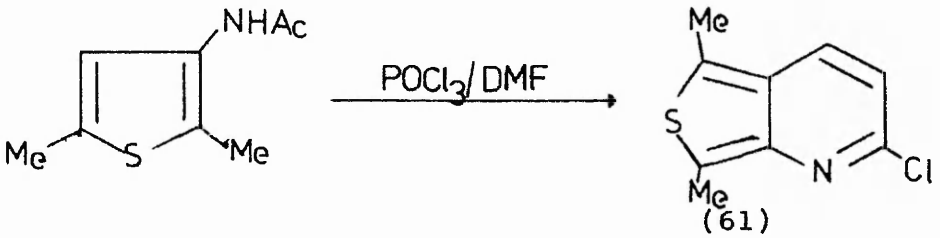
A few thieno(3,4-b)pyridine derivatives have been prepared by Jones[82] (Trent Polytechnic) by application of the Gould-Jacobs and Conrad-Limpach reactions- typical quinoline syntheses discussed earlier. (Scheme 24) shows the general approach employed by Jones;



Scheme 24

A series of stable derivatives was made from (59) and (60).

Meth-Cohn[32] has prepared the unstable thieno(3,4-b)-pyridine (61) (Eq. 11), by modification of the Vilsmeier reaction; the synthesis of thieno(2,3-b) and (3,2-b)pyridines by this route has been referred to earlier (P. 10).



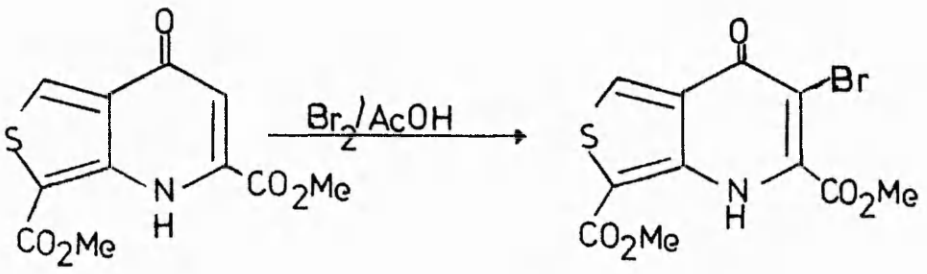
(61) (11)

1.3.2. Properties and Reactions.

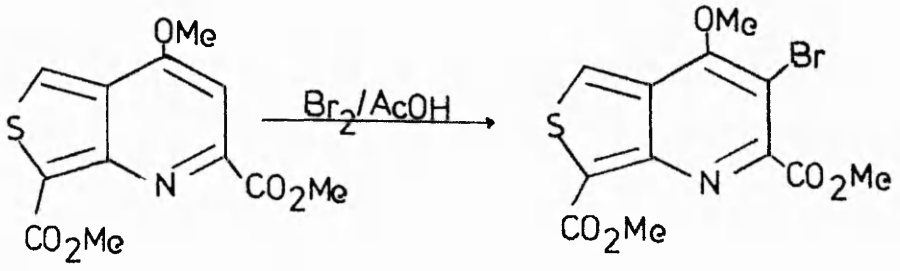
Most of the studies of thieno(3,4-b)pyridines so far reported have dealt with either syntheses of the compounds, theoretical studies, or the preparation of complex derivatives to be tested for biological activity. The few reactions performed on the system suggest that the thieno(3,4-b)pyridines differ from the other thieno(b)pyridines.

Electrophilic Substitution.

Bromination[82] of the elaborate system (60) resulted in substitution at C-3, i.e. in the pyridine ring; the same position was attacked in the methoxy derivative (62), (Scheme 25);



(60)



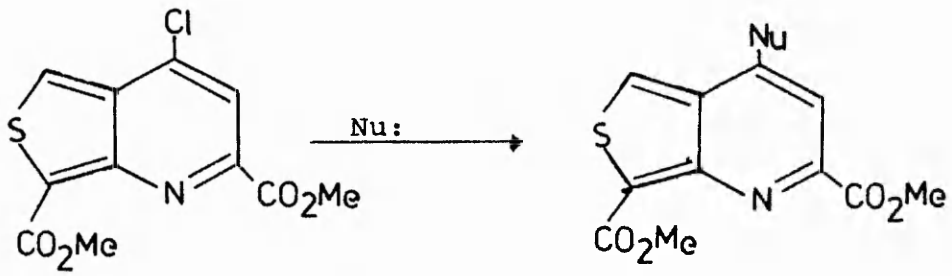
(62)

Scheme 25

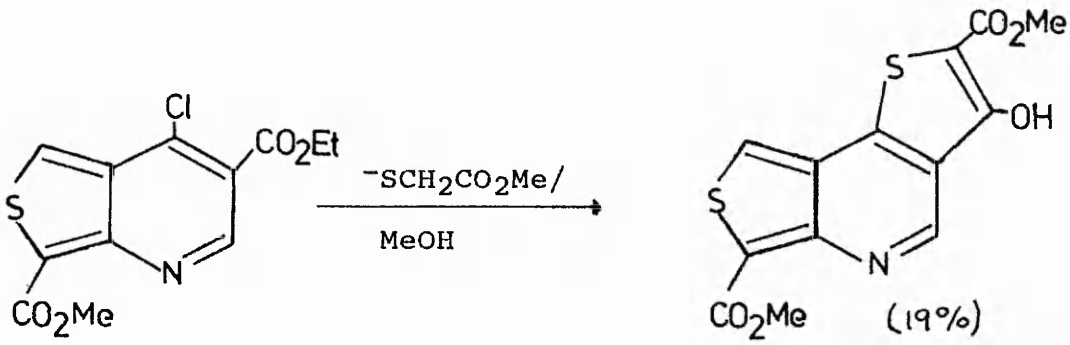
The related thieno(3,4-b)pyridine (59) failed to undergo bromination at all in acetic acid, probably due to the fact that the vacant position is now meta- rather than ortho- to the activating oxygen function.

Nucleophilic Substitution

The nucleophilic substitution reactions of a few 7-chlorinated thieno(3,4-b)pyridines were investigated by Jones[82]. A variety of nucleophiles was studied, as depicted in Scheme 26;



(63) Nu: = OMe^- (59%), morpholine (8%)



(64) (65)

Scheme 26

Transfer of the ester linkage in (60) from α- to β- to nitrogen has a pronounced effect on the rates of substitution. Attempted replacement of the γ-chlorine atom in (59) by methoxide led to long reaction times and degradation products. However, the tricyclic compound (65) was isolated in low yield by using the stronger thioglycolate nucleophile.

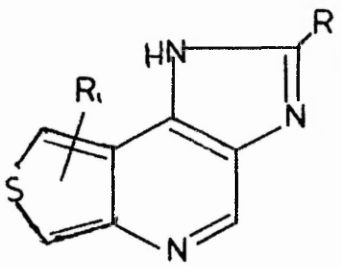
1.3.3. Keto-Enol Tautomerism.

Each of the 4-oxygenated compounds above exists predominantly in the keto form, as in the case with the corresponding 4-quinolones. The infra red spectra of (58) and (60) show strong absorptions at ~3300cm^{-1} due to N-H, ring C=O in the region 1610-1630cm^{-1} and a strong C=C band at 1580cm^{-1}. In the spectra of (63) and (64) (where the

pyridine ring is benzenoid and ring C=O is no longer present), there is still a third peak in the 1600-1700cm^{-1} region, due to ring C=C and C=O vibrations. Assignments of ^{13}C n.m.r. peaks by Barker have confirmed the tautomeric states, with good agreement with the quinoline and other thieno(b)pyridine analogues. A more detailed study of the tautomerism in these systems will be given later in this thesis (P. 86).

1.3.4. Miscellaneous

Elaborate 5,7-dihydrothieno(3,4-b)pyridines[85] systems have recently been prepared and shown to have antibacterial and antihypertensive properties. Some examples of these are shown in Fig. 4;



R = aryl, heteroaryl

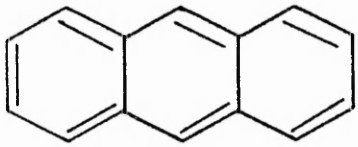
R_1 = H, Halogen, alkoxy, haloalkoxy

Figure 4

1.4. The unstable nature of thieno(3,4-b)pyridine.

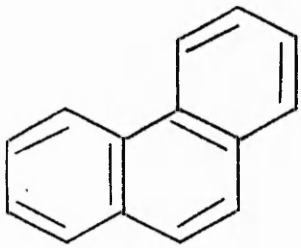
It has already been mentioned (see P. 35) that thieno(3,4-b)pyridine is considerably less stable its isomeric thieno(2,3-b)- and -(3,2-b)pyridines. Evidence will be provided here to suggest that this reduced stability is as a result of the quinonoid structure of the pyridine ring; in the (2,3-b)- and -(3,2-b)pyridines the pyridine ring exists in the classical Kekule form.

It is well-known that the resonance energy of an aromatic system is lower in its quinonoid state than in its related Kekule state;



Anthracene

352kJMol^{-1}



Phenanthracene

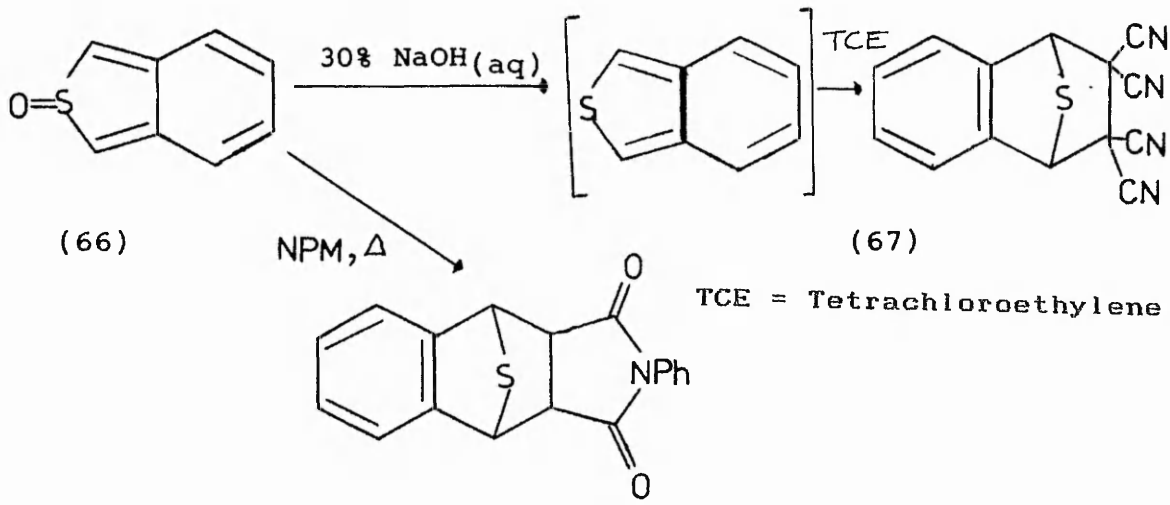
380kJMol^{-1}

STABILISATION ENERGIES.

Thus benzo(b)thiophene (which exists in the Kekule form) is a stable compound whose chemistry has been well-documented. In a review by Klemm[86], the chemistries of thieno(2,3-b)- and -(3,2-b)pyridines were shown to be interpretable as amalgamations of the chemistries of benzo(b)thiophene and quinoline.

In contrast, benzo(c)thiophene (where the benzene ring exists in the quinonoid form) was found by Cava[87] to be a highly reactive heterocycle, readily self-polymerising or forming Diels-Alder type adducts. Cava prepared benzo(c)thiophene by heating the stable dihydro sulphoxide

(66) in 30% aqueous sodium hydroxide (Scheme 27);

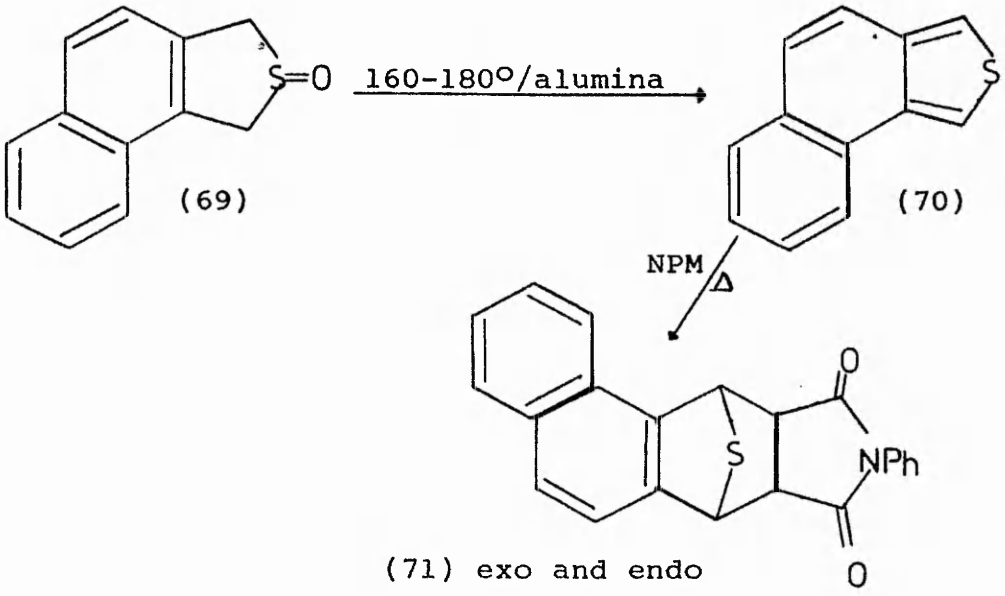


Scheme 27

Steam-distillation of the crude-product returned mainly polymer, but in the presence of tetracyanoethylene low yields of the adduct (67) were formed. In an earlier attempt[89] to prepare benzo(c)thiophene, the sulphoxide was heated on neutral alumina at 100-120°, but again only a very low yield of the compound was obtained. Heating a mixture of the sulphoxide (66) and N-phenyl maleimide (NPM) at 220°C returned the exo and endo Diels-Alder adducts (68). The same mixture was obtained more conveniently and in excellent yields by a mixture of the sulphoxide (66) and NPM in acetic anhydride.

Cava[88] et al prepared naphtho(1,2-c)thiophene (70), a stable compound, by heating its dihydro-sulphoxide (69) over neutral alumina at 160-180°C. At 100°C, (70) formed a mixture of the endo and exo Diels-Alder adducts (71) with N-phenyl maleimide (NPM) (Scheme 28). Benzo(c)thiophene reacts readily with NPM at room

temperature.

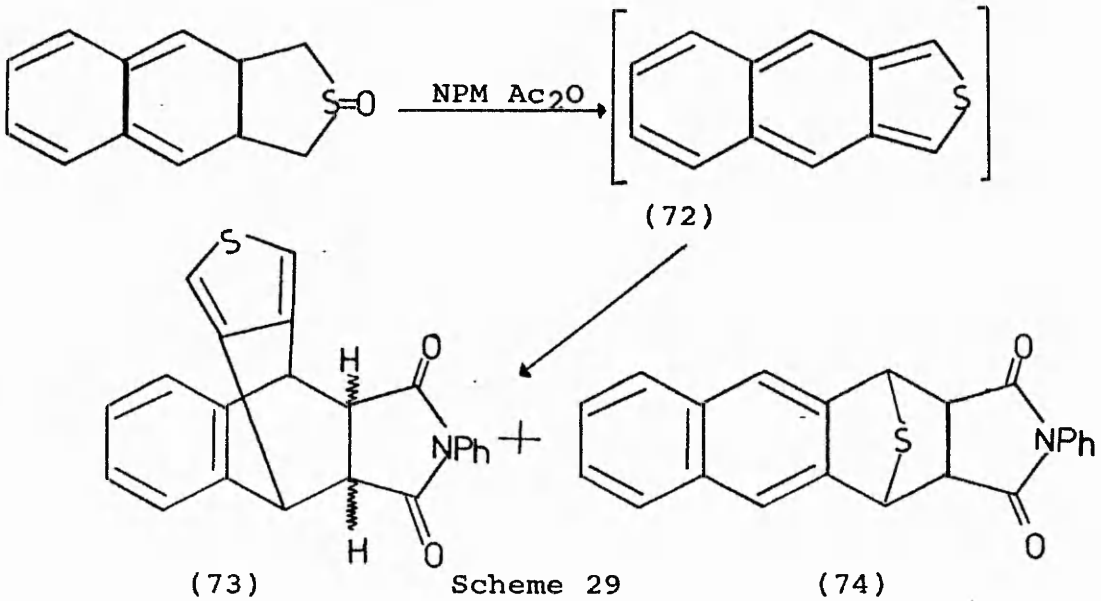


(69) (70)

(71) exo and endo

Scheme 28

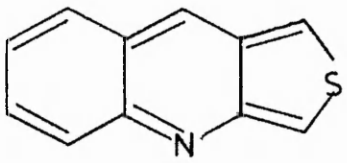
Attempts to isolate the naphthoquinonoid isomer of (70), naphtho(2,3-c)thiophene (72) by heating its dihydrosulphoxide failed. However, on heating in a mixture of acetic anhydride and NPM, three adducts were isolated; the endo and exo compounds (74) formed by addition of NPM across the thiophene ring and an adduct (73) formed by addition of NPM across the central ring (Scheme 29);



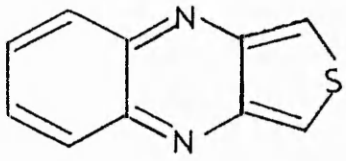
(72)

(73) Scheme 29 (74)

Attempts[89,90] to prepare the quinolino- and pyrimidino-(c)thiophenes (75) and (76), by heating their respective sulphoxides over alumina failed, both of these compounds being considerably less stable than thieno(3,4-b)pyridine. However, their NPM adducts could be isolated by heating their respective sulphoxides in a mixture of NPM and acetic anhydride.



(75)



(76)

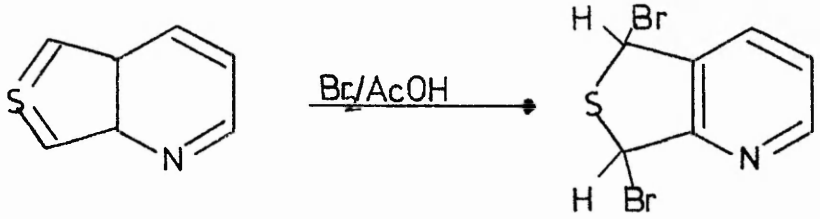
Reasons for the difference in stability between the Kekule and quinonoid form of heteroaromatic compounds above were suggested by the work of Palmer and Kennedy[91]. They investigated the photoelectronic spectra of quinonoid systems, namely benzo(c)thiophene, benzo(c)furan and isoindole and concluded that instability in these systems is attributed to a combination of a low resonance energy and a low lying excited state. Comparison of the resonance energies of this quinonoid series with the corresponding Kekule structures shows that the former are considerably destabilised.

This leads to the probability that some thieno(3,4-b)-pyridine derivatives may be found to be unstable. Indeed this is the case; several compounds prepared by the present author decomposed rapidly, in contrast to the stability of their counterparts in the other thieno(b)-

pyridine systems. It has been suggested[3] that d-orbital participation of the sulphur atom could occur, resulting in a Kekule form of the pyridine ring as in (77);

(3) (77)

In this case, the thiophene ring would be expected readily to undergo 1,3-addition reactions of the type given in Equation 12, but to date no experiments of this kind have been reported.



(12)

CHAPTER TWO

DISCUSSION

THIENO(3,4-b)PYRIDINES

2.1. Preparation.

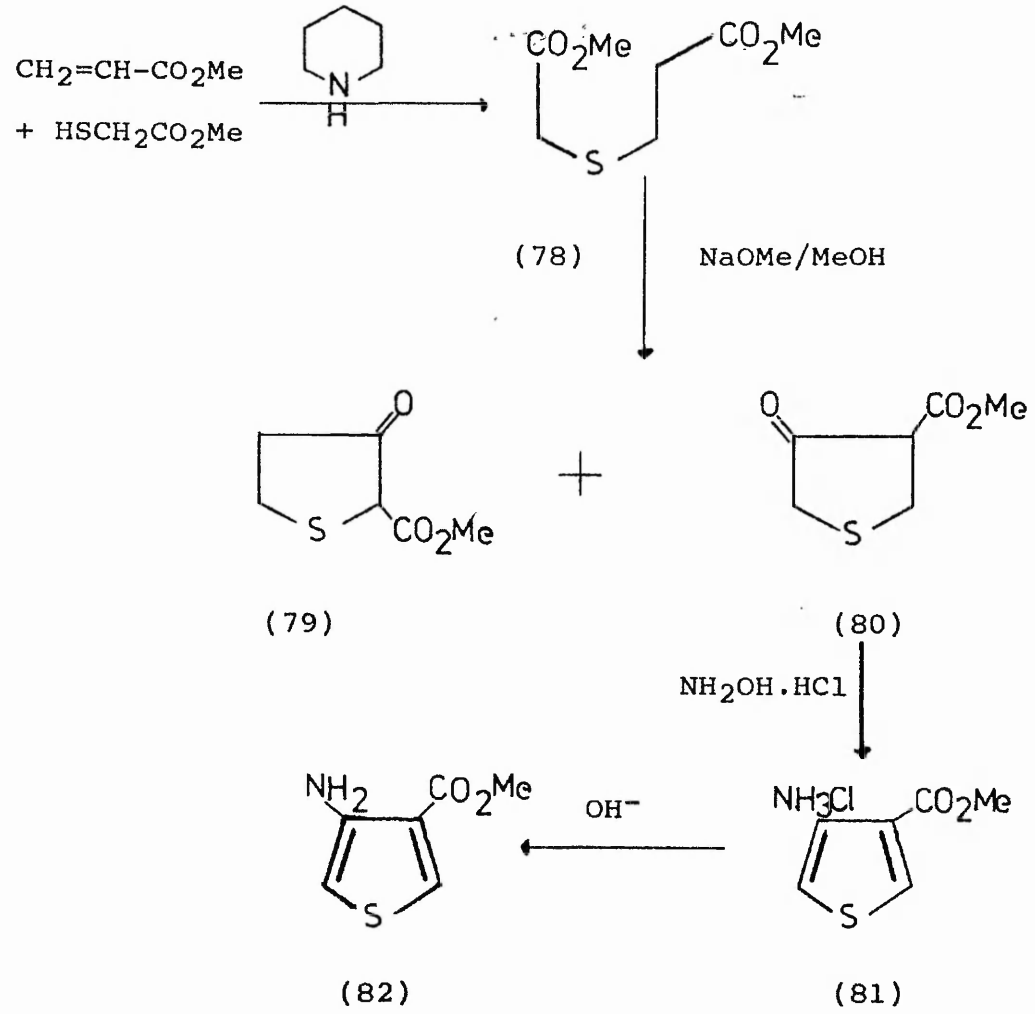
The author has investigated five routes which were adopted from well documented syntheses of the 2,3-fused thieno(b)pyridine and quinoline series, to thieno(3,4-b)-pyridine compounds. Of the five, two provided convenient routes to novel 2,4-dioxygenated and 4-oxygenated thieno(3,4-b)pyridine compounds, although the reaction conditions employed were often very different to those used in the preceding series. Also, a published route to a thieno(3,4-b)pyridine system was extended in order to prepare novel members of the series. Most of the thieno(3,4-b)pyridine compounds prepared in this work were found to be stable under normal laboratory conditions, but certain patterns of substitution rendered the ring system unstable. All of the thieno(3,4-b)pyridine compounds prepared exhibited blue fluorescence under u.v. light, except those containing sodium salts of hydroxylic or carboxylic acid groups (which gave a green colour). It was assumed that the thieno(3,4-b)pyridine ring had degraded if such fluorescence was not observed after a reaction.

Route 1.

Thieno(3,4-b)pyridin-4(1H)-one-3,7-dicarboxylic acid (59)

This was a repeat of work by Barker[82] who prepared the thieno(3,4-b)pyridinone (59) by the Gould-Jacobs synthesis already described (p. 37). The synthesis of (59) was scaled up fourfold with little reduction in overall yield.

The remaining five proposed routes to thieno(3,4-b)-pyridine compounds required methyl 4-aminothiophene-3-carboxylate (82), or its hydrochloride salt (81) as starting material. Unlike its 2,3- and 3,2- substituted isomers, this was not readily available commercially, and was prepared according to Scheme 30 below;



Scheme 30

The thioether[92] (78) was prepared in almost quantitative yield by the piperidine-catalysed addition of methyl acrylate to methyl thioglycolate. During the early part of this work the subsequent cyclisation and aromatisation steps returned low yields of (80) and (81) respectively.

Much development work was done to find improved conditions for these two reactions;

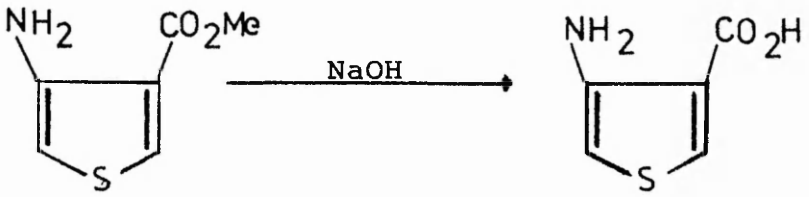
(i) Base-catalysed cyclisation of (78) proceeds *via* a thermodynamic- (leading to the required 3-oxo-4-ester (80)) *versus* kinetic-controlled mechanism[93] (giving the 3-oxo-2-ester isomer (79) and the separation of these two isomers proved to be the "bottle-neck" of the reaction. Initially, the desired product was separated from its 2,3-isomer by fractional-distillation under vacuum, but considerable degradation of material occurred and only low yields (<20%) of (80) were isolated. In a modification, the 2,3-isomer in the mixture was destroyed by stirring in alkaline solution; the required 3,4-substituted product (>35%) was then isolated by simple vacuum-distillation. Pure samples of (80) were often isolated as oils which failed to crystallise, even though the crude product before distillation was usually solid at room temperature. It has been shown that (80) can exist as both the keto and enol forms and the oil was a mixture of these two forms. Washing this mixture with ice-cold ethanol removed the enol form to leave the pure keto tautomer, mp 37-38^{o}C.

(ii) Early attempts to aromatise (80) to (81) with hydroxylamine hydrochloride were performed in DMF at 100^{o}C, but only low yields of product (<10%) were returned after lengthy work-up procedures. When DMF was replaced by acetonitrile as solvent then, under refluxing conditions the hydrochloride salt (81) was obtained in very high yields, without any need for further purification. The salt was found to be unstable, darken-

ing after a few days under normal conditions but having a shelf-life of a few weeks in the dark. This very efficient route to the rare 3,4-disubstituted thiophene series is subject to a patent application.

The free amine (82) was isolated in high yield by extraction from an alkaline solution of its hydrochloride salt (81). There was no sign of hydrolysis of the ester linkage. In contrast to its 3,2- and 2,3- substituted isomers, (82) is an unstable yellow oil which degrades rapidly in the dark, the process being photo-catalysed. Consequently, in reactions employing the free amine it was either generated in situ, from a mixture of the hydrochloride salt and a suitable base (for reactions at elevated temperatures) or, (for reactions at ambient temperature or lower) was freshly prepared before use.

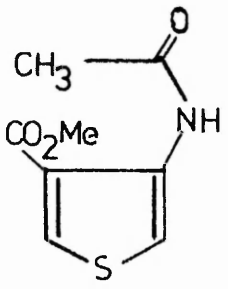
Attempted isolation of the amino-acid (83) by hydrolysis of the free amine (82), in 4M sodium hydroxide (Eq. 13) resulted only in decomposition.



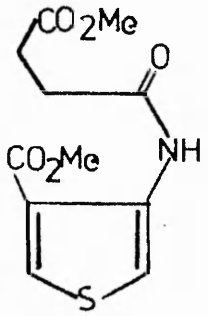
(13)

(83)

The acetamide (84) (unstable) and succinamide (85) derivatives of (82) were prepared in high yields by reaction of the free amine with acetyl chloride and 3-methoxycarbonylpropanoyl chloride respectively;



(84)

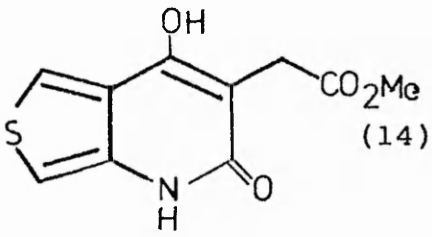


(85)

Route 2.

Attempted preparation of Methyl (2,3-dihydro-4-hydroxy-2-oxothieno[3,4-b]pyrid-3-yl)acetate (86)

In an approach to the thieno(3,4-b)pyridine (86), base-induced cyclisation of the succinamide (85) was attempted under a range of conditions, (Eq. 14); see Experimental Section. Either hydrolysis of an ester group took place or the starting material was recovered.

(85) —base→  (14)

(86)

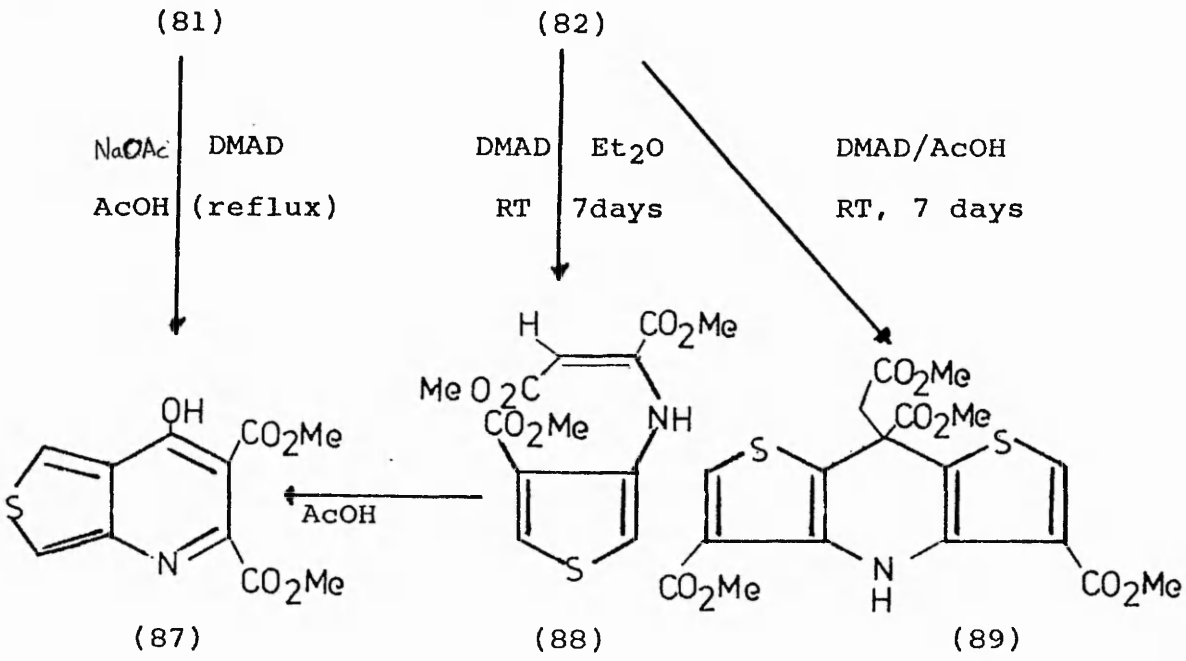
Route 3.

4-hydroxy-2,3-bismethoxycarbonylthieno(3,4-b)pyridine (87)

The third route to thieno(3,4-b)pyridines was an application of the Conrad-Limpach synthesis, already an established route to thieno(3,2-b)pyridines[5] (Scheme 3) and quinoline compounds[18-24]. In each of these cases, the β-aryl-α-amino acrylates were isolated in high yields, prior to cyclisation, by reaction of their respective aryl amines with DMAD.

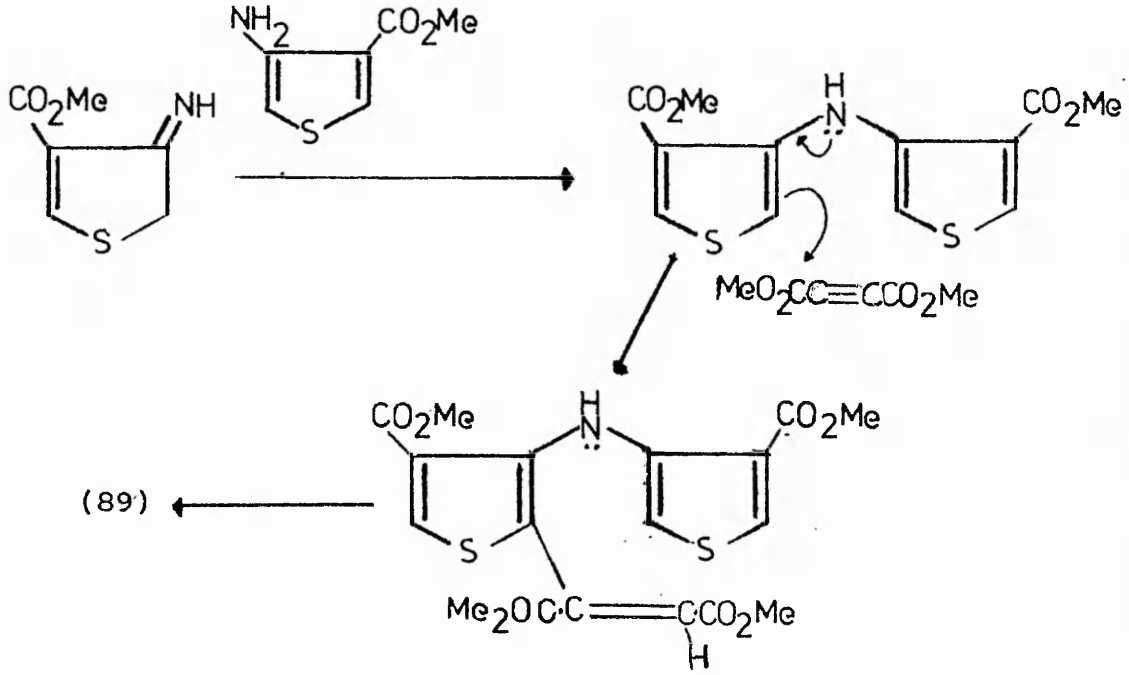
Attempts to prepare the analagous Michael adduct (88)

from the 3,4-disubstituted amine (82) by allowing a solution of the free amine and DMAD in glacial acetic acid to stand at room temperature afforded only a very small quantity (<1%) of a yellow, highly crystalline material. The high melting point of this compound (199°C) suggested it not to be the simple Michael adduct (88), (the related 3,2-substituted isomer[5] (13) and its benzene analogue[22] melt at 96°C and 92°C respectively) and subsequent micro-analysis indicated its molecular formula to be $C_{18}H_{17}NS_2O_8$. Its ^1H n.m.r. spectrum showed <u>four</u> OMe groups, from which it was deduced that the compound was formed by condensation of two molecules of the amine (82) with one molecule of DMAD, with loss of ammonia. The ^1H n.m.r. spectrum also showed a singlet (2H) at δ4.9 and another (1H) at δ6.6. From this information and from its ^{13}C n.m.r. spectrum the compound was assigned the tri-cyclic structure (89), (Scheme 31).



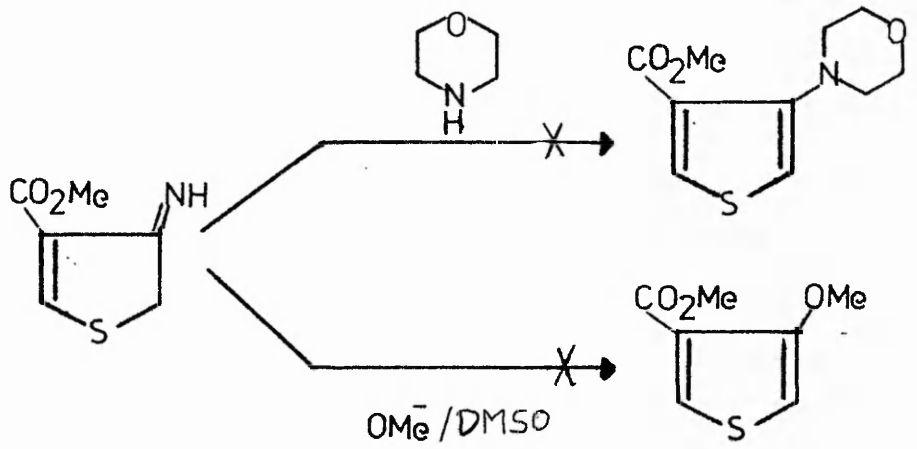
Scheme 31

A proposed mechanism for the formation of (89) is outlined in Scheme 32. This involves the condensation of (82) with its imine tautomer followed by addition to DMAD, then cyclisation. It is possible that a different sequence of events to those given in the mechanism given below may actually occur.



Scheme 32

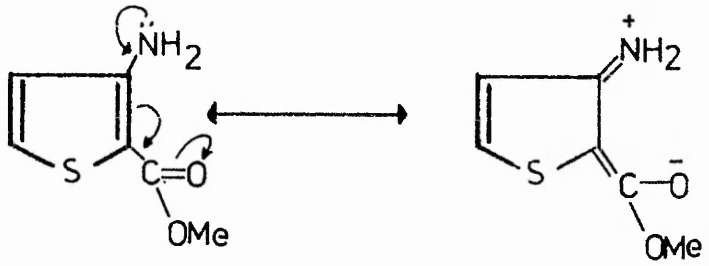
Attempts to "trap" the imine tautomer with morpholine or with methoxide ion failed (Scheme 33);



Scheme 33

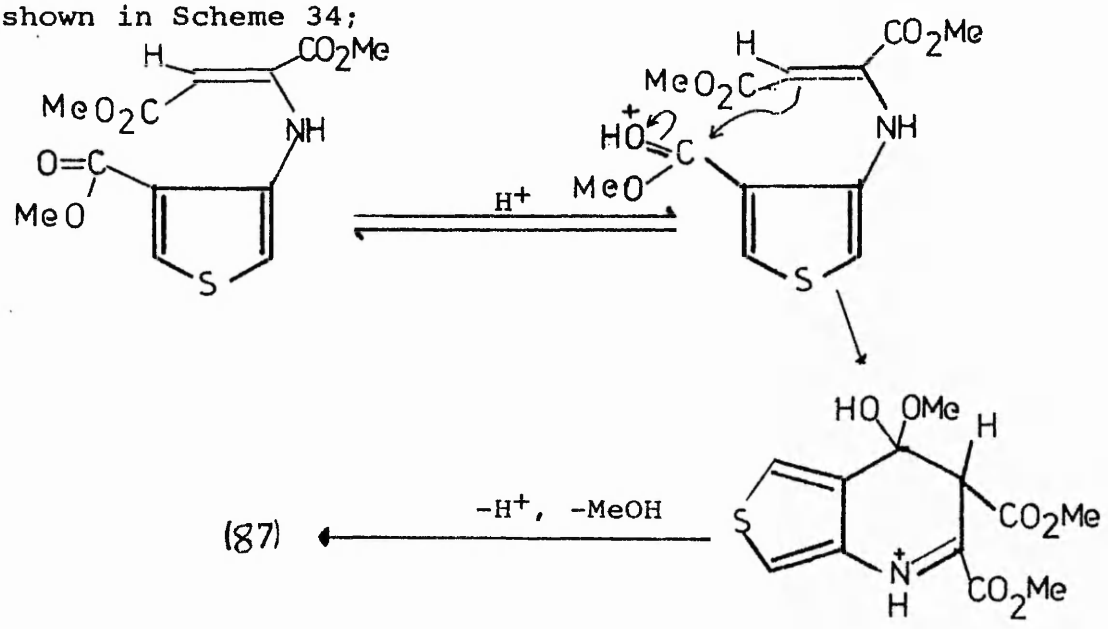
On heating a solution of (82) and DMAD in acetic acid, dark multi-component systems were isolated. Similar results were obtained if the solvent was refluxing methanol.

In ether at room temperature, reaction between the free amine (82) and DMAD proceeded very slowly, to give the true Michael adduct (88), (mp 99°C), in low yields (<10%). During the reaction time much of the unreacted free amine had degraded. ^{1}H n.m.r. evidence suggests that adducts of the type (88) exist in the fumarate[94-96] configuration and this appears to be no exception. The n.m.r. signal for the lone alkenic proton lies in the region characteristic of the vinyl resonance of such aryl amino-fumarates, (δ 5.6). The very slow rate of formation of (88) was a surprise, as the rate of addition of DMAD to the free amine (82) would be expected to be faster than the rate of addition of DMAD to its 3,2-substituted isomer (12) (Scheme 13), where there is a direct mesomeric interaction between the two ring substituents;



Very surprisingly, the Michael adduct (88) was cyclised in glacial acetic acid at room temperature overnight to give a quantitative yield of the thieno(3,4-b)pyridine (87). The 3,2-substituted thiophene[5] was cyclised by base to the respective thieno(3,2-b)pyridine. A proposed

mechanism for the acid-induced cyclisation of (88) is shown in Scheme 34;



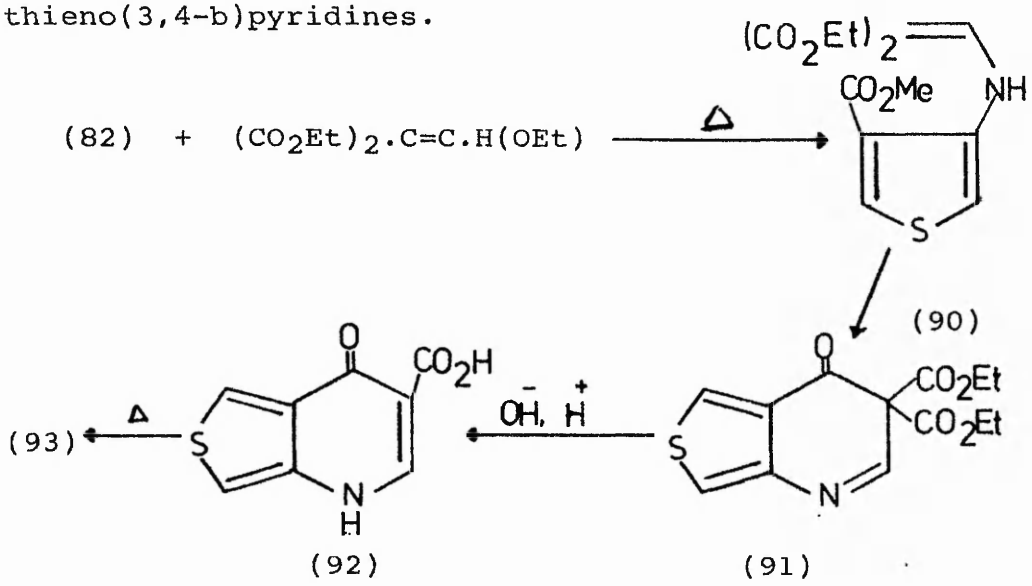
Scheme 34

The very slow rate of formation of (88) at room temperature meant that this did not offer a convenient route to the thieno(3,4-b)pyridine (87). After many different conditions had been investigated, acceptable yields (50%) of (87) were obtained in a "one-pot" synthesis by refluxing a mixture of the amine hydrochloride (81) and DMAD in acetic acid with a suitable base, usually sodium acetate. Presumably, these conditions allowed the amine formed in situ to react with DMAD before degradation could occur.

Route 4.

Thieno(3,4-b)pyridin-4(1H)-one (93).

In consideration of the ease of acid-catalysed cyclisation of the Michael adduct (88), the related enamine (90) was prepared by the condensation of diethyl ethoxymethylene malonate with (82) in toluene at 60°C. Surprisingly high yields (75%) of (90) were isolated, with only limited formation of decomposition products. No observable reaction occurred on leaving a solution of the enamine in glacial acetic acid at room temperature, (Scheme 35). Heating the same solution had no effect, but addition of a few drops of concentrated sulphuric acid resulted in the appearence of a faint blue fluorescent spot on tlc. Attempted isolation of this product failed, due to the very small quantity produced; u.v. fluorescence provides a very sensitive test for the presence of thieno(3,4-b)pyridines.

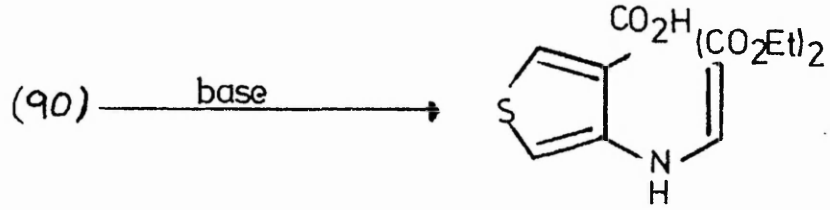


Scheme 35

In light of the proposed mechanism for acid-catalysed cyclisation of (88) (Scheme 34), two reasons are offered

to suggest why the enamine (90) was not readily cyclised under acid-conditions. Firstly, the bulky nature of the two ester groups attached to the α-aminoacrylate function would inhibit carbocation attack at this position, i.e. steric hindrance. Secondly, it is possible that one of the α-aminoacrylate ester functions, or the amino group is more easily protonated than in the Michael adduct (88), thus inhibiting cyclisation, but the author can offer no reasons why this should be so.

Attempts to achieve base-catalysed cyclisation of (90) also proved futile, with methoxide and then with hydride in various solvents and at a range temperatures. In many cases, hydrolysis of one of the ester groups occurred on work-up to give the acid (94), (Eq. 15)



(15)

(94)

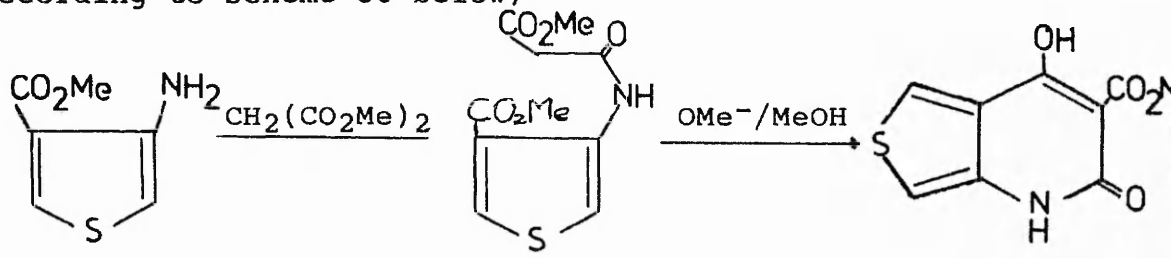
Successful cyclisation of (90) would have provided a convenient route to thieno(3,2-b)pyridin-4(1H)-one (93), (via decarboxylation of the acid (92)), and hence to 4-chlorothieno(3,4-b)pyridine (101), a key compound for kinetic and other studies.

Route 5.

2,4-Dioxygenatedthieno(3,4-b)pyridines

The 2,4-dioxygenated thieno(3,4-b)pyridine (96) was prepared by base-induced cyclisation of the amide (95)

formally derived from (82) and dimethyl malonate, according to Scheme 36 below;



(82) (95) (96)

Scheme 36

In identical routes to the thieno(2,3-b)- and (3,2-b)-pyridine analogues of (96), the corresponding malonamides were prepared in high yields by heating the appropriate amines [(12) and (15), respectively] in refluxing dimethyl malonate, b.p. 151^{0}C. Under these conditions the amine (82) degraded completely before reaction with dimethyl malonate could occur. A wide range of temperatures was explored, with some returning low yields of product after lengthy work-up procedures. Generally, this route behaved capriciously and no acceptable reproducible conditions were found. A summary of the various attempts that were made to prepare the malonamide (95) is now given.

(i) Below 55^{0}C, the reaction rate was slow and isolation of the product from decomposition products proved to be difficult,

(ii) Above 90^{0}C, amine degradation was high and no product was isolated,

(iii) On the assumption that degradation of (82) was photo-catalytic, a series of reactions was carried out in the dark at several different temperatures. Generally,

only marginal increases in yield were attained, with no apparent reduction in the formation of degradation products.

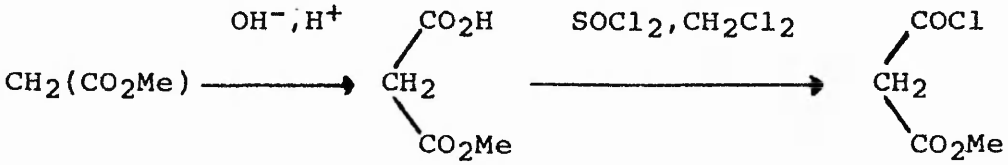
In each of the cases (i)-(iii) yields never exceeded 10%. Yields of the malonamide were improved by employing the amine-hydrochloride (81) and a suitable base in dimethyl malonate, shown in the table 4 below;

Table 4. Conditions for the preparation of (95) from 3-amino-4-methoxycarbonylthiophene hydrochloride (81) in dimethyl malonate with various organic bases.

BASE	TEMPERATURE/^{o}C	YIELD/%
TRIETHYLAMINE	95	30
QUINOLINE	100	30
PYRIDINE	95	30
N,N-DIETHYLANILINE	115	25

In all cases a two-fold excess of base was used. Under these conditions (as in preparation of the thieno(3,4-b)pyridine (87)), presumably the free amine is formed *in situ* and reacts with dimethyl malonate to form the stable amide before it can degrade.

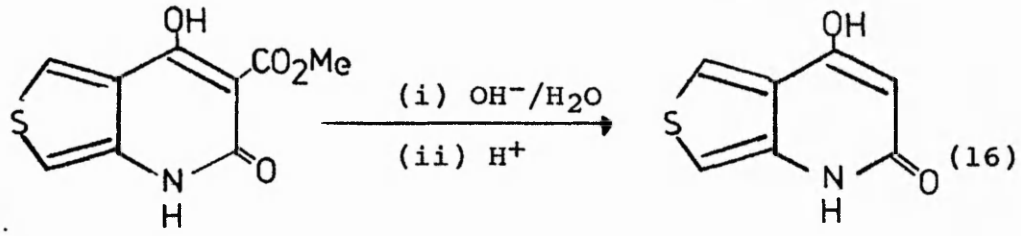
In a further modification, (95) was prepared by reaction of the free amine (82) with the half acid-chloride of dimethyl malonate, prepared according to the Scheme 37;



Scheme 37

Reaction of this acid-chloride with (82) provided good yields (<75%) of the required malonamide, although yields were not as high as would normally be expected for this type of reaction. The highest yields were attained at low temperatures (-10°C); in these conditions the possible formation of Friedel-Crafts by-products is less likely.

Cyclisation of the amide (95) proceeded smoothly with methoxide in refluxing methanol to give the dioxygenated thieno(3,4-b)pyridine (96) in high yield. In line with the quinoline, thieno(2,3-b)- and -(3,2-b)pyridine analogues, hydrolysis of the ester group in (96) gave the corresponding carboxylic acid which decarboxylated spontaneously at room temperature to give (97), (Eq. 16);



(96) (97)

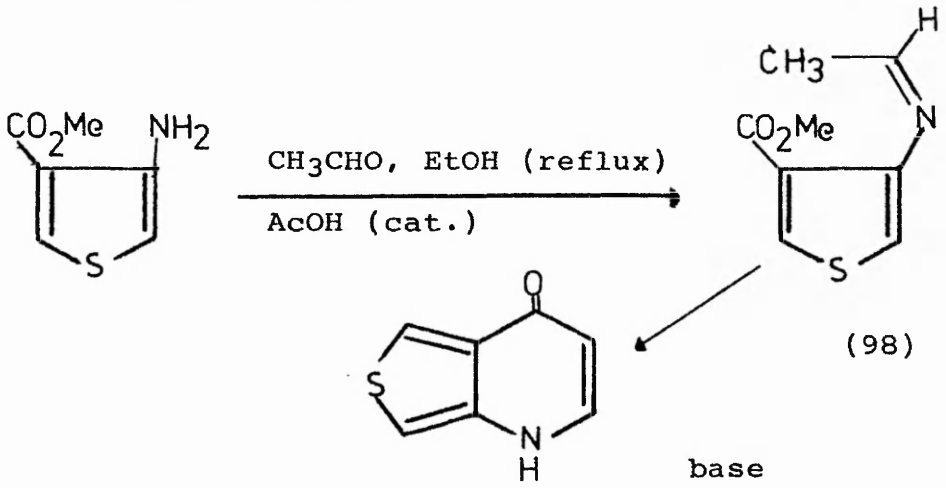
Both (96) and (97) are stable, high melting-point (>200°) compounds which exist predominantly in the α-one-γ-ol tautomeric states in the solid state, in line with their thieno(b)pyridine and quinoline counterparts. The infra-red spectra (KBr discs) of (96) and (97) showed

strong, rather broad bands in the region 1640-1660cm^{-1}, which is typical of the 2- rather than the 4-quinolone type. Strong evidence for this preferred tautomeric state is also found from the ^{13}C n.m.r. spectra of (96) and (97); see (P. 92).

Route 6.

Attempt to prepare Thieno(3,4-b)pyridin-4(1H)-one (93)

In a proposed route to thieno(3,4-b)pyridin-4(1H)-one (93) attempts were made to isolate the Schiffs base (98) derived from the free amine (82) and acetaldehyde. Base-induced cyclisation of the Schiffs base (98) would then provide a convenient route to (93), Scheme 38;



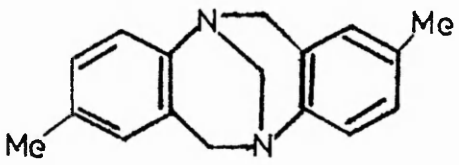
(93)

Scheme 38

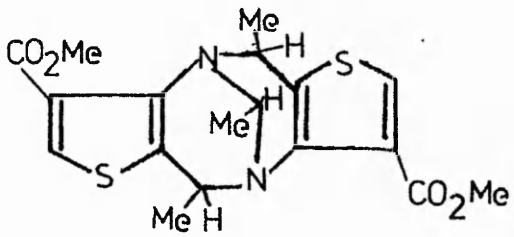
Under the usual conditions used for Schiff base formation, no observable reaction took place (on the evidence of tlc). On bubbling an excess of acetaldehyde through the refluxing ethanolic solution of (82) for a short time a small quantity of a colourless, crystalline compound was isolated. The high melting-point (158^{o}C) of

this compound suggested it not to be the simple Schiffs base and its ^{1}H n.m.r. and ^{13}C n.m.r. spectra indicated the presence of a high degree of aliphatic as well aromatic character. The mass spectrum and elemental analysis of the product indicated its molecular formula to be $C_{18}H_{20}N_2S_2O_4$; this is consistent with the condensation of two molecules of (82) with three molecules of acetaldehyde and loss of water.

In acid media[97-102], p-toluidine and formaldehyde react together to form a crystalline compound (mp. 160°C), known as Tröger's base whose structure was determined by Spielman[103] to be the tricyclic compound (99) 1,2-methylene-3-p-tolyl-6-methyl-1,2,3,4-tetrahydroquinazoline. The ^{13}C n.m.r. and ^{1}H n.m.r. spectra of the product formed between (82) and acetaldehyde suggest that the thienyl analogue (100) of Tröger's base was formed in this case.

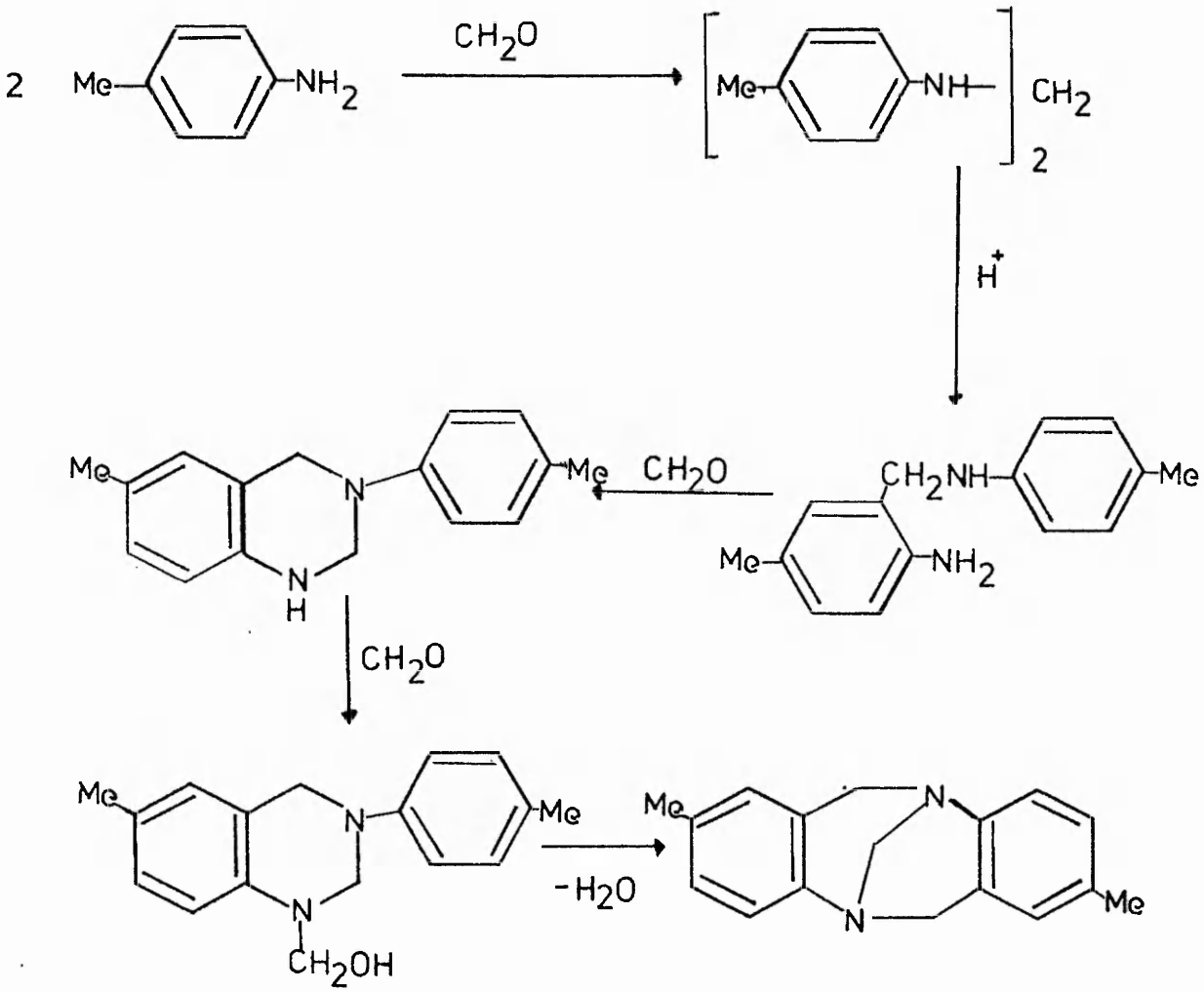


(99)



(100)

The mechanism for the formation of Tröger's Base was proposed by Wagner[104] and is depicted in Scheme 39



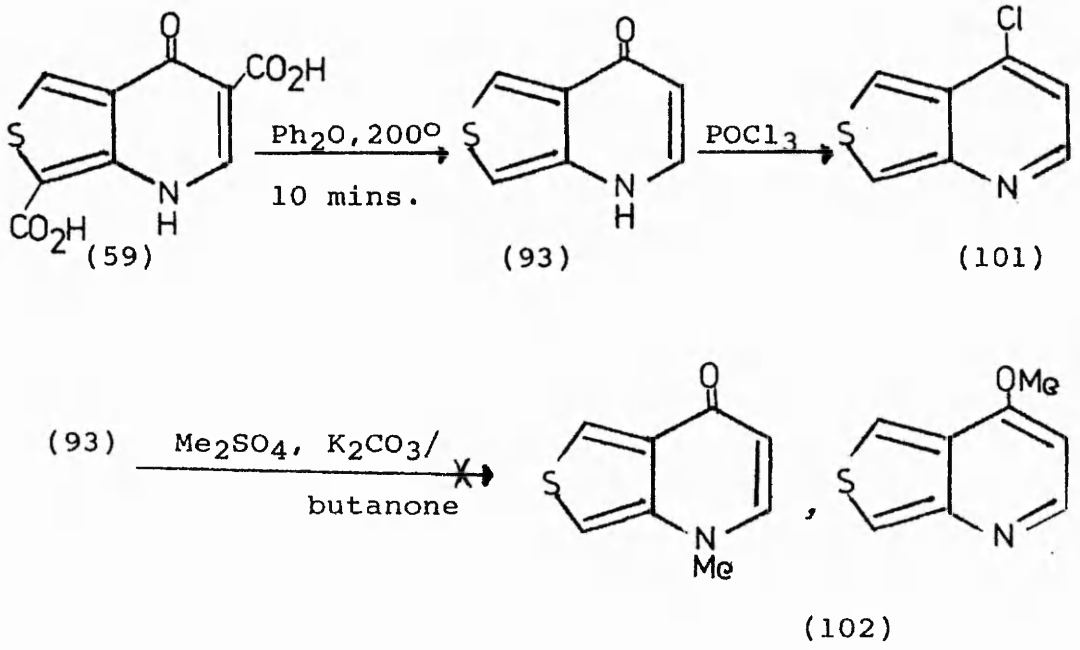
Scheme 39

2.2. Reactions

Thieno(3,4-b)pyridin-4(1H)-one-3,7-dicarboxylic acid (59)

A broad range of solvents and temperature conditions were applied in attempts to decarboxylate the di-acid (59) to (93), (Scheme 40). These usually resulted in either the recovery of starting material or degradation of the product (>220°). The highest yields (<15%) were attained by heating (59) for a short time in diphenyl ether at 200°C, the product being separated from the di-acid (which was re-cycled) by ordinary column-chromatography. As in the case of its thieno(3,2-b)pyridine and quinoline isosteres (93) exists predominantly as the keto tautomer, strong evidence being provided by ^{13}C n.m.r. data (see later).

In phosphoryl chloride at room temperature, (93) formed 4-chlorothieno(3,4-b)pyridine (101), an unstable yellow oil which could be kept as its picrate. High yields of (101) were attained, with no difficulty in the work-up; this is in contrast to similar attempted chlorinations in the thieno(2,3-b)pyridine series, in which phosphoryl chloride did not effect conversion of the oxygenated functions into chlorine.

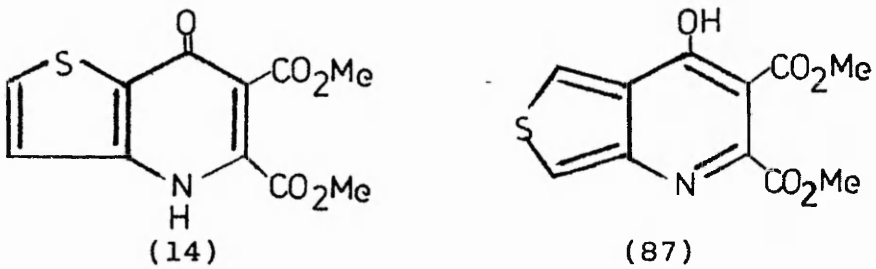


Scheme 40

Attempted methylation of (93) with dimethyl sulphate at room temperature gave a dark, complex mixture which did not fluoresce under u.v. light. The 2,3-fused thieno(b)-pyridine and quinoline analogues of (93) give the stable N-methylated products in each case. For further reactions in this system see sections "Nucleophilic Substitution" and "Electrophilic Substitution".

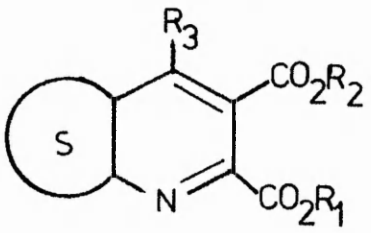
4-hydroxy-2,3-bismethoxycarbonylthieno(3,4-b)pyridine (87)

Strong evidence from the ^{13}C n.m.r. spectrum of (87) suggests that it exists predominantly in the enol state, in contrast to its thieno(3,2-b)pyridine counterpart (14).



As expected from this disparity, the chemical properties of (87) were found to differ markedly from those of (14) particularly in those reactions that involved the nitrogen or C-4 oxygen functions. Table 5 illustrates the contrast in properties of the thieno(3,2-b)- and -(3,4-b)pyridines (14) and (87).

Table 5: Comparison of the properties of the thieno-(3,2-b)[5] and -(3,4-b)pyridines;



R-1	R-2	R-3	reagents	(3,2-b)	(3,4-b)
CH_3	CH_3	=O,(OH)	Br_2/AcOH	3-bromo product	no reaction
			HNO_3/AcOH	3-nitro product	no reaction
			Me_2SO_4	N-methylation	O-methylation
			MeI	quat. ammonium salt	no reaction
CH_3	CH_3	Cl	OMe^-/MeOH	facile substitution	very slow reaction
H	H	=O,(OH)	heat, 275°C	$-2CO_2$	no reaction
			Ac_2O	forms	no reaction
			(reflux)	anhydride	

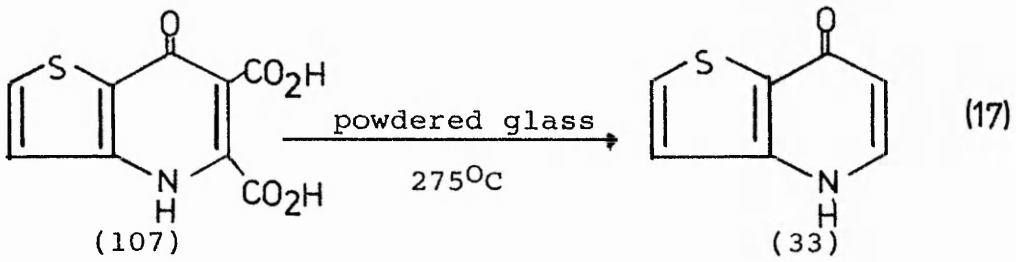
Reaction of dimethyl sulphate with (87) gave the O-methylated product (103) in high yield, with no sign of N-methylation taking place. In contrast, the (3,2-b)-isomer (14) (in line with many other oxygenated 2,3-fused thieno(b)pyridines and quinoline derivatives where there

are two possible sites for methylation) gives only the N-methylated product under similar conditions. This difference in the site of methylation is probably explained in terms of the relative electron-densities on the nitrogen and oxygen functions. In the case of (14), the lone pair of pi-electrons on the sp^2 hybridised nitrogen atom is more loosely bound than that on the sp^2 hybridised oxygen atom. The hydroxyl function in (87) is acidic (phenolic in nature), can dissociate and the anion formed will readily attack a dimethyl sulphate molecule. This explanation is probably an over-simplification as in the case of 4-hydroxythieno-(2,3-b)pyridine (36) N-methylation occurs on reaction with dimethyl sulphate. On treatment with hot 4M sodium hydroxide solution, 4-methoxy-2,3-bismethoxycarbonylthieno(3,4-b)pyridine (103) gave the bis-acid (104) which although authenticated, exhibited no carbonyl band in its i.r. spectrum.

4-Hydroxy-2,3-bismethoxycarbonylthieno(3,4-b)pyridine (87) in refluxing phosphoryl chloride gave 4-chloro-2,3-bismethoxycarbonylthieno(3,4-b)pyridine (105) in high yield. Attempted reductive dechlorination of (105) with zinc in acetic acid at room temperature gave a dark complex mixture which did not fluoresce under u.v. light on tlc. The nucleophilic substitution reactions of (105) will be discussed later (P. 73).

In 4M sodium hydroxide, 4-hydroxy-2,3-bismethoxycarbonylthieno(3,4-b)pyridine (87) was hydrolysed to give the corresponding di-acid (106), (mp>300^{0}C) for which no solvent for crystallisation could be found. Many

conditions were tried in attempts to decarboxylate (106), all of which failed, resulting in either recovery of starting material or, above ~250°C, evolution of hydrogen sulphide (as evidenced by testing with lead acetate paper). Thieno(3,4-b)pyridin-4(1H)-one (93) is known to decompose above ~220°C. The high temperature required for decarboxylation of its 2,3-disubstituted acid (106) probably resulted in decomposition of the product as it was formed. The (3,2-b)- isomer of (106), (107) has been decarboxylated to (33) by heating it at 275°C with powdered glass (Eq. 17);



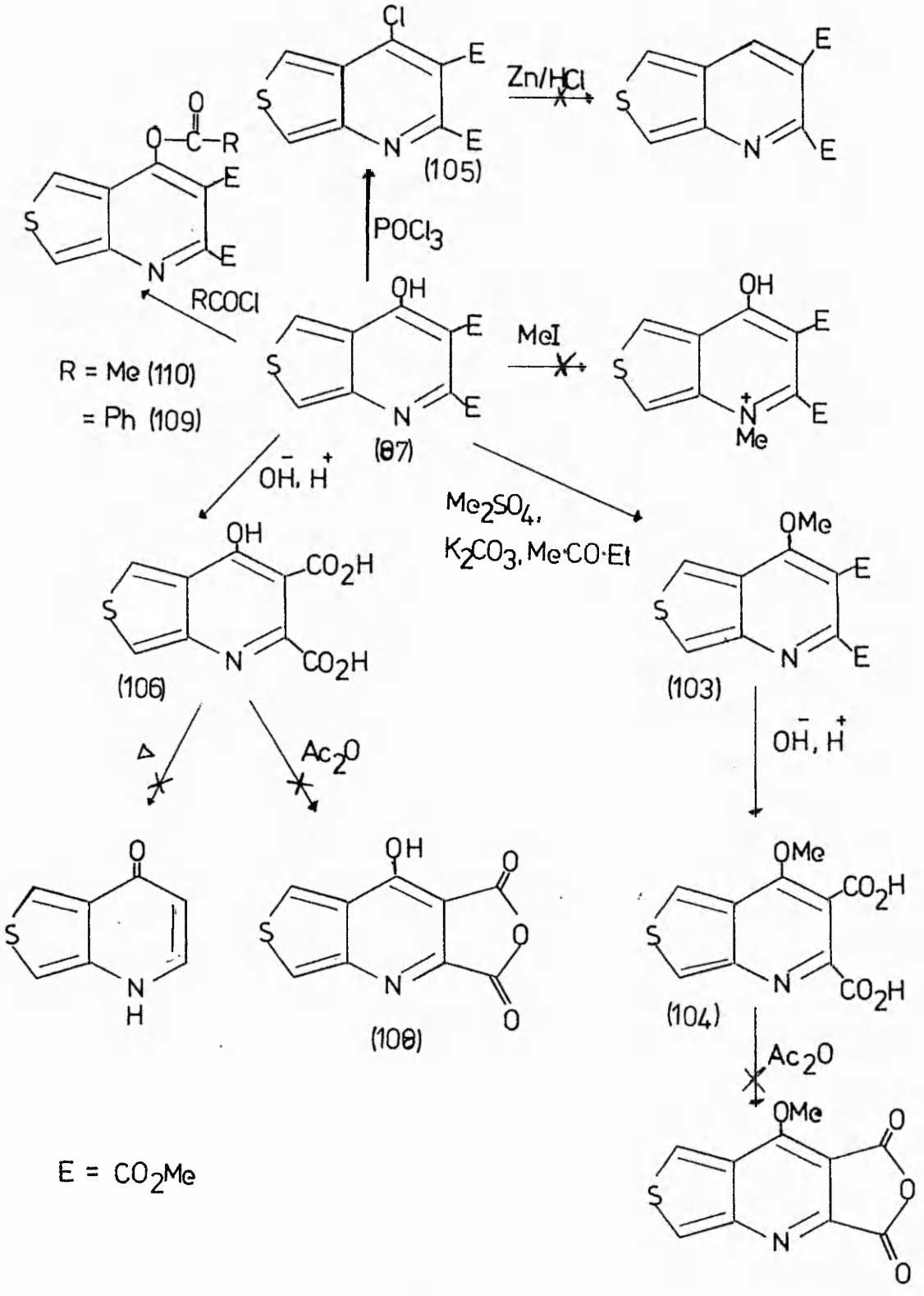
(107) (33) (17)

Attempted preparation of the anhydride (108) by heating the di-acid (106) in refluxing acetic anhydride resulted only in recovery of starting material.

The O-benzoyl (109) and O-acetyl (110) derivatives of (87) were prepared in high yields by reaction with the appropriate acid chlorides. There was no sign of N-substitution in either case.

With methyl iodide, (87) formed no quaternary ammonium salt, in contrast to the thieno(3,2-b)pyridine analogue (14), which forms the expected salt. This is another reflection of the more basic nature of the nitrogen atom in the keto form of (14) over the enol form of (87), (see methylation, P. 66).

The reactions described above are outlined in Scheme 41;

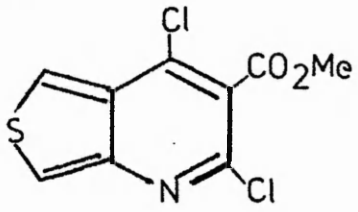


Scheme 42

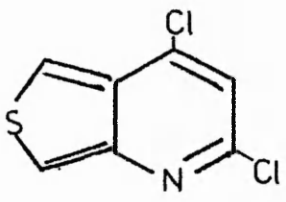
4-hydroxy-3-methoxycarbonylthieno(3,4-b)pyridin-2(1H)-one (96) and 4-hydroxythieno(3,4-b)pyridin-2(1H)-one (97)

The ^{13}C n.m.r. spectra (P. 94) of (96) and (97) indicate that they exist in their γ-hydroxy α-quinolone forms, in line with their quinoline and 2,3-fused thieno(b)pyridine analogues. Reactions of dimethyl sulphate with (96) and with (97) resulted in the formation of intractable black tars, which did not fluoresce under u.v. light. Under similar conditions their thieno(2,3-b)- and -(3,2-b)-pyridine and quinoline analogues provided stable N-methylated products.

In refluxing phosphoryl chloride, (96) and (97) were converted smoothly into their respective dichloro-derivatives (112) and (113). This is in contrast to the thieno(2,3-b)pyridine analogues of (96) and (97), (where reaction with phosphoryl chloride gave complex mixtures and phenyl phosphonic chloride gave low yields of the dichloro compounds) and the thieno(3,2-b)pyridine analogues (where phosphoryl chloride gave mainly γ-chloro-α-oxygenated products, and only low yields of the dichloro compounds).



(112)



(113)

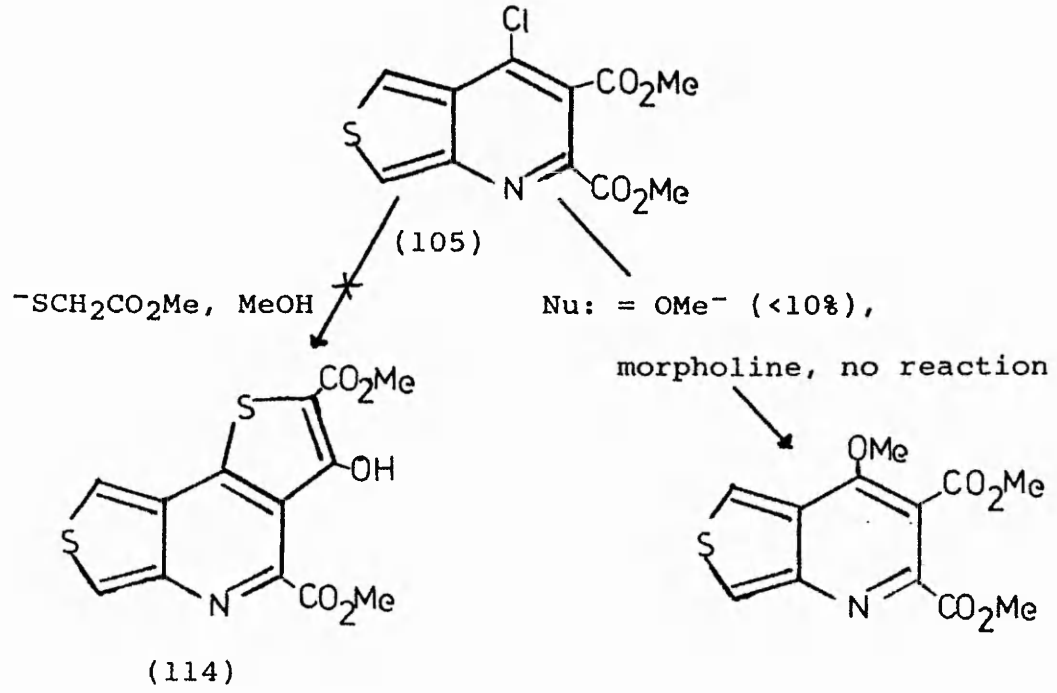
The crude products were isolated as intensely coloured (purple) oils, which resinified after a few days under normal conditions of storage. Attempted purification by

bubble-distillation under vacuum resulted in the formation of insoluble tars which did not fluoresce under u.v. light, again indicating that the thieno(3,4-b)pyridine ring system had been destroyed. Flash- and ordinary-column-chromatography on alumina were not successful in effecting purification, leading only to high melting-point mixtures. The latter retained their purple colour and solubility in chloroform and dichloromethane, but failed to fluoresce under u.v. light. The ^{1}H n.m.r. spectra of these mixtures indicated a high ratio in the number of aliphatic:aromatic protons and their ^{13}C n.m.r. spectra suggested that some aromatic or alkenic material was present. It is possible that (112) and (113) had undergone self Diels-Alder type reactions, although this was not confirmed. Thieno(3,4-b)pyridine is unstable and the ease with which the related quinonoid benzo[c]thiophene and naphtho(2,3-c)thiophene systems undergo Diels-Alder reactions (see P. 43) suggest that it is quite likely that (112) and (113) may behave similarly. As far as the author is aware no work on the Diels-Alder reactions of thieno(3,4-b)pyridines has been published. Pure samples of (112) and (113) were isolated as purple oils by ordinary column-chromatography of the crude products on neutral silica. They formed intensely coloured solutions in chloroform and in dichloromethane which fluoresced under u.v. light. After a few weeks at room temperature, both compounds were transformed into mixtures of high melting-point solids whose physical properties were very similar to those of the compounds isolated after elution through an alumina column.

Nucleophilic Substitution.

A yellow solution of 4-chlorothieno(3,4-b)pyridine (101) and sodium methoxide in DMSO darkened after a few hours at room temperature; tlc of the mixture showed no fluoresence under u.v. light, and it was assumed that the thieno-(3,4-b)pyridine ring had degraded. Subsequent work-up resulted in the isolation of a small quantity of brown tar, having a complex ^1H n.m.r. spectrum which indicated the absence of any aromatic protons. It was hoped that the kinetics of this nucleophilic substitution reaction could be studied and comparisons then made with its thieno-(2,3-b)- and -(3,2-b)pyridine and quinoline analogues. Obviously, the decomposition prevented any meaningful kinetic studies.

The γ-chlorine atom in 4-chloro-2,3-bismethoxycarbonyl-thieno(3,4-b)pyridine (105) was found to be almost inert towards nucleophilic attack. After prolonged heating in refluxing methanol with a great excess of methoxide a very low yield of the methoxy substituted product (103) was isolated, identical in all respects to the product isolated on reaction of 4-hydroxy-2,3-bismethoxycarbonyl-thieno(3,4-b)pyridine with dimethyl sulphate, (Scheme 41). Surprisingly, no substitution was observed with the more nucleophilic thioglycolate anion in refluxing methanol in an attempt to prepare the tricyclic compound (114). No reaction was observed on heating a solution of (105) and morpholine in DMSO.

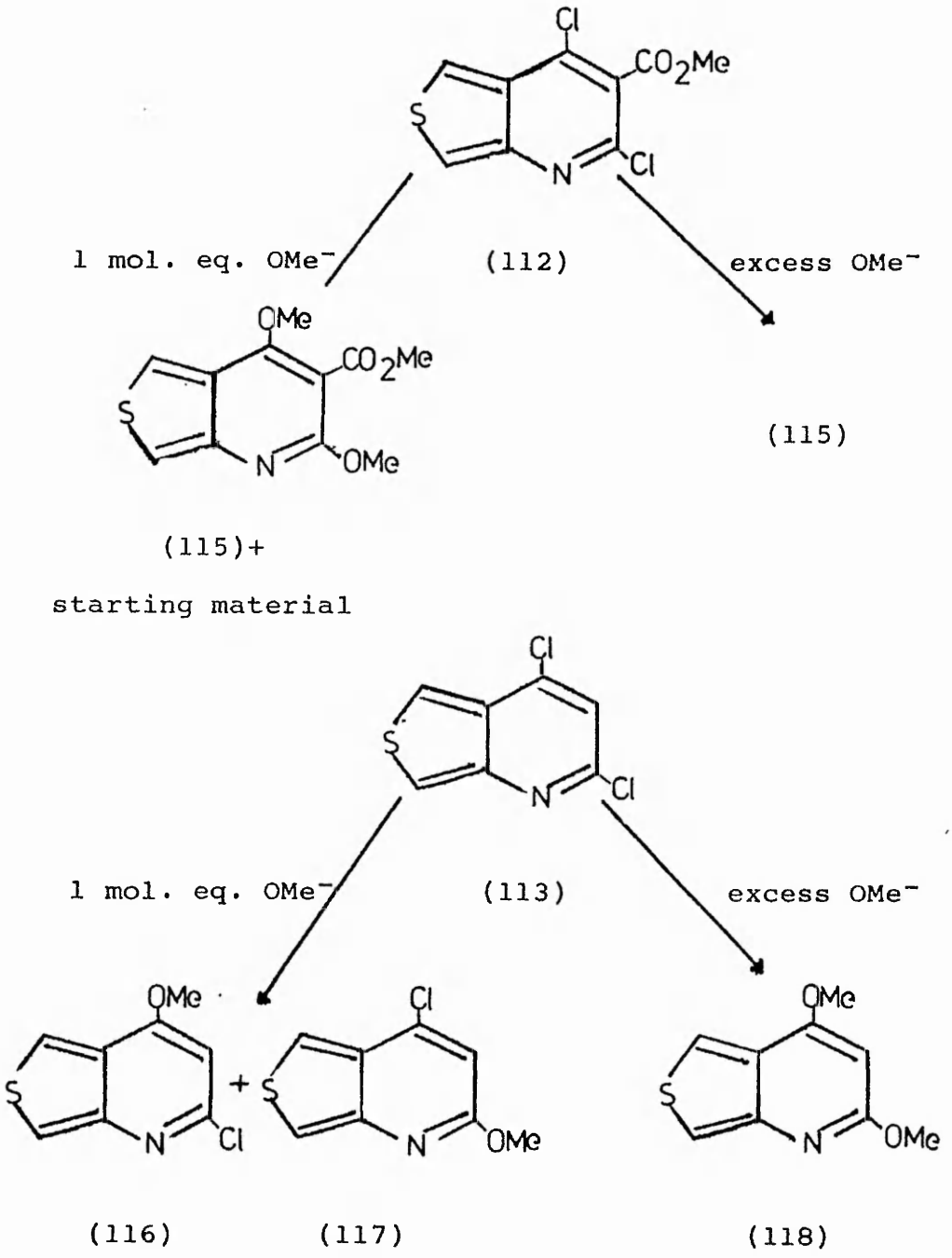


(114)

Scheme 42

The nucleophilic substitution reactions of 2,4-dichloro-3-methoxycarbonylthieno(3,4-b)pyridine (112) and 2,4-dichlorothieno(3,4-b)pyridine (113) were investigated using the methoxide and thioglycolate anions, and morpholine. A summary of their methoxydechlorination reactions is given in Scheme 43. In view of the unstable nature of (112) and (113), the reactions were performed at room temperature in the dark. Such reactions in the 2,3-fused thieno(b)-pyridine and quinoline series were carried out in refluxing methanol (see P. 25). In methanol the reactions of methoxide with (112) and (113) proceeded very slowly and the products, themselves unstable, were isolated in very low yields from the mixtures of decomposition products. Work performed during the last few decades has discovered that polar, aprotic solvents (particularly DMSO) significantly increase the rates of nucleophilic substitution reactions (see Section for further

discussion). Replacement of methanol by DMSO in the reactions above did indeed accelerate the rates substantially. In all cases substitution was complete overnight, allowing easier purification of the final product since much lower quantities of degradation products were formed. An equimolar ratio of 2,4-dichloro-thieno(3,4-b)pyridine (113) and methoxide in DMSO led to an equal ratio of the 2- and 4-mono- substituted products (116) and (117) in the crude mixture, according to its ^{1}H n.m.r. spectrum. Roughly equal proportions of the pure mono-substituted compounds were isolated as purple oils from the crude mixture by flash-chromatography on neutral silica. Under identical conditions, 2,4-dichloro-3-metho-xycarbonylthieno(3,4-b)pyridine gave only the disubstit-uted product (115); the di-chloro compound was recovered, together with some products of decomposition. With a two-fold excess of methoxide both dichloro compounds (112) and (113) yielded the dimethoxy products (115) and (118), respectively.

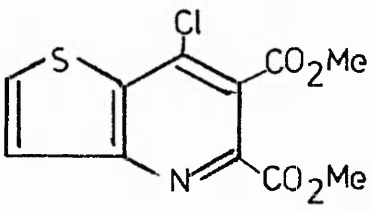


Scheme 42

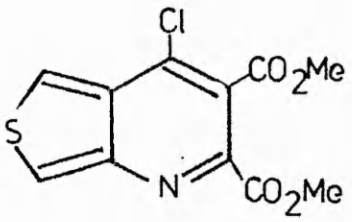
Reactions of thioglycolate with (112) and (113) in methanol resulted in the formation of insoluble, high melting-point mixtures which exhibited very little or no fluorescence under u.v. light. Similar reactions with morpholine resulted in the isolation of purple oils which did fluoresce under u.v. light. ^{1H} n.m.r. and ^{13C} n.m.r.

spectra of the crude products in each case provided firm evidence to indicate that both α- and γ- chlorine atoms in (112) and (113) were replaced. Unfortunately, the products were unstable and it was not possible to isolate any pure components from the complex mixtures.

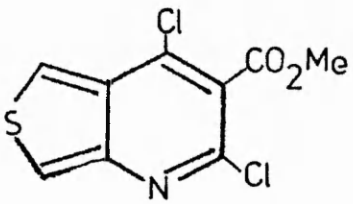
The anomalous nature of the thieno(3,4-b)pyridines.



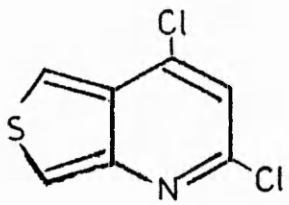
(46)



(105)



(112)



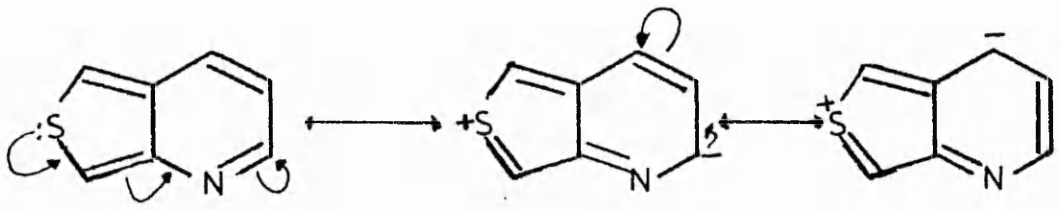
(113)

The results of the methoxydechlorination reactions of the chlorothieno(3,4-b)pyridine compounds (105), (112) and (113) are interesting for two reasons. Firstly, the dichloro compounds (112) and (113) behave much more like the quinoline analogues in that both of the α- and γ-chlorine atoms are easily replaced under mild conditions. In the 2,3-fused thieno(b)pyridine analogues (see Table 3, P. 25) the α-chlorine atom is much more difficult to replace than the γ-chlorine atom. Secondly, the ease of replacement of the γ-chlorine atom in the thieno(3,4-b)pyridine compounds is very dependent on the α- (i.e. meta-) substituent. The ready displacement of the γ-chlorine atom in compound (112) (where there is an α-

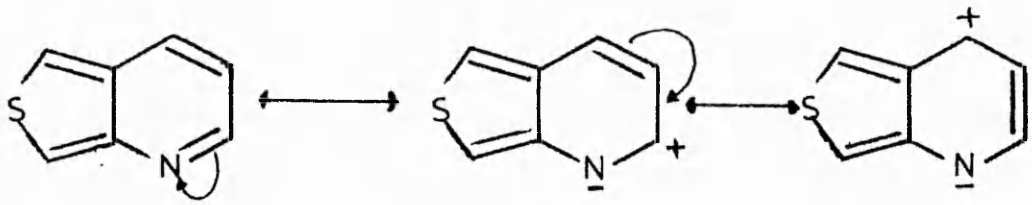
chlorine atom) is in contrast to the difficulty found in compound (105) (where there is an β-ester group), with both possessing a β-ester function. The γ-chlorine atoms in the thieno(3,2-b)pyridine analogues of (105) and (112) are easily replaced under mild conditions in both cases. Also, attempted mono-methoxydechlorination of the dichloro compound (113) giving only the disubstituted product, is anomalous to both the quinoline and 2,3-fused thieno(b)-pyridines.

Consideration of the canonical forms of the molecules before nucleophilic attack and the intermediate Wheland intermediates is given below;

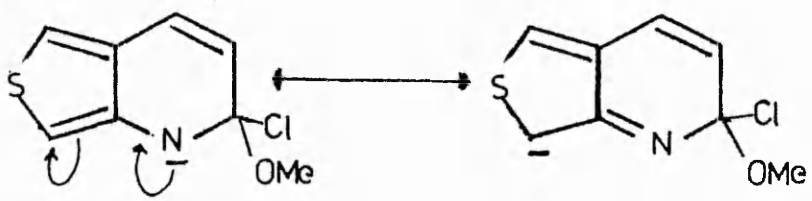
electron-releasing effect of the sulphur atom;



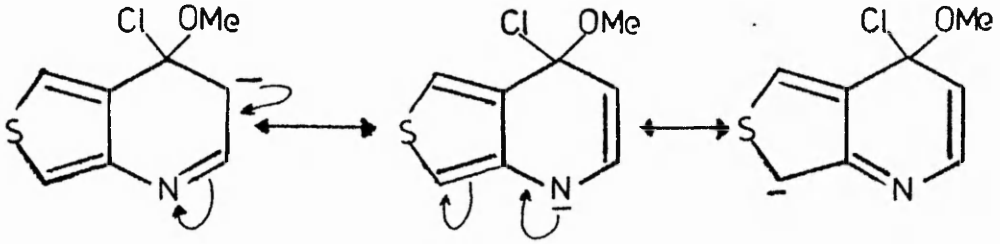
electron-withdrawing effect of the nitrogen atom



nucleophilic attack at the α-position



nucleophilic attack at the γ-position



These structures show that in all cases it is possible to draw canonical forms in which electron release from the sulphur atom increases the electron density and electron withdrawal to the nitrogen atom decreases the electron density at both the α- and γ-positions. There is no significant difference in the stabilities of the Wheland intermediates for nucleophilic attack at the α- and γ-sites. In the most important forms, i.e. those having the negative charge delocalised on the nitrogen atom neither possesses a stable Kekule form (unlike those in the other thieno(b)pyridine and quinoline series). On these grounds, the similar reactivities of the α- and γ-chlorine atoms in (112) and (113) are explained, although they would be expected to be more difficult to replace than those in the 2,3-fused thieno(b)pyridine and quinoline analogues.

The formation of only a disubstituted product during attempted preparation of a mono-methoxy derivative from 2,4-dichloro-3-methoxycarbonylthieno(3,4-b)pyridine (112), cannot be explained in the electronic terms presented above. Here, it seems that a methoxy substituent (which could be in either the α- or the γ-position) activates its meta- position towards nucleophilic attack. This effect is contrary to that observed by Illuminati[65] in the

quinoline series (see Table 6), where kinetic studies showed that electron-releasing groups meta- to a γ-chlorine atom decrease the rates of nucleophilic attack.

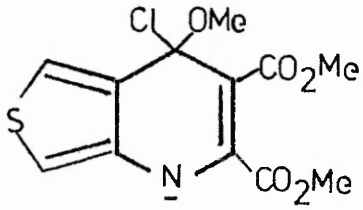
Table 6 : Reaction rates[65] for the methoxydechlorination of some 2-substituted 4-chloroquinolines in methanol at 75.2°

R	$10^4 k/l.mol^{-1}.sec^{-1}$	R	$10^4 k/l.mol^{-1}sec^{-1}$
OEt	0.159	SCH_3	1.17
OMe	0.143	H	2.47
CH_3	0.776	Cl	74.7

The γ-chlorine atom is replaced 500 times faster with a C-2 chlorine substituent than with a C-2 methoxy group. No kinetic studies in the nucleophilic substitution reactions of the 2,3-fused chlorothieno(b)pyridine compounds have been published. Qualitatively, no evidence has been found to suggest that a α- or γ-methoxy substituent activates its meta- position towards nucleophilic attack.

The virtually inert character of the γ-chlorine atom in 4-chloro-2,3-bismethoxycarbonylthieno(3,4-b)pyridine (105) cannot be explained in the simple electronic terms detailed above. The ready replacement of the α-chlorine atom in the dichloro compound (112) disproves any steric factors proposed to be induced by the β-ester function. Illuminati studied the effect of an α-ester function on the nucleophilic displacement of a γ-chlorine atom in the quinoline series. Although the rate of nucleophilic attack was of the expected order (rapid) for this electron-withdrawing group, reproducible results could not

be obtained and the reactions failed to go to completion. The difficulty in replacement of the γ-chlorine atom in (105) may be explained by reference to the canonical structure with the nitrogen atom possessing the negative charge;



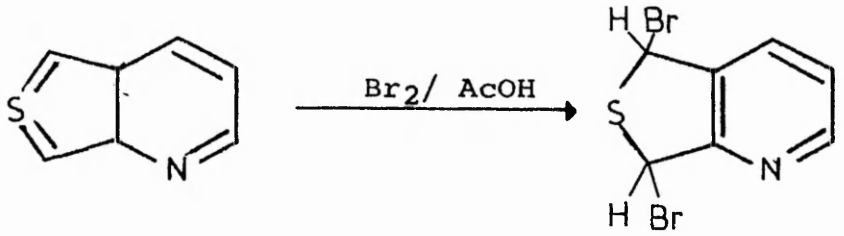
It is possible that a strong C2 - C3 single-bond fixation in the 2,3-bis ester compounds exists and so the presence of a double-bond at this position has a high destabilising effect. Evidence for this is found from the fact that the hydroxy compound (87) exists in the enol form, forms only the O-methylated compound with dimethyl sulphate and does not form a quaternary ammonium salt with methyl iodide.

Finally, it must be remembered that the intrinsic quinonoid structure of the thieno(3,4-b)pyridine ring, is not yet fully understood. The electronic structure within the bicyclic ring system has not been observed experimentally and few calculations have been performed. It is possible that the anomalous results above can be explained by reference to this enigmatic structure.

Electrophilic substitution.

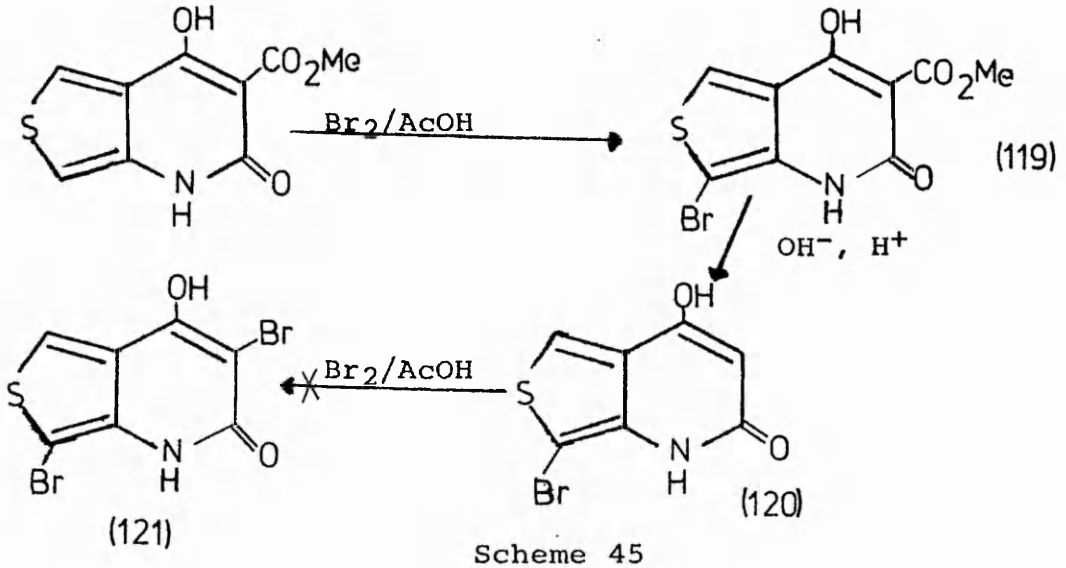
Once again, the thieno(3,4-b)pyridine series appeared to be anomalous not only to the other thieno(b)pyridine series, but also to quinolines. Reactions were carried out on four different systems, of which only one reacted smoothly.

Attempted bromination of 7-hydroxy-2,3-bismethoxycarbonylthieno(3,4-b)pyridine (87) in hot acetic acid resulted in recovery of the starting material only; the same results were found when chloroform was employed as solvent. This was quite surprising, since substitution into the thiophene ring of the thieno(2,3-b)pyridine analogue takes place without undue difficulty (p. 20). The lack of reaction rather disproves the prediction by Barker (P. 46) that the system would have a considerable tendency to undergo addition reactions at the 5,7-positions, since the product would then contain a normal Kekule pyridine ring (Eq. 18);



(18)

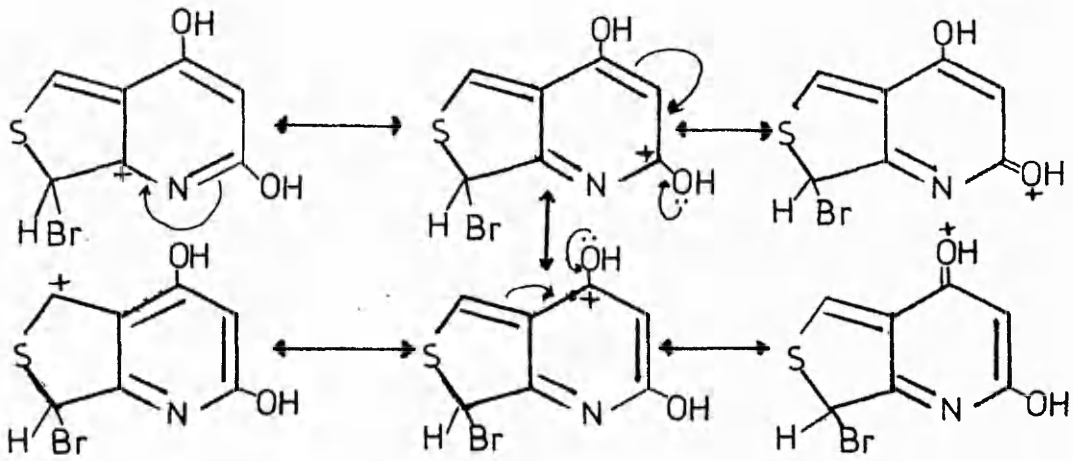
In acetic acid at 80°, 4-hydroxy-3-methoxycarbonylthieno(3,4-b)pyridin(2H)-1-one (96) was brominated to give the mono-substituted product (119) Scheme 45;



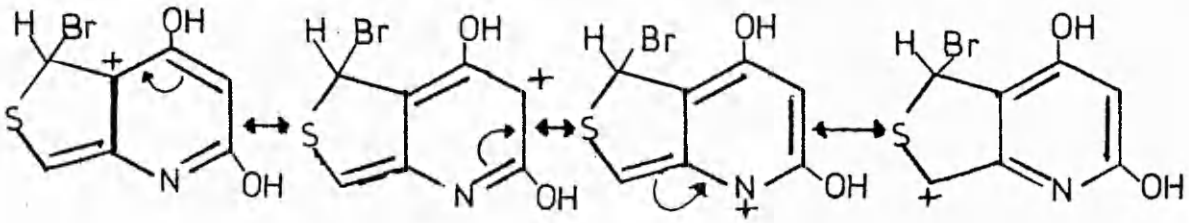
Scheme 45

The intermediate σ-complexes formed by electrophilic attack at the thiophene C-5 and C-7 positions on the di-hydroxy forms are given below;

attack at the C-7 position



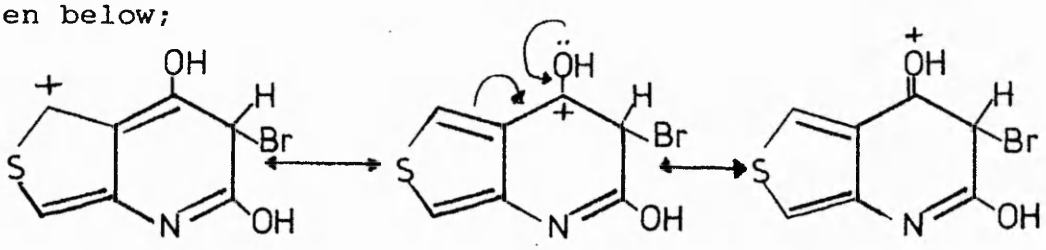
attack at the C-5 position



In each of the cases, for attack at either C-5 and C-7 the positive charge can be delocalised over the pyridine

ring. However, the σ-complex formed in the case of attack at C-7 would be the more stable of the two since the positive charge can be delocalised to the oxygen atoms, and there is no canonical form with the unfavourable location of the positive charge on the nitrogen atom. For attack at the C-5 position, the canonical forms possesses a high-energy nitrogen atom with a positive charge, and the oxygen atoms are unable to accept the charge.

In 4M sodium hydroxide, the ester group in (119) was hydrolysed to the intermediate carboxylic acid which decarboxylated spontaneously to give (120) in high yield. Attempts to introduce a second bromine atom into (120) under the same conditions used to prepare (119) resulted in the formation of a complex (fluorescent) mixture from which it proved impossible to isolate any pure compounds. The canonical forms for electrophilic attack at C-3 are given below;



Although there is no highly unstable form where a positive charge resides on the nitrogen atom, the charge distribution is limited to only one oxygen atom and two carbon atoms. If this limited delocalisation inhibits attack at the C-3 position, it is not possible to explain why (97) could not be brominated at either C-3 or C-7.

Under similar conditions to those used for the bromination of (96), 4-hydroxythieno(3,4-b)pyridin-(1H)2-

one (97) gave a complex mixture of intractable high mp solids (>250^0), fluorescing under a u.v. lamp. Attempted separation of products by column, flash and medium-pressure chromatography failed and crystallisation proved to be equally futile. Various solvents (pyridine, chloroform) were also used, and a wide range of temperatures employed, but either the starting material was recovered or the mixtures isolated were too complicated to be resolved. This is in contrast to the quinoline and 2,3- fused thieno(b)pyridines where mono-substitution readily occurred at the β-position of the pyridine ring in each case, followed by di-substituion with an excess of bromine. The compounds isomeric with (93) in the other thieno(b)pyridines undergo a Mannich reaction with formaldehyde and diethylamine in ethanol, but (93) (at room temperature) gave only a small quantity of colourless material, which became a tar after a few hours. Attempted diazo-coupling of (93) with p-nitro-benzenediazonium chloride gave a complex mixture which could not be resolved.

Reductive Dechlorination Reactions.

Various conditions were investigated in attempts to dechlorinate (105), (112) and (113) with zinc. All resulted in the formation of complex mixtures which did not fluoresce under u.v. light.

2.3. ^{13}C N.M.R. Studies

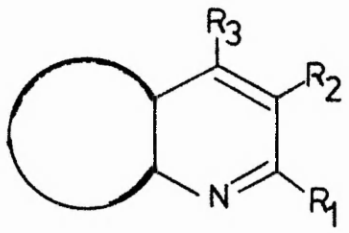
The proton-decoupled ^{13}C n.m.r. spectra of the compounds prepared in this work have been recorded. By applying data from the spectra of thieno(2,3-b)- and -(3,2-b)- pyridine and quinoline isosteres the spectra of most of the thieno(3,4-b)pyridines have been interpreted. Thus the author has been able to distinguish between the isomeric chloromethoxythieno(3,4-b)pyridines (116) and (117) and to determine the preferred tautomeric states in the various oxygenated compounds that were made.

Since much of the chemistry of the thieno(2,3-b)- and -(3,2-b)pyridines has been carried out since the advent of ^{13}C n.m.r., the spectra of many compounds in both series have been recorded and assignment of the ring carbon atom signals has been made. In order to interpret the spectra of substituted thieno(2,3-b)- and -(3,2-b)pyridines Barker assumed that the incremental chemical shifts (I.C.S.), defined as the difference in chemical shifts of a carbon atom in a substituted ring system and the parent heterocycle, on the pyridine ring atoms are very similar to those in their quinoline counterparts.

$$\text{I.C.S.} = \begin{bmatrix}\text{chemical shift at C-n in} \\ \text{the substituted system}\end{bmatrix} - \begin{bmatrix}\text{chemical shift at C-n} \\ \text{in the parent system}\end{bmatrix}$$

For each of the thieno(2,3-b)- and -(3,2-b)pyridines and quinoline systems the I.C.S. of the pyridine ring carbon atoms in some simple derivatives are given in Table 7;

Table 7. I.C.S. values of the pyridine ring carbon atoms in some simple quinoline and thieno(b)pyridine derivatives.



substituent	system	I.C.S. produced at C-a	C-b	C-c	C-d	C-e
R-1 = Cl	Q	+1.4	+0.3	+3.0	-1.2	0
R-2 = H	2,3-b	+1.4	-0.5	+2.0	-1.2	c
R-3 = H	3,2-b	+1.8	+0.8	+2.4	-1.5	-0.2
	MEAN	+1.5	+0.2	+2.5	-1.3	-0.1
R-1 = OMe	Q	+12.5	-14.0	+2.3	-7.8	-4.0
R-2 = H	2,3-b	+15.7	-12.9	+2.2	-5.6	c
R-3 = H	3,2-b	+15.7	-9.8	+2.2	-6.9	-2.6
	MEAN	+14.6	-12.2	+2.2	-6.8	-2.2
R-1 = H	Q	+0.1	-14.7	+28.5	-14.7	+0.1
R-2 = H	2,3-b	+2.1	-20.6	+30.1	-9.0	c
R-3 = OMe	3,2-b	+2.4	-18.4	+30.9	c	+2.1
	MEAN	+1.5	-17.9	+29.8	-7.9	+0.7
R-1 = H	Q	-0.5	+0.1	+6.4	-1.9	+0.8
R-2 = H	2,3-b	+0.4	-1.8	+7.5	-1.0	c
R-3 = Cl	3,2-b	+0.8	0	+8.0	-0.1	+1.3
	MEAN	+0.2	-0.6	+7.3	-1.0	+0.7

contd...

Oxygenated Series.

substituent	system	I.C.S. at produced C-a	C-b	C-c	C-d	C-e
R-3 = =O	Q	-10.8	-8.6	+39.3	-8.6	-10.8
	3,2-b	-9.8	-6.7	+42.2	-5.2	-11.7
	MEAN	-10.3	-7.7	+40.8	-6.9	-11.3
R-3 -OH	Q	+1.4	-12.7	+26.9	-12.7	+1.4
	2,3-b	-1.3	-14.5	+32.2	-7.9	c
	MEAN	0	-13.6	+29.6	-10.3	+1.4
R-1 = =O	Q	+11.7	-4.7	+4.4	-19.7	-15.4
	3,2-b	+14.2	-3.0	+2.3	-15.2	-14.3
	2,3-b	+15.1	+0.3	+2.0	-9.2	c
	MEAN	+13.7	-2.5	+2.9	-14.6	-14.9

Generally, agreement in the I.C.S. values within each of the three groups already studied is very good. In systems containing more than one substituent, the I.C.S values for each substituent can be treated independently as additive properties.

As far as the author is aware, no ^{13}C n.m.r. spectrum for thieno(3,4-b)pyridine has been published, so that predictions of the spectra of substituted thieno(3,4-b)-pyridine analogues from the parent heterocycle and the I.C.S. above cannot be made. However, it is possible to apply the I.C.S. values listed to the interpreted spectra of some simple thieno(3,4-b)pyridine derivatives prepared in this work, and to predict the spectrum of the parent

heterocycle. This can then be used to predict the spectra of the more elaborate thieno(3,4-b)pyridine compounds. What follows shows that this approach is successful to a reasonable degree.

The following points refer to interpretation of the ^{13}C n.m.r. spectra;

(i) due to the Nuclear Overhauser Effect (N.O.E.), carbon atoms bonded to hydrogen showed large peaks,

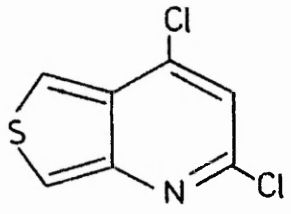
(ii) the bridge-head carbons (C-d and C-e) usually gave very small signals in the regions of 130-150ppm and 120-130ppm respectively.

(iii) Substituents have a significant effect on the positions of signals of the pyridine carbon atoms,

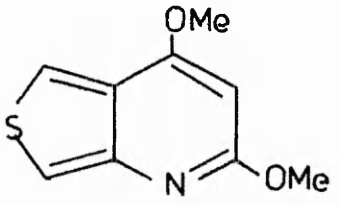
(iv) the signals due to the thiophene ring carbons C-5 and C-7 in the (3,4-b) series are sometimes altered very significantly by substituents in the pyridine ring. This has led to difficulty in the assignments of such peaks and in some cases, no firm conclusions can be made.

Predictions of the ^{13}C n.m.r. spectrum of thieno(3,4-b)pyridine itself were made by applying the established I.C.S. introduced by chloro- and methoxy- substituents at the α- and γ- positions to 2,4-dichlorothieno(3,4-b)pyridine (113) and its dimethoxy derivative (119). The spectra of these two substances were readily interpreted.

Prediction of the chemical shifts of the pyridine ring carbon atoms in thieno(3,4-b)pyridine from the interpreted spectra of (113) and (119);



(113)



(119)

	Compound	C-a	C-b	C-c	C-d	C-e
observed	(113)	148.8	118.2	138.9	129.0	150.2
I.C.S.		+1.7	-0.4	+9.8	-2.3	+0.6
predicted		147.1	118.6	129.1	131.3	149.6
observed	(119)	160.9	88.7	164.9	125.1	148.6
I.C.S.		+16.1	-30.1	+32.0	-14.7	-1.5
predicted		144.8	118.8	132.9	139.8	150.1
mean		146.0	118.7	131.0	135.6	149.9

where;

the "observed" row shows the observed signals of the pyridine carbons in the thieno(3,4-b)pyridine compounds.

the "I.C.S." row shows the combined I.C.S. values of the pyridine carbons in the other series.

the "predicted" row gives the predicted spectrum of thieno(3,4-b)pyridine.

the "mean" row gives the mean of the two predicted chemical shifts for each of the pyridine ring carbons.

Table 8 below compares the predicted chemical shifts of the pyridine carbons in thieno(3,4-b)pyridine with those observed in the 2,3-fused thieno(b)pyridines and quinoline

Table 8.

Comparison of the observed pyridine ring carbon chemical shifts in quinoline and the 2,3-fused thieno(b)pyridines with the predicted values for thieno(3,4-b)pyridine.

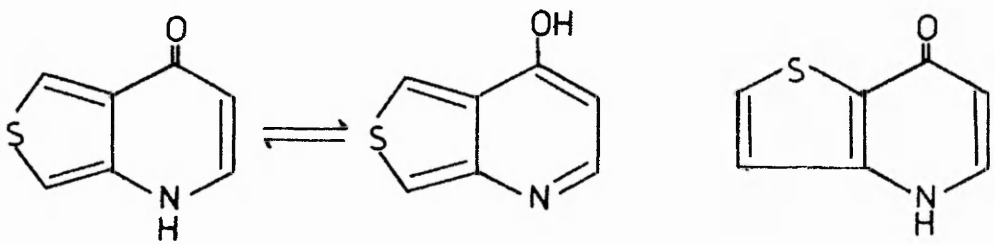
System	C-a	C-b	C-c	C-d	C-e
quinoline	150.3	121.0	136.0	128.3	148.3
thieno(2,3-b)pyridine	146.4	119.3	130.9	132.4	161.8
thieno(3,2-b)pyridine	147.1	118.4	130.2	133.0	156.0
thieno(3,4-b)pyridine	146.0	118.7	131.0	135.6	149.9

The predicted values of the chemical-shifts at the C-a, C-b and C-c positions are very similar to those in the 2,3-fused thieno(b)pyridines and quinoline. The chemical shifts at C-d and C-e vary, as expected, since they form part of the second fused ring.

Application of ^{13}C n.m.r. to structure elucidation.

(a) Determination of the preferred tautomeric states in the oxygenated thieno(3,4-b)pyridines.

The 4-oxygenated thieno(3,4-b)pyridine (93) could exist in either the keto or the enol form;



(93) (33)

The I.C.S. values of the pyridine carbon atoms for each of the keto and enol forms at C-4 are given in Table 7. Application of these values to the predicted spectrum of thieno(3,4-b)pyridine above allows the ^{13}C n.m.r. spectrum of each of the 4-oxygenated tautomers to be predicted;

	C-a	C-b	C-c	C-d	C-e	Dif.
Enol	146.5	105.4	159.4	125.1	151.8	32.7
Keto	136.2	111.3	170.6	128.5	139.1	22.5
Observed	140.2	104.4	176.5	133.4	c	--
(33)	137.3	109.3	173.4	127.8	144.3	--

where "Dif."= sum of the differences in chemical shifts between the predicted and observed spectra at C-a to C-e.

The signals of the pyridine ring carbons in the (3,2-b) analogue of (93), (33) (which exists as the keto form) are also given and are in good agreement with the observed and predicted spectrum for the keto tautomer of (93). In particular, the high chemical shift at C-c suggests very strongly that the keto tautomer is preferred.

Similarly, the spectrum of the 4-hydroxythieno(3,4-b)-pyridin-2(1H)-one (97) is predicted below. The assumption that, like the 2,3-fused thieno(b)pyridines and quinoline analogues, it exists as the γ-enol, α-keto form is almost certainly correct;

	C-a	C-b	C-c	C-d	C-e	Dif.
Predicted	159.7	102.6	163.5	110.7	136.4	
Observed	159.5	96.0	165.8	123.6	138.6	24.2
3,2-b	160.6	95.6	164.2	112.3	144.5	
2,3-b	162.2	94.5	164.6	115.9	149.6	

The chemical shifts of the pyridine ring carbons in (96) are also very similar to those observed in the 2,3-fused thieno(b)pyridines, suggesting that this also exists as the γ-enol, α-keto form.

system	C-a	C-b	C-c	C-d	C-e
2,3-b	160.5	95.2	170.0	114.3	152.3
3,2-b	160.7	95.0	169.1	a	146.1
3,4-b	161.4	95.4	169.5	122.1	138.0

(b) Bromination of 4-Hydroxy-3-methoxycarbonylthieno-(3,4-b)pyridine (96).

So far, only the chemical shifts of the pyridine ring carbons have been discussed. By assuming that bromination of 4-hydroxy-3-methoxycarbonylthieno(3,4-b)pyridin-2(1H)-one (96) occurred at the C-7 position (see P. 83), then it is possible to assign the thiophene ring signals. The I.C.S. values imposed by bromine at C-2 of a thiophene ring are known. Application of these shifts to the C-5 and C-7 signals in (96) and (97) allows those signals to be identified. For example, the signals in (96) occur at 125.2 and 101.3ppm. There are two possibilities;

(a) the C-5 signal is 125.2 and the C-7 signal is 101.3

(b) the C-5 signal is 101.3 and the C-7 signal is 125.2

The I.C.S. values at C-2 and C-5 caused by bromine at C-2 are -18.1 and -2.5 ppm. Applying these values to each of the cases (a) and (b) above and accepting that the bromine atom is at C-7, we arrive at the following predictions;

possibility (a)

C-5 signal at 125.2-2.5 = 122.7ppm (large due to NOE)

C-7 signal at 101.3-18.1 = 93.2ppm

possibility (b)

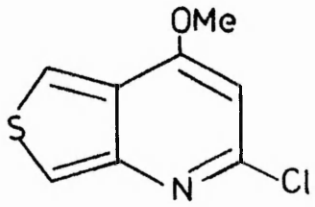
C-5 signal at 101.3-2.5 = 98.8ppm (large due to NOE)

C-7 signal at 125.2-18.1 = 107.1ppm

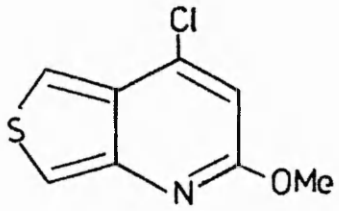
The observed values for (96) are 125.8 (large) and 86.9ppm in good agreement with possibility (a). The same type of calculation gives values of 119.1 and 100.4 ppm for the chemical shifts at C-5 and C-7 respectively in compound (97). The assigned signals for the thiophene carbons in (96) and (97), allow complete interpretation of the spectrum of thieno(3,4-b)pyridin-4(1-H)-one (93), as given on (P. 93).

<u>(ii) To distinguish between 2-chloro-4-methoxythieno-(3,4-b)pyridine (116) and its 4,2-isomer (117).</u>

By applying the I.C.S. values in Table 7 to the predicted ^{13}C n.m.r. spectrum of thieno(3,4-b)pyridine (Table 8), the spectrum of the monomethoxydechlorinated compounds (116) and (117) can be forecast;



(116)



(117)

Structure		C-a	C-b	C-c	C-d	C-e
(116)	(Predicted)	149.0	101.0	163.3	126.4	150.5
(117)	(Predicted)	160.8	107.1	140.5	127.8	148.4
Product A*	(Observed)	162.6	111.6	138.4	118.6	147.8
Product B**	(Observed)	152.5	97.1	160.6	124.8	149.7

* = product of higher Rf on tlc (chloroform)

** = product of lower Rf on tlc (chloroform)

It is clear that the values for product A and (117) are closer than those of A and (116) and similarly for (B) and (117). The total differences collected below, confirm the point;

observed	predicted	Diff.
A	(116)	10.6
A	(117)	28.1
B	(116)	26.2
B	(117)	11.5

Once again, the chemical shifts of the pyridine ring carbons are close to those in the 2,3-fused thieno(b)-pyridines;

For compound (116) and analogues

system	C-a	C-b	C-c	C-d	C-e
2,3-b	162.3	108.6	139.7	125.7	a
3,2-b	163.2	108.2	139.0	126.0	154.1
3,4-b	162.6	111.6	138.4	128.6	147.8

For compound (117) and analogues

System	C-a	C-b	C-c	C-d	C-e
2,3-b	149.5	101.3	162.1	122.9	161.5
3,2-b	150.5	100.6	162.1	121.8	156.4
3,4-b	152.5	97.1	160.6	124.8	149.7

Table 9. 13C n.m.r. Spectra of the other thieno(3,4-b)pyridines prepared in this work.

R-1	R-2	R-3	C-5	C-7	C-2	C-3	C-4	C-9	C-8
H	H	Cl	117.5,116.9		150.1	119.2	137.8	150.7	123.2
Cl	CO_2Me	Cl	119.5,119.7		146.0	124.2	136.9	147.8	128.1
OMe	CO_2Me	OMe	113.3,117.7		157.6	103.2	160.7	148.2	124.6
CO_2Me	CO_2Me	Cl	120.4,143.8		150.8	127.0	133.8	153.6	131.2
CO_2Me	CO_2Me	OMe	110.1,141.7		151.7	125.4	162.5	133.9	126.5
CO_2Me	CO_2Me	OH	121.6,139.7		141.5	115.8	162.1	135.5	118.8
CO_2Me	CO_2Me	OAc	113.7,143.4		152.7	130.8	157.2	157.2	127.2
CO_2Me	CO_2Me	OBz	114.0,143.4		152.7	129.0	157.6	152.7	127.3

Due to the unstable nature of 4-chlorothieno(3,4-b)-pyridine, its ^{13}C n.m.r. spectrum contained extra signals due to decomposition products and the spectrum could not be interpreted with certainty.

Since no substituent could be introduced into the thiophene ring in the 2,3-bis ester thieno(3,4-b)pyridine system (87), it is not possible to assign the thiophene ring carbon signals.

CHAPTER THREE

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 the ^{1}H on a Hitachi Perkin Elmer R-24B. Melting-points were uncorrected. Unless otherwise stated, solvents were dried over $MgSO_4$ and were evaporated under reduced pressure. The stationary phase for flash-column chromatography was Merck Keiselgel 60, 230-400 mesh. Light petroleum, unless otherwise stated refers to fraction b.p. 60-80°. The activated zinc used for reductive dechlorinations was first prepared with 10% hydrochloric acid as described by Vogel[106]. The ^{13}C n.m.r. spectra of the compounds prepared in this work are detailed in Chapter 2.

3.1. Thieno(3,4-b)pyridin-4(1H)-one and derivatives.

Thieno(3,4-b)pyridin-4(1H)-one (93) -

(a) Thieno(3,4-b)pyridin-4(1H)one-3,7-dicarboxylic acid (59) (2g) was added in one portion to boiling diphenyl ether (80ml). The mixture was boiled under reflux for 10 minutes, cooled, diluted to 200ml with light petroleum and filtered. The residue was washed with light petroleum, dried, and digested in refluxing methanol for 10 minutes. The mixture was filtered hot and the crude product, shown by tlc (ethanol) to contain mainly starting material, was isolated from the filtrate. Ordinary column-chromatography (elution with ethanol) gave the title pyridone (0.2g, 16%) m.p. 220°C (dec.). δ (DMSO); 8.37(d, H-5, J=3.5Hz), 7.92(d, H-2, J=8Hz), 7.62(d, H-7, J=3.5Hz), 5.81 (d, H-3, J=8Hz). ν_{max}: 3400(broad, N-H), 1570cm^{-1} (broad,C=O).

(b) The experiment was repeated as in (a), except that the pure pyridone (0.3g, 24%), was isolated from the crude-product by Soxhlet extraction into ethyl acetate instead of by chromatography.

(c) The di-acid (59) (2.0g) was added in one portion to boiling 1,2,4-trichlorobenzene (80ml) and the mixture was boiled under reflux for 20 minutes. The cooled mixture was diluted to 300ml with light petroleum and then filtered to give a yellow solid (1.8g). After being washed with light petroleum, then dried, tlc (ethanol) showed this to contain starting material only.

(d) A mixture of the di-acid (59) (1.0g) and copper-bronze (1.0g) in quinoline (50ml) was heated at 200° for 30 minutes, then cooled and filtered. The filtrate was evaporated to dryness under vacuum to leave a dark residue, to which cold ether (60ml) was added. The precipitate was filtered off, washed with ether on the funnel and dried. The product did not fluoresce under u.v. light on tlc (ethanol); it was assumed that the thieno(3,4-b)pyridine ring had degraded, so the reaction was abandoned.

(e) An intimate mixture of the di-acid (59) (0.5g) and powdered glass (1.5g) was heated at 150° for 15 minutes, cooled, and added to 4M sodium hydroxide (50ml). The glass was filtered off, the filtrate was acidified to pH 4 with concentrated hydrochloric acid and filtered. Tlc (ethanol) of the dried residue indicated that only starting material was present. The same procedure was repeated at different temperatures upto 250°, but the starting material was recovered or ring degradation occurred with hydrogen sulphide

being evolved (confirmed with lead acetate).

4-Chlorothieno(3,4-b)pyridine (101) -

Thieno(3,4-b)pyridin-4(1H)-one (93) (1.0g) in phosphoryl chloride (5ml) was left to stand at room temperature for seven days in the dark. The excess of reagent was evaporated off under vacuum at room temperature and the dark residue was added to water (20ml). The mixture was neutralised (saturated aqueous sodium bicarbonate) and the product was extracted into dichloromethane. After being dried, the solvent was evaporated off at room temperature to give the title chlorocompound as a yellow oil (700mg, 63%), which darkened after a few hours to a tar which did not fluoresce under u.v. light. δ ($CDCl_3$); 8.45 (H-2, d, J=5Hz), 8.00 (H-5, d, J=3Hz), 7.85 (H-7, d, J=3Hz), 6.95 (H-3, d, J=5Hz). The chlorothieno(3,4-b)pyridine formed a picrate salt (m.p. 210-215^{0}C).

Attempt to prepare 3-dimethylaminomethylthieno(3,4-b)-**pyridin-4(1H)-one**

Thieno(3,4-b)pyridin-4(1H)-one (93) (0.8g, 5.3mmol) was added to aqueous formaldehyde (40%, 1ml) and diethylamine (1.0g, 13.8mmol) in ethanol (30ml). After being left to stand at room temperature in the dark for 10 days, the brown solution was evaporated to dryness under vacuum. The resulting grey solid gave a complex ^{1}H n.m.r. spectrum and tlc (ethanol) showed mainly base-line material with a weak fluorescent spot at Rf ~0.5. After being left overnight in the dark, the solid was transformed into a black tar which did not fluoresce under u.v. light; the reaction was abandoned.

4-Methoxythieno(3,4-b)pyridine (102) -

(a) To freshly prepared 4-chlorothieno(3,4-b)pyridine (101)(0.9g, 5,3mmol) in DMSO (5ml) was added a solution of 25% sodium methoxide in methanol (Aldrich; 3.5g, 16mmol), and the solution was left to stand at room temperature in the dark for 24 hours. The dark mixture was poured into water (15ml) which contained glacial acetic acid (1.4g) and the whole was extracted with dichloromethane. Tlc in a range of solvents of the material extracted into the dichloromethane indicated that a complex mixture of components was present, none of which fluoresced under u.v. light. Degradation of the ring system was assumed and the reaction was abandoned.

Attempted methylation of thieno(3,4-b)pyridin-4(1H)-one -

A mixture of the pyridone (93), (1.0g, 6.6mmol), sodium carbonate (1g, 7.2mmol) and dimethyl sulphate (1g,7.9mmol) in butanone (15ml) was stirred at room temperature overnight and then poured into water (30ml). Extraction with dichloromethane gave a brown tar which did not fluoresce under u.v. light on tlc and whose complex ^{1}H n.m.r. spectrum ($CDCl_3$) indicated a very low ratio in the number of aromatic:aliphatic protons. Again it was assumed that the ring system had degraded, and the reaction was abandoned.

Attempted diazo-coupling of pyridone (93)

with p-nitrobenzene diazonium chloride -

A suspension of p-nitroaniline (0.2g, 1.4mmol) in water (20ml) containing 2M hydrochloric acid (0.2g) was heated on a steam-bath for five minutes. The solution was cooled to 0^0 and, with stirring, sodium nitrite was added until

nitrous acid was present in excess (starch-KI paper). After being left for 10 minutes at 0^0 the solution was added to ice-cold thieno(3,4-b)pyridin-4(1H)-one (93) (0.2g, 1.3mmol) in water (10ml) which containing 2M sodium hydroxide (2ml). The deep red solution which formed immediately was stirred for 10 minutes at room temperature and then neutralised with 2M sodium hydroxide. Extraction with ethyl acetate gave a small quantity of red solid whose tlc (ethyl acetate) indicated a complex mixture of components, one of which was weakly fluorescent under u.v. light. Chromatography (neutral silica), (elution with methanol; no other common solvent eluted anything from the column) gave a small quantity (30mg) of impure fluorescent material, which was insoluble in all common solvents, and the reaction was abandoned.

Attempted bromination of thieno(3,4-b)pyridin-4(1H)-one -

To a stirred solution of the thieno(3,4-b)pyridone (93) (0.3g, 2mmol) in acetic acid (6ml) was added bromine (0.3g 1.9mmol) in the same solvent (3ml). After 10 minutes the solution was poured into water and a yellow solid (0.2g) was isolated by extraction into ethyl acetate. Tlc showed that four major components were present, all of which fluoresced under u.v. light. Medium-pressure chromatography (silica) (elution with ethyl acetate) resulted in the isolation of two of these products in reasonably pure conditions. One of these was identified as the starting material (0.1g), but the very small quantity of the second component did not allow its structure to be determined. The same reaction was repeated at 80^0 in glacial acetic

acid, and also at room temperature in chloroform (sodium acetate as buffer), and in pyridine, but all produced complex mixtures of products which could not be separated using ordinary-column, flash-column or medium-pressure chromatography.

3.2. Methyl 4-aminothiophene-3-carboxylate hydrochloride (81) and derivatives.

4-Carboxymethyl-3-oxotetrahydrothophene (80) -

(a) To a stirred, boiling solution of sodium methoxide (3 mol, from sodium 69g) in methanol (500ml) was added dropwise α-,β-dicarboxymethylmethylethyl sulphide[92] (78) (190g, 1 mol), and the solution was boiled under reflux for a further 45 minutes. The cooled solution was poured into ice/water(500ml) which contained concentrated hydrochloric acid (150ml) and the product was extracted into dichloromethane. The organic layer was washed with water (3x), saturated aqueous sodium bicarbonate (3x), water (2x), dried and the solvent was removed. Vacuum-distillation of the residue gave the pure keto-ester (35g, 20%) b.p. 95-100°C/1mmHg. The oil-bath temperature was not allowed to exceed 120° to inhibit degradation of the product. $\delta(CDCl_3)$; 3.79(s, all protons). ν_{max}:3100 (broad, H-bonded O-H), 1750 (ester C=O), 1740 cm^{-1} (ring C=O). The product was isolated as a colourless slurry which contained a mixture of the keto and enol tautomers, but which was used directly in the next step. Washing the mixture with ice-cold ethanol removed the keto form, to give the pure enol tautomer having a mp 37-38°C (lit.[106] 37.8°C).

(b) The preparation was repeated as in (a), but after

being refluxed for 45 minutes, the cooled solution was added to ice/water (500ml) and the solution was stirred at room temperature for 20 minutes; this destroyed the 2,3-substituted by-product. The solution was then acidified to pH 1 with concentrated hydrochloric acid and worked up as in (a) above, to give the keto-ester (40g, 25%).

Methyl 3-aminothiophene-4-carboxylate hydrochloride (81) -

(a) To the keto-ester (80) (3.9g, 24mmol) in DMF (7mls) at 100^0 was added hydroxylamine hydrochloride (1.6g, 23mmol) in small portions. The mixture was heated for a further 10 minutes (a deep red colour formed) then cooled, and triturated with ether (20ml). A brown residue (1.7g) was filtered off, washed with ether on the funnel and sucked dry. Crystallisation from methanol gave the title hydrochloride in variable yields (<10%), m.p. 157^0C (dec.), (lit.107 $203-205^o$). (DMSO); 9.4(broad, NH), 8.45(d, H-2, J=4Hz), 7.80 (d, H-5, J=4Hz), 3.83(s, CO_2CH_3). ν_{max} 2600-3100 (broad, NH_3^+), 1725, ester C=O)cm $^{-1}$.

(b) To a stirred, boiling solution of the keto-ester (80) (5g, 31.3mmol) in acetonitrile (15mls) was added hydroxylamine-hydrochloride (2.1g, 30.2mmol). After being boiled under reflux for one hour (prolonged refluxing gave a dark coloured product containing decomposition products) the mixture was poured into ether (50ml), filtered and the residue was washed with ether on the funnel, and sucked dry. The title hydrochloride (5.2g, 87%), m.p. 159^0C(dec.) thus obtained was shown to be pure by ^{1}H n.m.r. and by tlc (methanol) and no further purification was necessary.

Methyl 3-aminothiophene-4-carboxylic acid (82) -

The hydrochloride (81) (10g) was dissolved in the minimum quantity of water with stirring, and the solution was basified to pH 14 with 4M sodium hydroxide. The free amine was isolated as a yellow oil (8g, >90%) with dichloromethane, the solvent being removed at room temperature to reduce product degradation. The freshly prepared amine was shown to be pure by ^1H n.m.r. and by tlc, but darkened after a few hours at room temperature. δ ($CDCl_3$); 7.90(d, H-2, J=4Hz), 6.05(d, H-5, J=4Hz), 4.5(broad NH), 3.81(s,$CO_2\underline{CH_3}$). ν_{max}: 3360 and 3460 (double peak, primary amine), 1600 (primary amine), 1700cm^{-1} (ester C=O).

4-Aminothiophene-3-carboxylic acid (83) -

A mixture of the amine hydrochloride (82) (3.0g) and 2M sodium hydroxide (50ml) was left to stand at room temperature for two hours and then filtered. The filtrate was acidified to pH 5 (ice-bath, concentrated hydrochloric acid) but no precipitate formed. The solution was extracted with ethyl acetate from which a brown tar (2.1g) was isolated which had a complex ^1H n.m.r. spectrum and showed several spots on tlc; the reaction was abandoned.

Methyl 4-methoxythiophene-3-carboxylate -

(a) A solution of the free amine (82) (2g, 13mmol) and 25% sodium methoxide/methanol (Aldrich; 5g, 23mmol) in DMSO (20ml) was left to stand at room temperature for three days in the dark. The dark solution was poured into water (30ml) which contained glacial acetic acid (2.5g, 42mmol) and extracted with dichloromethane. Removal of the solvent left a residue, which was shown to be a mixture of the

free amine and decomposition products by tlc and ^{1}H n.m.r. (b) The attempted preparation was carried out as in (a) above, but the solution was heated at 40^0 for 20 minutes. A dark solution resulted whose tlc indicated that a complex mixture was present. This was confirmed by the complex ^{1}H n.m.r. spectrum of the isolated product.

Methyl 4-morpholinothiophene-3-carboxylate -

A solution of the free amine (82) (1.5g, 9.6mmol) and morpholine (10g, 115mmol) in ether (30ml) was allowed to stand at room temperature in the dark for four weeks. Tlc (dichloromethane) showed only base-line material (i.e. the amine had degraded) and the reaction was abandoned. In further experiments, elevated temperature conditions resulted in only faster degradation of the free amine.

Methyl 4-N-acetylthiophene-3-carboxylate (84) -

To a stirred ice-cold solution of methyl 4-aminothiophene-3-carboxylate (82) (5g, 32mmol) and triethylamine (10g) in chloroform (80ml) was added dropwise acetyl chloride (4.0g, 51mmol) in chloroform (50ml). After being stirred for 10 minutes at room temperature, the dark solution was washed with water (2x), saturated aqueous sodium bicarbonate (3x), water (2x) and then dried. Evaporation of the solvent left a brown oil which solidified overnight. The acetamide formed dark brown needles (4.2g, 67%), m.p. 31-33^{o}C from light petroleum (b.p. 40-60^o)/ethyl acetate which degraded to a dark tar after seven days at room temperature. δ ($CDCl_3$); 7.95(s, H-2, H-5 superimp.), 3.85(s,$CO_2\underline{CH_3}$), 2.16(s, $CO\underline{CH_3}$).

Methyl 4-N-(2-methoxycarbonylpropanoyl)-3-carboxylate (85)

To the free amine (82) (5g, 32mmol) and triethylamine (10g, 99mmol) in chloroform (50ml) was added dropwise a solution of 3-methoxycarbonylpropanoyl chloride (5.5g, 37mmol) in chloroform (20ml), the temperature not being allowed to exceed 40°. After being stirred for 10 minutes, the solution was washed with water (3x), saturated aqeous sodium bicarbonate (3x), water (3x), and dried. Evaporation of the solvent left a yellow residue which was crystallised from light petroleum/ethanol to afford the title amide as pale yellow needles (6.1g, 71%), m.p. 142-144°C. (Found: C, 48.5; H, 4.8; N, 5.0. Required for $C_{11}H_{13}NO_5S$: C, 48.7; H, 4.8; N, 5.2%). δ($CDCl_3$); 8.00(s, H-2, H-5, superimp.), 3.69, 3.83(2xs, 2x$CO_2\underline{CH_3}$), 2.73(s, $\underline{CH_2CH_2}$, superimp.). ν_{max}: 1700, 1720 (2x ester C=O), 1670cm^{-1} (amido C=O).

Attempted cyclisation of the amide (85) -

(a) To a boiling solution of sodium methoxide (22mmol, from sodium 0.5g) in methanol (50ml) was added the foregoing amide (2.0g, 7.4mmol). After being boiled under reflux for three hours (tlc showed no fluorescent spot) the cooled solution was poured into water (200ml) which contained acetic acid (4g, 67mmol) and the precipitate was filtered off and dried. A small quantity of the crystallised material (from light petroleum/ethanol) gave an ^1H n.m.r. spectrum identical to that of starting material and there was no depression in the mixed melting-point.

(b) To a stirred solution of the amide (85) (2.0g, 7.4 mmol) in dry ether (30ml) was added sodium hydride (1.0g,

42mmol). The mixture was boiled under reflux for one hour (tlc indicated no reaction), the solvent was evaporated and the residue was poured into water (20ml) which contained glacial acetic acid (3g, 50mmol); no precipitate formed and extraction with a range of solvents failed to yield a product. The solution was acidified further (2M hydrochloric acid) to give a small quantity of solid. This was filtered off and dried; it effervesced with sodium bicarbonate solution and its ^{1}H n.m.r. spectrum indicated the CH_2-CH_2 linkage to be present. The reaction was abandoned.

3.3. 4-hydroxy-2,3-bismethoxycarbonylthieno(3,4-b) pyridine (87) and derivatives.

E-Dimethyl 2-N-(3-carboxymethyl-4-thienyl)butene-1,4-dioate (88) -

(a) A solution of the free amine (82) (2.0g, 13mmol) and DMAD (5.1g, 36mmol) in ether (30ml) was left to stand at room temperature in the dark for three weeks. The resulting dark brown mixture was filtered, the solid was washed with warm ether to leave a residue which contained a complex mixture (as evidenced by tlc, in a variety of solvents). From the filtrate was isolated a small quantity of yellow crystals which gave the title Michael-adduct (0.4g,11%), m.p. 97-99^{0}C from cyclohexane/acetone. (Found: C, 48.2; H, 4.3; N, 4.6. Required for $C_{12}H_{13}NO_6S$:C, 48.2; H, 4.4; N, 4.7%). δ($CDCl_3$); 9.0 (broad NH), 8.01(d, H-2, J=4.5Hz), 6.79(d, H-5, J=4.5Hz), 5.60(s, C H), 3.92, 3.87, 3.68(3xs, 3xCO_2CH_3). ν_{max}: 3300 (broad, H-bonded N-H), 1680, 1710, 1740cm^{-1} (ester C=O).

(b) A solution of the free amine (82) (2g, 13mmol) and DMAD (2.5g, 18mmol) in methanol was boiled under reflux for one hour. A dark solution was formed from which it was impossible to isolate any pure compounds. Tlc of the residue in various solvents indicated that the product was a complex mixture, and the reaction abandoned.

Methyl (2,5,8-trismethoxycarbonyldithieno(3,2-b:2,3-e)-pyridin-(1H)-yl) acetate (89)

Methyl 4-aminothiophene-3-carboxylate (82)(3g, 19mmol) and DMAD (3.0g, 21mmol) in acetic acid (20ml) was left to stand at room temperature in the dark for three weeks. A small quantity of crystals was filtered off, washed with ether on the funnel, and sucked dry. Crystallisation from acetone gave the title tricyclic product (0.1g, 2%), m.p. 198-199°C. (Found: C, 49.2; H, 3.9; N, 3.1. Required for $C_{18}H_{17}NO_8S_2$: C, 49.2; H, 3.9; N, 3.2%). δ ($CDCl_3$); 8.90, 8.95 (2xs, H-3, H-7), 6.61(N-H), 5.88(s,-CH_2-), 4.00, 4.02, 3.88, 3.70(4xs, 4xCO_2CH_3). ν_{max}: 1710, 1720, 1740 (ester C=O), 3400-3600 (N-H). The original acetic acid filtrate was poured into water (20ml), but no precipitation occurred; the solution was basified with 40% sodium hydroxide and then extracted with chloroform; removal of the solvent gave a complex mixture of products.

4-Hydroxy-2,3-bismethoxycarbonylthieno(3,4-b)pyridine (87)

(a) A solution of the Michael adduct (88) (30mg, 0.1mmol) in glacial acetic acid was left to stand at room temperature in the dark for three days. Tlc (chloroform) showed a single fluorescent spot, and the solution was poured into water (10ml). The mixture was extracted with chloroform,

the organic solution was washed with saturated aqueous sodium bicarbonate (2x), water (2x), and evaporated to dryness to give the title thieno(3,4-b)pyridine as a brown powder (15mg). The i.r. spectrum of this product was identical to that of an authentic sample prepared from (c) (see below) and there was no depression in the mixed melting-point.

(b) A solution of methyl 4-aminothiophene-3-carboxylate (82) (3.1g, 20mmol) and DMAD (2.8g, 20mmol) in acetic acid (20ml) was heated at 50° for 20 minutes, then cooled and poured into water. The solution was extracted with chloroform, the organic layer was washed with saturated aqueous sodium bicarbonate (3x), water (2x), dried and the solvent was removed, to give a dark brown tar. Tlc (chloroform) of the residue indicated it to contain a complex mixture, with a single weakly fluorescent component; the reaction was therefore abandoned.

(c) A mixture of the amine-hydrochloride (81) (20g, 0.1 mol), sodium acetate (10g, 0.1mol) and DMAD (15g, 0.1mol) in acetic acid (50ml) was boiled under reflux for three hours. The cooled slurry was poured into water (250ml) the mixture was filtered, the residue was washed with water at the funnel and dried. Crystallisation from light petroleum/acetone (charcoal) gave the thieno(3,4-b)pyridine as a pale brown powder (15.2g, 54%), m.p. 196-199°C. (Found: C, 49.1; H, 3.5; N, 5.8. Required for $C_{11}H_9NO_5S$: C, 49.4; H, 3.4; N, 5.2%). δ($CDCl_3$); 8.41(s, H-7), 7.23(s, H-5), 4.01, 3.96(2xs, 2x$CO_2\underline{CH_3}$). ν_{max}:2800-3600 (H-bonded O-H, N-H), 1720 (ester C=O), 1650cm^{-1} (ring C=O).

4-O-Acetyl-2,3-bismethoxycarbonylthieno(3,4-b)pyridine (111) -

To a cold, stirred solution of the hydroxythieno(3,4-b)-pyridine (87) (3g, 11mmol) and triethylamine (4g, 40mmol) in chloroform (50ml) was added acetyl chloride (5g, 64 mmol) in the same solvent. The mixture was stirred at room temperature for 20 minutes, washed with water (3x), dried, then the solvent was removed. The residue was crys-tallised from cyclohexane/acetone to give the acetate as white needles (3.1g, 91%), m.p. 140-142°C (Found: C, 50.5; H, 3.7; N, 4.6. Required for $C_{13}H_{11}NO_6S$: C, 50.5; H, 3.6; N, 4.5%). δ ($CDCl_3$); 8.80(s, H-7), 7.81(s, H-5), 3.97, 4.02(2xs, 2*CO_2CH_3), 2.42 (s,$COCH_3$).

4-O-Benzoyl-2,3-bismethoxycarbonylthieno(3,4-b)pyridine (112) -

This compound was prepared as for the acetyl derivative (111) above, but benzoyl chloride, (6g, 40mmol) was used instead of acetyl chloride. The benzoate gave off-white needles from cyclohexane/acetone (3.6g, 86%), m.p. 188-189°C. (Found: C, 58.1; H, 3.7; N, 4.0. Required for $C_{18}H_{13}NO_6S$: C, 58.2; H, 3.5; N, 3.8%. δ ($CDCl_3$); 8.89(s, H-7), 8.00(s, (H-5), 8.5, 7.8 (multpl. benzene H's), 4.02, 4.11(2xs, 2xCO_2CH_3). ν_{max}: 1730cm^{-1} (broad, ester C=O).

4-Chloro-2,3-bismethoxycarbonylthieno(3,4-b)pyridine (105) -

The hydroxythieno(3,4-b)pyridine (87) (3.1g) in phosphoryl chloride (20ml) was boiled under reflux for three hours. The excess of solvent was removed, the residue was poured into water (30ml), and the mixture was neutralised with

saturated aqueous sodium carbonate. The crude material was filtered off and crystallised from cyclohexane/acetone (charcoal) to give the chlorocompound (105) as colourless crystals (2.2g, 67%) m.p. 131-134°C. (Found: C, 46.3; H, 2.9; N, 5.2. Required for $C_{11}H_8ClNO_4S$: C, 46.2; H, 2.8; N, 4.9%). δ ($CDCl_3$); 8.70(s, H-7), 7.90(s, H-5), 4.01, 3.92(2xs, 2x$CO_2\underline{CH_3}$. ν_{max}: 1710, 1730cm^{-1} (ester C=O).

4-Methoxy-2,3-bismethoxycarbonylthieno(3,4-b)pyridine (103) -

(a) A mixture of 4-hydroxy-2,3-bismethoxycarbonylthieno-(3,4-b)pyridine (87) (5.0g, 19mmol), potassium carbonate (3.0g, 22mmol) and dimethyl sulphate (3.5g, 28mmol) in butanone (40ml) was boiled under reflux for four hours, then cooled and poured into ice-water; facile hydrolysis of an ester linkage occurred at room temperature. The product was filtered off, dried and crystallised (charcoal) from cyclohexane/acetone to provide the methoxycompound as a white powder, (3.8g, 72%), m.p. 136-38°C. (Found: C, 50.8; H, 4.2; N, 5.2. Required for $C_{12}H_{11}NO_5S$: C, 51.2; H, 3.9; N, 5.0%). δ ($CDCl_3$); 8.41(s, H-7), 7.23(s, H-5), 4.01, 3.92, 3.85(3xs, 3x$CO_2\underline{CH_3}$). ν_{max}: 1710, 1720, 1740, (ester C=O), 1100cm^{-1} (ether C=O).

(b) To a boiling solution of sodium methoxide (43mmol, from sodium,1.0g) in methanol (15ml) was added the chlorothieno(3,4-b)pyridine (105) (2.0g, 7mmol), and the mixture boiled under reflux for 48 hours. The cooled mixture was poured into a solution of glacial acetic acid (4g, 67mmol) in water (50ml), with stirring and the precipitate was filtered off and sucked dry. Tlc (chloroform) of the res-

idue indicated a mixture of starting material and a second fluorescent material at a similar Rf value to that of the known methoxy derivative. Ordinary column-chromatography (alumina), (elution with light petroleum/ethyl acetate (6:1)) gave the methoxy compound (0.2g, 10%) m.p. 134-37°C after crystallisation from cyclohexane/acetone.

4-Methoxythieno(3,4-b)pyridine-2,3-dicarboxylic acid (104) -

A mixture of 4-methoxy-2,3-bismethoxycarbonylthieno(3,4-b)pyridine (103) (5g) and 4M sodium hydroxide was boiled under reflux for one hour. The cooled solution, which had a green fluorescence was filtered, acidified to pH 4 with concentrated hydrochloric acid and the precipitate was filtered off and dried. The residue was crystallised (with difficulty) from glacial acetic acid to give the title di-acid as a light brown solid (3.2g, 71%) m.p. >300°C. (Found: C, 47.0; H, 2.9; N, 4.6. Required for $C_{10}H_7NO_5S$: C, 47.4; H, 2.8; N, 5.5%). δ(TFA); 8.91 (s, H-5), 7.70 (s, H-7), 4.03 (s, O-CH_3). ν_{max}: 2800-3600 (H-bonded O-H), 1600cm^{-1} (acid C=O).

Unsuccessful attempts to prepare compounds derived from 4-hydroxy-2,3-bismethoxycarbonylthieno(3,4-b)pyridine (87)

4-Methoxythieno(3,4-b)pyridine-2,3-dicarboxylic acid anhydride -

A mixture of 4-methoxythieno(3,4-b)pyridine-2,3-dicarboxylic acid (1g) and acetic anhydride (20ml) was boiled under reflux for 24 hours. The excess of reagent was evaporated off and the residue was added to dry ether (15ml). The

mixture was filtered, and the residue was washed with ether and dried, when it had m.p. > 300°C. The ^{1}H n.m.r. and i.r. spectra indicated that only starting material was present.

4-Hydroxy-1-methyl-2,3-bismethoxycarbonyl-thieno(3,4-b)pyridinium iodide -

A mixture of thieno(3,4-b)pyridine (87) (2.0g) and methyl iodide (20ml) was warmed for one hour. Tlc (chloroform) of the residue revealed a single fluorescent spot, whose Rf value was very similar to that of the starting material. Evaporation of the solvent left a residue which gave no depression of m.p. with an authentic sample of the starting material, confirming that no reaction had taken place.

Bromination of thieno(3,4-b)pyridine (87) -

To a refluxing mixture of (87) (2.0g, 7mmol) and potassium carbonate (2.0g, 15mmol) in chloroform (50ml) was added bromine (1.5g, 9.4mmol) in the same solvent (10ml). After 30 minutes,tlc (chloroform) indicated that no reaction had occurred, and the cooled mixture was stirred with dilute sodium metadithionite solution, washed with 2M hydrochloric acid (2x), water (2x) and then dried. The solution was evaporated to dryness to leave a brown residue, shown by its ^{1}H n.m.r. spectrum to be starting material. In acetic acid under similar conditions the starting material was again recovered.

Nitration of thieno(3,4-b)pyridine (87) -

To (87) (1.5g, 5.6mmol) in acetic acid (15ml) was added concentrated nitric acid (0.4g, 6.3mmol) and the whole was heated at 50° for one hour. Tlc (chloroform and ethyl

acetate) of the solution showed base-line material and no precipitation occurred when a small quantity of the solution was poured into water. The excess of solvent was distilled off under vacuum to leave a dark brown residue which was washed with ether and dried, when it had m.p. >250°C (dec.). No suitable solvent for crystallisation could be found, but the i.r. spectrum of the material suggested the presence of a protonated pyridine system. Subsequent mass-spectroscopic analysis indicated the starting material to be the main component, and the reaction was abandoned.

4-Hydroxythieno(3,4-b)pyridine-2,3-dicarboxylic acid -

The thieno(3,4-b)pyridine (87) (10g) was heated with 4M sodium hydroxide (70ml) at 80° for three hours and the fluorescent (green) solution was cooled to room temperature and filtered. The ice-cold filtrate was acidified (concentrated hydrochloric acid) with stirring and the precipitate which formed was filtered off and dried; it had m.p. >300°C. No solvent system was found for crystallisation and so n.m.r. spectra could not be obtained. (Found: C, 44.2; H, 2.4; N, 6.1. Required for $C_9H_5NO_5S$; C, 45.2; H, 2.1; N, 5.9%). m/e = 475. ν_{max}: 2000-3200 (H-bonded OH), 1620,1680 (2x C=O)cm^{-1}.

Decarboxylation of 4-Hydroxythieno(3,4-b)pyridine-2,3-dicarboxylic acid -

(a) The foregoing di-acid (2.0g) was added to refluxing 1,2,4-trichlorobenzene and the mixture was heated for a further 30 minutes; no effervescence was observed. The cooled mixture was poured into ether (200ml), filtered and

the residue was washed with ether at the funnel, and dried. The i.r. spectrum of the solid was identical to that of the starting material.

(b) The procedure described in (a) was repeated, but 1,2,4-trichlorobenzene was replaced by diphenyl ether as solvent. Again only starting material was recovered.

(c) The di-acid (2.5g) was heated with a mixture of copper bronze (5.1g) in refluxing quinoline (50ml) for one hour, then cooled and filtered. The filtrate was distilled almost to dryness, cooled and diluted to 250ml with light petroleum. The precipitate was filtered off, washed with light petroleum at the funnel and dried; the solid effervesced with saturated aqueous sodium bicarbonate solution. The i.r. spectrum of the residue was identical to that of the di-acid starting material.

(d) The temperature af an intimate mixture of the di-acid (29) (2.1g) in ground-glass (4g) was increased slowly from 100 to 200°; no sign of decarboxylation was observed. After being heated above 230°, degradation of the material was observed, the gases evolved giving a positive test for hydrogen sulphide (lead acetate solution).

Anhydride of 4-hydroxythieno(3,4-b)pyridine-2,3-dicarboxylic acid -

4-Hydroxythieno(3,4-b)pyridine-2,3-dicarboxylic acid(1.3g) was heated with refluxing acetic anhydride (25ml) for 24 hours, and the excess of solvent was removed. The dark residue was taken into dry chloroform, the solution was treated with charcoal and evaporated to dryness. Tlc of the residue (ethyl acetate) indicated a fluorescent spot

(Rf 0.4, methanol) as well as base-line starting material. The residue was stirred with dry ether and the yellow filtrate was evaporated to dryness to give a small quantity of (30mg) of yellow powder, m.p. 120-128^{0}C. The n.m.r. spectrum of the product indicated that O-acetylation had occurred and the i.r. spectrum indicated the presence of an anhydride, both to very small extents. Micro-analysis of the product indicated starting material to be the main component and the reaction was abandoned.

Attempted reductive dechlorination of 4-chloro-2,3-bismethoxycarbonylthieno(3,4-b)pyridine (105) -

(a) Finely powdered activated zinc (3g, 48mmol) was added to the chlorothieno(3,4-b)pyridine (105) (1.5g, 5.3mmol) in glacial acetic acid (30ml) and the mixture was heated on a steam-bath for two hours. Tlc of the black mixture (in a range of solvents) showed it to contain many non-fluorescent components and the reaction was abandoned.

(b) The experiment was repeated as in (a) above, but instead of being heated, the mixture was left to stand at room temperature for two days; again a complex mixture formed and the reaction was abandoned.

Failed nucleophilic substitution reactions on 4-chloro-2,3-bismethoxycarbonylthieno(3,4-b)pyridine (105) -

(a) A solution of the chlorothieno(3,4-b)pyridine (105) (1.5g, 8.1mmol) and morpholine (2.0g, 23mmol) in chloroform (20ml) was boiled under reflux for three hours. Tlc (chloroform) indicated that no reaction had taken place and the solution was cooled, washed with 0.1M hydrochloric acid (3x20ml) and dried to give a brown residue, which was

shown to be the starting material by ^1H n.m.r.

(b) A solution of the chloro-compound (105) (2g) in morpholine (20ml) was heated on a steam-bath for two hours. Tlc (chloroform) indicated no reaction had occurred and the ^1H n.m.r. spectrum of the residue isolated after removal of the solvent under vacuum confirmed this.

(c) To a solution of sodium methoxide (22mmol, from sodium 0.5g) in dry methanol (50ml) was added methyl thioglycolate (2.75g, 26mmol). The solution was stirred for 10 minutes then the chloro-compound (105) (2.0g, 7mmol) was added and the solution was boiled under reflux for six hours. Tlc of the solution indicated that no reaction had occurred and the subsequent work-up (mixed m.p. and proton n.m.r. spectrum) confirmed only starting material (1.85g).

3.4. Attempted synthesis of thieno(3,4-b)pyridin-4(1H)-one 3-(2,2-Bisethoxycarbonylvinylamino)-4-methoxycarbonylthiophene (90) -

Methyl 4-aminothiophene-3-carboxylate (82) (4g,25mmol) and diethyl ethoxymethylenemalonate (6g, 28mmol) in toluene (20ml) was heated at 80°C for one hour. The solvent was removed and the residue was poured into light petroleum (50ml). The mixture was stirred for five minutes, filtered and the residue was crystallised from light petroleum/acetone to give the enamine as a white powder (4.6g, 55%), m.p. 111-113°C. (Found: C, 51.4; H, 5.2; N, 4.2. Required for $C_{14}H_{17}NO_6S$: C, 51.4; H, 5.2; N, 4.3%). δ ($CDCl_3$); 8.60(d, CH NH, J=13Hz), 8.02(d, H-2, J= 3Hz), 6.81(d, H-5,

J=3Hz), 4.25(multipl. OCH_2), 3.89(s, CO_2CH_3), 1.31(2xsuperimp. t. CH_2CH_3).

Attempted cyclisation of 3-(2,2-Bisethoxycarbonylvinylamino)-4-methoxycarbonylthiophene (90) -

(a) To the foregoing enamine (2g, 13mmol) in p-dioxane (15ml) was added Calcium hydride (1g, 42mmol). The mixture was stirred at room temperature for 20 minutes, poured into water (30ml), and then filtered. The dried residue was added to chloroform (30ml), the mixture was washed with dilute hydrochloric acid (to remove calcium hydroxide) and dried. The solvent was removed and the residue was identified as starting material by mixed m.p. with an authentic sample of the enamine.

(b) To the enamine (90) (2g, 13mmol) in ether (30ml) was added sodium hydride (2g, 84mmol). The mixture was stirred for one hour, washed with water (3x), and the ethereal solution was dried. Removal of the solvent gave a white residue (1.8g) whose mixed m.p. with an authentic sample of enamine (90) indicated only starting material to be present. Tlc of the aqueous extracts showed no organic material and the reaction was abandoned.

(c) To the enamine (90) (3g, 12mmol) in DMF (15ml) at 50^0 was added sodium hydride (1g, 42mmol) and the mixture was stirred for one hour. The solvent was evaporated under vacuum and the residue was poured into ether (30ml). The solution was washed with dilute hydrochloric acid (3x), and evaporated to dryness to leave a residue which, after crystallisation from light petroleum/acetone was identified as starting material.

(d) To a refluxing solution of sodium methoxide (0.22mol from sodium 0.5g) in methanol (100ml) was added the enamine (90) (7g, 0.03mol). The solution was boiled under reflux for eight hours, then poured into water (200ml) which contained glacial acetic acid (14g). A precipitate was filtered off, which was crystallised from methanol and identified as 4-(2,2-bisethoxycarbonylvinylamino)thiophene-3-carboxylic acid (94) (2.1g, 31%), m.p. 174-178°C (eff.) (Found: C, 49.6; H, 4.8; N, 4.3. Required for $C_{13}H_{15}NO_6S$: C, 49.8; H, 4.8; N, 4.5%). δ(DMSO); 8.10 (d, H-5, J=4Hz), 7.00 (d, H-7, J=4Hz), 3.82, 3.74 (s, 2xOCH_3). ν_{max}: 2500-3500cm^{-1} (H-bonded O-H). Tlc (methanol) of the filtrate indicated two components, one of which was fluorescent under u.v. light. Extraction of the solution with dichloromethane gave a mixture (400mg) of compounds, which contained the fluorescent material. Only a very small quantity of impure fluorescent solid (10mg) was isolated by column-chromatography (alumina) (elution with ethyl acetate). In view of the very low yield of product, the experiment was abandoned.

(e) The enamine (90) (5g) was heated in glacial acetic acid (10ml) at 80°. The excess of solvent was removed and the residue was poured into water (30ml). Extraction of the mixture with ether gave a quantity of white powder, showed to be starting material by m.p. and mixed m.p. with an authentic sample of the starting material.

(f) The experiment was repeated as in (e) but a mixture of concentrated sulphuric acid (1ml) and acetic acid (10ml) was used instead of glacial acetic acid. Tlc of the solut-

ion (chloroform) indicated mainly base-line material to be present, with a very weak fluorescent spot at Rf ~0.5. The impure fluorescent compound (20mg) was isolated by extraction with chloroform, but in view of the low return of material it was decided not to pursue the reaction.

(g) A solution of the enamine (0.2g) in ethereal hydrogen chloride (10ml) was left to stand at room temperature for one hour. Tlc of the solution indicated that no reaction had occurred. Similarly no reaction was observed on heating the solution upto 30°. Neutralisation with saturated aqueous sodium bicarbonate and evaporation of the organic layer returned starting material in almost quantitative yield.

3.5. 4-Hydroxy-3-methoxycarbonylthieno(3,4-b)pyridin-2(1H)-one (96) and its derivatives.

2-Methoxycarbonyl-N-(3-methoxycarbonyl-4-thienyl)acetamide (95) -

(i) From methyl 4-aminothiophene-3-carboxylate (82) and dimethyl malonate.

(a) The amine (82) (3g) and dimethyl malonate (50ml) were boiled under reflux for 30 minutes, when the unreacted ester was removed under vacuum. Tlc and ^{1}H n.m.r. of the residue indicated a complex mixture of products and the reaction was abandoned.

(b) The experiment was repeated as in (a) above, but the reaction was carried out at 70° for 10 minutes, instead of being boiled under reflux. No detectable reaction occurred (tlc); the cooled solution was washed with 2M hydrochloric acid (2x20ml), the aqueous solution was basified (4M sod-

ium hydroxide) and the free amine partially recovered, along with decomposition products by extraction into dichloromethane.

(c) The experiment was repeated as in (a), but the reaction mixture was heated at 90-100° for two hours, during which the solution darkened. The solvent was evaporated under vacuum to leave a dark tar from which the crude-product was isolated by trituation with cold methanol. Crystallisation from cyclohexane/acetone gave the amide as a white powder (0.15g, 3%), m.p. 88-89°C. (Found: C, 46.8; H, 4.4; N, 5.9. Required for $C_{10}H_{11}NO_5S$: C, 46.7; H, 4.3; N, 5.4%). δ($CDCl_3$); 8.01(s, H-1, H-3, superimp.), 3.89, 3.78(2xs, 2x$CO_2\underline{CH_3}$), 3.49(s,$\underline{CH_2}$). ν_{max}: 3250 (N-H), 1720, 1740 (ester C=O), 1670cm^{-1} (amido C=O).

(d) The amine-hydrochloride (81) (5g) was heated with pyridine (5ml) and dimethyl malonate for two hours at 90° with stirring. Tlc (methanol) indicated that reaction had occurred to some extent; the mixture was cooled and washed with 2M hydrochloric acid (2x). The excess of dimethyl malonate was evaporated under vacuum to leave a dark oil, which solidified overnight. It was crystallised from cyclohexane/acetone (charcoal) to give the amide as white needles (1.2g, 18%), m.p. 86-88°C.

(e) A mixture of the amine-hydrochloride (81) (4g), N,N-dimethylaniline (10ml) and dimethyl malonate (100ml) was boiled under reflux under an air condenser for six hours. The resulting dark red solution was distilled to dryness under vacuum and the residue was added to chloroform (50ml). The solution was washed with 2M hydrochloric acid

(2x20ml), water (2x) and dried. Evaporation of the solvent, and crystallisation of the residue from cyclohexane/ethanol gave the title amide, (0.2g, 4%), m.p. 86-88°C.

(f) Experiment (d) was repeated, but triethylamine was used as base instead of N,N-dimethylaniline, and the mixture was heated at 50° rather than being boiled under reflux. Low yields (<10%) of the malonamide were isolated.

(g) Experiment (e) was repeated, but the residue, obtained after evaporation under vacuum, in chloroform was not washed with acid, to inhibit hydrolysis of the amide linkage. The amide was isolated as a white powder (2.5g, 30%) m.p. 88-89°C after crystallisation from cyclohexane/ethanol.

(h) Reactions (a) to (g) were also performed in the dark, but this had little effect on the yield, and the degrees of degradation were similar in each case.

(ii) From methyl 4-aminothiophene-3-carboxylate (82) and 2-methoxycarbonylacetyl chloride.

2-Methoxycarbonylacetyl chloride -

To a refluxing solution of dimethyl malonate (100ml, 116g) in methanol (200ml) was added, with stirring, potassium hydroxide (20g) in the same solvent (250ml), over a 30 minute period. The solution was heated for a further 30 minutes then the methanol was removed. Ether (200ml) was added to the residue, the mixture was filtered, and the precipitate (30g) was washed with ether on the funnel, and sucked dry; Its ^1H n.m.r. spectrum ((DMSO), δ 3.72(s), 3.41(s)) indicated the major component (>90%) to be the required mono-potassium salt and no further purification

was applied. The mono-potassium salt was dissolved in the minimum quantity of water with stirring and the ice-cold solution was acidified with concentrated hydrochloric acid. The solution was extracted with ether, dried and the solvent was removed at room temperature to give 2-methoxy carbonylacetic acid (52g). To the acid (19g) in dichloromethane (50ml) was added thionyl chloride (45g). The solution was boiled under reflux for one hour, the solvent was removed, and the acid chloride was distilled as a colourless liquid, (55g, 46%, overall yield), b.p. 70°C/15mm Hg. δ($CDCl_3$) 4.20(s, CH_2), 4.17(s, CO_2CH_3). ν_{max} (liquid film) : 1750 (ester C=O), 1800cm^{-1} (C=O acid chloride), On attempted distillation at higher temperature (>100°C) the acid-chloride was found to degrade.

Reaction of 2-methoxycarbonylacetyl chloride with methyl 4-aminothiophene-3-carboxylate (82) -

(a) To the amino-ester (82) (5g, 32mmol) and triethylamine (5g, 50mmol) in chloroform (40ml) was added a solution of the foregoing acid chloride (5g, 37mmol) in chloroform (20ml) at room temperature. After being stirred for 20 minutes the solution was washed with water (3x), dried, and the solvent was removed to leave a yellow oil, which crystallised overnight. Re-crystallisation from light petroleum/acetone gave the amide, (2.1g, 26%), m.p. 87-88°C.

(b) Experiment (a) was repeated, but addition of the acid-chloride was performed at 0° instead of at room temperature. Higher yields of the amide were isolated (3.0g, 37%).

(c) Experiment (a) was repeated, but the amino-ester (82)

was dissolved in 1:1 triethylamine:chloroform (40ml) and addition of the acid-chloride in chloroform was performed at 0°C instead of at room temperature. Better yields of the title compound were obtained (5.0g, 62%).

4-Hydroxy-3-methoxycarbonylthieno(3,4-b)pyridin-2(1H)-one (96) -

To a refluxing solution of sodium methoxide (43mmol, from sodium 1.0g) in methanol (30ml) was added the foregoing amide (95) (5.2g, 20mmol), then the mixture was boiled under reflux for three hours, with stirring. The cooled mixture was poured into water (30ml) which contained glacial acetic acid (3g), then filtered. The residue was washed with water at the funnel and dried. The resulting dark brown powder was crystallised from acetone/methanol (charcoal) to give the pyridone as a brown powder (3.9g, 87%), m.p.>230°C. (Found:C, 46.4; H, 2.9; N, 6.0. Required for $C_9H_7NO_4S$: C, 48.0; H, 3.1; N, 6.2%). δ(DMSO); 8.25 (d, H-5, J=3Hz), 6.81 (d, H-7), J=3Hz), 3.80 (s, OCH_3). ν_{max}: 2500-3600 (H-bonded O-H, N-H), 1650cm^{-1} (ester, ring C=O).

4-Hydroxythieno(3,4-b)pyridin-2(1H)-one (97) -

(a) A solution of the foregoing ester (8.4g) in 4M sodium hydroxide (25ml) was left to stand at room temperature overnight. After neutralisation to pH 4 with concentrated hydrochloric acid (only a little effervescence was noted) the precipitate which formed was filtered off and dried. Tlc (methanol) of the residue showed two fluorescent spots, and its ^1H n.m.r. spectrum indicated approximately an equimolar ratio of starting material:product.

(b) A solution of the ester (96) (3g) in 4M sodium hydro-

xide was boiled under reflux for two hours, then cooled and filtered. The filtrate was acidified to pH 4 with concentrated hydrochloric acid; rapid effervescence took place. The pale brown precipitate was filtered off and dried. The solid gave a single fluorescent spot on tlc (methanol) and was crystallised from ethyl acetate to give the title pyridone (1.95g, 80%), m.p.> 200°C. (Found: C, 48.0; H, 2.9; N, 7.8. Required for $C_7H_5NO_2S$: C, 50.3; H, 3.0; N, 8.4%). δ(DMSO); 7.80 (d, H-5, J=5Hz), 6.75 (d, H-7, J=5Hz), 5.45 (s, H-3). ν_{max}: 2500-3500 (H-bonded O-H, N-H), 1650cm^{-1} (amido C=O).

2,4-Dichloro-3-methoxycarbonylthieno(3,4-b)pyridine (112)-

(a) A solution of the ester (96) (1g) in phosphoryl chloride (10ml) was boiled under reflux for three hours, then the excess of reagent was removed. The residue was poured into water (30ml) and, with stirring, the mixture was neutralised with saturated aqueous sodium carbonate. Attempted extraction of the product into chloroform gave an emulsion which did not separate. After filtration through Hyflo Supercell filter aid (B.D.H.), a two-layer system formed; the organic layer was washed with water (2x) and dried. A purple oil was isolated, but attempted purification by ordinary and then by flash-column chromatography (elution with dichloromethane), gave a high m.p. (140-160°C) complex mixture which did not fluoresce under u.v light on tlc (dichloromethane). The ^{1}H n.m.r. spectrum of the residue showed a high ratio in the number of aliphatic:aromatic protons, but its ^{13}C n.m.r. spectrum indicated, in part, retention of an aromatic system.

(b) Experiment (a) was repeated, but attempts were made to purify the crude product by bubble-distillation under vacuum instead of by chromatography. Again a complex mixture of high m.p. solids formed and the reaction was abandoned.

(c) Experiment (a) was repeated, but after removal of phosphoryl chloride the residue was poured into water and the mixture was neutralised with solid sodium carbonate. The mixture was evaporated to dryness at 30^0, and the residue was stirred with dichloromethane (75ml) for 10 minutes and then filtered. The organic layer was dried and evaporated to give a purple oil (300mg) which showed a single fluorescent spot under u.v. light. The compound was identified as 2,4-dichloro-3-methoxycarbonylthieno(3,4-b)-pyridine. (Found: C, 41.0; H, 2.5; N, 4.8. Required for $C_9H_5Cl_2NO_2S$:C, 41.2; H, 1.9; N, 5.3%). δ($CDCl_3$):7.93 (s, H-5, H-7), 4.00 (OCH_3).

(e) The ester (96) (2g) was heated in refluxing phosphoryl chloride (30ml) for four hours, then the solvent was removed at room temperature. The residue was added to dichloromethane/water (50ml/50ml) with stirring, the mixture was neutralised with solid sodium carbonate and then filtered through Hyflo Supercel filter-aid (B.D.H.). The organic layer was dried and a deep purple oil was isolated after removal of the solvent. The pure title compound was isolated by elution through a neutral silica column, the ^1H n.m.r. being identical to that above (1.7g, 74%).

2,4-Dimethoxy-3-methoxycarbonylthieno(3,4-b)pyridine (115) -

(a) To sodium methoxide (30mmol, from sodium 700mg) in methanol (30ml) was added a solution of 2,4-dichloro-3-methoxycarbonylthieno(3,4-b)pyridine (112) (3.5g, 13mmol) in the same solvent (10ml), the whole was left to stand at room temperature in the dark for one week and then poured into a solution of glacial acetic acid (2.0g) in water (50ml). The product was extracted into dichloromethane, washed with saturated aqueous sodium bicarbonate (2x), water (2x), then dried. Evaporation of the solvent at room temperature gave a purple oil from which the title dimethoxycompound (1.0g, 29%) was isolated by flash-chromatography (elution with dichloromethane). $\delta(CDCl_3)$: 8.00 (s, H-5), 7.60 (s, H-7), 4.05, 4.00, 3.94 (3xOCH_3). Attempts to isolate the by-products by chromatography were unsuccessful, and only insoluble complex mixtures of high melting-point solids were isolated, which did not fluoresce under u.v. light.

(b) To the di-chloro compound (112) (3.0g, 11mmol) in DMSO (10ml) was added 25% sodium methoxide in methanol (Aldrich 8g, 37mmol). The methanol was removed under vacuum, the mixture was left to stand at room temperature for 24 hours, and then poured into water (100ml) which contained glacial acetic acid (4g). The title dimethoxycompound was isolated as a purple oil (1.8g, 62%) by extraction into dichloromethane and was shown to be pure by ^1H n.m.r. and tlc. Attempts to prepare an analytical sample of the product by bubble-distillation and then by flash-chromato-

graphy (elution with dichloromethane) failed, and gave only decomposition products.

Attempted nucleophilic substituted reactions of 2,4-dichloro-3-methoxycarbonylthieno(3,4-b)pyridine (112)-

(a) Monomethoxydechlorination.

(i) To the di-chloro compound (112) (2.1g, 8mmol) in methanol (30ml) was added a solution of 25% sodium methoxide in methanol (Aldrich, 1.8g, 7mmol); the mixture was left to stand at room temperature in the dark for three days. Tlc (light petroleum) of the mixture showed two fluorescent spots, (corresponding to starting material and the dimethoxy comound (115) above) as well as non-fluorescent base-line material. Flash-chromatography (elution with light petroleum/ethyl acetate (20:1)) gave first the dimethoxycompound (0.55g, 28%) and then the starting material (0.6g). No mono-substituted product was isolated.

(ii) The experiment was repeated as in (i) above, but DMSO was used as solvent instead of methanol, and the solution was left for 24 hours in the dark. Again only a mixture of starting material and the dimethoxycompound (115) was recovered.

(b) Reaction with Morpholine

(b) A solution of the dichloro compound (112) (2.1g, 8mmol) and morpholine (2.1g, 24mmol) in chloroform (10ml) was left to stand at room temperature for three days. The purple mixture was filtered and the residue, after being washed with ether on the funnel and then dried was identified as morpholine hydrochloride. The chloroform layer was

washed with water (4x), dried and the volatile material was removed under vacuum. Tlc of the residue (range of solvents) indicated a complex mixture of components. Flash-chromatography (elution with a range of light petroleum/ethyl acetate (20:1-5:1) mixtures) gave a very small quantity of a purple oil, the ^1H n.m.r. spectrum of which indicated that substitution into the ring had occurred. Further purification proved to be long and difficult, so the reaction was abandoned.

(c) Reaction with thioglycolate.

Methyl thioglycolate (2.0g,19mmol) was added to a solution of sodium methoxide (38mmol, from sodium 0.9g) in methanol (25ml). The dichloro compound (112) (3.1g, 12mmol) in DMSO (20ml) was then added, the mixture was stirred at room temperature for three hours, then poured into ether (100ml) which contained glacial acetic acid (3ml). The precipitate (4.3g) was filtered off, washed with ether on the funnel and sucked dry. The residue (a brown powder, 4.3g) was stirred in water (50ml) for 10 minutes, filtered off, washed with water on the funnel, and then dried to give a solid (2.3g) m.p.>250^{0}C which was crystallised with difficulty from glacial acetic acid and whose tlc showed no fluorescent spot under u.v. light. The ^1H n.m.r. spectrum of the residue indicated it to contain a very low ratio in the number of aromatic:aliphatic protons, so the reaction was abandoned.

Attempted reductive dechlorination of 2,4-dichloro-3-methoxycarbonylthieno(3,4-b)pyridine (112) -

(a) A mixture of the dichloro compound (112) (0.5g) and

zinc (1g) in acetic acid (10ml) was heated at 50° for 20 minutes. Tlc (methanol) showed a non-fluorescent spot near the baseline and the mixture was poured into water (50ml). Extraction with dichloromethane failed to remove the products from the mixture, and gave only a small quantity of acetic acid. Neutralisation of the aqueous layer with 4M sodium hydroxide and subsequent extraction into chloroform gave a brown solution which exhibited a complex tlc (no fluorescence under u.v. light) in a variety of solvents; the reaction was abandoned.

(b) The experiment was repeated as in (a) above, but the mixture was left to stand at room temperature for two days. Although there was no evidence of the formation of sulphide ions (lead acetate paper), tlc revealed a complex mixture (which included one weak fluorescent spot); the reaction was abandoned.

(b) A mixture of the dichloro compound (112) (800mg) and activated zinc[105] (1.0g) in acetic acid (10 ml) was left to stand at room temperature for one day. The mixture changed colour from purple to brown, and a smell of hydrogen sulphide was noted. Tlc (variety of solvents) showed no fluorescent spot and the reaction was abandoned.

2,4-Dichlorothieno(3,4-b)pyridine (113) -

A mixture of 4-hydroxythieno(3,4-b)pyridin-4(1H)-one (97) (1.5g) and phosphoryl chloride was boiled under reflux for 3.5 hours. The excess of reagent was removed, and the residue was added to dichloromethane (50ml)/water (50ml). With stirring, the mixture was neutralised with solid sodium carbonate, washed with water (4x), then filtered

through Hyflo Supercell filter aid (B.D.H.). Evaporation of the dried organic layer at room temperature gave a purple oil, which exhibited a single fluorescent spot and some base-line material on tlc (chloroform). Flash-chromatography (elution with dichloromethane) gave the pure di-chlorocompound, (0.5g, 28%) as a purple oil. Found: C, 41.7; H, 1.9; N, 6.8. Required for $C_7H_3Cl_2NS$: C, 41.2%; H, 1.9%; N, 6.8%. $\delta(CDCl_3)$ 7.80 (s, H-5, H-7), 6.95(s, H-3). Attempted bubble-distillation (<100°C/0.1mmHg) gave a complex mixture of high melting-point solids whose ^1H n.m.r. spectrum revealed a total absence of aromatic protons, but ^{13}C n.m.r. indicated some aromatic character. After two weeks at room temperature the pure title compound had degraded to a complex mixture of high m.p. (120-130°C) solids.

2,4-Dimethoxythieno(3,4-b)pyridine (118) -

The dichloro compound (113) (3.2g, 11mmol) and 25% sodium methoxide/methanol solution (Aldrich; 5.0g, 31mmol) in DMSO (10ml) was left to stand at room temperature in the dark for 24 hours. The brown mixture was poured into water (30ml), and the product was extracted with dichloromethane. The solvent was removed at room temperature to leave a purple oil which exhibited a single fluorescent spot on tlc (chloroform) and a small quantity of base-line material. The pure dimethoxycompound (2.0g, 65%) was isolated by flash-chromatography (elution with dichloromethane). The product was unstable, and had decomposed after three days at room temperature, or when bubble-distillation was attempted. $\delta(CDCl_3)$: 7.75 (d, H-5, J=4Hz),

7.49 (d, H-7, J=4Hz), 5.81 (s, H-3), 3.90, 4.00 (OCH_3).

Monomethoxydechorination of (113) -

The dichloro compound (113) (3.5g, 11.5mmol) and a 25% solution of sodium methoxide/methanol (Aldrich; 2.4g, 11.5mmol) in DMSO (10ml) was left to stand at room temperature in the dark overnight. The dark solution was poured into water (50ml) and the whole was extracted with dichloromethane. From the dried organic layer was isolated a purple oil which showed a single fluorescent spot on tlc (chloroform). The ^1H n.m.r. spectrum of the product showed two methoxy peaks of equal intensity and a complex aromatic region. The product was subjected to flash-chromatography. Elution with dichloromethane gave 4-chloro-2-methoxythieno-(3,4-b)pyridine (116) as a purple oil (0.9g, 27%). $\delta(CDCl_3)$: 7.72 (d, H-5, J=4Hz), 7.53 (d, H-7, J=4Hz), 6.60 (s, H-3), 3.91 (s,OCH_3). 2-chloro-4-methoxythieno(3,4-b)pyridine (117) was then isolated as a purple oil (1.0g, 30%) by elution with ethyl acetate. $\delta(CDCl_3)$: 7.89 (d, H-5,J=3Hz), 8.73 (d, H-7, J=3Hz), 6.65 (s, H-3), 3.95 (s, OCH_3).

Each of the mono- and di- substituted methoxy derivatives of (112) and (113) were less stable than their dichloro precursors. Attempted nucleophilic substitution reactions of the 2,4- dichlorothieno(3,4-b)pyridine (113) with morpholine and with the thioglycolate anion were run in parallel with those for (112), already described. Again, complex mixtures resulted, and ^1H n.m.r. provided evidence that reaction had occurred, but the small amounts of individual products present and the difficulties in

separation made further work impractical.

Attempted reductive dechlorinations of 2,4-dichlorothieno-(3,4-b)pyridine (113) -

(a) A mixture of the dichloro compound (113) (500mg) and zinc (900mg) in acetic acid (10ml) was allowed to stand at room temperature overnight, during which the colour had changed from purple to dark brown. Tlc of the solution indicated a complex mixture and lead acetate paper indicated sulphide ions to be present, so the reaction was abandoned.

(b) The experiment was repeated as in (a) above, but the reaction was carried out at 0^{o}. Tlc of the solution showed a weak fluorescent spot corresponding to starting material, and the mixture was poured into water (50ml). The mixture was filtered and the filtrate was neutralised with 4M sodium hydroxide under ice-cold conditions. A small quantity of organic material was extracted into dichloromethane and was identified as starting material (~100mg) from its ^{1}H n.m.r. spectrum; the reaction was abandoned.

Nitration of 4-hydroxy-3-methoxycarbonylthieno(3,4-b)-pyridin-2(1H)-one (96)

To a hot solution of (96) (0.91g, 4mmol) in glacial acetic acid (20ml) was added, with stirring, concentrated nitric acid (0.5g, 5.6mmol). After being stirred at 70^{o} for 30 minutes the brown solution was poured into ice (30g) and water (50ml) was added. Very little precipitation occurred, but the product was extracted into ethyl acetate to give an orange organic layer. The dried solution was evaporated, and the residue was washed in cold ether and dried

to leave a pale brown powder (0.67g). Although the i.r. spectrum indicated the formation of a salt, subsequent n.m.r. and micro-analyses indicated the main component to be starting material and the reaction was abandoned.

Attempted acetylation of (96)-

A solution of the di-oxygenated compound (96) (0.9g) in acetic anhydride (20ml) was boiled under reflux for one hour. The solvent was removed, the residue was poured into water (80ml) which contained 4M hydrochloric acid (2ml) and the solution was washed with dichloromethane (4x). The organic layer was dried and the solvent was evaporated to leave a dark tar. Tlc (variety of solvents) indicated a complex mixture, which did not not fluoresce under u.v. light. The ^{1}H n.m.r. spectrum of the tar showed vitually no aromatic protons to be present and the reaction was abandoned.

Attempted methylations of (96) and (97)-

(a) A mixture of 4-hydroxy-3-methoxycarbonylthieno(3,4-b)-pyridin-2(1H)one (96) (1.2g,5.3mmol), potassium carbonate (1.0g, 7.2mmol) and dimethyl sulphate (2.0g, 16mmol) in butanone (30ml) was stirred overnight at room temperature. The brown mixture was evaporated to one-quarter of its original volume, and then poured into water (25ml). Tlc of the residue obtained by extraction into ethyl acetate indicated a complex mixture (no fluorescence) and its ^{1}H n.m.r. spectrum showed absence of aromatic protons; the reaction was abandoned.

(b) The reaction was repeated as in (i) above, but an equimolar ratio of dimethyl sulphate (700mg) was used.

Again a complex mixture was formed, whose tlc exhibited a weak fluorescent spot of identical Rf to starting material. The reaction was abandoned.

(c) Reactions (a) and (b) were applied to 4-hydroxy-thieno(3,4-b)pyridin-2(1H)-one (97). Again only complex mixtures were isolated and the reactions were abandoned.

7-Bromo-4-hydroxy-3-methoxycarbonylthieno(3,4-b)pyridin-2-(1H)-one (119) -

To a hot solution of 4-hydroxy-3-methoxycarbonylthieno(3,4-b)pyridin-2(1H)-one (96) (2.1g, 9mmol) and sodium acetate (1.0g, 12 mmol) in acetic acid (25ml) was added bromine (1.6g, 10mmol) in acetic acid (10ml). After 10 minutes the solution was cooled, poured into water (100ml) and the mixture was filtered. Crystallisation of the dried residue from ethanol gave the title bromocompound as a brown powder (0.9g, 32%), m.p. 246°C (dec.). (Found: C, 35.4; H, 2.1; N, 3.8. Required for $C_9H_6BrNO_4S$: C, 35.5; H, 2.0; N, 4.6%). δ(DMSO): 8.60 (s, H-5), 4.03 (s, OCH_3).

7-Bromo-4-hydroxythieno(3,4-b)pyridin-2(1H)-one (120)-

A solution of the foregoing bromo ester (119) (2g) in 4M sodium hydroxide (50ml) was boiled under reflux for one hour, then cooled and neutralised with 2M hydrochloric acid. The title bromocompound (0.90g, 56%), m.p.>200°C was filtered off, washed with cold water on the funnel and crystallised (with difficulty) from methanol/acetone. (Found: C, 37.8; H, 2.0; N, 6.1. Required for $C_7H_4BrNO_2S$: C, 34.2; H, 1.6; N, 5.7%). δ(DMSO): 8.10 (s, H-5), 5.65 (s, H-3).

3.6. Reaction of methyl 4-aminothiophene-3-carboxylate (82) with acetaldehyde -

A solution of the free amine (82) (4.0g, 25mmol), glacial acetic acid (four drops) and acetaldehyde (2.0g, 43mmol) in dichloromethane (30ml) was left to stand overnight at room temperature. Tlc of the solution (dichloromethane) indicated that no reaction had occurred and ethanol (40ml) was added. The dichloromethane was evaporated and acetaldehyde was bubbled through the refluxing ethanolic solution for 10 minutes. On cooling in an ice-bath, colourless crystals formed; these were filtered off and crystallised from ethanol to give the Tröger's base analogue (100), (0.25g, 3%), m.p. 150-52°C. Found: C, 55.1; H, 5.2; N, 7.2. Required for $C_{18}H_{20}N_2O_4S_2$, C, 55.1; H, 5.1; N, 7.1%. δ($CDCl_3$): 8.00 (s in=2 J=3Hz), 4.60(q, J=7Hz, int=3), 3.91(s,int=6), 1.4-1.9 (multi, int=10).

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PART 2.

KINETIC STUDIES OF THE

AROMATIC NUCLEOPHILIC SUBSTITUTION REACTIONS

OF SOME CHLORO- QUINOLINE AND THIENO(b)PYRIDINE COMPOUNDS.

CHAPTER 1

INTRODUCTION

Introduction.

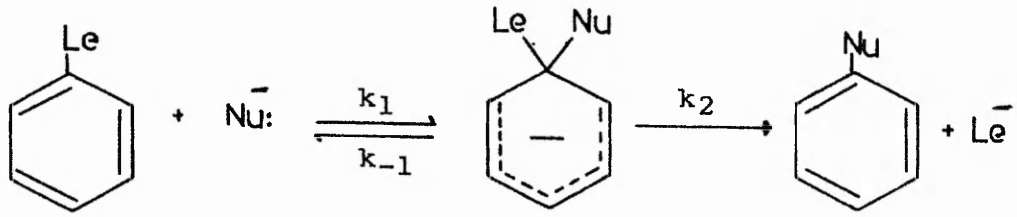
Although nucleophilic aromatic substitution reactions were recognised as early as 1854[1], detailed kinetic studies were not reported until almost 100 years later[2,3]. The nucleophilic displacements in various activated (i.e. electron-deficient) ring systems such as nitrobenzene, pyridine and quinoline compounds were initially studied. These reactions are now well-understood and have been the subject of excellent reviews by Bunnett[4], Illuminati[5] and Shepherd[6]. Kinetic studies of nucleophilic aromatic substitution reactions of other systems, for example benzothiazole[7], s-triazine[8], thiophene[9], furan[10], and benzo(b)-thiophene[11] involving a wide range of attacking groups and reaction conditions have since been reported and have been the subject of a number of reviews[2,12].

1.1.1. The Mechanisms of Nucleophilic Displacement.

Three different ionic mechanisms[13] have been observed in aromatic nucleophilic substitution reactions. The first is a rare unimolecular (S_N1) process, which has been observed only in the thermal decomposition of diazonium salts[14]. The second is an elimination-addition mechanism[15] which proceeds *via* a highly reactive aryne (for example benzyne) intermediate. Although well-established this mechanism has been observed mainly in the nucleophilic substitution reactions of non-activated substrates (typically with various aniline compounds) with strong bases, such as sodamide. The third and by far the most common mechanism is the bimolecular process (S_N2) which will now be discussed in some detail.

1.1.2. The Bimolecular Mechanism.

The majority of aromatic nucleophilic substitution reactions of "activated" systems are found to follow second-order kinetics overall[16], being first order with respect to each reactant. The reactions are formally similar to those which occur at a saturated carbon atom (i.e. S_N2 mechanism) but differ substantially in that nucleophilic attack takes place at an unsaturated aromatic carbon atom, with aromatic substitution. The most widely accepted mechanism[17] for nucleophilic aromatic substitution, is illustrated in Scheme 1;



1

Le = leaving group, Nu = nucleophile

Scheme 1

This involves a change from sp^2 to sp^3 hybridisation of the attacked carbon atom. The essential difference between this mechanism (sometimes referred to as S_NAr) and that of S_N2, (i.e. at an aliphatic carbon atom) is that system 1 is now not a transition state, but an intermediate charge-transfer (or Meisenheimer[18]) complex of finite stability. It is indeed now widely accepted that Meisenheimer complex formation can play an important role in the mechanism of nucleophilic aromatic substitution reactions. Such complexes, which form brightly coloured solutions, have been studied extensively during the last 20 years and have been

the subject of a number of reviews[19]. The reaction co-ordinate diagram[20] for the S_NAr mechanism involving this intermediate contains two maxima (transition states) separated by a minimum (Meisenheimer complex). In contrast, the reaction co-ordinate for the S_N2 mechanism contains only one maximum. The rate determining-step in the S_NAr mechanism (and hence the observed reaction) is determined by the stability of the Meisenheimer complex. If this has a long life-time (i.e. $k_1 >> k_2$) (Scheme 1) the rate of reaction would depend on the equilibrium concentration of the intermediate complex. If $k_2 >> k_1$ (i.e. the complex behaves like a transition state) then a bimolecular rate-determining step would ensue and simple second-order kinetics would be observed. The life-time of the Meisenheimer intermediate 1 is dependent on the reaction conditions employed. The nature of the substrate, attacking group, and leaving group and the temperature and solvent used each play important roles. Specific conditions can be established to favour either the "normal" S_N2 process or the more complicated mechanism involving the equilibrium concentration of the Meisenheimer complex.

1.2. Kinetic Studies In The Quinoline Compounds.

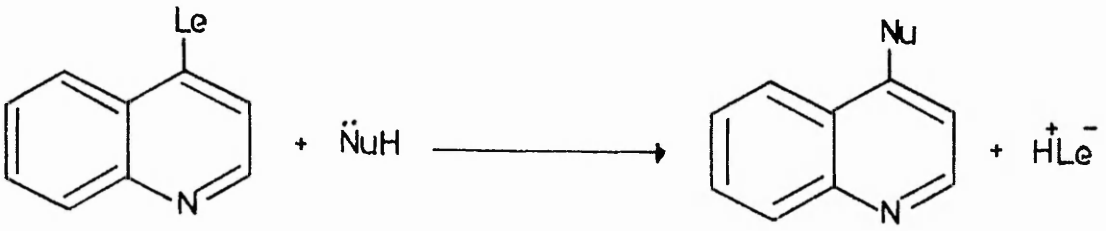
1.2.1. Factors which affect the rates of nucleophilic displacement.

The nucleophilic substitution reactions of many quinoline compounds have been studied and an excellent review has been written by Illuminati[5]. The electron-withdrawing inductive and mesomeric effects of the aza-function in quinoline activate the C-2 and C-4 positions

towards nucleophilic attack. However, presence of the aza-function can lead to complications in these reactions. The basic nitrogen atom, if protonated, is responsible for the occurrence of acid-catalysis[21], which has a pronounced effect on the observed rate-constants. Generally[22], the rates of nucleophilic substitution are dependent on the pKa of the solvent and the ring-substituents in the quinoline ring, which affect the pKa of the quinoline substrate. These factors and others which affect rates of nucleophilic substitution are detailed below.

1.2.1. (a) The attacking group[5,23].

Both the anionic (for example alkoxide[21(c),24] and arene thiolate[22(b,c),25]) and the neutral (amines[21(a),22(a)] piperidine[21(c),26] nucleophilic attack on quinoline compounds have been studied. Generally, with anionic nucleophiles, normal second-order kinetics have been observed. In some cases, a large excess of alkoxide anions[27] has been used to create pseudo first-order conditions. Reactions with uncharged species have often been studied under pseudo first-order conditions since many of these reagents also act as suitable solvents for the reaction. Reaction with amines[21(a)] have often been investigated in alcohols and have been found to follow second order kinetics. Generally however, reactions with uncharged species are more complicated than those with anions. Initial reaction usually results in the formation of a proton (Scheme 2) which can then combine with either the solvent or the aza-function of the quinoline ring.



Scheme 2

If protonation of the aza-function occurs, the strongly electron-attracting $=NH^+$ function is formed which has a pronounced effect on the reaction rates, and autocatalysis may result[21]. The results observed are then similar to those for attack on a system containing a quaternised nitrogen group. Hence relative base strengths and concentrations of substrate and reagent play a major role during the reaction.

1.2.1. (b) The leaving group[5,28].

The halide ions are by far the most studied leaving-group in reactions of the quinoline series. Numerous substrates have been studied and chloride, bromide and iodide are usually displaced at rates differing only by one order of magnitude from each other. The most frequent order of ease of replacement in the halogenoquinolines is Br>Cl>I[29] Fluorine is a much better leaving group than the other halogens, its ease of replacement being similar to a nitro group. Since the work carried out by the author involved study of the displacement of chloride ions only, leaving group effects will not be discussed in detail here.

1.2.1. (c) The solvent effects[30].

The type of solvent employed plays a very important role

in determining the rates of the nucleophilic substitution reactions. The degree of solvation of the substrate and of the nucleophile are particularly important since these determine the readiness with which the two can approach each other. Miller[31] has shown that the nucleophilicity of anionic reagents changes drastically depending on whether the solvent is able to hydrogen-bond with the reagent (hydroxylic solvents) or not (dipolar aprotic solvents). The fluoride ion acts as a strong nucleophile (can displace chloride ion) in a non-hydroxylic solvent, but can easily be replaced in the substrate in hydroxylic solvents. Also, the stability of the intermediate Meisenheimer complex is very dependent on the solvent employed. Dimethyl sulphoxide (DMSO) tends to be a good solvent for stabilising ionic species and Meisenheimer complexes have been studied in this solvent[32]. Dipolar,aprotic solvents[33] (e.g. acetonitrile N,N-dimethylformamide, acetone) tend to accelerate the rates of nucleophilic displacement substantially. DMSO is found to be easily the most effective solvent for reaction of this type and it increases the rates of ionic reactions, in general, by a great degree, compared to other solvents.

1.2.2. Rate Constants and Activation Parameters in the methoxydechlorination reactions of 2-chloroquinoline and 4-chloroquinoline.

The activation parameters for the nucleophilic substitution reactions of various 2- and 4-chloroquinoline compounds were determined by Illuminati[24]. In all cases, the reactions were found to be second-order and proceeded

smoothly to completion. The values given below relate to the methoxydechlorination reactions of 2- and 4- chloroquinoline only, along with a comparison of rates at specific temperatures are given in Table 1 below.

Table 1.

Kinetic data[24] for the methoxydechlorination reactions of 2-chloroquinoline and 4-chloroquinoline in methanol.

	10^4k,/l.mol^{-1}sec^{-1} at various temperatures,/°C			Ea	$\Delta H^{\ddagger}$	$-\Delta S^{\ddagger}$
	75.2	86.5	99.5	/kJ mol^{-1}		/Jmol^{-1}K^{-1}
2-chloroquinoline	2.22	6.76	19.38	101.3	100.0	29.3
4-chloroquinoline	2.47	6.31	17.81	88.7	84.9	72.0

In the reactions above Illuminati observed a simple one-stage bimolecular mechanism and no evidence was found for the intervention of stable intermediates. The reactions proceeded to completion and there was no sign of any products other than the desired monomethoxy compounds. Similar results were found for the ethoxydechlorination[21(c)] and piperidinodechlorination[26] reactions of 2- and 4-chloroquinoline. The reactions were studied either by of loss of nucleophile or by formation of chloride ion with respect to time.

1.3. The thieno(b)pyridines

Although the chemistry of the 2,3-fused thieno(b)-pyridines is well-understood, only the electrophilic substitution reactions[35] of the parent heterocycles have been studied quantitatively. The nucleophilic aromatic substit-

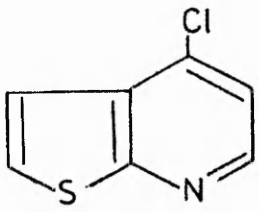
ution reactions of various α- and γ-chlorothieno(2,3-b)- and -(3,2-b)pyridine compounds with various nucleophiles has already been discussed (see P. 24). In contrast to the quinoline series (where the α- and γ-chlorine atoms are both easily displaced by nucleophiles) the α-chlorine atom is much more difficult to replace than the γ-chlorine atom in the thieno(b)pyridines series.Competitive experiments[35] indicate that the ease of nucleophilic displacement of γ-chlorine atoms in the 2,3-fused thieno(b)pyridines and the quinoline isosteres is 4-chloroquinoline > 4-chlorothieno(2,3-b)pyridine > 7-chlorothieno(3,2-b)pyridine.

CHAPTER 2

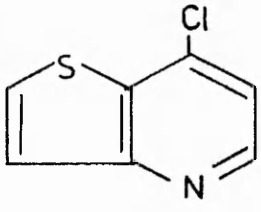
DISCUSSION

2.1. Objectives and Preliminary Work.

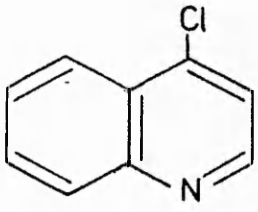
The object of the present work was to find a common, mild set of conditions which could be applied to determine the rate constants for the nucleophilic displacements of the chlorine atoms in compounds (1) -(7). A comparison of the rate constants within the series could then be made.



(1)



(2)



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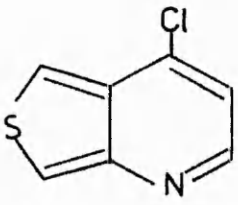

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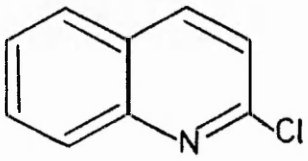
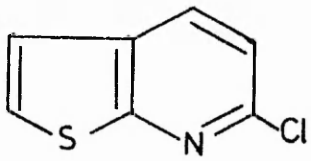
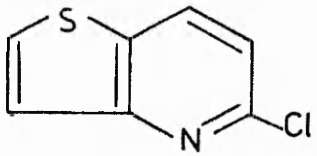


(5)



(6)



(7)

In view of the unstable nature of 4-chlorothieno(3,4-b)-pyridine (4) (P. 65), particular emphasis was placed on selecting a nucleophile and solvent which would allow the reactions to be studied under milder conditions to those used by Illuminati (Table 1).

2.1. (a) Nucleophile

It has been mentioned that neutral nucleophiles such as morpholine and thiols complicate halogen displacements in quinoline compounds, leading to auto-catalysis. The work by Illuminati described previously has shown that the methoxy-dechlorination reactions of chloroquinoline compounds are free from such complexities. It was decided therefore to use

methoxide ion as the nucleophile exclusively in this work.

2.1. (b) Solvent

The ten pi-electrons in the thieno(b)pyridine ring are delocalised over nine ring atoms whereas they are delocalised over ten ring atoms in the quinoline ring. In view of this, the pi-electron density in the pyridine ring is greater in the thieno(b)pyridine compounds and so displacement of the chlorine atoms in this series would be expected to be more difficult than in the quinoline analogues. Clearly, methanol could not be employed as solvent alone, since the temperatures required to observe convenient rate-constants would be even higher than those used by Illuminati (Table 1). The presence of DMSO in solution is known to increase the rates of nucleophilic substitution reactions very considerably and initial studies were performed in this solvent alone. Soon after mixing the reagent solutions together, an intense yellow colour formed which disappeared after approximately 20 minutes, the time taken depending on the temperature. It is highly likely that stable Meisenheimer complexes were being formed under these conditions so that "normal" second-order kinetics were not obeyed. No further work was performed in DMSO alone. Preliminary studies of the nucleophilic substitution reactions of compounds (1), (2) and (5) in 1:1(v/v) DMSO:methanol gave encouraging results (i.e. close to a "normal" second-order reaction) and this system was formally adopted. Although the reactions were too slow to be studied at room temperature, convenient rate-constants could be determined in the temperature range 39-54^{o}C.

2.2 Results

The possibility of side-reactions competing with the true nucleophilic displacement reactions was considered. Tlc of the solutions at infinity readings gave no indication of the formation of by-products. The compounds (1), (2), (3) and (5) were each boiled with a great excess of methoxide in methanol for prolonged periods. In each case, the methoxy compounds were isolated in high yields without any sign of the formation of any by-products. It was assumed that the reactions followed "normal" bimolecular second-order processes, as already described.For reactions of this type, where the initial concentrations of starting materials are not identical, the integrated rate-equation has the form;

$$kt = \frac{1}{(a-b)} \; LN\left[\frac{b(a-x)}{a(b-x)}\right] = X$$

where k, t, and x have their usual meanings.

In the series of reactions studied here;

a = [NaOMe] at time, t=0

b = [R-Cl] at time, t=0

The results were interpreted by computer programs written by the author. For interpretations of individual runs and listings of the programs used, see appendices 1 and 3. Table 2 gives the observed rate-constants for the individual runs for compounds (1), (2), (3), (5), (6) and (7) in 1:1(v/v) DMSO:methanol. 4-Chlorothieno(3,4-b)pyridine (4) was found to be too unstable to obtain any results.

Table 2: Observed rate constants in the aromatic nucleophilic substitution reaction of compounds (1) - (7).

Substrate	Temperature, /^{o}C	$10^{5}k$, /mol^{-1}dm^{3}sec^{-1}	S.D.
1	39.3	14.1	0.2
1	45.3	30.4	1.1
1	53.0	80.4	2.9
1	53.2	83.3	2.4
2	39.5	8.6	0.2
2	46.5	18.7	0.3
2	47.8	17.6	0.9
2	53.0	42.1	1.5
2	54.0	41.4	1.5
3	39.5	15.1	0.5
3	46.9	31.0	0.6
3	47.8	32.4	0.9
3	53.0	106	1.6
3	54.0	127	1.5
5	46.2	31.3	0.5
5	53.5	55.8	1.5
6	46.2	2.3	0.04
6	53.5	5.9	0.2
7	46.2	1.5	0.07

where "S.D." gives the calculated standard deviation of the best-line fit (least squares method) rate-constant.

Using the equations given in Appendix 2, the activation parameters for some of these reactions were calculated. The results are shown in Table 3.

Table 3

Activation Parameters Calculated From Kinetic Results.

4-Chlorothieno(2,3-b)pyridine (1)

Run	1.	2.	3.	4.
T/^{o}C	39.3	45.3	53.0	53.2
10^{5}k,/mol^{-1}dm^{3}sec^{-1}	14.1	30.4	80.4	83.3

Runs	Ea /kJ mol^{-1}	$\Delta H^{\ddagger}$ /kJ mol^{-1}	$\Delta G^{\ddagger}$ /kJ mol^{-1}	$\Delta S^{\ddagger}$ /J mol^{-1} K^{-1}	S.D. Ea	S.D. $\Delta S^{\ddagger}$
1-2	106.0	103.3	99.7	+11.6	5.4	17.0
1-3	107.7	105.0	99.6	+16.9	2.4	7.5
1-4	108.4	105.7	99.6	+19.1	2.0	6.1
2-3	109.1	106.4	99.6	+21.3	5.7	17.8
2-4	110.3	107.6	99.5	+25.0	5.1	15.7

7-Chlorothieno(3,2-b)pyridine (2)

Run	1.	2.	3.	4.
T/^{o}C	39.5	46.5	53.0	54.0
10^{5}k,/mol-1dm^{3}sec-1	8.6	18.7	42.1	41.4

Runs	Ea /kJ mol^{-1}	$\Delta H^{\ddagger}$ /kJ mol^{-1}	$\Delta G^{\ddagger}$ /kJ mol^{-1}	$\Delta S^{\ddagger}$ /J mol^{-1} K^{-1}	S.D. Ea	S.D. $\Delta S^{\ddagger}$
1-2	92.2	89.6	101.2	-36.6	3.4	10.6
1-3	99.8	97.1	101.2	-12.7	2.7	8.4
1-4	92.1	89.5	101.4	-37.0	2.5	7.9
2-3	108.2	105.6	101.3	-13.3	5.2	16.1
2-4	92.2	89.5	101.5	-37.0	4.6	14.2

4-Chloroquinoline (3)

Run	1.	2.	3.	4.
T/^{o}C	39.5	46.9	53.0	54.0
10^{5}k/ mol-1dm^{3}sec-1	15.1	31.0	106	127

Runs	Ea	$\Delta H^{\#}$	$\Delta G^{\#}$	$\Delta S^{\#}$	S.D.	
	/kJ mol^{-1}	/kJ mol^{-1}	/kJ mol^{-1}	/J mol^{-1} K^{-1}	Ea	$\Delta S^{\#}$
1-2	80.9	78.3	99.8	-68.2	4.3	13.6
1-3	122.4	119.8	99.2	+64.4	2.3	7.2
1-4	125.0	122.3	99.1	+72.4	2.0	6.1
2-3	175.0	172.3	99.4	+225.5	5.7	17.8
2-4	173.0	170.3	99.3	+219.2	5.1	15.7

6-Chlorothieno(2,3-b)pyridine (6)

Run	1.	2.
T/^{o}C	46.2	53.5
10^{5}k,/mol-1dm^{3}sec-1	2.3	5.9

Runs	Ea	$\Delta H^{\#}$	$\Delta G^{\#}$	$\Delta S^{\#}$	S.D.	
	/kJ mol^{-1}	/kJ mol^{-1}	/kJ mol^{-1}	/J mol^{-1} K^{-1}	Ea	$\Delta S^{\#}$
1-2	112.0	109.3	106.8	+7.8	4.5	14.0

2-Chloroquinoline (5)

Run	1.	2.
T/^{o}C	46.2	53.5
10^{5}k,/mol^{-1}dm^{3}sec^{-1}	31.3	55.8

Runs	Ea	$\Delta H^{\ddagger}$	$\Delta G^{\ddagger}$	$\Delta S^{\ddagger}$	S.D.	
	/kJ mol^{-1}	/kJ mol^{-1}	/kJ mol^{-1}	/J mol^{-1} K^{-1}	Ea	$\Delta S^{\ddagger}$
1-2	68.7	66.0	100.2	-105.9	3.7	11.5

2.3. Conclusions

2.3.1. Comparison of rate constants.

At each of the temperatures studied the relative rates of displacements of the γ-chlorine atoms are in the order;

4-chloroquinoline > 4-chlorothieno(2,3-b)pyridine > 7-chlorothieno(3,2-b)pyridine.

These results are in agreement with the semi-quantitative observations by Barker[35], mentioned earlier. This order in ease of displacement can be explained in electronic terms and has been dealt with (see P. 27). The observed rate constants for the displacements of the α-chlorine atoms in the thieno(b)pyridines compounds (6) and (7) are much lower than those observed for their γ-chloro isomers (2) and (3). This reduced reactivity of the α-position towards nucleophilic attack has been qualitatively observed by Barker[35,39], but has not been explained.

The rate-constants for the displacements of the chlorine atoms in 2-chloroquinoline and 4-chloroquinoline were very similar; such observations were made by Illuminati[24(b)], who used methanol as solvent.

2.3.2. Comparison of activation parameters.

(i) The Activation Energy.

The calculated activation energies in the nucleophilic substitution reactions of 2-chloro- and 4-chloroquinoline in 1:1 DMSO:methanol in the range 39-45°C are of the expected order, i.e. about 80kJmol^{-1} as observed by Illuminati (Table 1) for the same reactions in methanol. Unfortunately, above 45°, although good second-order plots were attained, the value of the activation energy in the 4-chloroquinoline case in the present work was erroneous and the necessary data were not collated for the nucleophilic displacement in 2-chloroquinoline. In contrast, the activation energies in the nucleophilic substitution reactions of the γ-chlorothieno(2,3-b)- and -(3,2-b)-pyridine compounds (2) and (3) were good between the temperature range of 39-54°C. The values, as expected were higher than those observed in the quinoline analogues. These results represent the first citing of activation parameters in the nucleophilic displacement of chlorine in thieno(b)pyridines. The activation energy calculated for nucleophilic displacement of the α-Cl atom in the thieno-(b)pyridine compound (6) is, within experimental error approximately equal to the values obtained in the displacement of the γ-chlorine atom in compound (2). This is surprising, since under identical conditions the γ-chlorine atom is replaced almost 15 times faster than the α-chlorine atom.

(ii) Entropy.

In the nucleophilic displacement reactions generally, the entropy of activation would be expected to be negative, since formation of the charged Meisenheimer intermediate would increase the order of the solvent "cage" surrounding it. Indeed the observed entropies of activation in the quinoline compounds are negative, and again except at higher temperatures, are of the same order as those observed by Illuminati (Table 1) with methanol as solvent. However, the observed entropies of activation in most of the reactions of the thieno(b)pyridines are close to zero or maybe even positive. This suggests that the entropy increases as the Meisenheimer intermediate is formed, an observation which is not readily explained. However, a more extensive investigation may clarify this.

2.3.3. Summary.

A convenient set of conditions has been established which allow the nucleophilic displacement of chlorine at C-2 and at C-4 in quinoline and at the comparable positions in the 2,3-fused thieno(b)pyridine (compounds (1) to (7)) to be studied. The reactions were observed to be second-order. The rate-constants obtained were generally reproducible. Calculations were performed to determine the activation parameters for these reactions, and in most cases, acceptable results were found. Future work would involve a more accurate determination of the rate-constants, to allow more accurate values for the activation parameters to be evaluated.

CHAPTER 3

EXPERIMENTAL

3.1. Preparation Of The Solvents.

Dry methanol was prepared by stirring a suspension of sodium hydride in pure methanol (Aldrich) for 24 hours and collecting the median fraction on distillation. Dry DMSO was prepared by standing pure DMSO (Aldrich) over molecular sieves for 48 hours and collecting the median fraction on distillation under vacuum. The solvent for the runs was prepared by thoroughly mixing freshly prepared dry methanol (1ℓ) and dry DMSO (1ℓ) and allowing the solution to stand over molecular sieves for 24 hours.

3.2. Preparation Of The Substrates.

2-Chloroquinoline (mp 37-38°) and 4-chloroquinoline (mp 30-31°) were obtained from Aldrich and were purified by bubble-distillation under vacuum. 7-Chlorothieno(3,2-b)-pyridine[37] (mp 46-47°) and 4-chlorothieno(2,3-b)pyridine[38] (mp 31-32°) were prepared as described in the literature and were purified by bubble-distillation under vacuum. Samples of 5-chlorothieno(3,2-b)pyridine[39] (mp 64-65°) and 6-chlorothieno(2,3-b)pyridine[36] (mp 49-50°) were already prepared in the laboratory by D. Holmes (Ph.D. 1985, Trent Polytechnic) and were purified by bubble-distillation under vacuum.

3.3. Preparation of the reacting solutions and following the course of the reactions.

The methoxide solutions were prepared by dissolving freshly cut sodium (~1.2g) in the solvent (50ml) at 0°C. The substrate solution was prepared by dissolving an accurately weighed amount of the substrate (~0.47g) and adding it to the solvent (50ml). The two solutions were allowed

to reach equilibrium in a thermostatically controlled (precision to 0.001^{o}C) oil-bath, then 5ml of the methoxide solution was quickly pipetted into 50mls of the substrate solution. Immediately, a sample (3ml) was withdrawn, cooled in an ice-bath, and distilled water (20ml) was added. This solution was titrated against HCl solution using phenolphthalein as indicator. This procedure was repeated throughout the course of the reaction at selected time intervals.

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APPENDICES

Appendix 1.

Calculations Of The Rate Constants For The Methoxydechlorination Reactions Of α- and γ- chlorinated Quinoline And Thieno(b)pyridine Compounds.

The calculations that follow were based on the assumption that the reactions that were studied had followed second order kinetics, being first order with respect to the substrate and to the nucleophile (p. 156). The integrated rate equation for this type of reaction, where the concentrations of the reagents are not equal is given below;

$$kt = \frac{1}{(a-b)} LN\left[\frac{b(a-x)}{a(b-x)}\right] = X$$

In the calculations that follow the terms are defined as;

$$a = [NaOMe] \text{ at time, } t = 0$$

$$(a-x) = [NaOMe] \text{ at time, } t$$

$$b = [substrate] \text{ at time, } t = 0$$

$$(b-x) = [substrate] \text{ at time, } t$$

For each run a graph of time, t versus function, X is given. The slope of the line (which was calculated by least squares method) is equal to the rate constant.

Reaction of methoxide anion with
4-chlorothieno(2,3-b)pyridine
in 1:1 DMSO:Methanol (v/v) at 39.3°C

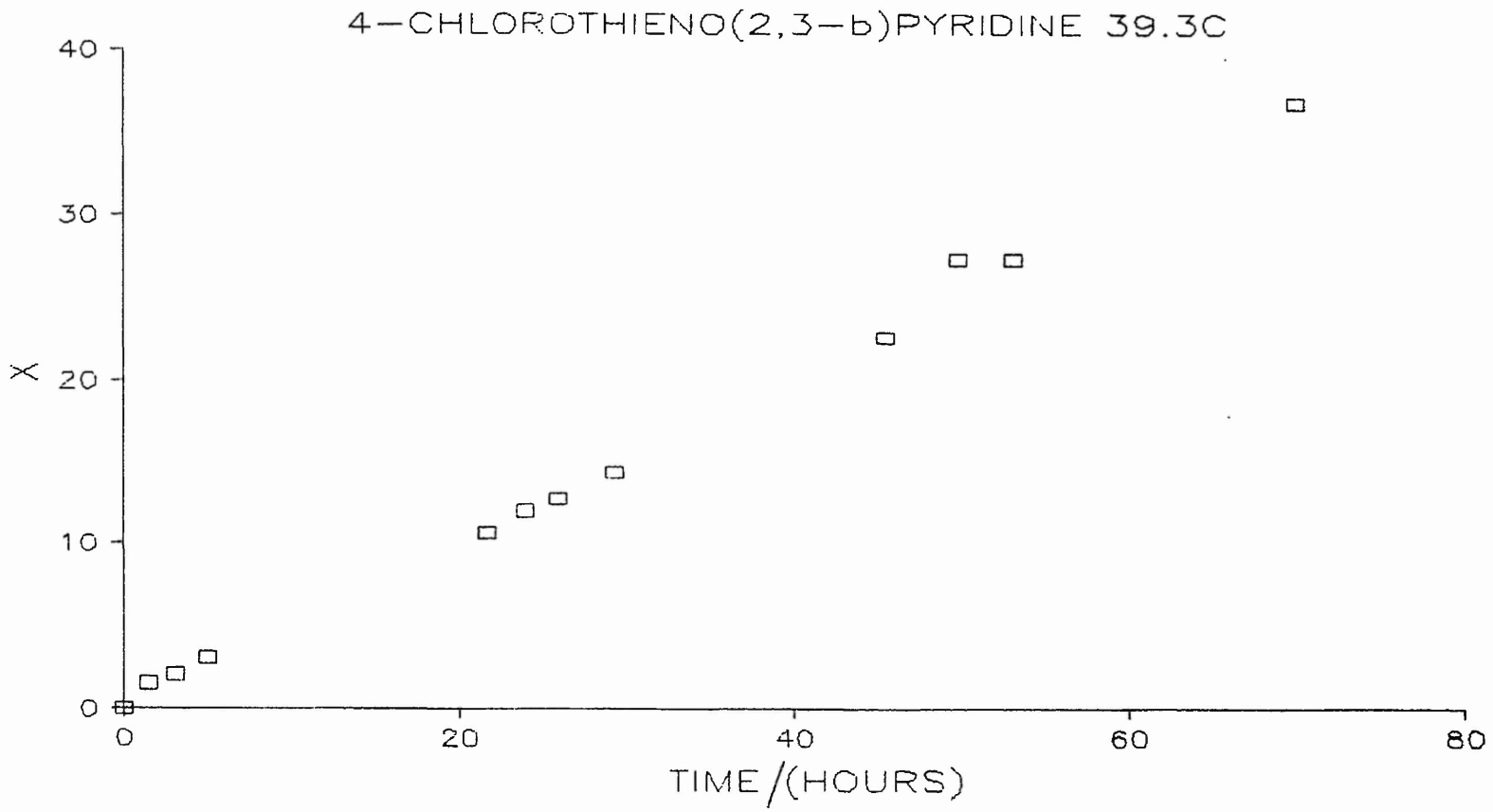
a=.1083mol dm^{-3}
b=5.78E-2mol dm^{-3}
Factor HCl=1.08E-2

n.	time /hrs	titre /mls	100(a-x) /mol	100(b-x) dm^{-3}	X $/mol^{-1} dm^3$	% reaction
1	0	30.1	10.83	5.78	-1E-2	-1
2	1.5	27.7	9.97	4.92	1.54	14
3	3.1	27	9.71	4.66	2.08	19
4	5	25.8	9.28	4.23	3.1	26
5	21.7	20.4	7.34	2.29	10.6	60
6	24	19.8	7.12	2.07	11.97	64
7	26	19.5	7.01	1.96	12.72	65
8	29.3	18.9	6.8	1.75	14.4	69
9	45.5	16.9	6.08	1.03	22.65	82
10	49.8	16.2	5.83	.78	27.35	86
11	53.1	16.2	5.83	.78	27.35	86
12	70	15.3	5.5	.45	36.81	92

SLOPE=.518$mol^{-1} dm^3 hr^{-1}$
BEST FIT RATE CONSTANT=1.43E-4$mol^{-1} dm^3 s^{-1}$
INTERCEPT=1.6E-2$mol^{-1} dm^3$
STANDARD DEVIATION OF SLOPE=1.04E-2$mol^{-1} dm^3 hr^{-1}$
STANDARD DEVIATION OF INTERCEPT=.368$mol^{-1} dm^3$
CORRELATION COEFFICIENT=.997

RE-CALCULATION OMITTING THE FOLLOWING PAIRS OF POINTS;
10

SLOPE=.51$mol^{-1} dm^3 hr^{-1}$
BEST FIT RATE CONSTANT=1.41E-4$mol^{-1} dm^3 s^{-1}$
INTERCEPT=5.5E-2$mol^{-1} dm^3$
STANDARD DEVIATION OF SLOPE=8.6E-3$mol^{-1} dm^3 hr^{-1}$
STANDARD DEVIATION OF INTERCEPT=.289$mol^{-1} dm^3$
CORRELATION COEFFICIENT=.998


4—CHLOROTHIENO(2,3—b)PYRIDINE 39.3C
X
TIME/(HOURS)
0
10
20
30
40
0
20
40
60
80

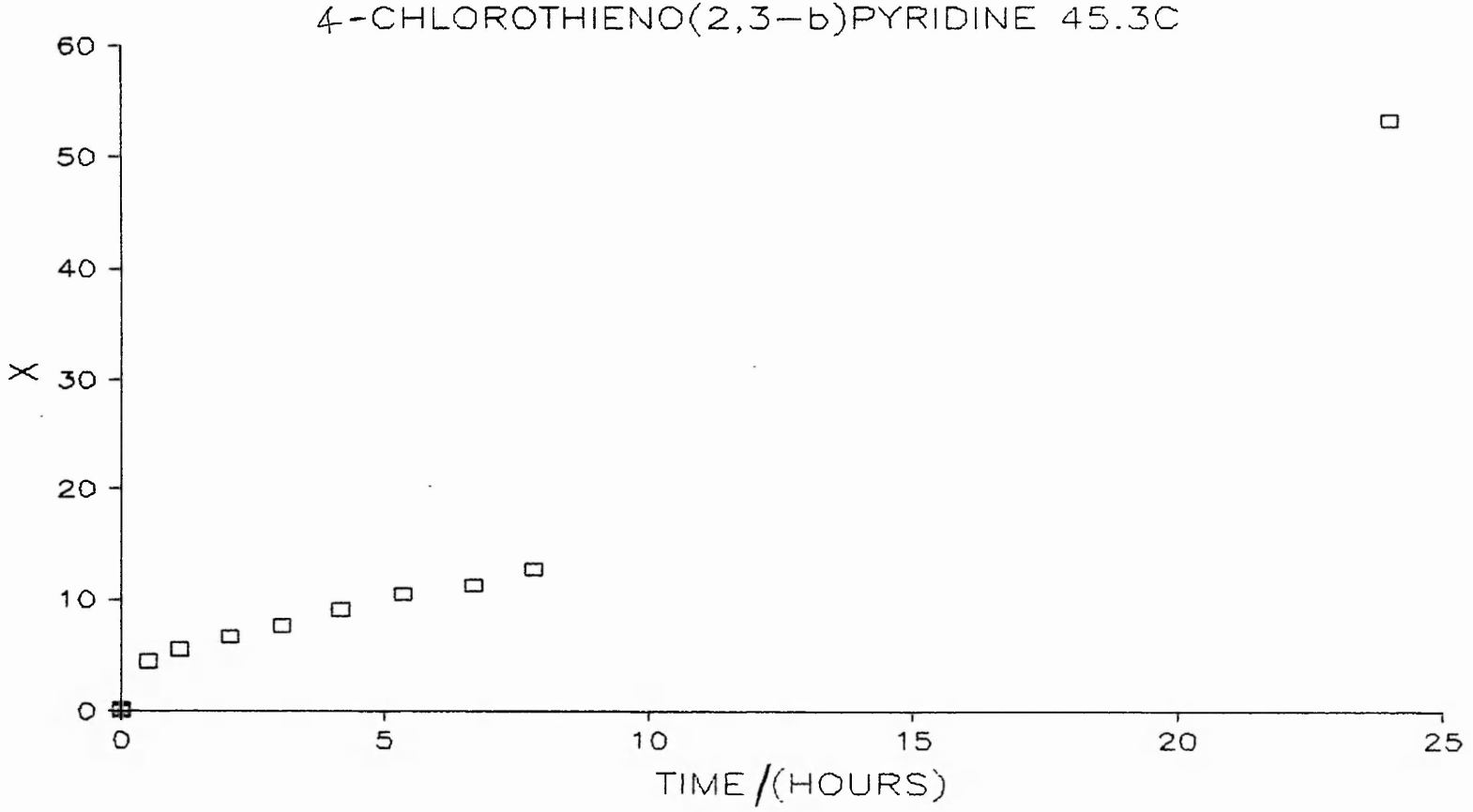
Reaction of methoxide anion with
4-chlorothieno(2,3-b)pyridine
in 1:1 DMSO:Methanol (v/v) at 45.3°C

a=.1164mol dm^{-3}
b=4.66E-2mol dm^{-3}
Factor HCl=1.09E-2

n.	time /hrs	titre /mls	100(a-x) /mol dm^{-3}	100(b-x) dm^{-3}	X /$mol^{-1} dm^3$	% reaction
1	0	31.8	11.55	4.57	.16	1
2	.5	27.2	9.88	2.9	4.43	37
3	1.1	26.4	9.59	2.61	5.52	43
4	2.05	25.7	9.33	2.35	6.6	49
5	3.05	25.1	9.11	2.13	7.65	54
6	4.18	24.4	8.86	1.88	9.06	59
7	5.35	23.8	8.64	1.66	10.46	64
8	6.68	23.5	8.53	1.55	11.25	66
9	7.83	23	8.35	1.37	12.72	70
10	24	19.4	7.04	6E-2	53.23	98

SLOPE=2.094$mol^{-1} dm^3 hr^{-1}$
BEST FIT RATE CONSTANT=5.81E-4$mol^{-1} dm^3 s^{-1}$
INTERCEPT=.647$mol^{-1} dm^3$
STANDARD DEVIATION OF SLOPE=.1246$mol^{-1} dm^3 hr^{-1}$
STANDARD DEVIATION OF INTERCEPT=1.074$mol^{-1} dm^3$
CORRELATION COEFFICIENT=.986

RE-CALCULATION OMITTING THE FOLLOWING PAIRS OF POINTS;
1 10
SLOPE=1.097$mol^{-1} dm^3 hr^{-1}$
BEST FIT RATE CONSTANT=3.04E-4$mol^{-1} dm^3 s^{-1}$
INTERCEPT=4.249$mol^{-1} dm^3$
STANDARD DEVIATION OF SLOPE=3.87E-2$mol^{-1} dm^3 hr^{-1}$
STANDARD DEVIATION OF INTERCEPT=.177$mol^{-1} dm^3$
CORRELATION COEFFICIENT=.996


4-CHLOROTHIENO(2,3-b)PYRIDINE 45.3C
60
50
40
30
20
10
0
X
0
5
10
15
20
25
TIME /(HOURS)

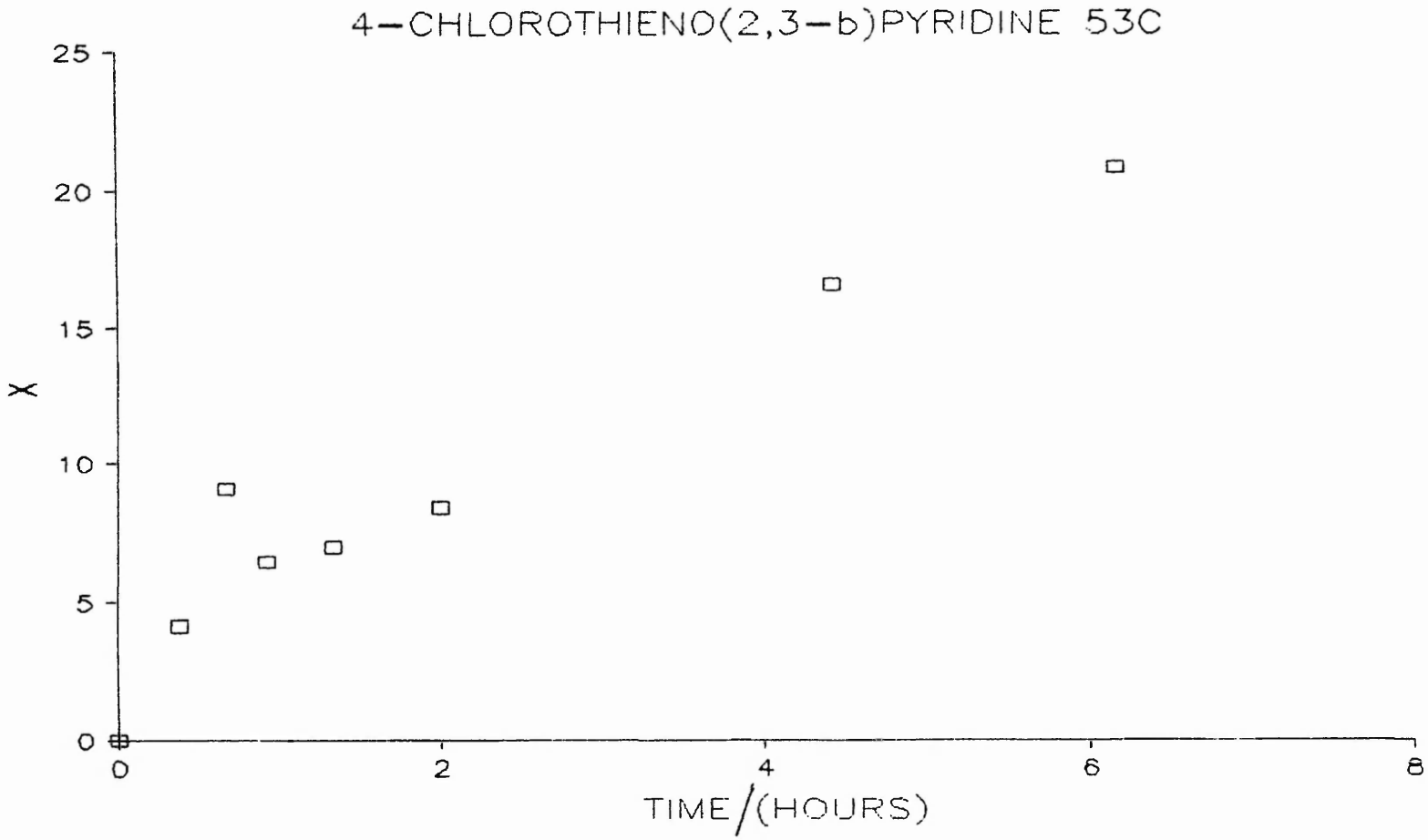
Reaction of methoxide anion with
4-chlorothieno(2,3-b)pyridine
in 1:1 DMSO:Methanol (v/v) at 53 °C

a=.1204mol dm^{-3}
b=4.52E-2mol dm^{-3}
Factor HCl=1.16E-2

n.	time /hrs	titre /mls	100(a-x) /mol dm^{-3}	100(b-x) dm^{-3}	X $/mol^{-1}dm^{3}$	% reaction
1	0	31.2	12.06	4.54	-5E-2	-1
2	.38	26.8	10.36	2.84	4.17	37
3	.67	24	9.27	1.75	9.08	61
4	.92	25.3	9.78	2.26	6.44	49
5	1.33	25	9.66	2.14	6.98	52
6	2	24.3	9.39	1.87	8.39	58
7	4.42	21.8	8.42	.9	16.58	79
8	6.17	21.1	8.15	.63	20.84	85

SLOPE=2.937mol^{-1} dm^{3} hr^{-1}
BEST FIT RATE CONSTANT=8.15E-4mol^{-1} dm^{3} s^{-1}
INTERCEPT=3.222mol^{-1} dm^{3}
STANDARD DEVIATION OF SLOPE=.3678mol^{-1} dm^{3} hr^{-1}
STANDARD DEVIATION OF INTERCEPT=1.047mol^{-1} dm^{3}
CORRELATION COEFFICIENT=.956

RE-CALCULATION OMITTING THE FOLLOWING PAIRS OF POINTS;
1 3
SLOPE=2.897mol^{-1} dm^{3} hr^{-1}
BEST FIT RATE CONSTANT=8.04E-4mol^{-1} dm^{3} s^{-1}
INTERCEPT=3.219mol^{-1} dm^{3}
STANDARD DEVIATION OF SLOPE=.1029mol^{-1} dm^{3} hr^{-1}
STANDARD DEVIATION OF INTERCEPT=.337mol^{-1} dm^{3}
CORRELATION COEFFICIENT=.997


4-CHLOROTHIENO(2,3-b)PYRIDINE 53C
25
20
15
10
5
0
X
0
2
4
6
8
TIME/(HOURS)

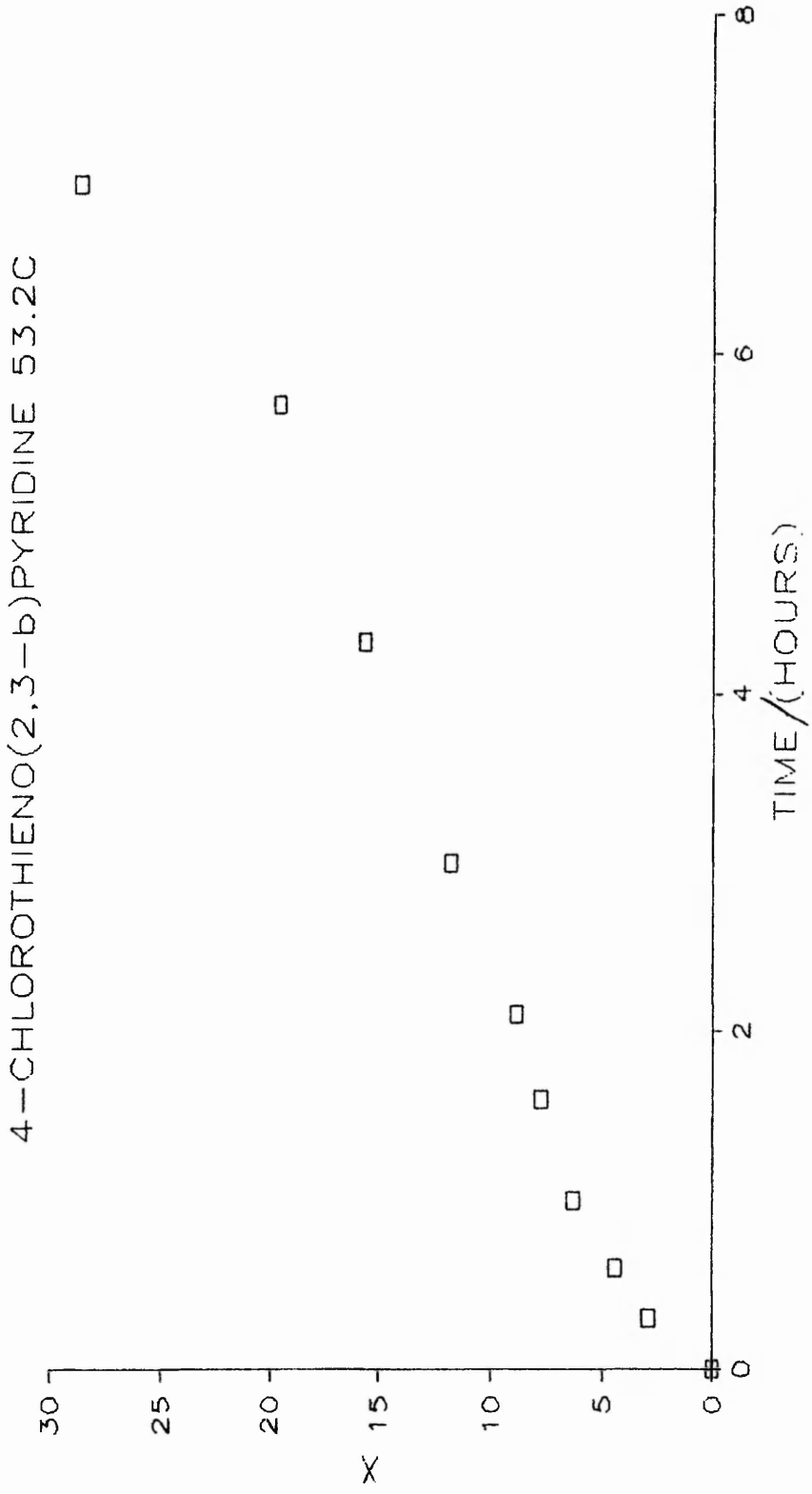
Reaction of methoxide anion with
4-chlorothieno(2,3-b)pyridine
in 1:1 DMSO:Methanol (v/v) at 53.2 °C

a=.125mol dm^{-3}
b=4.31E-2mol dm^{-3}
Factor HCl=1.1E-2

n.	time /hrs	titre /mls	100(a-x) /mol	100(b-x) dm^{-3}	X $/mol^{-1}dm^3$	% reaction
1	0	34.1	12.5	4.31	-1E-2	-1
2	.3	30.7	11.25	3.06	2.87	28
3	.6	29.4	10.78	2.59	4.41	39
4	1	28.1	10.3	2.11	6.34	50
5	1.6	27.3	10	1.81	7.81	57
6	2.1	26.8	9.82	1.63	8.88	62
7	3	25.7	9.42	1.23	11.82	71
8	4.3	24.7	9.05	.86	15.65	79
9	5.7	24	8.79	.6	19.58	85
10	7	23.1	8.46	.28	28.62	93

SLOPE=3.556mol^{-1} dm^3 hr^{-1}
BEST FIT RATE CONSTANT=9.87E-4mol^{-1} dm^3 s^{-1}
INTERCEPT=1.497$mol^{-1}dm^3$
STANDARD DEVIATION OF SLOPE=.1975mol^{-1} dm^3 hr^{-1}
STANDARD DEVIATION OF INTERCEPT=.676$mol^{-1}dm^3$
CORRELATION COEFFICIENT=.987

RE-CALCULATION OMITTING THE FOLLOWING PAIRS OF POINTS;
1 10
SLOPE=3.001mol^{-1} dm^3 hr^{-1}
BEST FIT RATE CONSTANT=8.33E-4mol^{-1} dm^3 s^{-1}
INTERCEPT=2.695$mol^{-1}dm^3$
STANDARD DEVIATION OF SLOPE=8.61E-2mol^{-1} dm^3 hr^{-1}
STANDARD DEVIATION OF INTERCEPT=.251$mol^{-1}dm^3$
CORRELATION COEFFICIENT=.997


4-CHLOROTHIENO(2,3-b)PYRIDINE 53.2C
X
TIME/(HOURS)
0
5
10
15
20
25
30
0
2
4
6
8

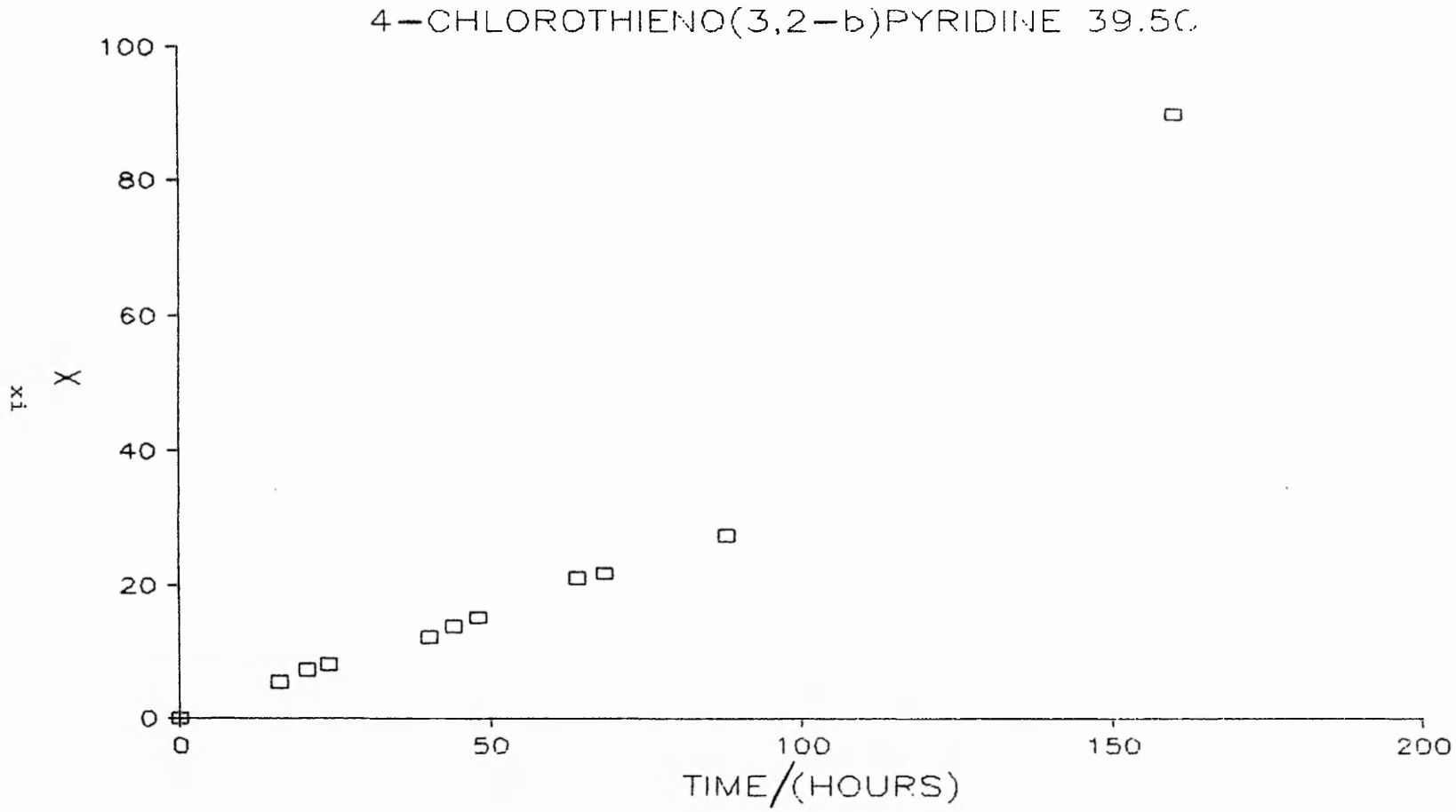
Reaction of methoxide anion with
4-chlorothieno(3,2-b)pyridine
in 1:1 DMSO:Methanol (v/v) at 39.5 °C

a=7.43E-2mol dm^{-3}
b=4.83E-2mol dm^{-3}
Factor HCl=1.3E-2

n.	time /hrs	titre /mls	100(a-x) /mol	100(b-x) dm^{-3}	X $/mol^{-1} dm^3$	% reaction
1	0	17.2	7.45	4.85	-7E-2	-1
2	16	13.8	5.98	3.38	5.37	30
3	20.5	13	5.63	3.03	7.24	37
4	24	12.7	5.5	2.9	8.03	39
5	40.3	11.4	4.93	2.34	12.17	51
6	44.2	11	4.76	2.16	13.76	55
7	48	10.7	4.63	2.03	15.07	57
8	64	9.6	4.15	1.56	21.15	67
9	68.3	9.5	4.11	1.51	21.84	68
10	88.2	8.8	3.81	1.21	27.47	74
11	160.2	6.4	2.77	.17	90.07	96

SLOPE=.533$mol^{-1} dm^3 hr^{-1}$
BEST FIT RATE CONSTANT=1.48E-4$mol^{-1} dm^3 s^{-1}$
INTERCEPT=-7.639$mol^{-1} dm^3$
STANDARD DEVIATION OF SLOPE=5.27E-2$mol^{-1} dm^3 hr^{-1}$
STANDARD DEVIATION OF INTERCEPT=3.534$mol^{-1} dm^3$
CORRELATION COEFFICIENT=.958

RE-CALCULATION OMITTING THE FOLLOWING PAIRS OF POINTS;
11
SLOPE=.312$mol^{-1} dm^3 hr^{-1}$
BEST FIT RATE CONSTANT=8.6E-5$mol^{-1} dm^3 s^{-1}$
INTERCEPT=.268$mol^{-1} dm^3$
STANDARD DEVIATION OF SLOPE=6.3E-3$mol^{-1} dm^3 hr^{-1}$
STANDARD DEVIATION OF INTERCEPT=.307$mol^{-1} dm^3$
CORRELATION COEFFICIENT=.998


4-CHLOROTHIENO(3,2-b)PYRIDINE 39.50
100
80
60
40
20
0
X
xi
0
50
100
150
200
TIME/(HOURS)

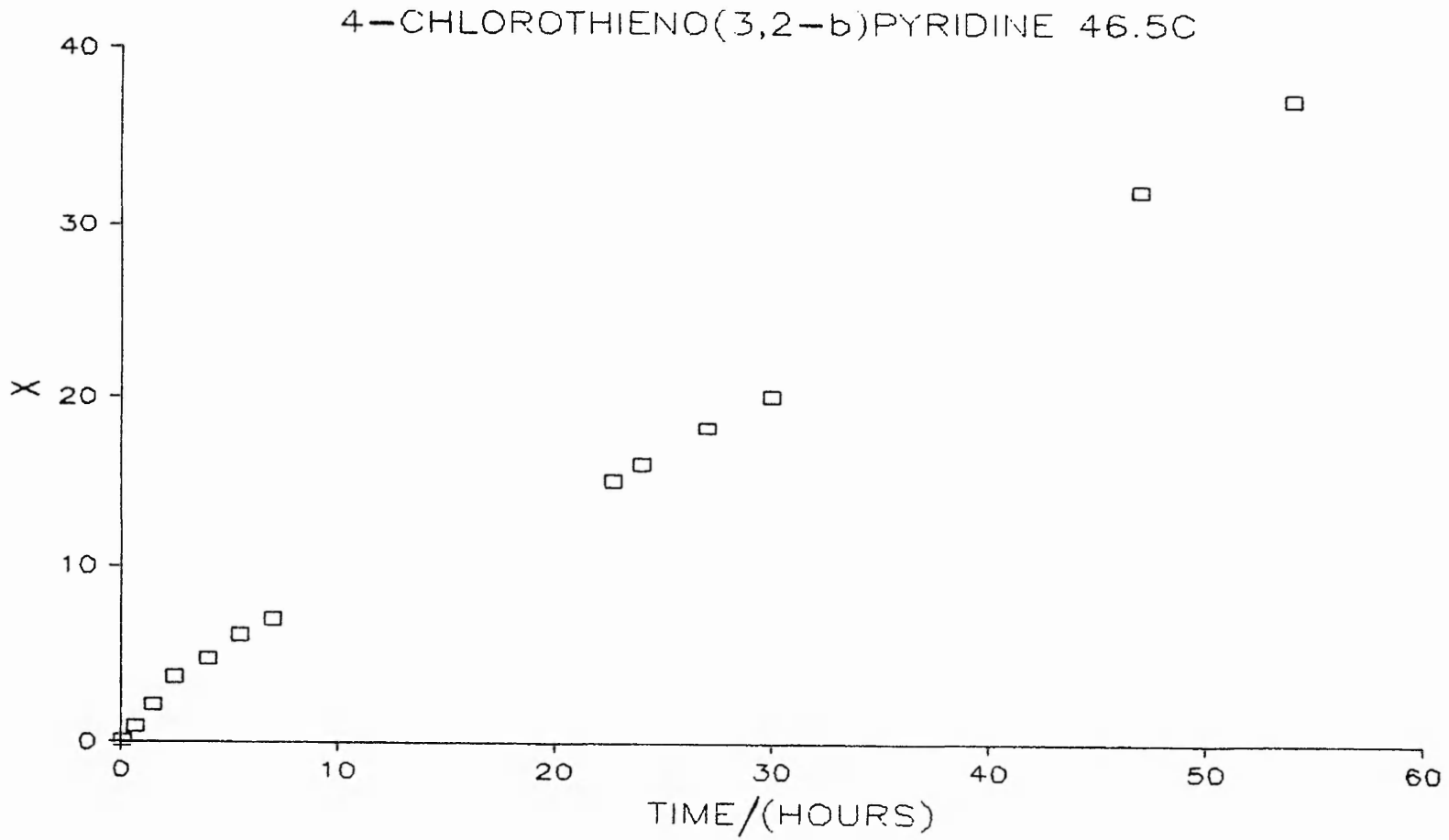
Reaction of methoxide anion with
4-chlorothieno(3,2-b)pyridine
in 1:1 DMSO:Methanol (v/v) at 46.5°C

$a=9.55E-2 mol\ dm^{-3}$
$b=4.53E-2 mol\ dm^{-3}$
Factor HCl=1.3E-2

n.	time /hrs	titre /mls	100(a-x) /mol dm^{-3}	100(b-x) dm^{-3}	X /$mol^{-1} dm^3$	% reaction
1	0	22.1	9.57	4.55	-7E-2	-1
2	.67	21.2	9.18	4.16	.89	8
3	1.5	20.2	8.75	3.73	2.11	17
4	2.5	19.1	8.27	3.25	3.72	28
5	4	18.5	8.01	2.99	4.74	33
6	5.5	17.8	7.71	2.69	6.1	40
7	7	17.4	7.54	2.52	6.97	44
8	22.7	14.9	6.45	1.43	15.07	68
9	24	14.7	6.36	1.35	16.04	70
10	27	14.3	6.19	1.17	18.23	74
11	30	14	6.06	1.04	20.14	76
12	47	12.8	5.54	.52	32.04	88
13	54	12.5	5.41	.39	37.21	91

SLOPE=.65$mol^{-1} dm^3 hr^{-1}$
BEST FIT RATE CONSTANT=1.8E-4$mol^{-1} dm^3 s^{-1}$
INTERCEPT=1.259$mol^{-1} dm^3$
STANDARD DEVIATION OF SLOPE=1.49E-2$mol^{-1} dm^3 hr^{-1}$
STANDARD DEVIATION OF INTERCEPT=.369$mol^{-1} dm^3$
CORRELATION COEFFICIENT=.997

RE-CALCULATION OMITTING THE FOLLOWING PAIRS OF POINTS;
4 5 6 7
SLOPE=.674$mol^{-1} dm^3 hr^{-1}$
BEST FIT RATE CONSTANT=1.87E-4$mol^{-1} dm^3 s^{-1}$
INTERCEPT=.242mol dm
STANDARD DEVIATION OF SLOPE=8.9E-3$mol^{-1} dm^3 hr^{-1}$
STANDARD DEVIATION OF INTERCEPT=.263$mol^{-1} dm^3$
CORRELATION COEFFICIENT=.999

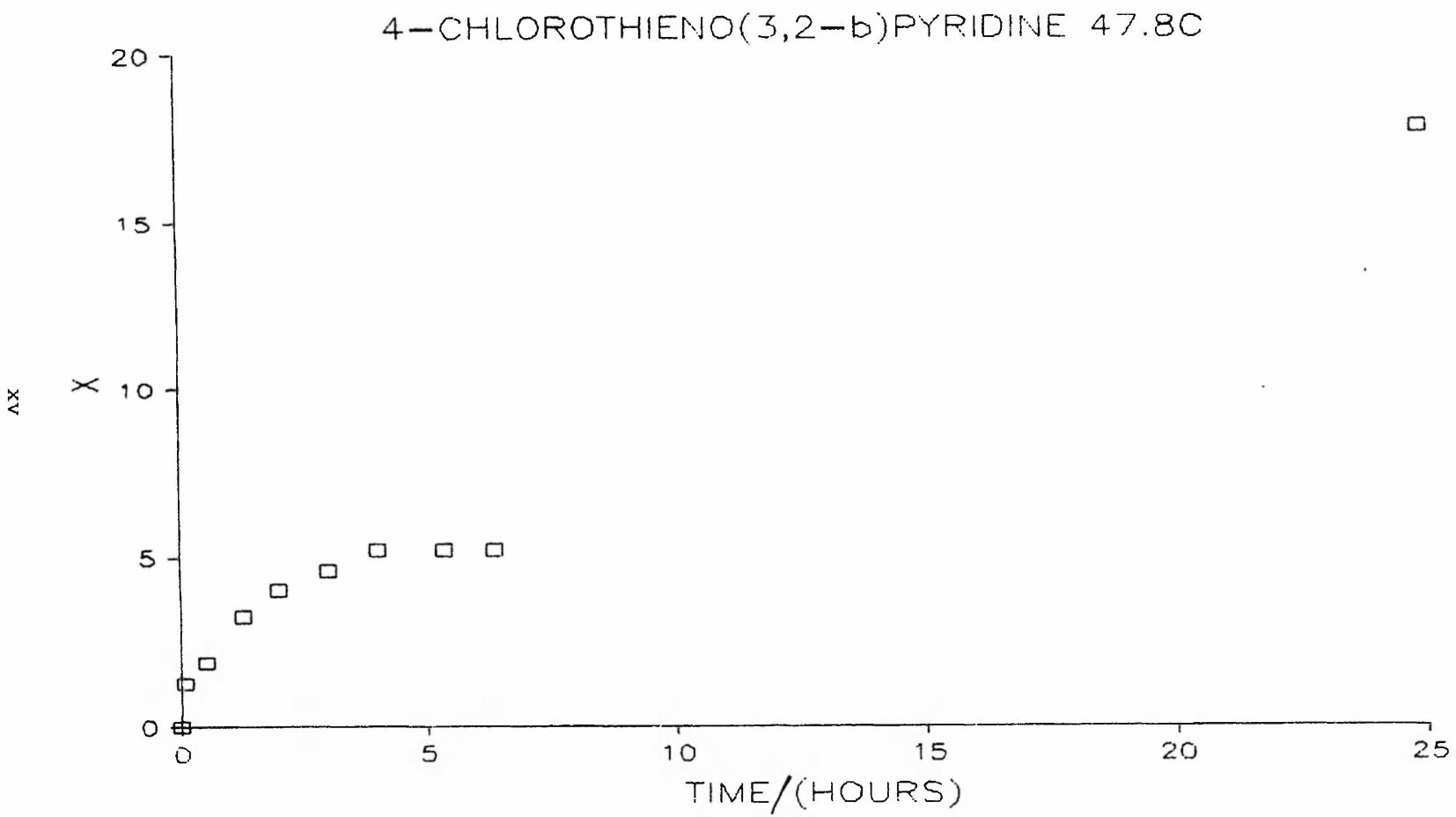

4-CHLOROTHIENO(3,2-b)PYRIDINE 46.5C
X
TIME/(HOURS)
0
10
20
30
40
50
60

Reaction of methoxide anion with
4-chlorothieno(3,2-b)pyridine
in 1:1 DMSO:Methanol (v/v) at 47.8°C

a=9.2E-2mol dm^{-3}
b=5E-2mol dm^{-3}
Factor HCl=2.26E-2

n.	time /hrs	titre /mls	100(a-x) /mol dm^{-3}	100(b-x) /mol dm^{-3}	X /$mol^{-1} dm^3$	% reaction
1	0	11.5	8.66	4.46	1.27	10
2	.5	11.2	8.43	4.23	1.88	15
3	1.25	10.6	7.98	3.78	3.25	24
4	2	10.3	7.75	3.55	4.03	28
5	3	10.1	7.6	3.4	4.6	31
6	4	9.9	7.45	3.25	5.2	34
7	5.33	9.9	7.45	3.25	5.2	34
8	6.33	9.9	7.45	3.25	5.2	34
9	24.8	7.5	5.65	1.44	17.86	71

SLOPE=.636$mol^{-1} dm^3 hr^{-1}$
BEST FIT RATE CONSTANT=1.76E-4$mol^{-1} dm^3 s^{-1}$
INTERCEPT=2.052$mol^{-1} dm^3$
STANDARD DEVIATION OF SLOPE=3.09E-2$mol^{-1} dm^3 hr^{-1}$
STANDARD DEVIATION OF INTERCEPT=.275$mol^{-1} dm^3$
CORRELATION COEFFICIENT=.991


4-CHLOROTHIENO(3,2-b)PYRIDINE 47.8C
20
15
10
5
0
X
0
5
10
15
20
25
TIME/(HOURS)

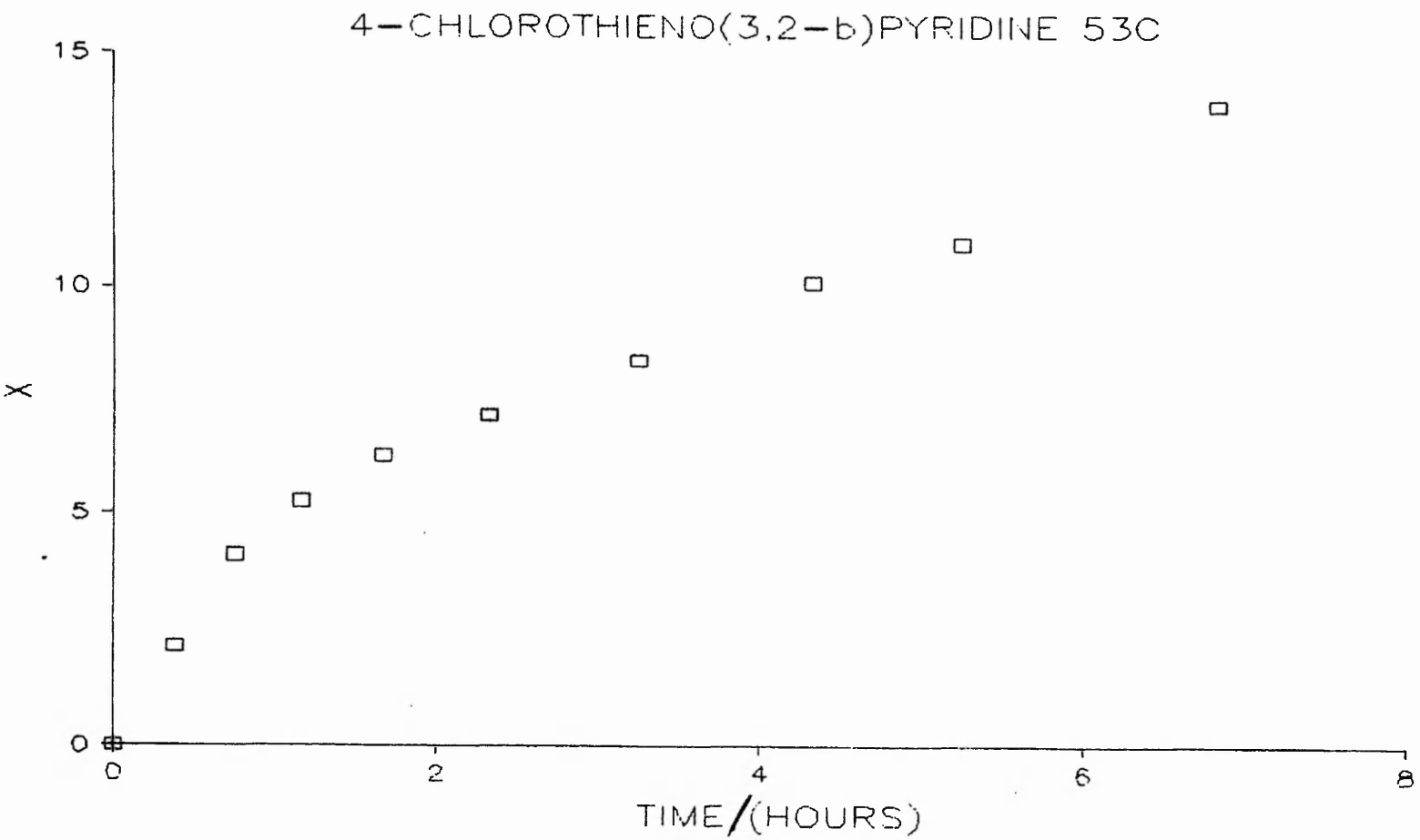
Reaction of methoxide anion with
4-chlorothieno(3,2-b)pyridine
in 1:1 DMSO:Methanol (v/v) at 53°C

a=.1148mol dm^{-3}
b=5.18E-2mol dm^{-3}
Factor HCl=1.3E-2

n.	time /hrs	titre /mls	100(a-x) /mol dm^{-3}	100(b-x) dm^{-3}	X /mol^{-1} dm^3	% reaction
1	0	26.5	11.48	5.18	-1E-2	-1
2	.38	24	10.4	4.09	2.14	20
3	.75	22.3	9.66	3.36	4.12	35
4	1.17	21.5	9.31	3.01	5.26	41
5	1.67	20.9	9.05	2.75	6.24	46
6	2.33	20.4	8.84	2.54	7.16	50
7	3.25	19.8	8.58	2.28	8.4	55
8	4.33	19.1	8.27	1.97	10.09	61
9	5.25	18.8	8.14	1.84	10.92	64
10	6.83	17.9	7.75	1.45	13.91	71

SLOPE=1.795mol^{-1} dm^3 hr^{-1}
BEST FIT RATE CONSTANT=4.98E-4mol^{-1} dm^3 s^{-1}
INTERCEPT=2.165mol^{-1} dm^3
STANDARD DEVIATION OF SLOPE=.1583mol^{-1} dm^3 hr^{-1}
STANDARD DEVIATION OF INTERCEPT=.534mol^{-1} dm^3
CORRELATION COEFFICIENT=.97

RE-CALCULATION OMITTING THE FOLLOWING PAIRS OF POINTS;
1 2
SLOPE=1.515mol^{-1} dm^3 hr^{-1}
BEST FIT RATE CONSTANT=4.21E-4mol^{-1} dm^3 s^{-1}
INTERCEPT=3.421mol^{-1} dm^3
STANDARD DEVIATION OF SLOPE=5.45E-2mol^{-1} dm^3 hr^{-1}
STANDARD DEVIATION OF INTERCEPT=.205mol^{-1} dm^3
CORRELATION COEFFICIENT=.996

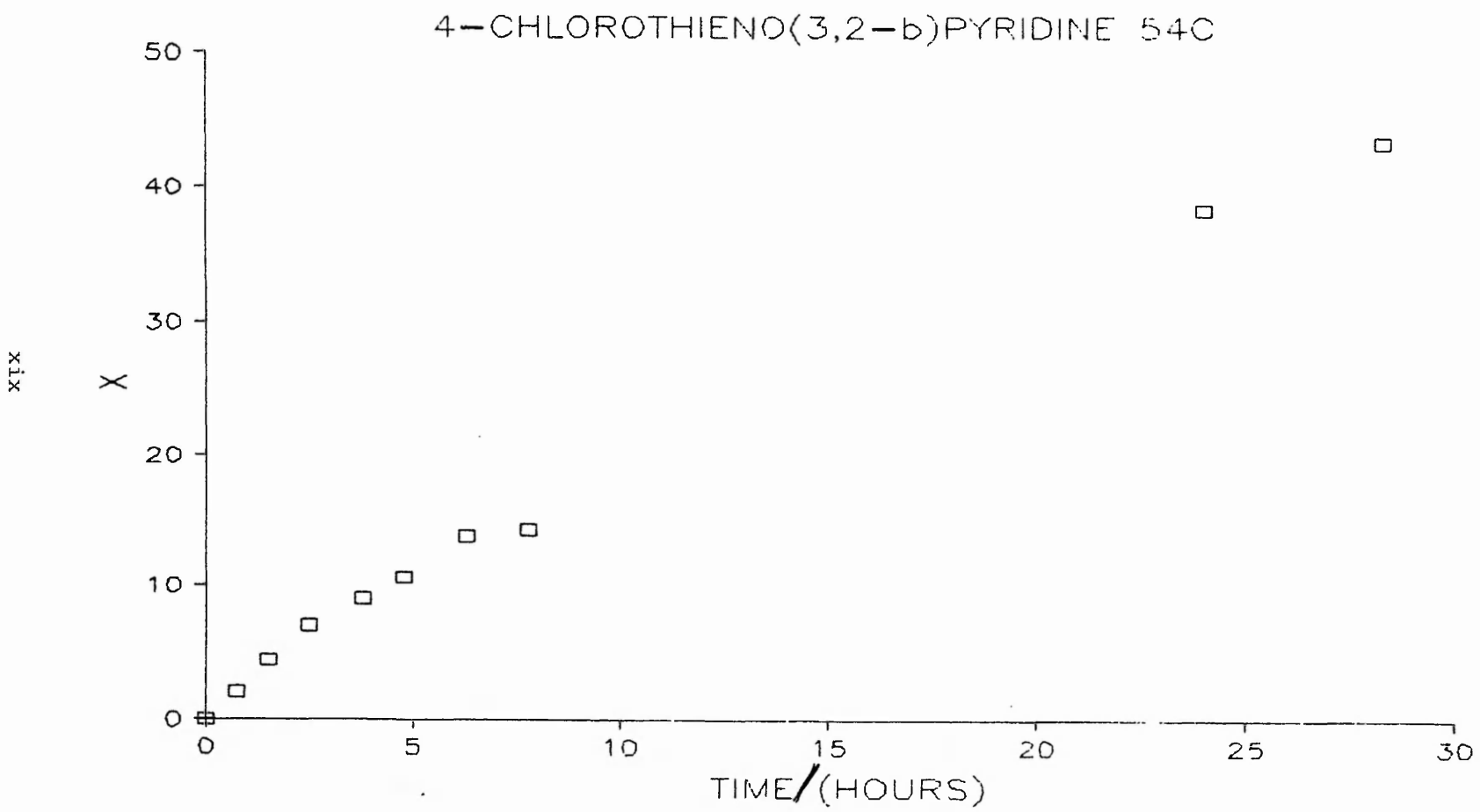

4-CHLOROTHIENO(3,2-b)PYRIDINE 53C
15
10
5
0
X
0
2
4
6
8
TIME/(HOURS)

Reaction of methoxide anion with
4-chlorothieno(3,2-b)pyridine
in 1:1 DMSO:Methanol (v/v) at 54 ^{o}C

a=4.44E-2mol dm^{-3}
b=5.55E-2mol dm^{-3}
Factor HCl=1.3E-2

n.	time /hrs	titre /mls	100(a-x) /mol dm^{-3}	100(b-x) /mol dm^{-3}	X /mol^{-1} dm^{3}	% reaction
1	0	10.7	4.63	5.74	-.77	-4
2	.75	9.2	3.98	5.09	2.02	8
3	1.5	8.2	3.55	4.66	4.38	15
4	2.5	7.3	3.16	4.27	6.99	23
5	3.8	6.7	2.9	4.01	9.06	27
6	4.8	6.3	2.73	3.83	10.63	30
7	6.3	5.6	2.42	3.53	13.83	36
8	7.8	5.5	2.38	3.49	14.34	37
9	24	2.8	1.21	2.32	38.42	58
10	28.3	2.5	1.08	2.19	43.44	60

SLOPE=1.493mol^{-1} dm^{3} hr^{-1}
BEST FIT RATE CONSTANT=4.14E-4mol^{-1} dm^{3} s^{-1}
INTERCEPT=2.326mol^{-1} dm^{3}
STANDARD DEVIATION OF SLOPE=5.41E-2mol^{-1} dm^{3} hr^{-1}
STANDARD DEVIATION OF INTERCEPT=.668mol^{-1} dm^{3}
CORRELATION COEFFICIENT=.994


4-CHLOROTHIENO(3,2-b)PYRIDINE 54C
50
40
30
20
10
0
X
0
5
10
15
20
25
30
TIME (HOURS)

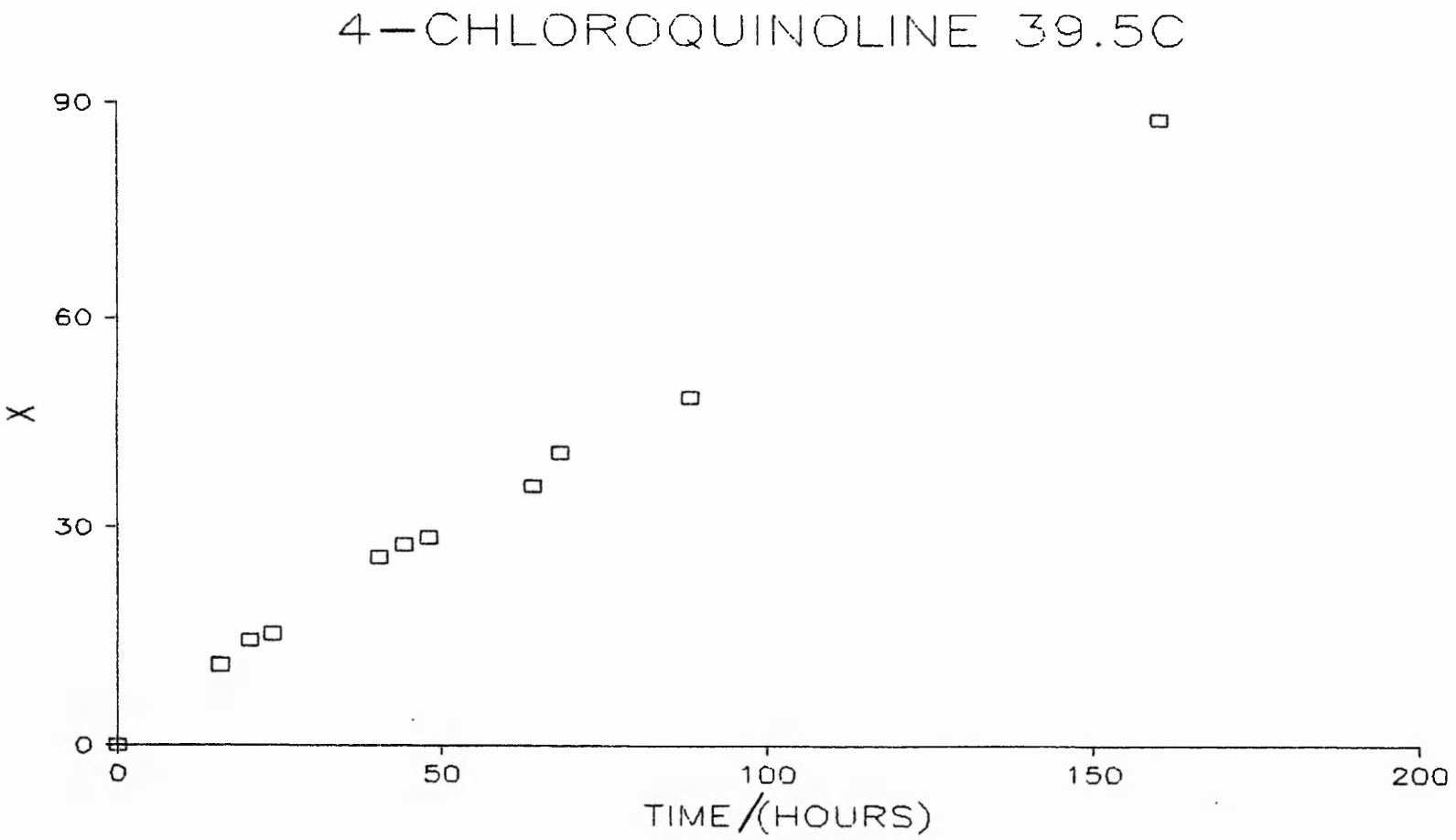
Reaction of methoxide anion with
4-chloroquinoline
in 1:1 DMSO:Methanol (v/v) at 39.5°C

$a=7.19E-2 mol\ dm^{-3}$
$b=4.6E-2 mol\ dm^{-3}$
Factor HCl=1.3E-2

n.	time /hrs	titre /mls	100(a-x) /mol dm^{-3}	100(b-x) /mol dm^{-3}	X /$mol^{-1}\ dm^{3}$	% reaction
1	0	16.6	7.19	4.6	-2E-2	-1
2	16	11.5	4.98	2.39	11.07	47
3	20.5	10.7	4.63	2.04	14.33	55
4	24	10.5	4.55	1.96	15.27	57
5	40.3	8.9	3.85	1.26	25.74	72
6	44.2	8.7	3.77	1.18	27.6	74
7	48	8.6	3.72	1.13	28.6	75
8	64	8	3.46	.87	35.83	80
9	68.3	7.7	3.33	.74	40.55	83
10	88.2	7.3	3.16	.57	48.69	87
11	160.2	6.4	2.77	.18	87.63	96

SLOPE=.534$mol^{-1}\ dm^{3}\ hr^{-1}$
BEST FIT RATE CONSTANT=1.48E-4$mol^{-1}\ dm^{3}\ s^{-1}$
INTERCEPT=2.613$mol^{-1}\ dm^{3}$
STANDARD DEVIATION OF SLOPE=9.7E-3$mol^{-1}\ dm^{3}\ hr^{-1}$
STANDARD DEVIATION OF INTERCEPT=.651$mol^{-1}\ dm^{3}$
CORRELATION COEFFICIENT=.998

RE-CALCULATION OMITTING THE FOLLOWING PAIRS OF POINTS;
11
SLOPE=.545$mol^{-1}\ dm^{3}\ hr^{-1}$
BEST FIT RATE CONSTANT=1.51E-4$mol^{-1}\ dm^{3}\ s^{-1}$
INTERCEPT=2.233$mol^{-1}\ dm^{3}$
STANDARD DEVIATION OF SLOPE=1.71E-2$mol^{-1}\ dm^{3}\ hr^{-1}$
STANDARD DEVIATION OF INTERCEPT=.832$mol^{-1}\ dm^{3}$
CORRELATION COEFFICIENT=.996


4—CHLOROQUINOLINE 39.5C
90
60
30
0
X
0
50
100
150
200
TIME/(HOURS)

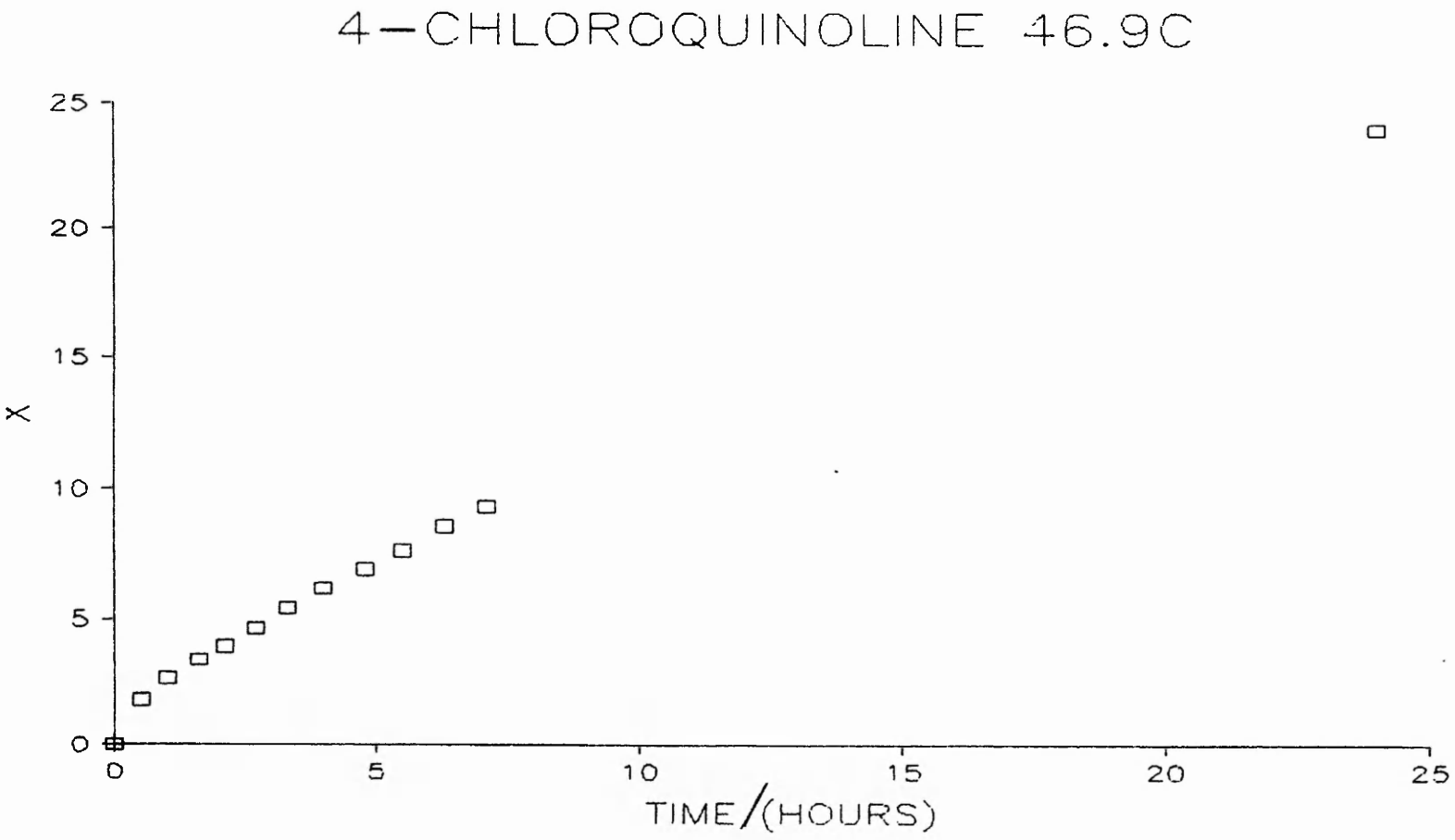
Reaction of methoxide anion with
4-chloroquinoline
in 1:1 DMSO:Methanol (v/v) at 46.9°C

a=.1574mol dm^{-3}
b=8.42E-2mol dm^{-3}
Factor HCl=1.28E-2

n.	time /hrs	titre /mls	100(a-x) /mol	100(b-x) dm^{-3}	X $/mol^{-1}dm^3$	% reaction
1	0	36.9	15.74	8.42	-1E-2	-1
2	.5	32.3	13.78	6.46	1.8	23
3	1	30.6	13.05	5.73	2.68	31
4	1.6	29.4	12.54	5.22	3.42	37
5	2.1	28.6	12.2	4.88	3.96	42
6	2.7	27.7	11.81	4.49	4.64	46
7	3.3	26.8	11.43	4.11	5.41	51
8	4	26	11.09	3.77	6.18	55
9	4.8	25.3	10.79	3.47	6.93	58
10	5.5	24.7	10.53	3.21	7.65	61
11	6.3	24	10.23	2.91	8.59	65
12	7.1	23.5	10.02	2.7	9.34	67
13	24	18.9	8.06	.74	24	91

SLOPE=.95$mol^{-1}dm^3hr^{-1}$
BEST FIT RATE CONSTANT=2.64E-4$mol^{-1}dm^3s^{-1}$
INTERCEPT=1.911$mol^{-1}dm^3$
STANDARD DEVIATION OF SLOPE=3.55E-2$mol^{-1}dm^3hr^{-1}$
STANDARD DEVIATION OF INTERCEPT=.272$mol^{-1}dm^3$
CORRELATION COEFFICIENT=.992

RE-CALCULATION OMITTING THE FOLLOWING PAIRS OF POINTS;
1 13
SLOPE=1.118$mol^{-1}dm^3hr^{-1}$
BEST FIT RATE CONSTANT=3.1E-4$mol^{-1}dm^3s^{-1}$
INTERCEPT=1.559$mol^{-1}dm^3$
STANDARD DEVIATION OF SLOPE=2.1E-2$mol^{-1}dm^3hr^{-1}$
STANDARD DEVIATION OF INTERCEPT=8.6E-2$mol^{-1}dm^3$
CORRELATION COEFFICIENT=.998


4—CHLOROQUINOLINE 46.9C
25
20
15
10
5
0
X
0
5
10
15
20
25
TIME/(HOURS)

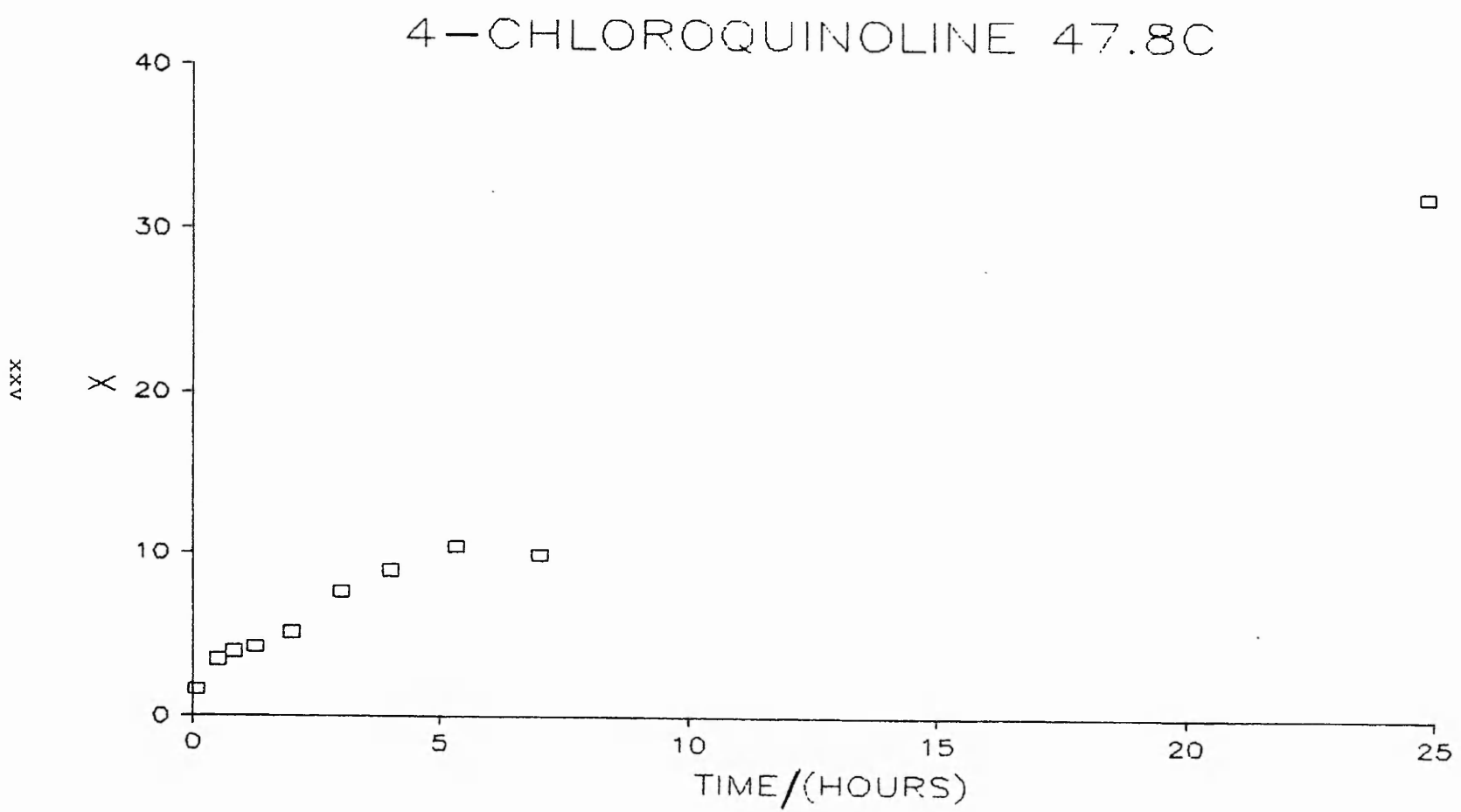
Reaction of methoxide anion with
4-chloroquinoline
in 1:1 DMSO:Methanol (v/v) at 47.8°C

$a=9.2E-2 mol\ dm^{-3}$
$b=4.99E-2 mol\ dm^{-3}$
Factor HCl=2.26E-2

n.	time /hrs	titre /mls	100(a-x) /mol dm^{-3}	100(b-x) /mol dm^{-3}	X /$mol^{-1} dm^3$	% reaction
1	0	11.3	8.51	4.3	1.67	13
2	.5	10.5	7.9	3.69	3.51	25
3	.83	10.3	7.75	3.54	4.04	28
4	1.25	10.2	7.68	3.47	4.32	30
5	2	9.9	7.45	3.24	5.21	34
6	3	9.2	6.93	2.72	7.67	45
7	4	8.9	6.7	2.49	8.95	50
8	5.33	8.6	6.47	2.26	10.39	54
9	7	8.7	6.55	2.34	9.89	53
10	24.8	6.5	4.89	.68	32.13	86

SLOPE=1.178$mol^{-1} dm^3 hr^{-1}$
BEST FIT RATE CONSTANT=3.27E-4$mol^{-1} dm^3 s^{-1}$
INTERCEPT=3.042$mol^{-1} dm^3$
STANDARD DEVIATION OF SLOPE=4.45E-2$mol^{-1} dm^3 hr^{-1}$
STANDARD DEVIATION OF INTERCEPT=.378$mol^{-1} dm^3$
CORRELATION COEFFICIENT=.994

RE-CALCULATION OMITTING THE FOLLOWING PAIRS OF POINTS;
1 9
SLOPE=1.168$mol^{-1} dm^3 hr^{-1}$
BEST FIT RATE CONSTANT=3.24E-4$mol^{-1} dm^3 s^{-1}$
INTERCEPT=3.441$mol^{-1} dm^3$
STANDARD DEVIATION OF SLOPE=3.24E-2$mol^{-1} dm^3 hr^{-1}$
STANDARD DEVIATION OF INTERCEPT=.298$mol^{-1} dm^3$
CORRELATION COEFFICIENT=.997


4—CHLOROQUINOLINE 47.8C
40
30
20
10
0
X
0
5
10
15
20
25
TIME/(HOURS)

Reaction of methoxide anion with
4-chloroquinoline
in 1:1 DMSO:Methanol (v/v) at 53°C

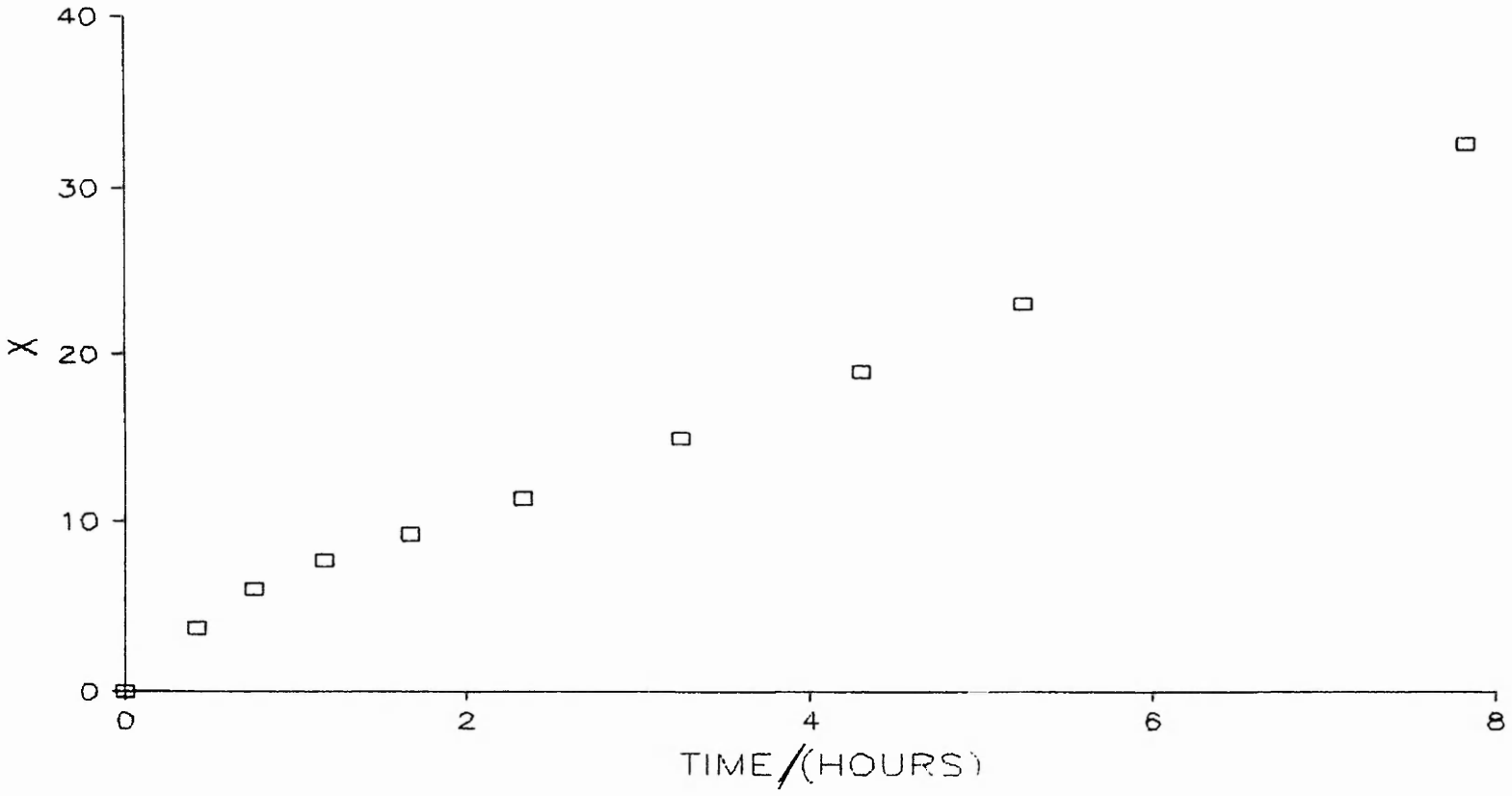
a=.1157mol dm^{-3}
b=5.19E-2mol dm^{-3}
Factor HCl=1.3E-2

n.	time /hrs	titre /mls	100(a-x) /mol	100(b-x) dm^{-3}	X $/mol^{-1} dm^3$	% reaction
1	0	26.7	11.57	5.19	0	0
2	.42	22.8	9.87	3.49	3.7	32
3	.75	21.2	9.18	2.8	6.01	45
4	1.17	20.3	8.79	2.41	7.68	53
5	1.67	19.6	8.49	2.11	9.23	59
6	2.33	18.8	8.14	1.76	11.39	65
7	3.25	17.8	7.71	1.33	14.94	74
8	4.3	17	7.36	.98	18.94	80
9	5.25	16.4	7.1	.72	23.17	85
10	7.83	15.6	6.76	.37	32.55	92

SLOPE=3.951$mol^{-1} dm^3 hr^{-1}$
BEST FIT RATE CONSTANT=1.097E-3$mol^{-1} dm^3 s^{-1}$
INTERCEPT=2.108$mol^{-1} dm^3$
STANDARD DEVIATION OF SLOPE=.1248$mol^{-1} dm^3 hr^{-1}$
STANDARD DEVIATION OF INTERCEPT=.446$mol^{-1} dm^3$
CORRELATION COEFFICIENT=.996

RE-CALCULATION OMITTING THE FOLLOWING PAIRS OF POINTS;
1

SLOPE=3.818mol dm hr
BEST FIT RATE CONSTANT=1.06E-3$mol^{-1} dm^3 s^{-1}$
INTERCEPT=2.741$mol^{-1} dm^3$
STANDARD DEVIATION OF SLOPE=5.84E-2$mol^{-1} dm^3 hr^{-1}$
STANDARD DEVIATION OF INTERCEPT=.22$mol^{-1} dm^3$
CORRELATION COEFFICIENT=.999

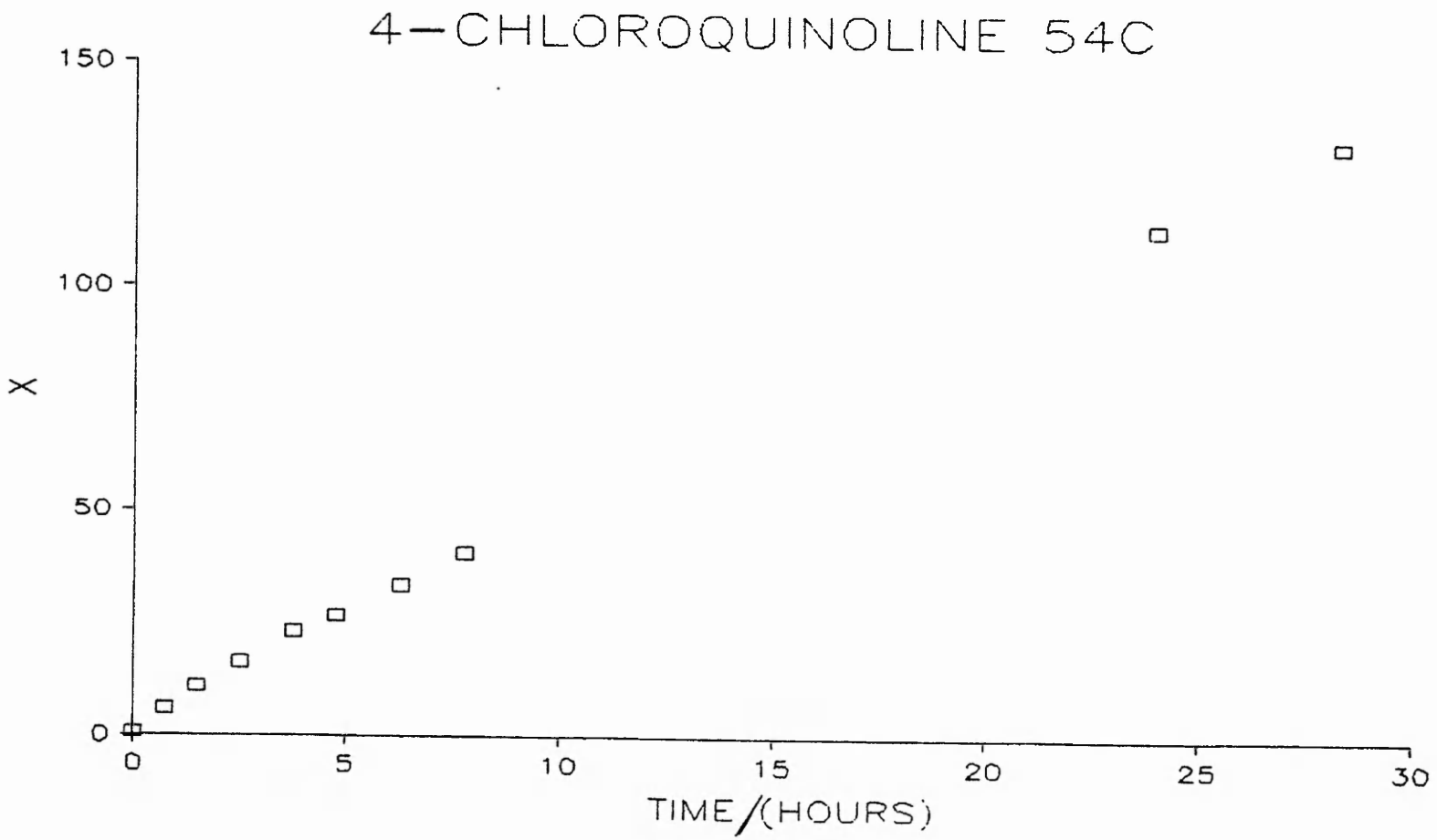

4—CHLOROQUINOLINE 53C
40
30
20
10
0
X
0
2
4
6
8
TIME (HOURS)

Reaction of methoxide anion with
4-chloroquinoline
in 1:1 DMSO:Methanol (v/v) at 54°C

$a = 4.62E-2 mol\ dm^{-3}$
$b = 5.25E-2 mol\ dm^{-3}$
Factor HCl = 1.3E-2

n.	time /hrs	titre /mls	100(a-x) /mol dm^{-3}	100(b-x) /mol dm^{-3}	X /$mol^{-1}\ dm^3$	% reaction
1	0	10.3	4.46	5.09	.66	2
2	.75	8.1	3.51	4.13	5.91	21
3	1.5	6.7	2.9	3.53	10.88	32
4	2.5	5.6	2.42	3.05	16.34	41
5	3.8	4.6	1.99	2.62	23.3	50
6	4.8	4.2	1.81	2.44	26.89	53
7	6.3	3.6	1.56	2.18	33.55	58
8	7.8	3.1	1.34	1.97	40.75	62
9	24	1.1	.47	1.1	113.4	78
10	28.3	.9	.39	1.01	132.31	80

SLOPE = $4.563 mol^{-1} dm^3 hr^{-1}$
BEST FIT RATE CONSTANT = $1.267E-3 mol^{-1}\ dm^3\ s^{-1}$
INTERCEPT = $4.004 mol^{-1}\ dm^3$
STANDARD DEVIATION OF SLOPE = $5.53E-2 mol^{-1}\ dm^3\ hr^{-1}$
STANDARD DEVIATION OF INTERCEPT = $.683 mol^{-1}\ dm^3$
CORRELATION COEFFICIENT = .999


4—CHLOROQUINOLINE 54C
150
100
50
0
X
0
5
10
15
20
25
30
TIME/(HOURS)

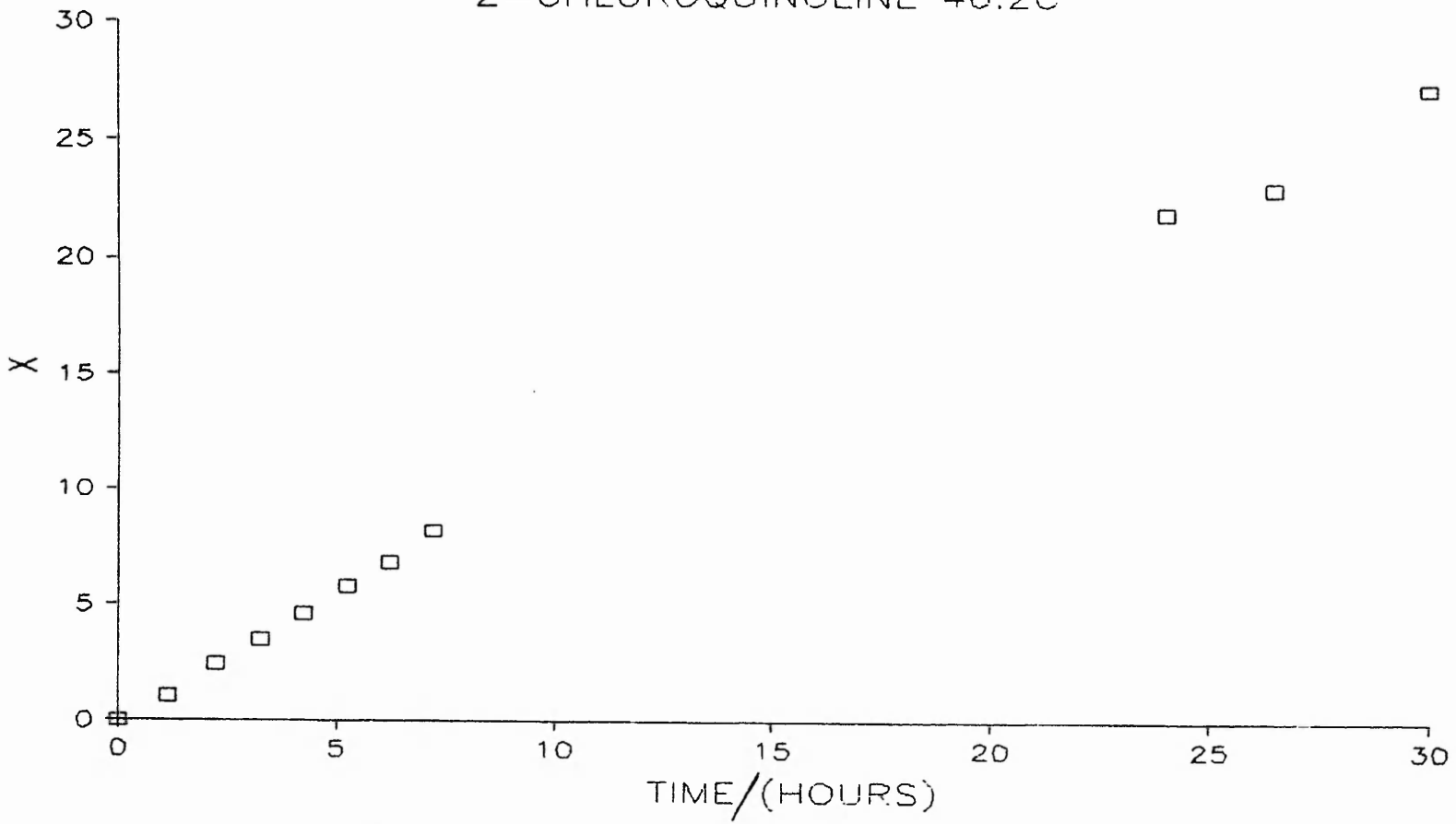
Reaction of methoxide anion with
2-chloroquinoline
in 1:1 DMSO:Methanol (v/v) at 46.2°C

a=.1638mol dm^{-3}
b=5.29E-2mol dm^{-3}
Factor HCl=1.08E-2

n.	time /hrs	titre /mls	100(a-x) /mol dm^{-3}	100(b-x) dm^{-3}	X /$mol^{-1} dm^3$	% reaction
1	0	45.5	16.37	5.28	0	0
2	1.17	43.2	15.55	4.46	1.06	15
3	2.25	40.8	14.68	3.59	2.49	31
4	3.25	39.4	14.18	3.09	3.53	41
5	4.25	38.2	13.75	2.66	4.61	49
6	5.25	37.1	13.35	2.26	5.8	57
7	6.25	36.3	13.06	1.97	6.83	62
8	7.25	35.4	12.74	1.65	8.22	68
9	24	31.7	11.41	.32	21.98	93
10	26.5	31.6	11.37	.28	23.02	94
11	30	31.3	11.26	.17	27.21	96

SLOPE=.874$mol^{-1} dm^3 hr^{-1}$
BEST FIT RATE CONSTANT=2.42E-4$mol^{-1} dm^3 s^{-1}$
INTERCEPT=.764$mol^{-1} dm^3$
STANDARD DEVIATION OF SLOPE=1.88E-2$mol^{-1} dm^3 hr^{-1}$
STANDARD DEVIATION OF INTERCEPT=.274$mol^{-1} dm^3$
CORRELATION COEFFICIENT=.997

RE-CALCULATION OMITTING THE FOLLOWING PAIRS OF POINTS;
9 10 11
SLOPE=1.129$mol^{-1} dm^3 hr^{-1}$
BEST FIT RATE CONSTANT=3.13E-4$mol^{-1} dm^3 s^{-1}$
INTERCEPT=-.12$mol^{-1} dm^3$
STANDARD DEVIATION OF SLOPE=1.69E-2$mol^{-1} dm^3 hr^{-1}$
STANDARD DEVIATION OF INTERCEPT=7.4E-2$mol^{-1} dm^3$
CORRELATION COEFFICIENT=.999


2-CHLOROQUINOLINE 46.2C
30
25
20
15
10
5
0
X
0
5
10
15
20
25
30
TIME/(HOURS)

xxxx

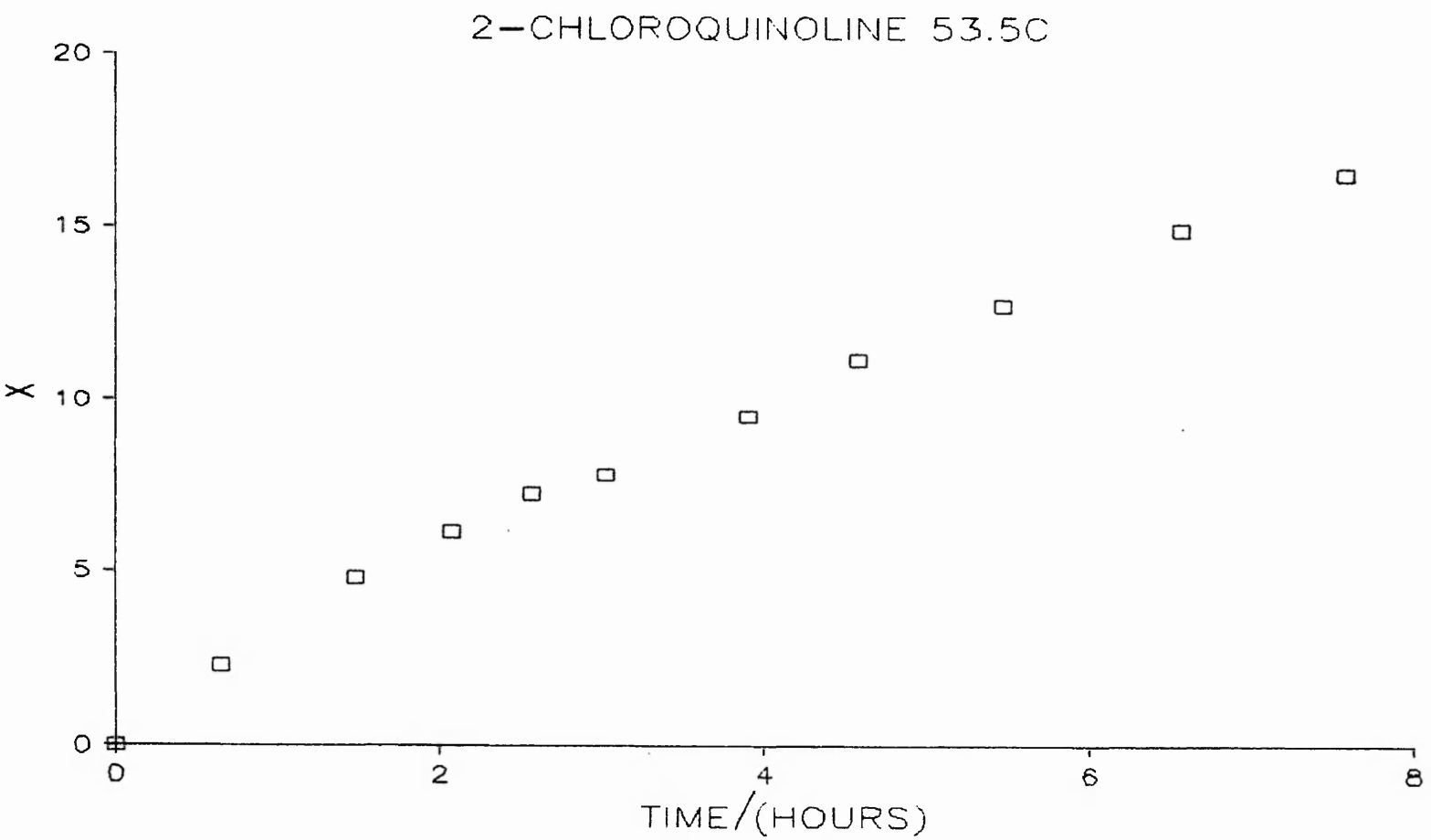
Reaction of methoxide anion with
2-chloroquinoline
in 1:1 DMSO:Methanol (v/v) at 53.5 °C

$a = .128 mol\ dm^{-3}$
$b = 6.46E-2 mol\ dm^{-3}$
Factor HCl = 1.09E-2

n.	time /hrs	titre /mls	100(a-x) /mol dm^{-3}	100(b-x) /mol dm^{-3}	X /$mol^{-1}\ dm^3$	% reaction
1	0	35.2	12.78	6.44	1E-2	0
2	.65	31	11.26	4.92	2.26	23
3	1.48	27.8	10.1	3.76	4.79	41
4	2.07	26.5	9.62	3.28	6.15	49
5	2.57	25.6	9.3	2.96	7.26	54
6	3.03	25.2	9.15	2.81	7.81	56
7	3.9	24.1	8.75	2.41	9.52	62
8	4.58	23.2	8.42	2.08	11.21	67
9	5.47	22.5	8.17	1.83	12.77	71
10	6.57	21.7	7.88	1.54	14.92	76
11	7.58	21.2	7.7	1.36	16.53	78

SLOPE=2.108 $mol^{-1}\ dm^3\ hr^{-1}$
BEST FIT RATE CONSTANT=5.85E-4 $mol^{-1}\ dm^3\ s^{-1}$
INTERCEPT=1.216 $mol^{-1}\ dm^3$
STANDARD DEVIATION OF SLOPE=7.68E-2 $mol^{-1}\ dm^3\ hr^{-1}$
STANDARD DEVIATION OF INTERCEPT=.318 $mol^{-1}\ dm^3$
CORRELATION COEFFICIENT=.994

RE-CALCULATION OMITTING THE FOLLOWING PAIRS OF POINTS;
1
SLOPE=2.008 $mol^{-1}\ dm^3\ hr^{-1}$
BEST FIT RATE CONSTANT=5.58E-4 $mol^{-1}\ dm^3\ s^{-1}$
INTERCEPT=1.714 $mol^{-1}\ dm^3$
STANDARD DEVIATION OF SLOPE=5.41E-2 $mol^{-1}\ dm^3\ hr^{-1}$
STANDARD DEVIATION OF INTERCEPT=.235 $mol^{-1}\ dm^3$
CORRELATION COEFFICIENT=.997


2—CHLOROQUINOLINE 53.5C
20
15
10
5
0
X
0
2
4
6
8
TIME/(HOURS)

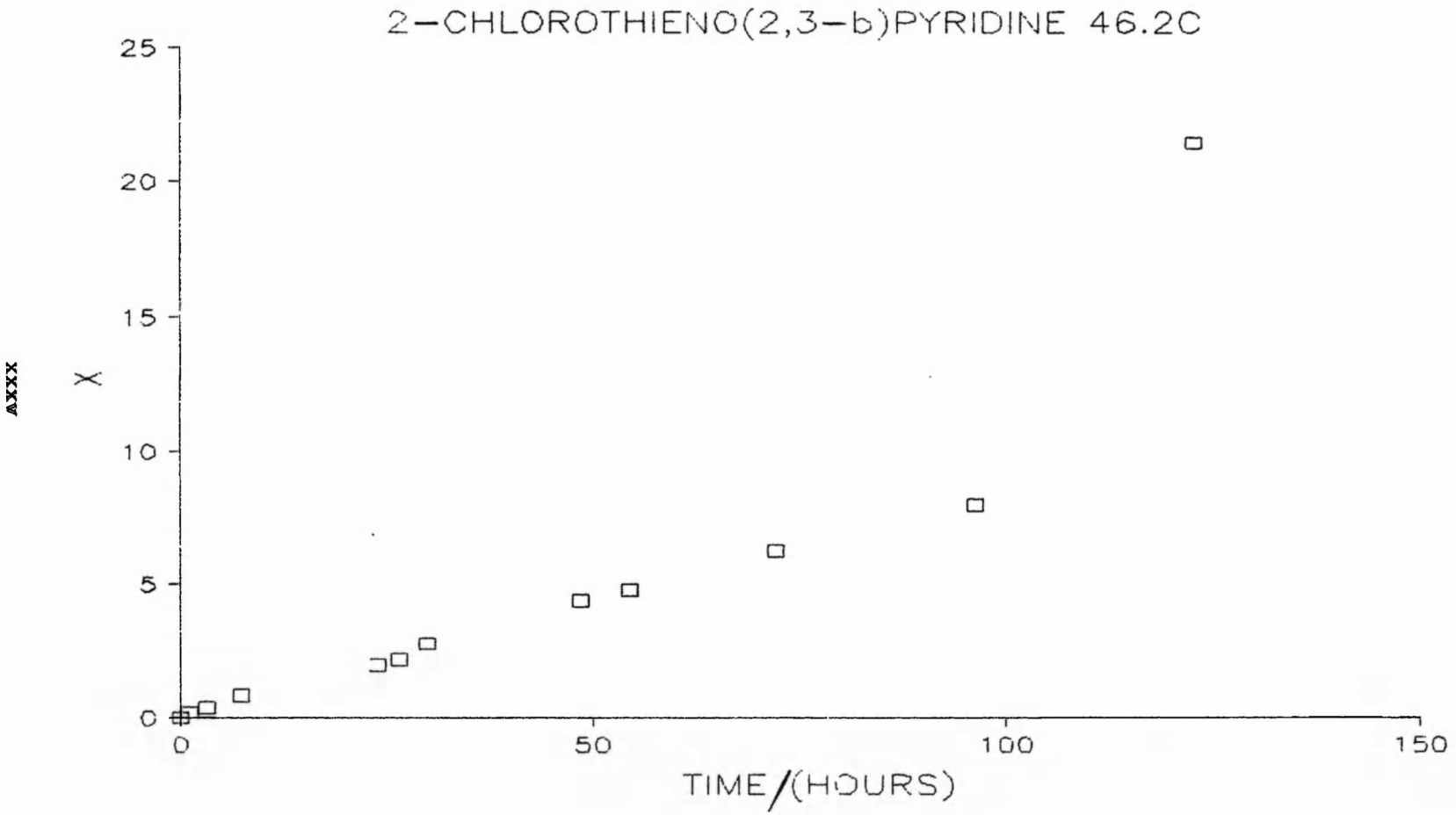
Reaction of methoxide anion with
2-chlorothieno(2,3-b)pyridine
in 1:1 DMSO:Methanol (v/v) at 46.2°C

a=.1701mol dm^{-3}
b=4.77E-2mol dm^{-3}
Factor HCl=1.08E-2

n.	time /hrs	titre /mls	100(a-x) /mol	100(b-x) dm^{-3}	X $/mol^{-1} dm^3$	% reaction
1	0	47.3	17.02	4.78	-3E-2	-1
2	1.17	46.8	16.84	4.6	.2	3
3	3.25	46.4	16.7	4.46	.39	6
4	7.25	45.5	16.37	4.13	.84	13
5	24	43.6	15.69	3.45	1.97	27
6	26.5	43.3	15.58	3.34	2.17	29
7	30	42.5	15.29	3.05	2.76	35
8	48.5	40.7	14.65	2.41	4.35	49
9	54.5	40.3	14.5	2.26	4.77	52
10	72	39.1	14.07	1.83	6.25	61
11	96.3	38	13.67	1.43	8	69
12	122.6	34.7	12.49	.25	21.5	94

SLOPE=.136$mol^{-1} dm^3 hr^{-1}$
BEST FIT RATE CONSTANT=3.7E-5$mol^{-1} dm^3 s^{-1}$
INTERCEPT=-1.089$mol^{-1} dm^3$
STANDARD DEVIATION OF SLOPE=1.94E-2$mol^{-1} dm^3 hr^{-1}$
STANDARD DEVIATION OF INTERCEPT=1.078$mol^{-1} dm^3$
CORRELATION COEFFICIENT=.911

RE-CALCULATION OMITTING THE FOLLOWING PAIRS OF POINTS;
12
SLOPE=8.3E-2$mol^{-1} dm^3 hr^{-1}$
BEST FIT RATE CONSTANT=2.3E-5$mol^{-1} dm^3 s^{-1}$
INTERCEPT=.112$mol^{-1} dm^3$
STANDARD DEVIATION OF SLOPE=1.4E-3$mol^{-1} dm^3 hr^{-1}$
STANDARD DEVIATION OF INTERCEPT=6.3E-2$mol^{-1} dm^3$
CORRELATION COEFFICIENT=.998


2-CHLOROTHIENO(2,3-b)PYRIDINE 46.2C
25
20
15
10
5
0
X
0
50
100
150
TIME/(HOURS)

Reaction of methoxide anion with
2-chlorothieno(2,3-b)pyridine
in 1:1 DMSO:Methanol (v/v) at 53.5 °C

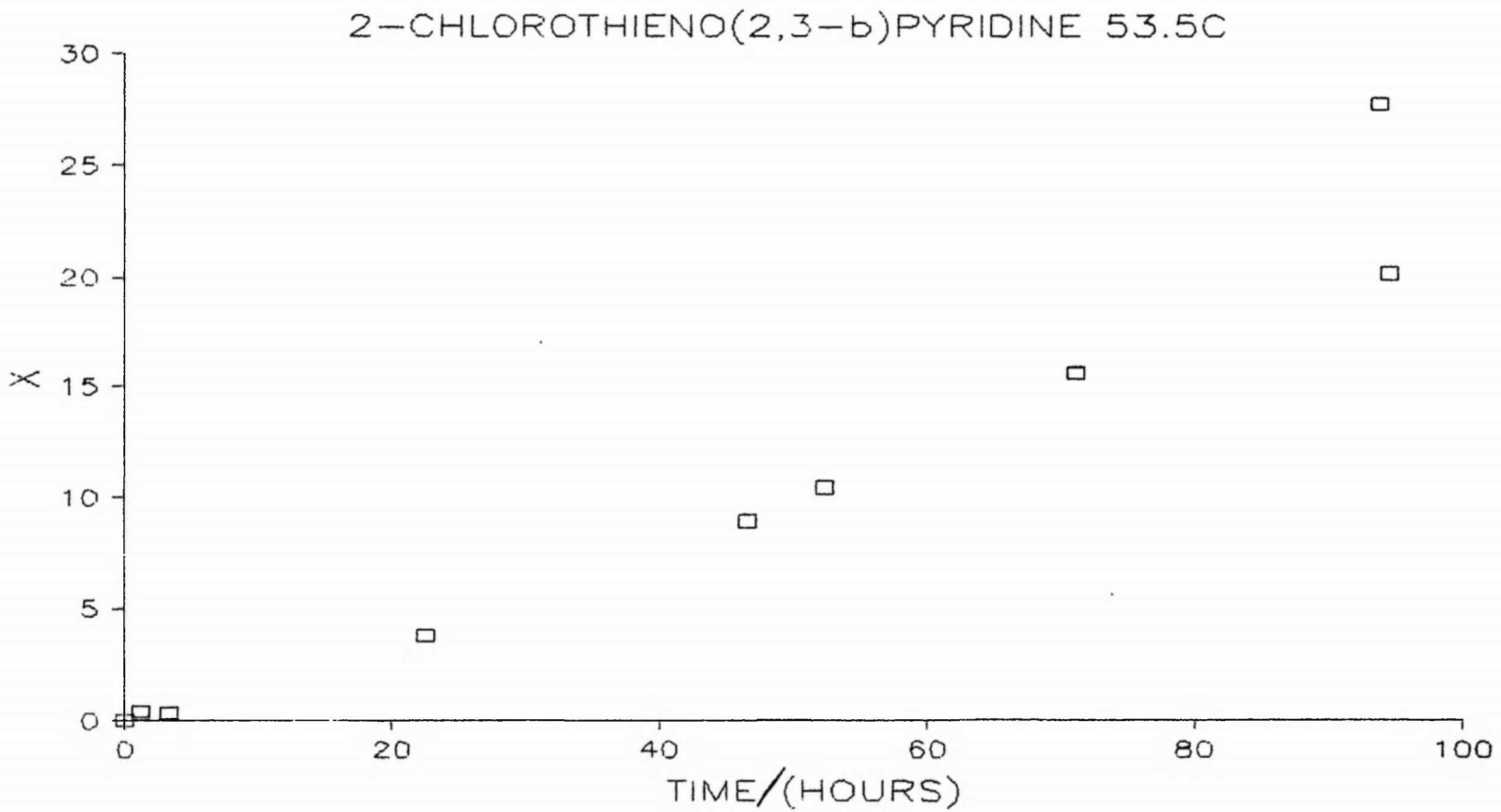
a=.1452mol dm^{-3}
b=4.31E-2mol dm^{-3}
Factor HCl=1.09E-2

n.	time /hrs	titre /mls	100(a-x) /mol dm^{-3}	100(b-x) dm^{-3}	X /mol^{-1} dm^3	% reaction
1	0	40	14.53	4.32	-3E-2	-1
2	1.25	39.3	14.27	4.06	.39	5
3	3.33	39.4	14.31	4.1	.33	4
4	22.6	35.2	12.78	2.57	3.78	40
5	46.6	31.9	11.59	1.38	8.94	67
6	52.4	31.3	11.37	1.16	10.44	73
7	71.2	29.9	10.86	.65	15.63	84
8	93.8	28.6	10.39	.18	27.75	95
9	94.6	29.2	10.6	.39	20.22	90

SLOPE=.249mol^{-1} dm^3 hr^{-1}
BEST FIT RATE CONSTANT=6.9E-5mol^{-1} dm^3 s^{-1}
INTERCEPT=-.994mol^{-1} dm^3
STANDARD DEVIATION OF SLOPE=2.32E-2mol^{-1} dm^3 hr^{-1}
STANDARD DEVIATION OF INTERCEPT=1.3mol^{-1} dm^3
CORRELATION COEFFICIENT=.971

RE-CALCULATION OMITTING THE FOLLOWING PAIRS OF POINTS;
8

SLOPE=.215mol^{-1} dm^3 hr^{-1}
BEST FIT RATE CONSTANT=5.9E-5mol^{-1} dm^3 s^{-1}
INTERCEPT=-.397mol^{-1} dm^3
STANDARD DEVIATION OF SLOPE=6.3E-3mol^{-1} dm^3 hr^{-1}
STANDARD DEVIATION OF INTERCEPT=.312mol^{-1} dm^3
CORRELATION COEFFICIENT=.997


2-CHLOROTHIENO(2,3-b)PYRIDINE 53.5C
30
25
20
15
10
5
0
X
0
20
40
60
80
100
TIME/(HOURS)

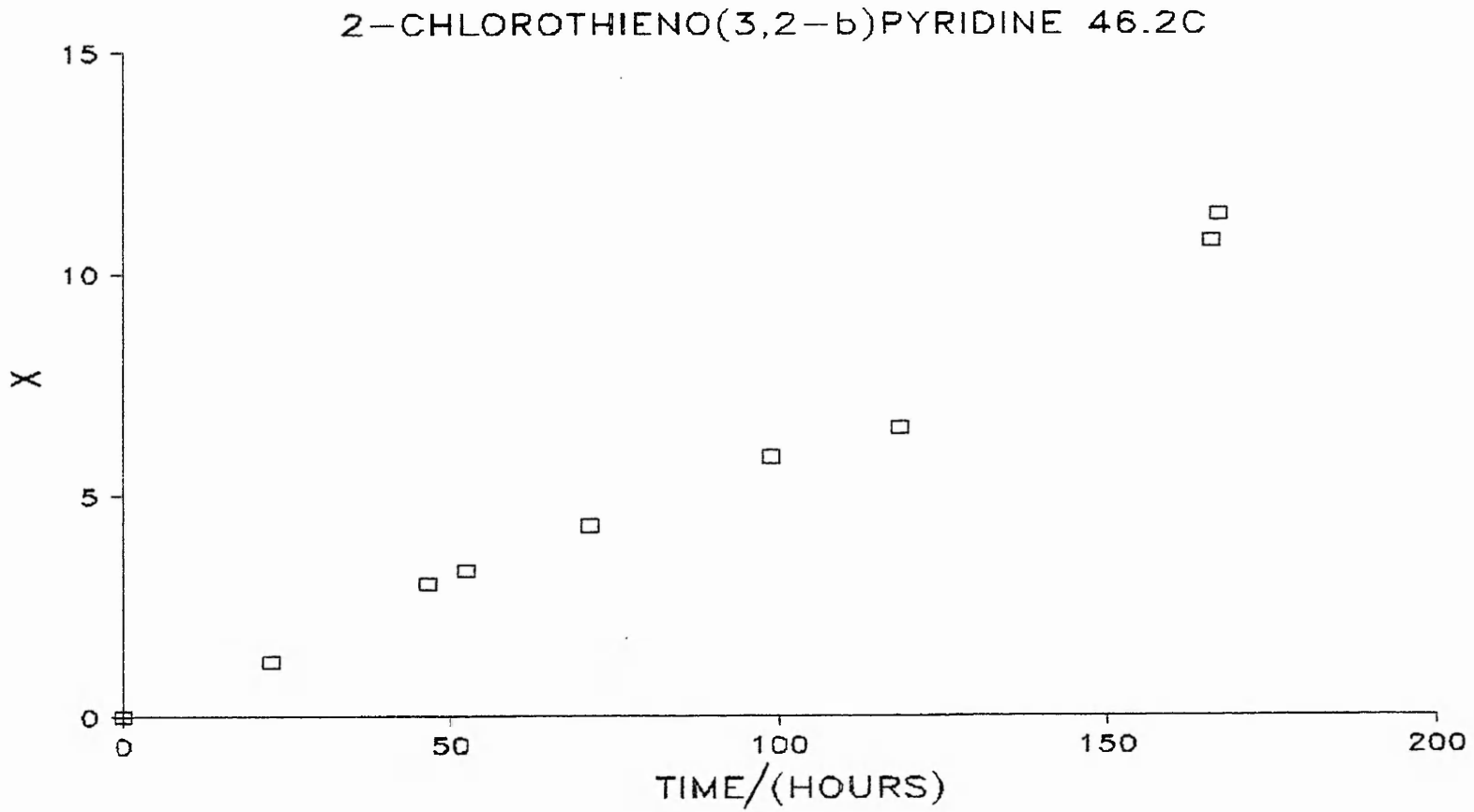
Reaction of methoxide anion with
2-chlorothieno(3,2-b)pyridine
in 1:1 DMSO:Methanol (v/v) at 46.2 C

a=.142mol dm^{-3}
b=4.16E-2mol dm^{-3}
Factor HCl=1.09E-2

n.	time /hrs	titre /mls	100(a-x) /mol dm^{-3}	100(b-x) /mol dm^{-3}	X /$mol^{-1} dm^3$	% reaction
1	0	39.1	14.2	4.16	-2E-2	-1
2	22.6	37.3	13.55	3.51	1.22	15
3	46.6	35.3	12.82	2.78	2.98	33
4	52.4	35	12.71	2.67	3.29	35
5	71.2	34.1	12.38	2.34	4.33	43
6	98.8	33	11.99	1.95	5.86	53
7	118.3	32.6	11.84	1.8	6.51	56
8	165.9	30.7	11.15	1.11	10.71	73
9	166.9	30.5	11.08	1.04	11.32	74

SLOPE=6.5E-2$mol^{-1} dm^3 hr^{-1}$
BEST FIT RATE CONSTANT=1.8E-5$mol^{-1} dm^3 s^{-1}$
INTERCEPT=-.25$mol^{-1} dm^3$
STANDARD DEVIATION OF SLOPE=2.8E-3$mol^{-1} dm^3 hr^{-1}$
STANDARD DEVIATION OF INTERCEPT=.285$mol^{-1} dm^3$
CORRELATION COEFFICIENT=.993

RE-CALCULATION OMITTING THE FOLLOWING PAIRS OF POINTS;
8 9
SLOPE=5.6E-2$mol^{-1} dm^3 hr^{-1}$
BEST FIT RATE CONSTANT=1.5E-5$mol^{-1} dm^3 s^{-5}$
INTERCEPT=.139$mol^{-1} dm^3$
STANDARD DEVIATION OF SLOPE=2.3E-3$mol^{-1} dm^3 hr^{-1}$
STANDARD DEVIATION OF INTERCEPT=.165$mol^{-1} dm^3$
CORRELATION COEFFICIENT=.995


2-CHLOROTHIENO(3,2-b)PYRIDINE 46.2C
15
10
5
0
X
0
50
100
150
200
TIME/(HOURS)

Appendix 2.

The equations used to calculate the activation parameters (whose values are given p. 158-160) are given below. For the observed rate constants k_1 and k_2 at temperatures T_1 and T_2;

$$\text{Activation Energy,} \quad Ea = \frac{T_1 * T_2 * 8.314}{(T_2 - T_1)} . \; LN\left(\frac{k_1}{k_2}\right)$$

$$\text{Enthalpy Of Activation,} \quad \Delta H^{\#} = Ea - (8.314 * T_m)$$

$$\text{Gibbs Free Energy, Of Activation} \quad \Delta G^{\#} = LN\left(\frac{1.38*10^{-23}*T_m}{6.626*10^{-34}*k_m}\right) * 8.314 * T_m$$

$$\text{Entropy Of Activation,} \quad \Delta S^{\#} = \frac{\Delta H^{\#} - \Delta G^{\#}}{T_m}$$

$$\text{where;} \quad T_m = \frac{(T_1+T_2)}{2} \quad , \quad k_m = e^{\wedge} \frac{(LOG_e\ k_1 + LOG_e\ k_2)}{2}$$

The equations used to the determine the standard deviation values of the energy and entropy of activation (S.D. Ea and S.D. $\Delta S^{\#}$ respectively) from the standard deviations of the rate-constants (S.D. k_1 and S.D. k_2) are given below;

$$\text{S.D. Ea} = \left[\left(\frac{\text{S.D. } k_1}{k_1}\right)^2 + \left(\frac{\text{S.D. } k_2}{k_2}\right)^2\right]^{1/2} * \frac{(8.314 * T_1 * T_2)}{(T_2 - T_1)}$$

$$\text{S.D. } \Delta S^{\#} = \frac{[\text{S.D. Ea}]^2}{(T_1+T_2)}$$

Appendix 3

Listings Of The Computer Programs Which Were Written By Author To The Interpret Experimental Results.

(a) The computer program used to calculate the best fit rate constants for individual runs (given on p. 157).

```
100 CSIZE 0,0:OPEN #5,ser1:CLS #0:CLS #1:CLEAR
110 PRINT "DETERMINATION OF RATE CONSTANT, kAND STATISTICAL
 ANALYSIS OF SECOND-ORDER PLOTS ON THE NUCLEOPHILIC SUBSTIT
UTION (METHOXIDE) OF     CHLORINATED THIENO(b)PYRIDINES   A
ND QUINOLINES"
120 INPUT "Reacting Substrate?";su$
130 INPUT "and initial concentration";rclin
140 INPUT "initial Methoxide concentration";metin
150 INPUT "Molarity of HCl used";HCl
160 INPUT "Temperature";temp
180 PRINT#5,TO 35; "Reaction of methoxide anion with "\,TO
35,su$\,TO 35,"in 1:1 DMSO:Methanol (v/v) at ";temp;" C"
190 PRINT #5
200 PRINT #5,TO 43, "a=";metin;"mol dm "
210 PRINT #5,TO 43,"b=";rclin;"mol dm "
220 PRINT #5,TO 43,"Factor HCl=";HCl
230 PRINT #5
240 INPUT "NUMBER OF PAIRS OF POINTS";N
250 DIM X(N),Y(N),time(N),base(N),RCl(N),titre(N)
260 PRINT "TIME,TITRE"
270 FOR I= 1 TO N
280 INPUT time(I),titre(I)
290 NEXT I
300 CLS
310 PRINT "N.","TIME","TITRE"
320 FOR I= 1 TO N
330 PRINT I,time(I),titre(I)
340 NEXT I
350 INPUT "WISH TO CHANGE ANY VALUES?(Y/N)";ANSWER$:IF ANSW
ER$="N" THEN GO TO 380
360 INPUT "TYPE IN N., TIME,TITRE";NUM,tim,tit:time(NUM)=ti
m:titre(NUM)=tit
370 GO TO 300
380 PRINT #5,TO 25;"n.";"     time";"    titre";" 100(a-x)"
;" 100(b-x)";"   X";"      %"
390 PRINT #5,TO 25;"        hrs      mls        mol dm      m
ol dm  reaction"
400 FOR I=1 TO N
410 LET base(I)=(HCl/3)*titre(I)
420 LET RCl(I)=rclin-(metin-base(I))
430 LET Y(I)=LN((base(I)*rclin)/(metin*RCl(I)))/(metin-rcli
n)
440 X(I)=time(I)
450 PRINT #5,TO 25;I,time(I),titre(I),INT(10000*base(I))/10
0,INT(10000*RCl(I))/100,INT(100*Y(I))/100,INT(100*(rclin-RC
l(I))/rclin)
460 NEXT I
470 T=0
480 I=0:Z=0:W=0:D=0:Q=0:R=0
490 FOR I = 1 TO N
500 IF titre(I)=0 THEN GO TO 540
510 Q=Q+Y(I):R=R+X(I)
520 Z=Z+Y(I)*X(I):W=W+Y(I)*Y(I)
530 D=D+X(I)*X(I)
```

```
540 NEXT I
550 N=N-T
560 L=Q/N:M=R/N
570 U=(Z-N*L*M)/(D-N*M*M)
580 V=((W-N*L*L)/(D-N*M*M)-U*U)/(N-2)
590 S=SQRT(V):P=L-U*M:F=S*SQRT(D/N)
600 COCO=(N*Z-Q*R)/((N*D-R^2)*(N*W-Q^2))^.5
610 PRINT #5
620 PRINT #5,TO 33, "SLOPE=";INT(U*1000)/1000;"mol dm hr"
630 K=U/3600
640 PRINT #5,TO 33,"BEST FIT RATE CONSTANT=";INT(1E6*K)/1E6
;"mol dm s"
650 PRINT #5,TO 33, "INTERCEPT=";INT(P*1000)/1000;"mol dm"
670 PRINT #5,TO 33,"STANDARD DEVIATION OF SLOPE=";INT(S*100
00)/10000;"mol dm hr"
680 PRINT #5,TO 33,"STANDARD DEVIATION OF INTERCEPT=";INT(1
000*F)/1000;"mol dm "
690 PRINT #5,TO 33, "CORRELATION COEFFICIENT=";INT(1000*COC
O)/1000
700 INPUT "WISH TO REPEAT CALCULATIONS OMITTING CERTAIN RES
ULTS";ANSW$
710 IF ANSW$="N" THEN STOP
720 INPUT "NUMBER OF PAIRS?";T
730 DIM OMIT(T)
740 PRINT "INPUT THE VALUE OF n. CORRESPONDING TO THOSE VAL
UES TO BE NEGLECTED"
750 FOR I= 1 TO T
760 INPUT OMIT(I)
770 NEXT I
780 PRINT #5
790 PRINT#5, TO 25,"RE-CALCULATION OMITTING THE FOLLOWING
PAIRS OF POINTS;"
800 FOR I=1 TO T
810 PRINT #5,TO 30,OMIT(I);
820 titre(OMIT(I))=0
830 NEXT I
840 GO TO 480
```

(b) The computer program used to calculate the activation parameters, whose values are given in Table 3, p. 158-160.

```
100 CLS #0:CLS #1:CLEAR
110 OPEN #5, SER1
120 PRINT "Determination of activation para-"\"meters"
130 INPUT "substrate";substrate$
140 PRINT #5, substrate$
150 INPUT "T1=";ta,"T2=";tb,"K1=";ka,"K2=";kb,"S.D. on K1="
;sdka,"S.D. on K2=";sdkb
160 ta=ta+273.2:tb=tb+273.2:z=(ta+tb)/2
170 ea=LN(ka/kb)*(8.314*ta*tb/(ta-tb))
180 h=ea-(8.314*z):f=EXP((LN(ka)+LN(kb))/2)
190 g=LN((1.38E-23*z)/(6.626E-34*f))*8.314*z
200 s=(h-g)/z
210 PRINT #5,"activation energy = ";ea;"kJ/Mol"
220 PRINT #5, "enthalpy of activation = ";h;"kJ Mol"
230 PRINT #5, "Gibbs free energy of activation=";g;"kJ/Mol"
235 PRINT #5, "entropy of activation=";s;"J mol K"
240 sdea=((sdka^2/ka^2)+(sdkb^2/kb^2))^.5*(8.314*ta*tb)/(tb
-ta)
250 sdea=sdea/1000
260 PRINT #5, "standard deviation on activation energy=";sd
ea;"kJ mol"
270 sds=2000*sdea/(ta+tb)
280 PRINT #5,"standard deviation on activation of entropy="
;sds;"J mol K"
```