SUMMARY

This Thesis reports attempts to prepare thienopyridine analogues of simple quinoline alkaloids, and a study of aspects of the chemistry of various thieno[3,2-b] and [3,4-b]pyridine derivatives that were obtained as a result.

In the first approach the intention was to prepare 6-methylthieno-[2,3-b]pyridin-4(7H)one, from 2-aminothiophen, by a method described in the literature, with a view to elaborating the 6-methyl group. Nitration of thiophen under a variety of conditions always gave mixtures of the 2- and 3-nitro-compounds and various techniques were examined in attempts to obtain material enriched in the 2-isomer. Reduction, and reaction of the aminothiophen with ethyl acetoacetate gave N-(2-thienyl)-3-keto-butanamide and not the product previously reported. Cyclisation then led to 4-methylthieno[2,3-b]pyridin-6(7H)one.

Approaches to isomer-free aminothiophens were next investigated. Both the Beckmann rearrangement of 2-acetylthiophen oxime and the nitration/reduction of thiophen-2-carboxylic acid and ethyl thiophen-2-carboxylate failed to produce acceptable yields of pure aminothiophens. Nitration of thiophen-3-carboxylic acid and its ethyl ester did provide isomer-free nitro derivatives, which, on reduction and subsequent reactions also gave thienopyridines isomeric with those required.

Next, the possibility of preparing thienopyridines by vapour phase techniques (that are successful for the synthesis of thiophen and benzothiophens) was explored. Although reaction of 2-vinyl pyridine with carbon disulphide did produce thienopyridines, the yields were too low to make the route synthetically useful.

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Finally, the application of 3-amino-2-acylthiophens to the synthesis of thienopyridines was explored. Syntheses of the Camps and Friedlander types were unsuccessful. Although the 3-aminothiophen derivatives failed to form adducts with methyl tetrolate, the 2-methoxycarbonyl compound provided excellent yields of the Michael adduct on reaction with dimethyl acetylene dicarboxylate. The adduct could be cyclised either to a thieno[3,2-b] or a thieno[3,4-b] pyridine, according to the conditions employed. The chemistry of the thienopyridines obtained from this intermediate was explored, and analogues of the alkaloids echinopsine and echinorine were prepared. Similar adducts were formed by addition of the 3-aminothiophen to ethoxymethylene malonate, and these, too, were cyclised to thieno[3,2-b]- or [3,4-b]pyridines.

TRENT POLYTECHNIC

Thienopyridine Analogues of Quinoline Alkaloids

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

ARWEL WYN JONES, BSc

January 1979

TABLE OF CONTENTS

PREFACE

The work described in this thesis was carried out by the author in the laboratories of the Department of Physical Sciences, Trent Polytechnic, Nottingham, between September 1975 and September 1978.

The author wishes to express his gratitude to Dr J. M. Barker for his constant encouragement and supervision throughout the course of the work. Thanks are also due to Dr.P. R. Huddleston for his enthusiasm and helpful advice.

The author is also indebted to Mr T. Webster, of Croda Synthetic Chemicals Limited, Four Ashes, Wolverhampton, for the use of facilities at their laboratories and to Dr R. Hull of ICI Pharmaceuticals Division, Alderley Edge, for the gifts of chemicals and elemental analyses. Thanks are also extended to Dr J. Adamczewska for Russian translation and to Mr M. Wood for technical assistance. Thanks are also extended to Mrs. S. McIntyre for the typing of this thesis.

ARWEL WYN JONES

TRENT POLYTECHNIC

To Sandra and Sarah

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CHAPTER ONE

INTRODUCTION

1.1 Introduction

Since the work described in this thesis had as its main aim the synthesis of thiophen analogues of quinoline alkaloids (in which a benzene ring is replaced by a thiophen ring) it seems appropriate to discuss the following topics as background material.

Firstly, the properties of thiophen and benzene are compared, and the justification of replacing one ring by the other in compounds of potential pharmacological interest is discussed. Secondly, an outline of the occurrence and structural variety of the quinoline alkaloids is given.

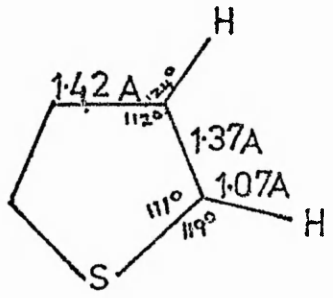
Further, the work has involved the synthesis and a study of some thieno*[b]*pyridines. A brief review of this area of chemistry is therefore also included.

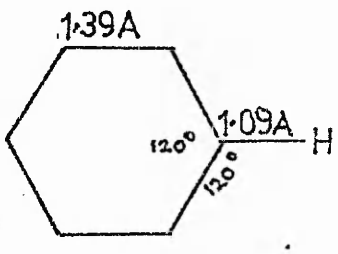
1.2 A comparison of the structural, physical and chemical properties of thiophen and benzene

The similarities in physical and chemical properties of thiophen and benzene have long been recognised. It therefore follows that the thiophen analogues of biologically active compounds containing benzene rings should have been prepared and examined for pharmacological activity.

The molecular dimensions of thiophen and benzene are very similar, illustrated in the scale drawing below:

(1) Molecular dimensions[1-3]



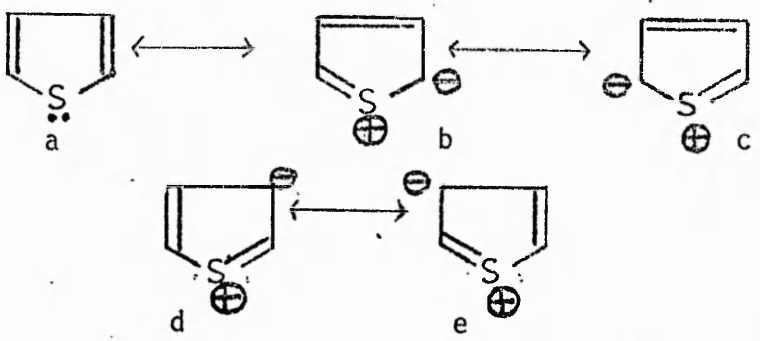


The physical constants for the two compounds tabulated below also reveal a broad similarity, although the densities and freezing points of the two substances are significantly different.

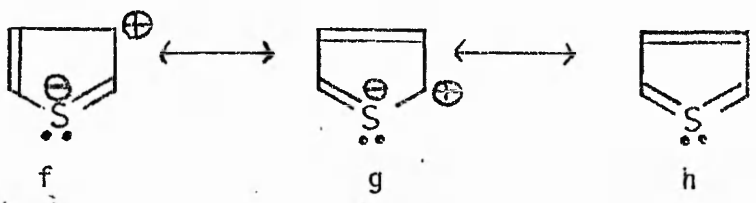
Physical constants

Property	Benzene	Thiophen
boiling point (760 mm), ^{o}C	80.1	84.1
freezing point, ^{o}C	5.5	-38.3
d_4^{20}, g cm^{-3}	0.8790	1.0644
Dn_0	1.5011	1.5287
Dn_{20}	0.650	0.662
molecular refraction (20^{o})	26.185	24.365

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



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

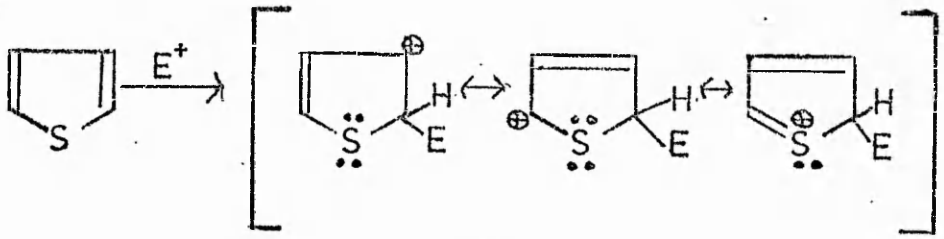


The simple molecular orbital representations of thiophen and benzene again reveal similarities and differences. In both systems there is a planar, σ bond framework of sp^2 hybridised atoms and a delocalised 6π electron system; however, in thiophen the sulphur 3p orbital is involved in the construction of the π-bonding molecular orbitals, whereas in benzene only 2p orbitals contribute.

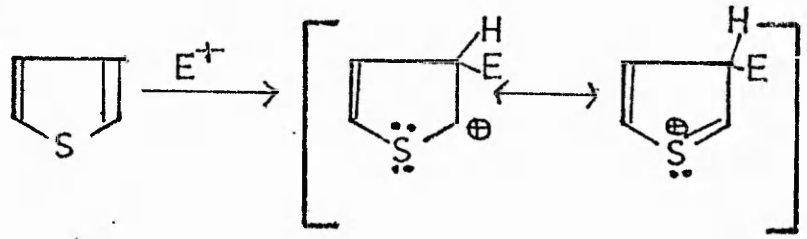
Chemical behaviour

Both thiophen and benzene react with electrophiles in substitution reactions. In the case of thiophen, consideration of the delocalization energies of the Wheland intermediates for the two possible positions of substitution helps to explain why the reaction takes place predominantly at the 2-position.[4,5]

2-substitution:



3-substitution:



As would be expected from its π excessive nature, thiophen is considerably more reactive towards electrophiles than is benzene; it can be brominated, acylated, formylated and chloromethylated under conditions

which fail to give a reaction with benzene. This is illustrated by the fact that typical Friedel-Crafts acylations of thiophen can be carried out in benzene as solvent.

In general, substituents attached to the thiophen ring show unexceptional behaviour; however, hydroxy and amino groups prove to be exceptions. Unlike their benzene counterparts, hydroxythiophens are inaccessible and unstable compounds, which exist predominantly in the keto form. The nmr spectrum of 2-hydroxythiophen, for example, indicated the dominance of 5[H]-thiophen-2-one.[6] Both 2- and 3-amino-thiophen are very unstable as free bases, although acyl derivatives and salts are stable.

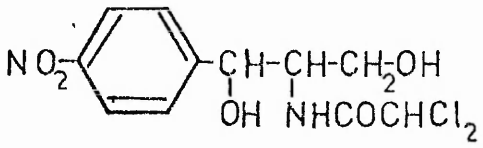
1.3 Biological activity of thiophen

The general conclusion to be drawn from the studies made of simple thiophen derivatives is that these compounds exert similar, but less pronounced pharmacological activity compared with their benzene analogues. In some cases, however, related compounds have different effects; for example, thienyl ketones are convulsants, whereas their benzene counterparts are hypnotics.[7]

Thiophen exerts a toxic action on the nervous system, and causes histological damage of the cerebellum,[8] as does benzene; it produces convulsions, muscular weakness, fall in blood pressure, and death when administered to experimental animals.[9] Thiophen has found use therapeutically as a bacteriostat, insecticide and anthelmintic and as an ingredient of ointments used for treatment of skin infections.[10]

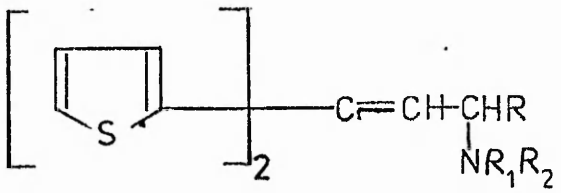
Many thiophen compounds have been tested for biological activity; as this number is particularly large, the following discussion considers only those thiophen compounds that are analogues of a benzene counterpart, with a comparison of their relative pharmacological activity.

β-2-Thienylethylamine[11] showed pronounced central nervous stimulating properties, of comparable activity to its benzene counterpart, but possessing a considerably lower threshold dose. Thiophen compounds structurally related to chloramphenicol (1) have been prepared;[12] however, the antibacterial activity of these was much lower than that of the natural antibiotic.[13]



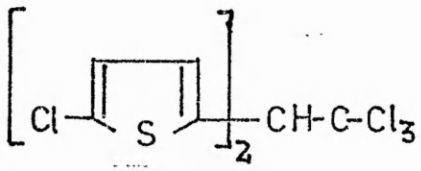
(1)

The thiophen analogues (2) of 3,3-diphenylallylamines were found to have antihistaminic and local anaesthetic properties,[14] as well as pronounced analgesic activity.[15] However, they also possess the same disadvantages as the benzenoid derivative in that they are addictive.[16]



(2)

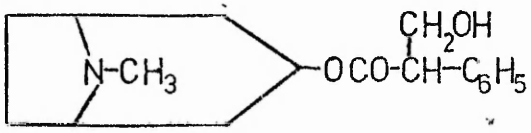
The thiophen analogues of methadone and isomethadone have been prepared and have been shown to be active analgesics.[17] The preparation of the thiophen analogue of 2,2-bis-(p-chlorophenyl)-1,1,1-trichloroethane (D.D.T.) was reported by Prill et al,[18] who discovered that 2,2-bis-(2-thienyl)-1,1,1-trichloroethane was inactive against the housefly. However, 2,2-bis-(2-chloro-5-thienyl)1,1,1-trichloroethane (3) has been reported to be effective against cockroaches.[19]



(3)

Considering the large number, structural diversity and pharmacological activity of the alkaloids it is rather surprising that so few thiophen analogues have been recorded. The instability of hydroxythiophens and the inaccessibility of methoxythiophens may be partially responsible for this, since the benzene rings in the majority of the simpler alkaloids carry these substituents.

Atropine (4) and cocaine (5) are obvious exceptions, and the synthesis of the 2-thienyl analogues of these substances was reported by Steinkopf and his co-workers.[20]



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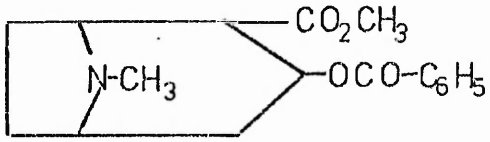
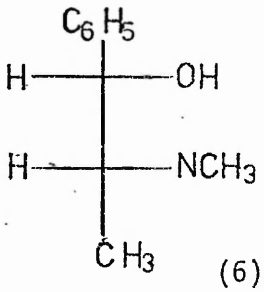


(5)

These analogues were shown to possess approximately the same pharmacological activity as the natural substances.

Barker, Huddleston and Byron[21] have prepared the 2-thienyl analogues of ephedrine (6) and ψ-ephedrine (7). It was found that the ephedrine analogues had about one-third the activity of ephedrine in its effect on the spinal cat, but the ψ-ephedrine analogue was inactive. The syntheses of the 3-thienyl analogue of ephedrine and a number of related halogenated substances have also been reported.[22]



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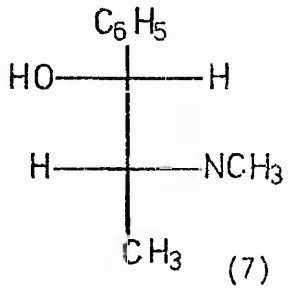
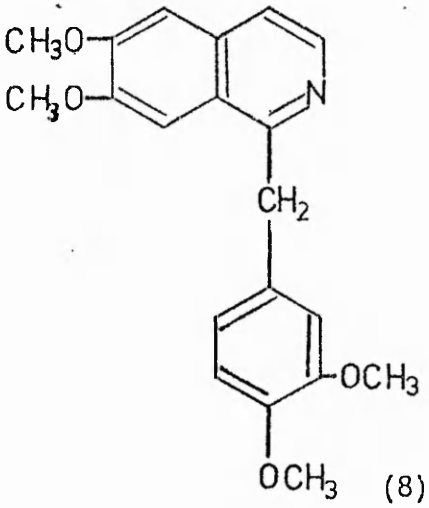


(7)

Hertz and Tsai[23] report attempts to prepare thienyl analogues of papaverine (8). The compound (9) obtained by these workers is not a true papaverine analogue since it lacks two methoxy groups (which should be sited on the vacant positions of the thiophen ring).



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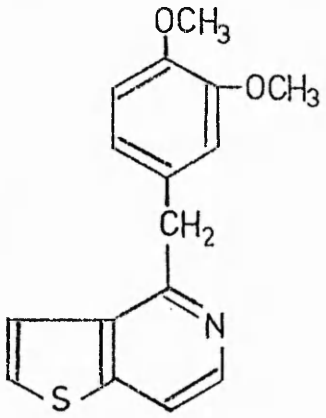
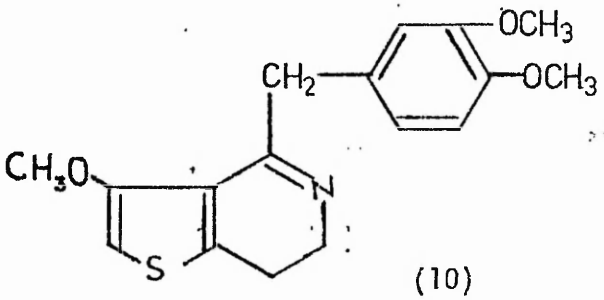


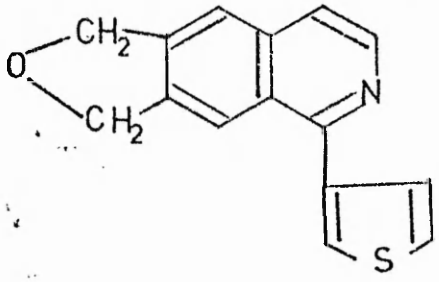
(9)

In an attempt to prepare a methoxythienopyridine analogue, Lawson[24] obtained the dihydrothienopyridine (10) shown below:-



(10)

Kametani and his co-workers[25] have carried out a great deal of work on the synthesis of substances related to papaverine; among the many compounds described are a number of 6,7-dioxygenated isoquinolines (for example compounds 11 and 12) bearing a thiophen substituent in the 1-position.



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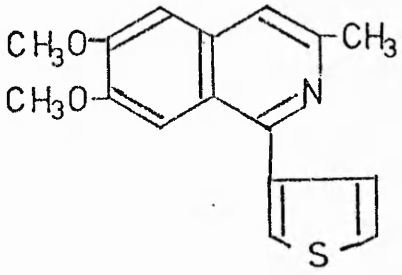


(12)

1.4 The Quinoline alkaloids

Introduction

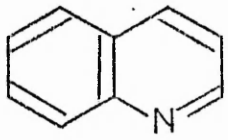
The alkaloids have been of great importance to man for centuries, long before they were recognised as a chemical class. Their influence on folklore, medicine and primitive cultures are immeasurable. The scientific study of alkaloids may be said to have begun with the isolation of morphine by Serturner in 1804.

The term "alkaloid" usually applies to basic nitrogen-containing compounds of plant origin. Usually (but not always) the nitrogen atom is incorporated into the structure as part of a heterocyclic ring, and the compounds manifest significant pharmacological activity.

It has been estimated that alkaloids are found in only 10-15% of all vascular plants; generally a given genus or related genera yield the same or structurally related alkaloids. The function of alkaloids in plants remains a subject for speculation. Many authorities regard them as by-products of plant metabolism, whilst others regard them as reservoirs for protein synthesis or as protective materials, discouraging animal or insect attack.

Alkaloids are commonly classified either according to the plant genera in which they occur, or on the basis of similarities in molecular structure. The latter classification is based on the skeletal features which members of a group possess in common (eg. the isoquinoline alkaloids).

Alkaloids possessing the quinoline nucleus (13) constitute one of the smallest groups. Several simple derivatives of quinoline are found in the family Rutaceae, as well as in the Compositae (genus Echinops). Quinoline itself has been reported to occur in *Peganium harmala*, together with 2-methylquinoline.[26]



(13)

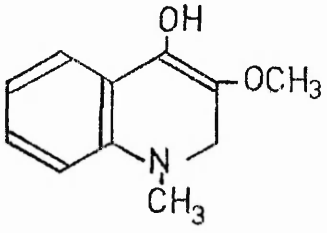
In the following discussion a general review of quinoline alkaloids is given; Echinopsine and Echinorine, of which thienopyridine analogues have been prepared in the present work (section IV) are discussed in greater detail.

The quinoline alkaloids can be conveniently divided into three broad structural types:

(i) simple substituted quinolines
(ii) simple substituted quinolin-4-ones
(iii) simple substituted quinolin-2-ones.

1.5 (i) Simple substituted quinolines

The occurrence of quinoline and 2-methyl quinoline has already been mentioned. From *Echinops ritro* some simple dihydroquinoline derivatives (eg. 14) have been isolated.[27] The rather more complex alkaloid japonine, from *Orixa japonica*, was shown to have the structure (15) by chemical studies and by spectroscopy, particularly by comparison of its spectra with those of synthetic 2- and 3-phenyl-quinolines.[28]



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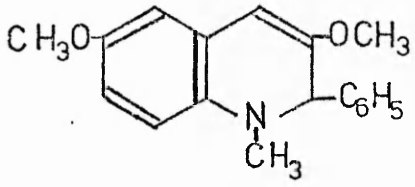
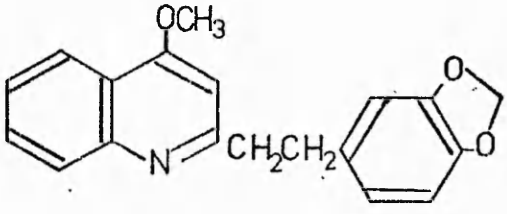


(15)

From the bark of *Galipea officinalis* the alkaloids cusparine (16) and galipine (17) have been isolated.[29] Both are tertiary bases and give methiodides, which on treatment with alkali give isocusparine (18) and isogalipine (19), respectively.



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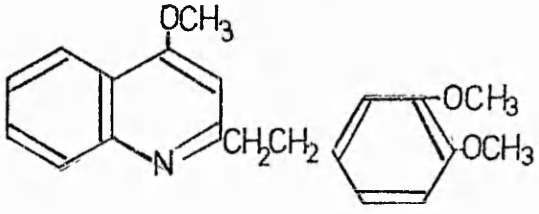

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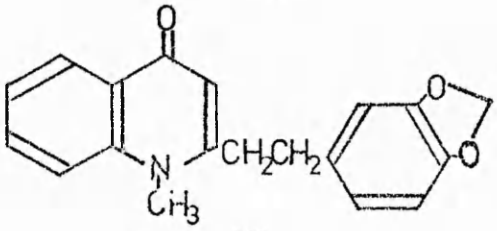

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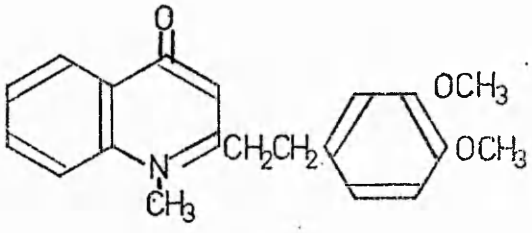
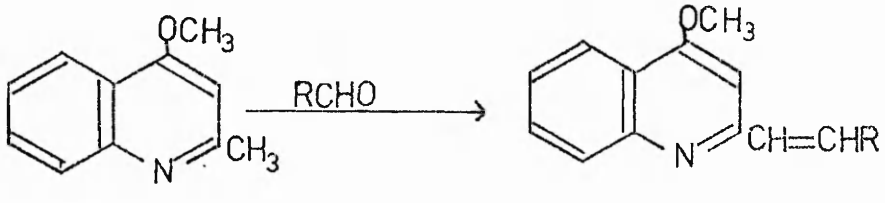


(19)

Oxidation of galipine with potassium permanganate gave veratic acid and 4-methoxyquinoline-2-carboxylic acid.[29] The two alkaloids (16) and (17) were synthesised by Späth and Eberstaller,[30] by condensation of 4-methoxy-2-methylquinoline (20) with piperonal or veratraldehyde, respectively, in the presence of zinc chloride, followed by catalytic hydrogenation:-



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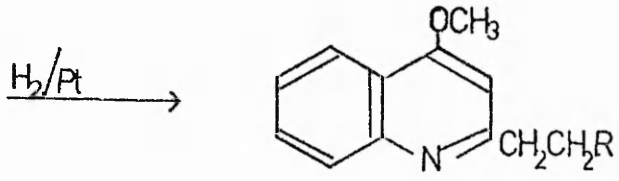
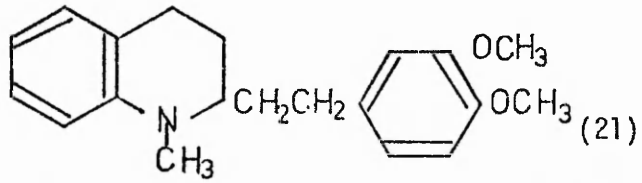


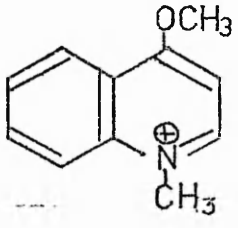
The closely related alkaloid cuspareine (21) was also isolated from the same source. It was synthesised by Stanĕk, by a similar procedure to that described above, from quinaldine methiodide and veratraldehyde.



(21)

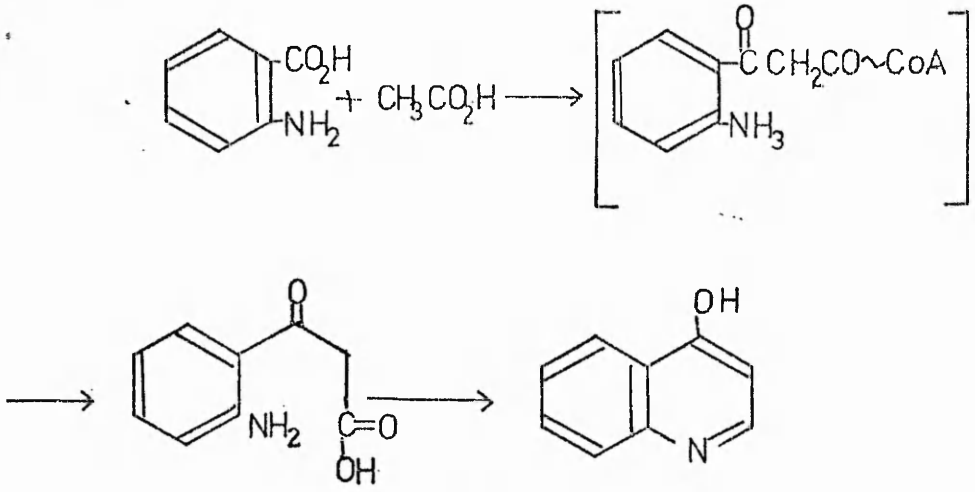
Echinorine (a 1-methyl-4-methoxy-quinolinium salt) (22) has been isolated from *Echinops communtatis*,[32] from *Echinops ritro L*[33] and from *Echinops sphaerocephalus*.[34]

The structure of echinorine was confirmed by Schroder[33] by comparison of its spectral data with those of a synthetic sample.



(22)

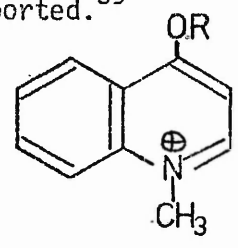
The biosynthesis of this alkaloid is suggested to follow the pathway from anthranilic acid, shown below:[34]



(22)

This is supported by the increase in echinorine content when *Echinops schaerocephalus* was fed extra tryptophan (precursor to anthranilic acid),[35] and by incorporation of ^{14}C labelled anthranilic acid.[36] This pathway is in general agreement with the accepted biosynthetic route to quinoline alkaloids.[37,38]

The syntheses of echinorine analogues of the type shown below (23) have been reported.[39]



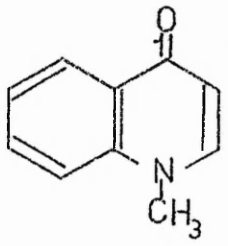
where R = CH_2CH_2OH or $CH_2C_6H_5$

(23)

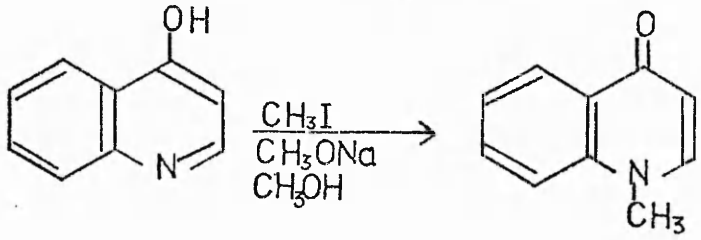
No appreciable pharamcological activity was found for these substances.

1.6 (i) Simple substituted Quinolin-4-ones

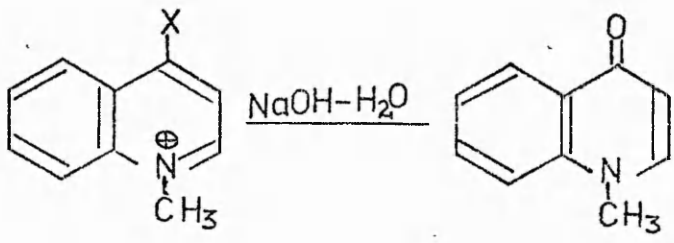
The simplest alkaloid in this group is Echinopsine(1-methylquinolin-4-one) (24), first isolated by Gershoff[40] in 1900.



This alkaloid has been isolated from a number of species of Echinops, eg. *Echinops schaerocephalus*[41] from *Echinops communtatis*,[42] from *Echinops ritro L*[40] and from *Echinops ritro ruthenicus*.[43] Its structure was determined by Späth[44] in 1922, who synthesised the compound by heating a mixture of 4-hydroxyquinoline, iodomethane and sodium methoxide in methanol in a sealed tube at 100°.



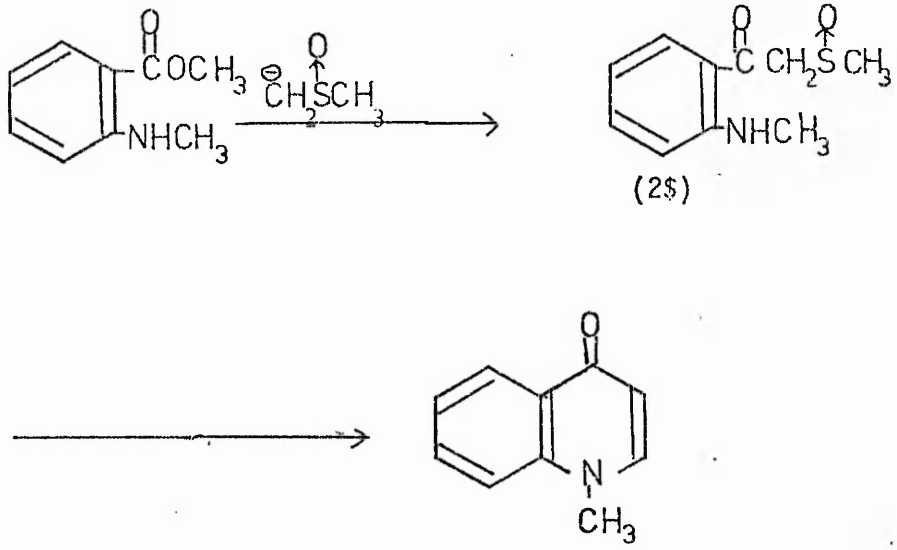
Several other syntheses of echinopsine have been reported; two involve nucleophilic displacements from the 4-substituted-1-methyl-quinolinium salts (25(a) *[echinorine]*[32] and 25(b)[20]).[45]



25(a) X = OCH_3, Y = I

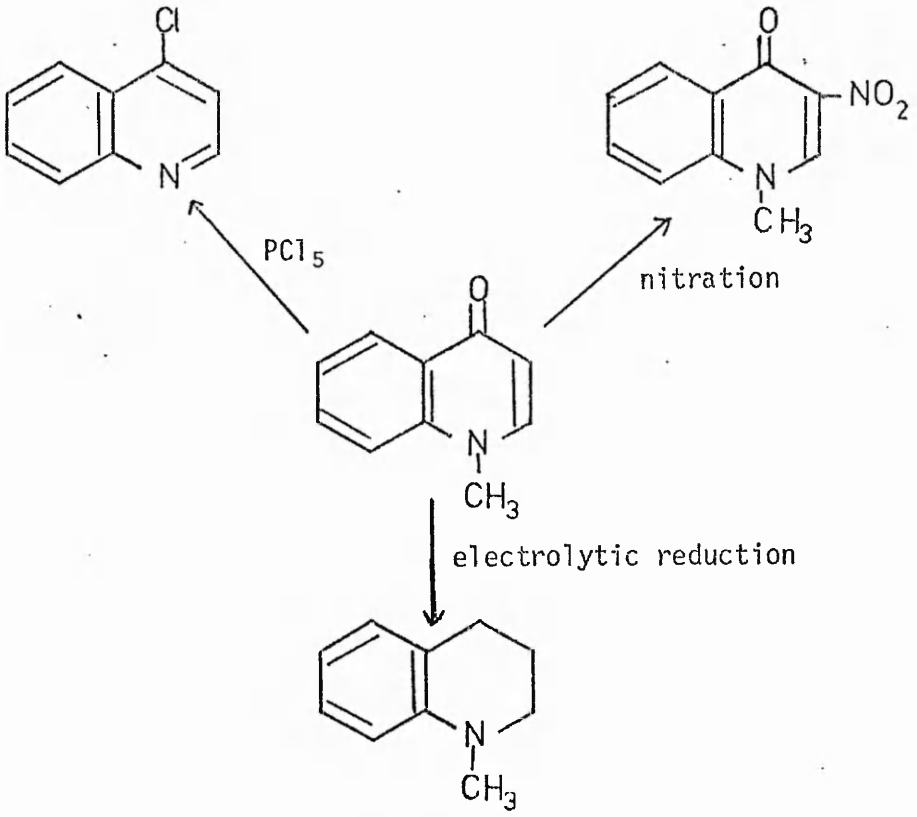
25(b) X = N_3, Y = CH_3SO_4

The reaction of (25(a) (echinorine)) is noteworthy (see section IV). A multi-step synthesis from quinoline itself was carried out by Kondo,[45] whilst Strandtmann[46] prepared the compound by the interesting route outlined below - in which condensation of o-amino-w(methylsulphonyl) acetophenone (26) with formaldehyde by refluxing in toluene in the presence of a catalytic amount of piperidine gave echinopsine:-



Echinopsine forms faintly yellow crystals which separate from water as a hydrate; it is sparingly soluble in ether, but readily soluble in chloroform and ethanol. It is optically inactive and gives an intense blood red colour with ferric chloride solution.

Echinopsine shows fairly typical quinolin-4-one behaviour. Due to the interaction between the carbonyl group and the nitrogen atom it is a very weak base; electrolytic reduction at a lead cathode gives 1,2,3,4-tetrahydro-1-methylquinoline (27),[44] nitration yields the 3-nitro derivative,[47] and treatment with phosphorus pentachloride at 150^{o} results in demethylation.

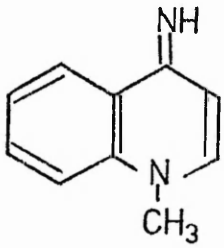


The complete biosynthesis of the alkaloid has not yet been elucidated. However, addition of probable precursors, ie. tryptophan, phenylalanine, and anthranilic acid[48,49] to seedlings of *Echinops sphaerocephalus* cultivated in sterile media led to an increase in the echinopsine content in the grown plants when compared with others not so treated.

The pharmacology of echinopsine has been the subject of much interest in Eastern Europe. An ultra-violet spectroscopic method of analysis, applicable to tablets, has been reported,[50] and a method for the quantitative determination of the alkaloid in globe thistle fruits (by titration of the extracts with 0.1 M perchloric acid in acetic acid solution) is available.[51] The oral LD_{50} in mice and rats were found to be 460 mg/kg and 290 mg/kg respectively.[52] The main effect of the alkaloid on the central nervous system is depressant,[53] and in high doses it induces narcosis; at low dosage in rats it causes decreased brain nor-adrenaline levels.[54] It has negligible anti-cholinesterase activity.[55] A combination of echinopsine and amphetamine induced convulsions when injected intravenously into mice.

In general substitution of a methyl, methoxy, ethoxy or chloro group at the 6- or 8-position of 2-methyl derivatives of echinopsine increased the activity and the toxicity of the compound,[57] eg. 2,6-dimethylechinopsine caused a non-specific central stimulation, followed by depression with myo-relaxation in mice. Phenyl-nor-echinopsine had some estrogenic effects in mice,[58] and phenacyl-nor-echinopsine had central nervous system depressant activity.[59]

A structurally similar alkaloid, Echinopsidine (28) was isolated from *Haplophylum perforatum* and from *Echinops schaerocephalus*.[60] Schroder,[61] however, disputes the presence of echinopsidine in these plants, his work indicating that the compound is formed during the isolation procedure or during storage of the plant material, by ammonolysis of echinopsine.

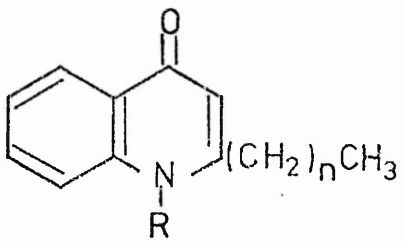


(28)

The activity of this compound has been investigated; it blocked autonomic ganglia, and had a mild hypotensive action and decreased neuromuscular activity, and was also a weak in vitro inhibitor of cholinesterase.[59]

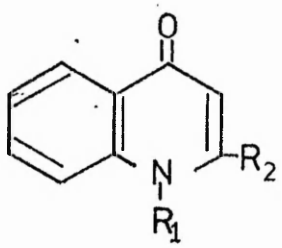
The 2,3-dihydro derivative of echinopsidine was found to be ten times more toxic than echinopsine to mice. It was shown to decrease arterial blood pressure, induced bradycardia and blocked ganglionic nerve impulse transmission.[62] 2-Methyl-6-ethoxy-echinopsidine had greater anticholinesterase activity than echinopsidine itself.[59]

Several alkaloids which possess the quinolin-4-one system carrying a long-chain alkyl substituent at C-2 (29) are known.[63]



(29)

These were first found in fungi, but in recent years have been shown to be present in higher plants. 2 -Undecylquinolin-4-one (29, R = H, n = 10) has been isolated from *Ptelea trifoliata*,[63] and the roots of *Rutus graveoleus* contain a mixture of compounds of this type (29, R = H, n = 10-13).[64] Extracts of the leaves and fruits of *Evodia rutaecarpa* yielded three 1-methyl substituted compounds (29, R = CH_3, n = 10, 12 and 14).[64] Alkaloids of the same general form, but carrying rather more elaborate side chains at C-2 have been characterised.



(30)

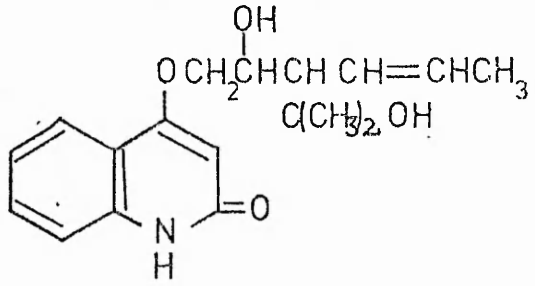
Thus, acutine[65] (30, R_1 = H, R_2 = $(CH_2)_3CH{=}CH{-}CH_2CH_3$) is present in *Haplophyllum acutifolium*, and *Vepris anipody*[66] has yielded compounds, so far not given trivial names, of general formula (30) where R_1 = H, R_2 = $-(CH_2)_9COCH_3$, $-(CH_2)_8CH_2OH$ and $(CH_2)_2CH{=}CH{-}CH_2{-}CH{=}CH{-}CH_2CH_3$.

In yet another group of alkaloids of general formula (30) the substituent at C-2 is aromatic. For example, in folinudine[67] (from *Haplophyllum foliosium*) R_1 is CH_3 and R_2 is 4-hydroxy-3-methoxyphenyl. Closely related is rutamine[67] (30, R_1 = CH_3, R_2 = 3,4-methylene-dioxyphenyl), found in both *Ruta bracteosis* and *Ruta groveolens*.

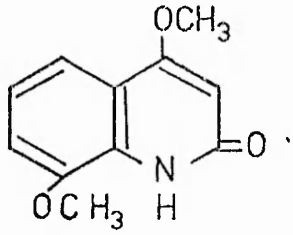
1.6 (ii) Simple substituted Quinolin-2-ones

The great majority of alkaloids based on the quinolin-2-one system have more complex substitution patterns. Detailed reviews of the quinolin-2-one alkaloids are available.[73,74] The formulae of a small selection of these compounds are presented in the following chart:

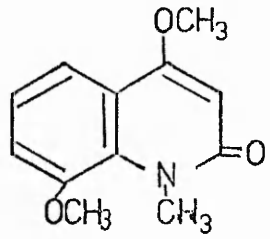
Quinolin-2-one alkaloids



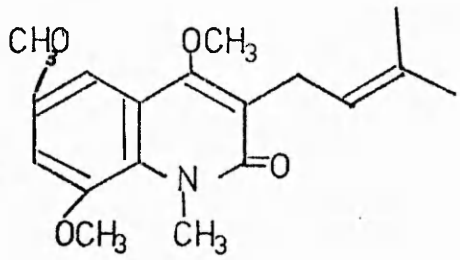
(31)



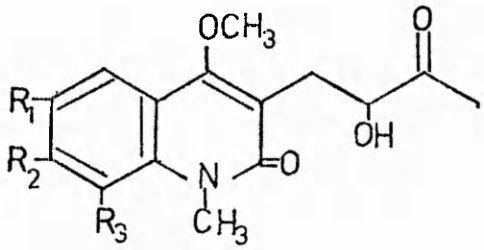
(32)



(33)



(34)



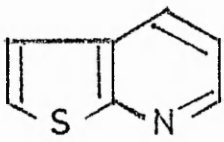
(35)

Bucharidine (31) isolated from *Haplophyllum bucharicum*,[68] is one of the simpler alkaloids in this group, having a substituent at C-4 only. From *Haplophyllum scleroxyla*, the alkaloid halfordamine (32) has been isolated; its structure was confirmed by synthesis.[69] The alkaloid foliudine (33) has been isolated from *Haplophyllum bucharicum*; there is some evidence that this compound is a plant growth inhibitor.[70] A large number of N-methylquinolin-2-one derivatives of general form (35) have been isolated from *Ptelea trifoliata*.[71] Typical are ptelefoline (35, $R_1 = R_3 = OCH_3$; $R_2 = H$), isoptelefoline (35, $R_1 = H$, $R_2 = R_3 = OCH_3$) and ptelefolidine (35, $R_1 = H$, R_2, $R_3 = O\text{-}CH_2\text{-}O$). Extracts of the root bark of this plant gave an alkaloid as yet un-named with structure (34).[72]

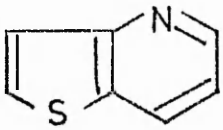
1.7 Thienopyridines

Introduction

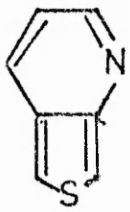
There are six possible thienopyridine systems, all of which have been prepared. The b-fused series are analogous to quinoline, and the c-fused to isoquinoline. In the following discussion only the b-fused systems will be considered, that is, the thieno[2,3-b]-,-[3,2-b]- and -[3,4-b]pyridines.



[2,3-b]



[3,2-b]



[3,4-b]

Thienopyridines have received considerable attention over the past few years, for two main reasons. Firstly, the close resemblance (sterically and electronically) of thienopyrdines to quinolines and isoquinolines has rendered them of considerable pharmacological interest. Secondly, there is the theoretical interest in the behaviour of systems in which a π-excessive and a π-deficient ring are fused together. The presence in thienopyridines of a ring susceptible to electrophilic substitution (thiophen) and one susceptible to nucleophilic substitution (pyridine) makes selective chemical functionalisation of the individual rings an interesting possibility.

Thienopyridine chemistry has previously been reviewed by Schneller,[75] and more recently, and in greater detail, by Barker.[76] The earliest report of a preparation of a thienopyridine was in 1913, by Steinkopf.[77] However, only since 1960 has a significant number of publications on thienopyridines appeared in the literature. Very little work has so far been reported on the thieno[3,4-b]pyridine system; the parent substance was prepared in 1970,[78] but was found to be much less stable than the other isomers.

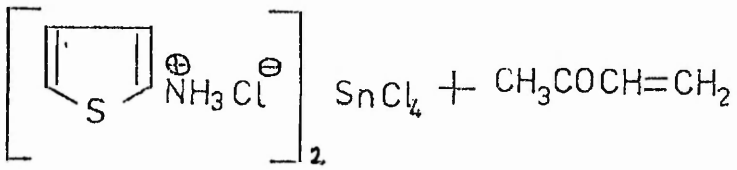
Unlike their benzene counterparts, thienopyridines do not occur widely in nature. The basic component of a shale oil of high sulphur content was found to contain certain methyl thieno[2,3-b] and [3,2-b] pyridines,[79] but no other natural occurrence of the compounds has been reported.

1.8 Synthesis

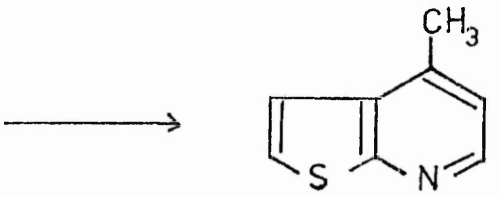
Synthetic approaches to thienopyridines are conveniently considered under two headings, according to which heterocyclic ring is constructed. Generally, syntheses involving formation of the pyridine ring have been adaptations of classical quinoline syntheses.

Syntheses involving formation of the pyridine ring

Steinkopf[77] applied the Skraup reaction to 2-amino thiophen to obtain a low yield of thieno[2,3-b]pyridine. Free 2-amino thiophen is an unstable substance, and it is usual to employ the tin double salt $(C_4H_5SNH_3^+Cl^-)SnCl_4$ (36) obtained directly by reduction of 2-nitrothiophen. Russian workers[80] reported that methylvinylketone reacts with (36) to give 4-methylthieno[2,3-b]pyridine (37).

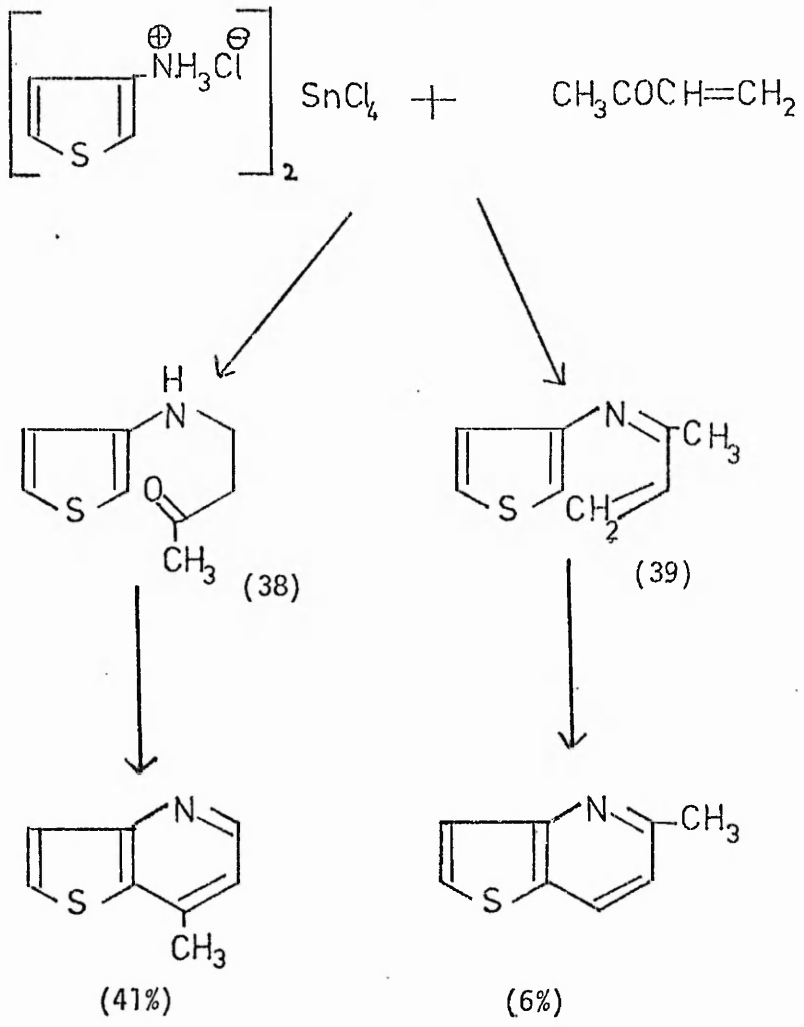


(36)

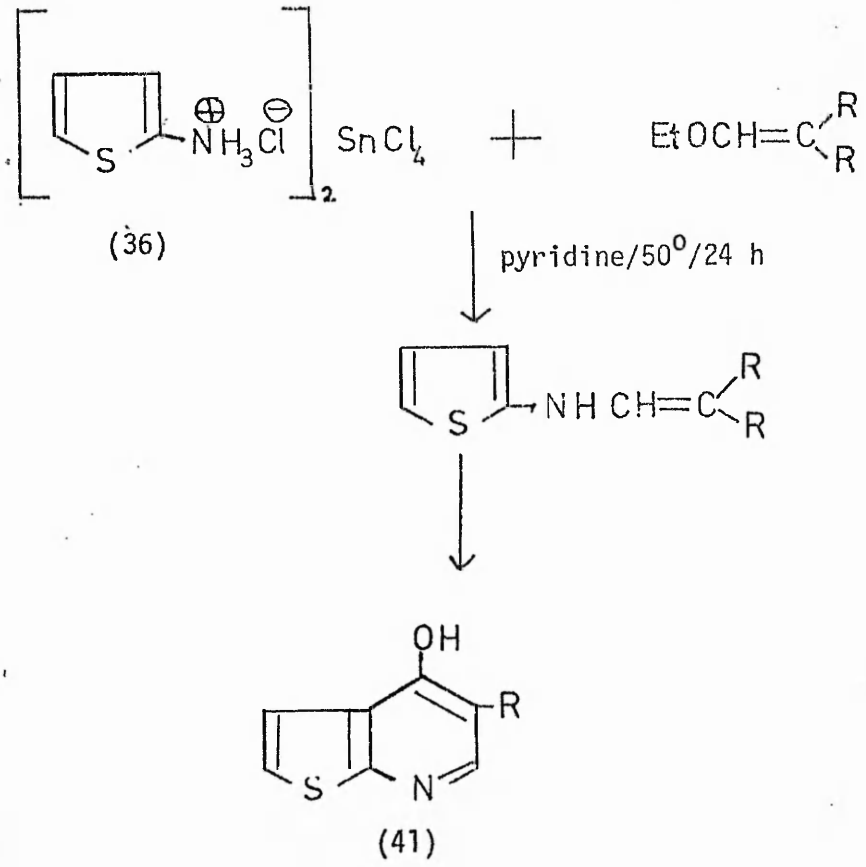


(37)

Klemm[81] showed that the 3-aminothiophen tin double salt reacts in a similar way, but gave a mixture of products, that arising from the Michael adduct (38) predominating over that from the Schiff's base (39).



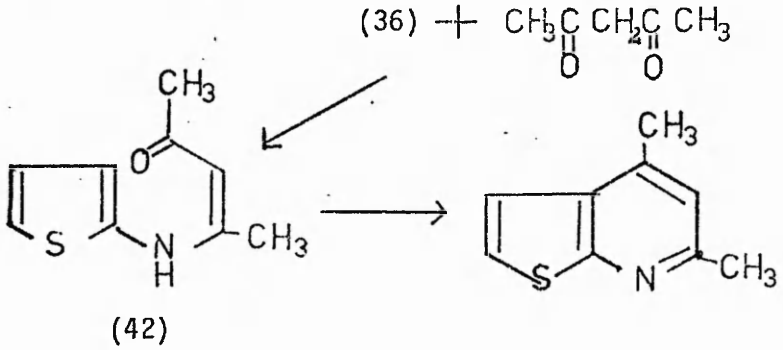
Khan[82] reported the preparation of thieno[2,3-b] and [3,2-b] pyridines by the application of the Gould-Jacobs quinoline synthesis to these systems. Thus, condensation of 2- and 3-aminothiophen tin double salts with ethoxymethylene derivatives of active methylene compounds in pyridine, followed by cyclization of the condensation products (40, R = eg. COOEt) by heating them under reflux in dowtherm or diphenyl ether, gave various 4-hydroxythieno[2,3-b]pyridines (41):—



(36) (41)

Reactions of aminothiophens with 1,3-dicarbonyl compounds

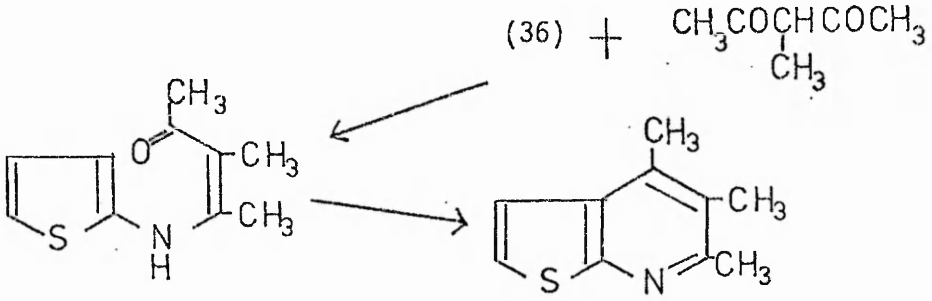
Klemm, Emerson and Holly[83] were the first to apply this approach to the thienopyridine system. Cyclization of the Schiff's base (42) with a variety of agents gave good yields of 4,6-dimethylthieno [2,3-b] pyridine.[83,84]



(42)

Similarly, the preparation of 4,5,6-trimethyl thieno[2,3-b] pyridine (44) via the 3-methylpentan-2, 4-dione/2-amino thiophen

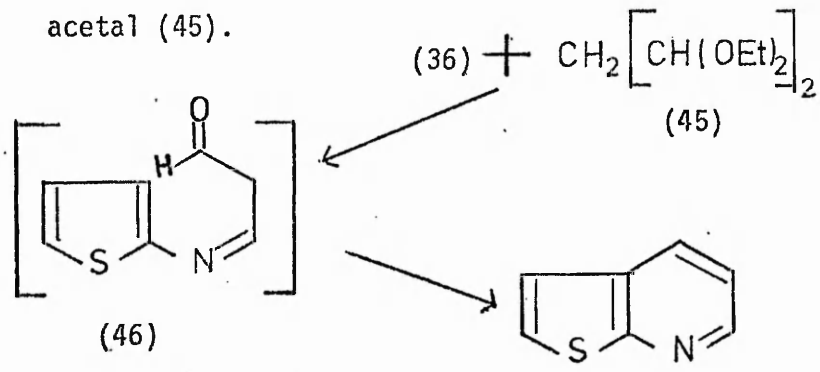
Schiff's base (43) has also been described.[81]



(43) (44)

The procedure has been applied,[81,85,86] with varying degrees of success, to the reaction of several 1,3-dicarbonyl compounds with both 2- and 3-aminothiophens. It seems, however, that with few exceptions yields are low, and this, coupled with the inaccessibility of simple aminothiophens, means that this is only rarely a good route to thieno *[2,3-b]* or *[3,2-b]* pyridines.

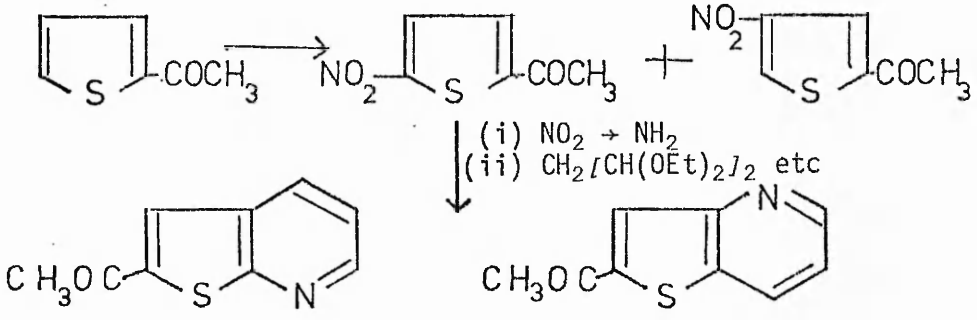
The acetals and ketals of 1,3-dicarbonyl compounds are also effective in this synthesis; thus Klemm[81] prepared the parent system by condensation-cyclisation of (36) with malondialdehydetetraethyl-acetal (45).



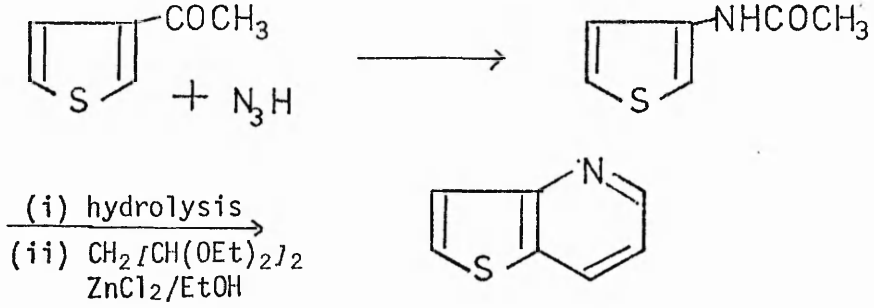
(46)

It has been suggested that this reaction proceeds by initial hydrolysis of malondialdehydetetraethylacetal to malondialdehyde, which condenses with the amine salt to form a 1:1 Schiff's base (46). Electrophilic substitution at C-3, followed by dehydration then leads to the thieno-pyridine.

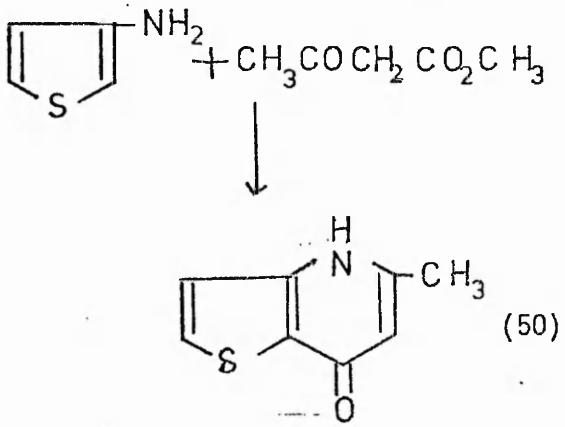
Surprisingly, the presence of a deactivating group on the thiophen ring does not prevent cyclisation. Thus, Klemm[81] showed that the mixture of amines formed on nitration and reduction of 2-acetylthiophen led to a mixture of 2-acetylthieno[2,3-b] (47, 10%) and [3,2-b]pyridines (48, 10%).



An alternative synthesis of thieno[3,2-b]pyridine from 3-acetylthiophen via the Schmidt reaction has been reported.[87]



Abramenko[88] found that 3-aminothiophen condensed with ethyl acetoacetate (49), in the presence of glacial acetic acid, to give 5-methylthieno[3,2-b]pyridin-7(4H)one (50).

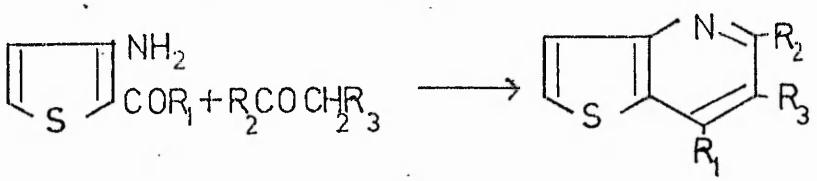


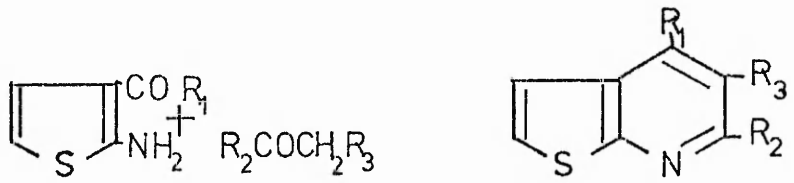
(50)

Numerous attempts by the present author to emulate this reaction with 2-aminothiophen were unsuccessful.

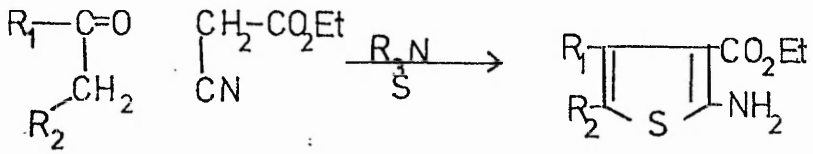
Cyclisations involving ortho-amino-carbonyl thiophens

This approach is summarised by the equations:-

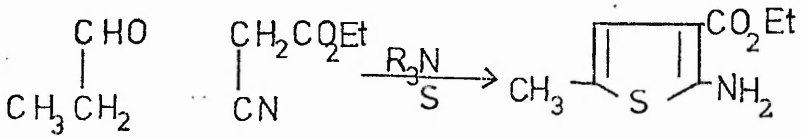




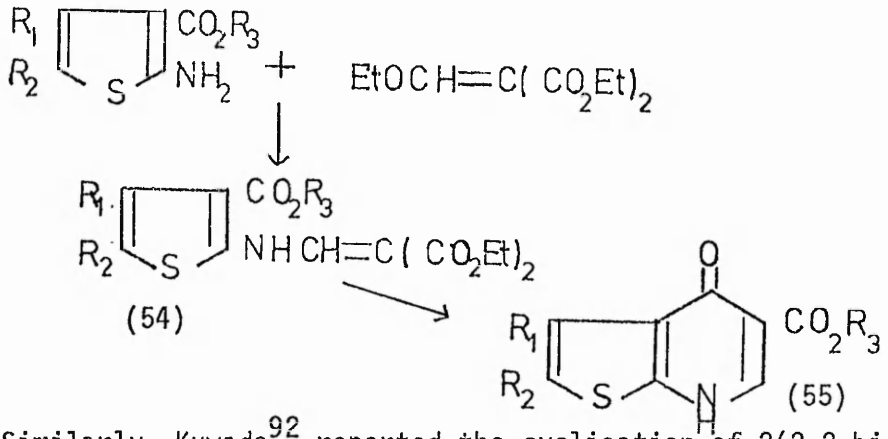
The principal difficulty originally lay in the preparation of appropriately substituted thiophens (51 and 52), but the work of Gewald,[89] in recent years, has, to a large extent, removed this objection for 2-aminothiophens. Thus, suitable thiophens are readily synthesised directly from the appropriate aldehyde or ketone, ethyl cyanoacetate and sulphur:-



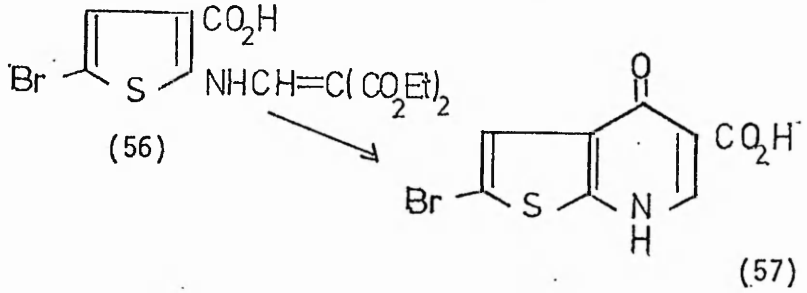
For example, using propionaldehyde, 2-amino-3-ethoxycarbonyl-5-methylthiophen (53) is readily prepared:



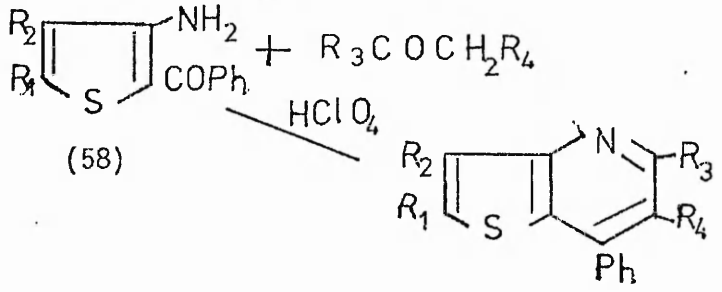
Blaskiewicz[90] and other workers[91] describe the preparation of compounds of the type (54) by reaction of an appropriately substituted 2-aminothiophen and with diethylethoxymethylenemalonate. The intermediate (54) was then cyclised by heating in polyphosphate ester or in diphenyl ether, to give substituted thieno[2,3-b]pyridin-4(7H)ones of type (55).



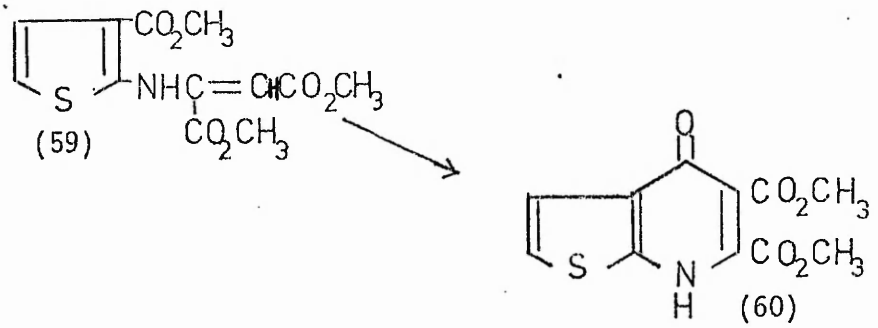
Similarly, Kuwada[92] reported the cyclisation of 2(2,2-bisethoxycarbonyl-vinylamino)-5-bromo-thiophen-3-carboxylic acid (56), by heating it in polyphosphate ester to give the thienopyridone (57) in 80% yield.



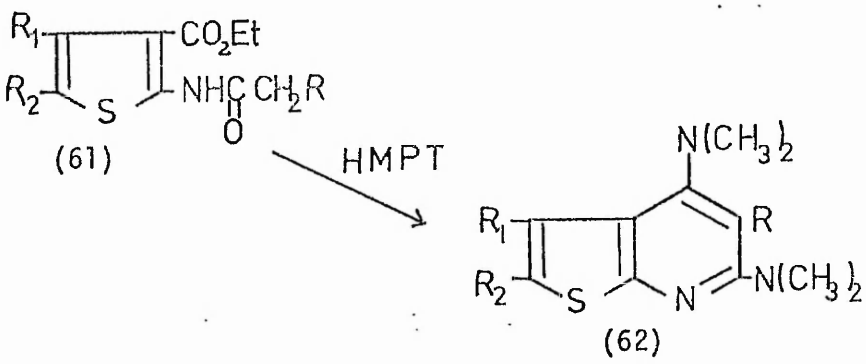
Perchloric acid has been used to effect condensations of 3-amino-2-benzoylthiophens (58) with ketones.[93]



Biere and Seelen[94] reported the preparation of the Michael adduct (59) by reaction of 2-amino-3-methoxycarbonylthiophen and dimethyl-acetylene dicarboxylate. Treatment of (59) with potassium butoxide in dimethyl sulphoxide gave the thienopyridone (60).



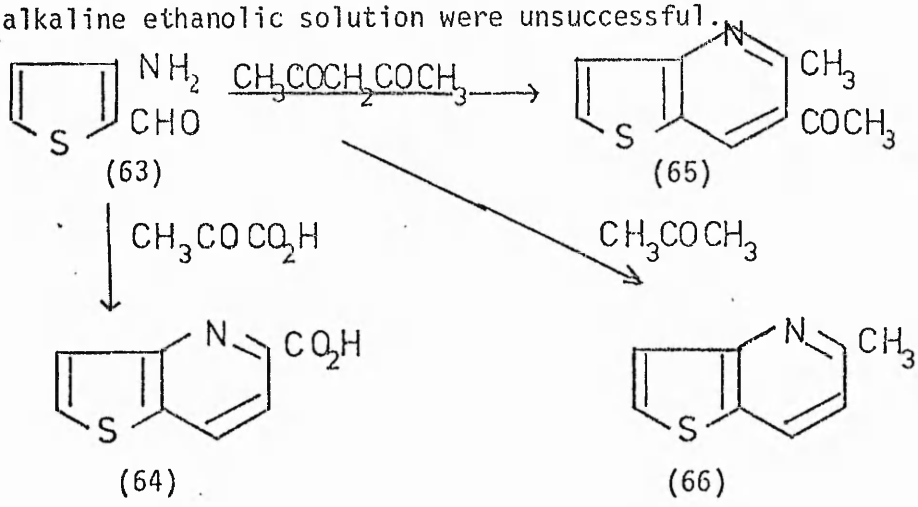
The preparation of 4,6-bis(dimethylamino)thieno[2,3-b]pyridines (62) by heating 2-acetamido-3-thiophencarboxylic acid ethyl esters (61) in refluxing hexamethylphosphorictriamide (HMPT) has been reported.[95]



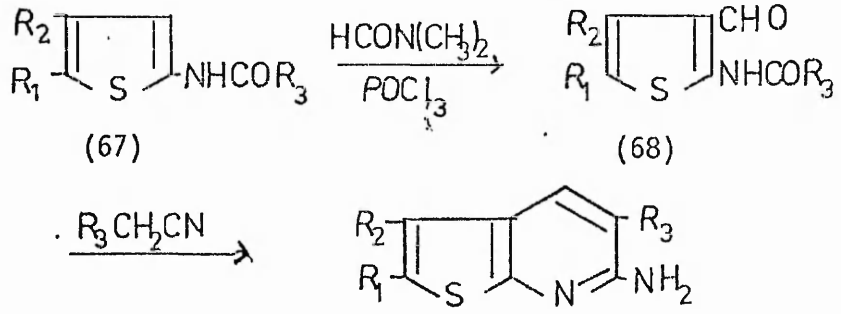
Gronowitz[96] describes the application of the Friedlander synthesis to 3-amino-2-formylthiophen (63) for the preparation of thieno[3,2-b] pyridines. The Friedlander synthesis involves the reaction (in alkaline or acidic media) of an aromatic ortho amino carbonyl compound and a carbonyl compound containing an active methylene group α-to the carbonyl function.

Under carefully controlled conditions, reactions with freshly distilled pyruvic acid, acetone and acetylacetone led to (64), (65)

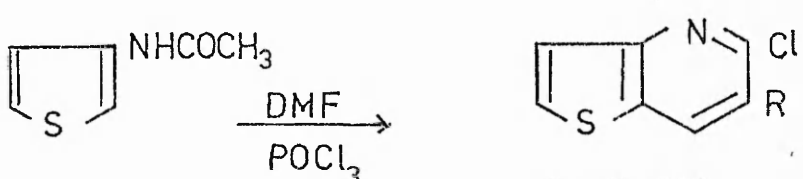
and (66) respectively. Attempts to react acetaldehyde with (63) in alkaline ethanolic solution were unsuccessful.



Shvedov et al[97,98] carried out Vilsmeier reactions on various 4,5-disubstituted-2-acetylthienylamines (67); cyclisation of the resulting formyl compounds (68) with a variety of compounds containing active methylene groups led to thieno[2,3-b]pyridines:-



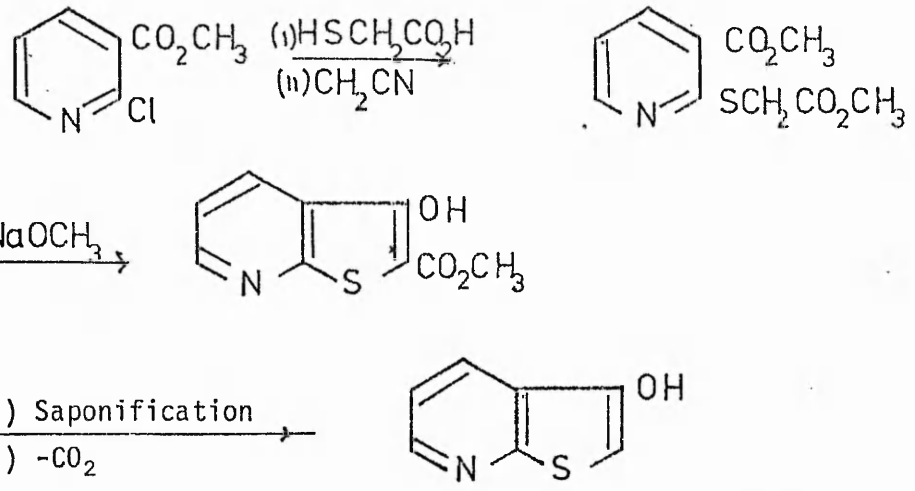
In a recent publication, Meth-Cohn[99] describes a modification of the Vilsmeier-Haack reaction, which, when applied to acetylaminothiophens, leads to thienopyridines. Thus, starting with 3-acetylaminothiophen, the products shown below are available.



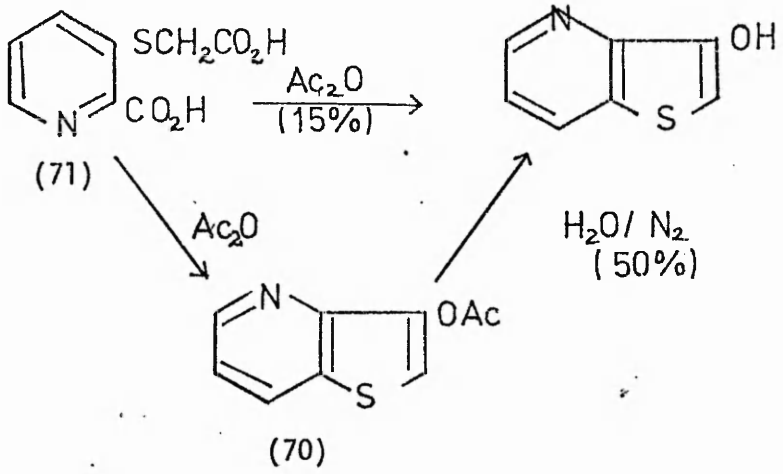
R = H, 23%
R = CHO, 5%

1.9 Synthesis involving formation of the thiophen ring

Chichibabin[100] reported the preparation of 3-hydroxythieno[2,3-b]pyridine (69) by the route shown below:-

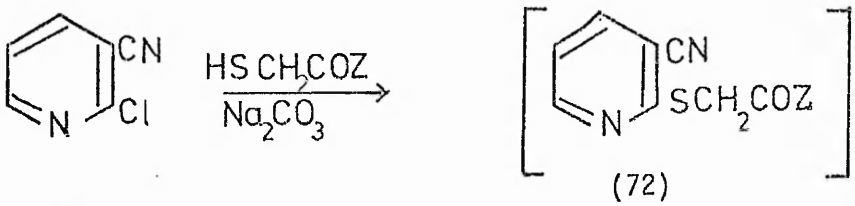


When the intermediate acetoxycompound (70) is isolated in the cyclisation of carboxypyridylthioacetic acid (71) with acetic anhydride, there is an improvement in the yield of the thienopyridine.[101]

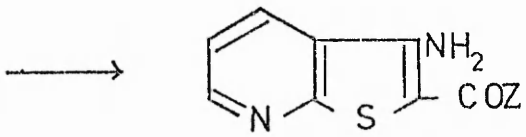


Similarly, Abramenko[84] prepared 3-hydroxy-6-methylthieno[2,3-b]pyridine from 6-carboxy-6-methyl-2-pyridylthioacetic acid.

Related syntheses use cyanopyridylthioacetic acids or esters (72, A = OH or alkyl); 3-amino-2-ethoxycarbonylthieno[2,3-b]pyridine (73, Z = OEt), for example, has been obtained by the route depicted below.[102]



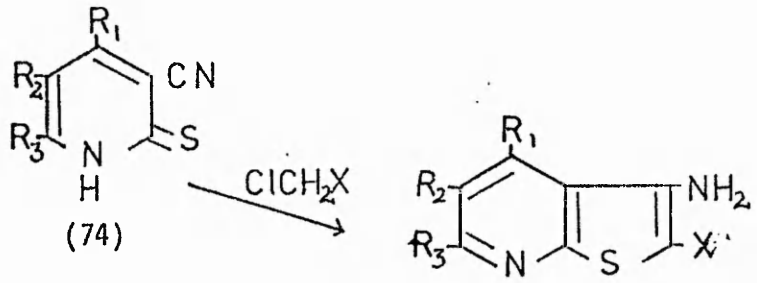
(72)



(73)

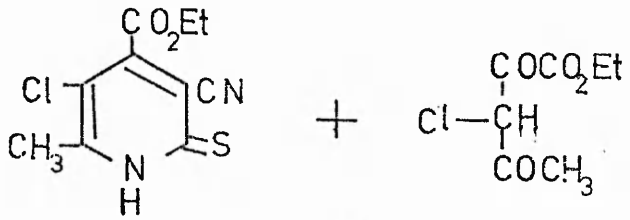
Use of mercaptoacetamide in this reaction leads to the corresponding amide[103] (73, Z = NH_2).

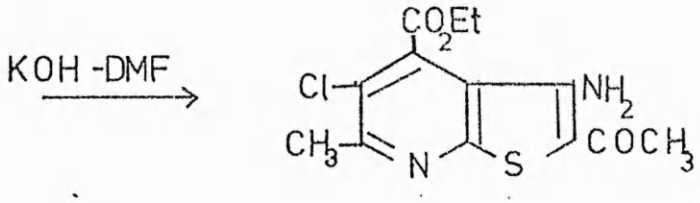
The synthesis has been extended to the preparation of more complex thieno[2,3-b]pyridine derivatives. Substituted pyridin-2-thiones (74, R^1 = CH_3, R^2 = H; R_1R_2 = $-(CH_2)_4-$; R^3 = CH_3) react with compounds of the type $ClCH_2X$, where X is an electron withdrawing group (X = CO_2Et;[103,104] $-COCH_3$, CN, NO_2[105]) to produce the appropriate thieno-pyridines (75):-



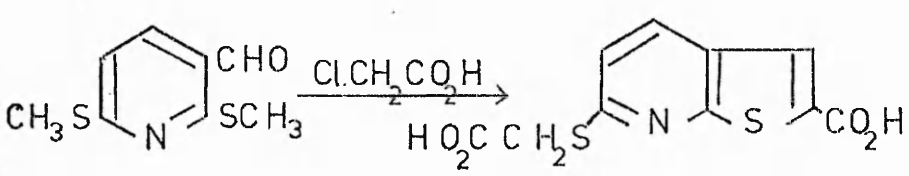
(74)

The successful use of a rather elaborate chloro-compound in a synthesis of this kind has been recorded by Tornetta[106]:-



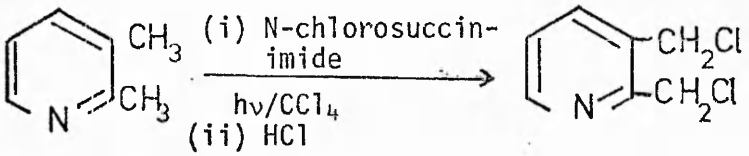


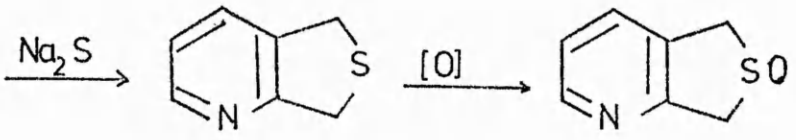
Martini[107] reports the preparation of 2,6-disubstituted thieno [2,3-b]pyridines (76) by reaction of chloroacetic acid with appropriately substituted 2-thiopyridines, eg.:-

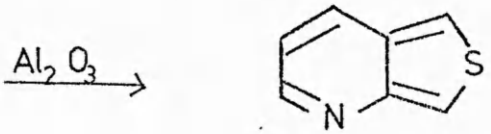


Thieno[3,4-b]pyridines

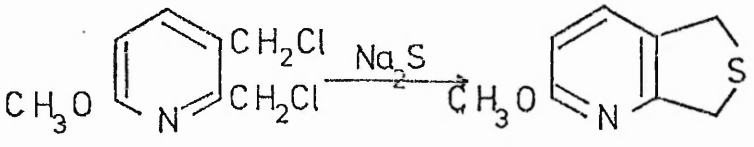
Very little work has been reported in this area. The parent system has been prepared by Klemm and co-workers,[78,109,110] by the following sequence:-



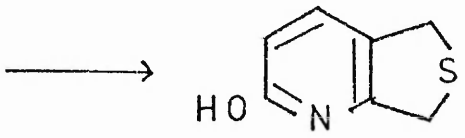




Spinner and Yeoh[111] have synthesised a number of 1,3-dihydro-derivatives of the system (eg. 77, 78), by a similar route to that shown above:

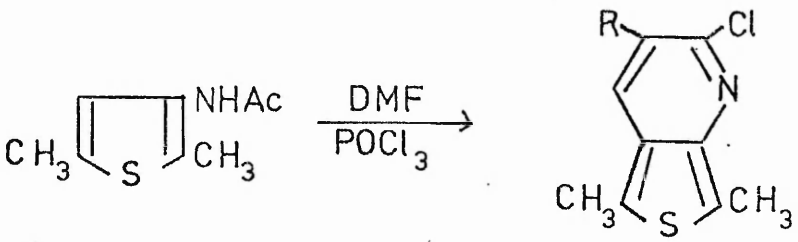


(77)



(78)

Meth-Cohn[99] has prepared thieno[3,4-b]pyridines of the type shown below (78b) by modification of the Vilsmeier-Haack reaction, as discussed previously:-

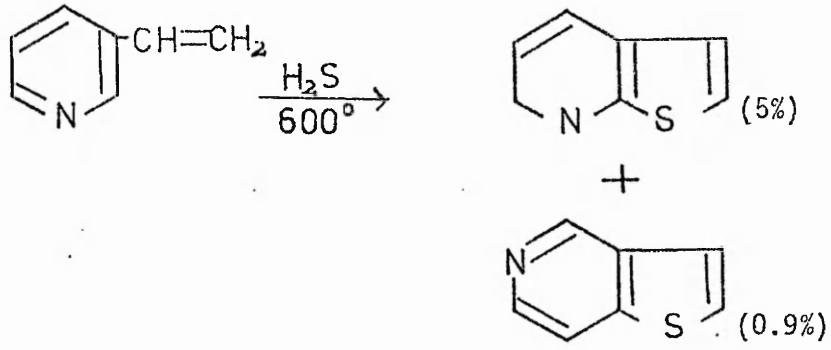


(78b)

R = H, 52% yield
R = CHO, 39% "

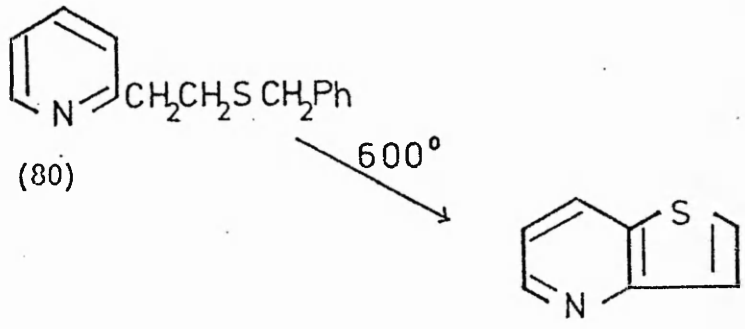
1.10 High temperature catalytic methods for the preparation of thienopyridines

An early attempt by Hansch[112] to prepare thienopyridines in a single-step process from 4-vinyl pyridines and hydrogen sulphide in the presence of an iron-aluminium oxide catalyst at 600° failed. Subsequently, however, thieno[2,3-b] and[3,2-b]pyridines were obtained in very low yields by reaction of suitably substituted pyridines with hydrogen sulphide.[113,114,115,116] Thus, in a typical case, 3-vinyl pyridine (79) gave a mixture of thieno[2,3-b] and [3,2-c]pyridines:-



Similarly, 2-vinyl pyridine provided thieno[3,2-b]pyridine by this process.

Improvements in yield were obtained if the vinyl pyridine was first converted into the corresponding benzyl pyridylethyl sulphide (80), followed by pyrolysis over glass helices.[115]



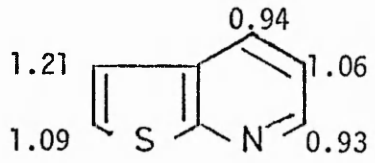
It seems likely that all these high temperature reactions involve free radicals. In the last one described above, for example, it is proposed that homolysis of the sulphur-benzyl bond gives $C_5H_4NCH_2CH_2S\cdot$

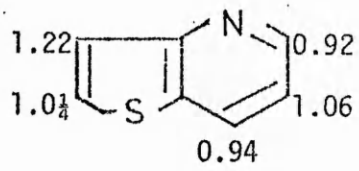
radicals which cyclise to the 2,3-dihydrothieno[3,2-b]pyridine. Dehydrogenation then yields the fully aromatic system.

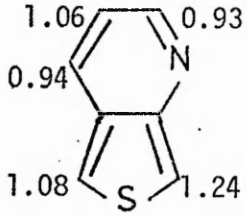
1.11 Physical Properties

(1) Electron distribution

One of the major points of interest in thienopyridines is the presence in them of a π-excessive and a π-deficient system. It is not surprising, therefore, that efforts have been made to calculate π-electron densities and to correlate them with experimental observations.[117,118] The following diagrams show some calculate π-electron densities for the three systems.



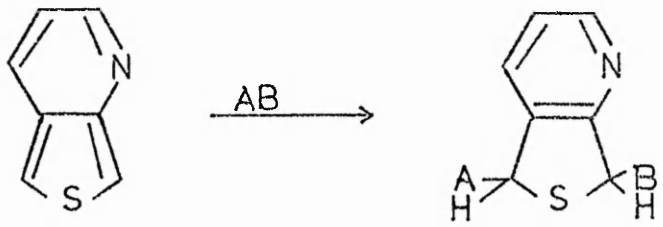




Efforts have also been made to calculate indices of reactivity of nucleophilic,[116] electrophilic and radical substitution[117] for thienopyridines. In general, the results obtained are in agreement with experimental observations. Electrophilic substitution is expected to occur in the thiophen ring β- to the sulphur atom when that position is free and nucleophilic substitution to occur in the pyridine ring, with a slight preference to the carbon atom γ over that α to the nitrogen atom, where such a choice exists. No systematic study of

nucleophilic substitution or free radical substitution in thienopyridines has been reported.

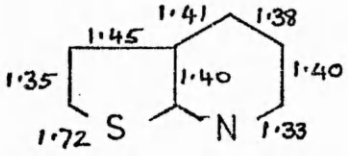
Little experimental evidence is available for the -[3,4-b] fused system, but it seems probable that they would have a considerable tendency to undergo addition reactions at the 1,3-positions, since the product would have a normal rather than a quinoid pyridine ring:-

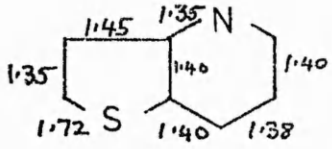


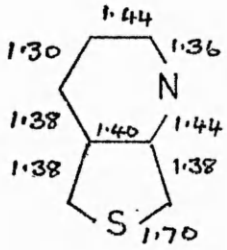
(2) Bond lengths

The bond lengths of the systems, estimated by modification of known (or calculated) bond lengths in related molecules are shown below:[117]

Bond lengths (Å) of thienopyridines



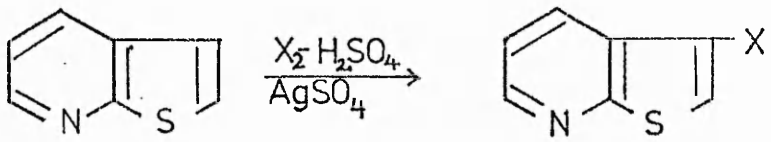




1.12 Reactions

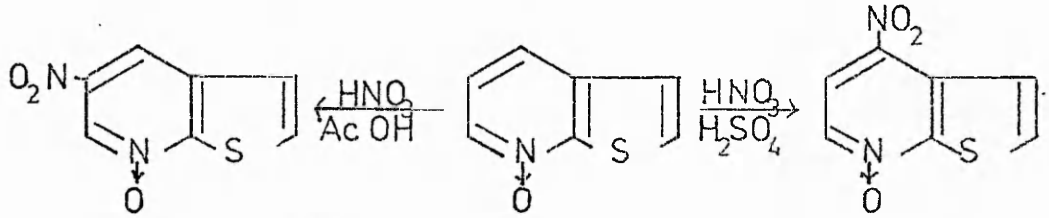
(1) Electrophilic substitution

A detailed study of electrophilic substitution of thieno[2,3-b]pyridines has been reported by Alunni and Clementi.[119] The results obtained enabled these workers to evaluate standard rate constants for reaction of the protonated species, and confirmed that substitution occurred preferentially β- to the sulphur atom. Deuterium exchange studies[110] indicated that for thieno[2,3-b]pyridine the proton at C-3 was replaced more rapidly than that at C-2. Bromination[120] and chlorination[121] of the system in carbon tetrachloride solution gave 2,3-disubstituted products, whilst halogenation in sulphuric acid-silver sulphate solution[121] gave exclusively the 3-halogeno-derivative (81).



(81) X = Cl, Br

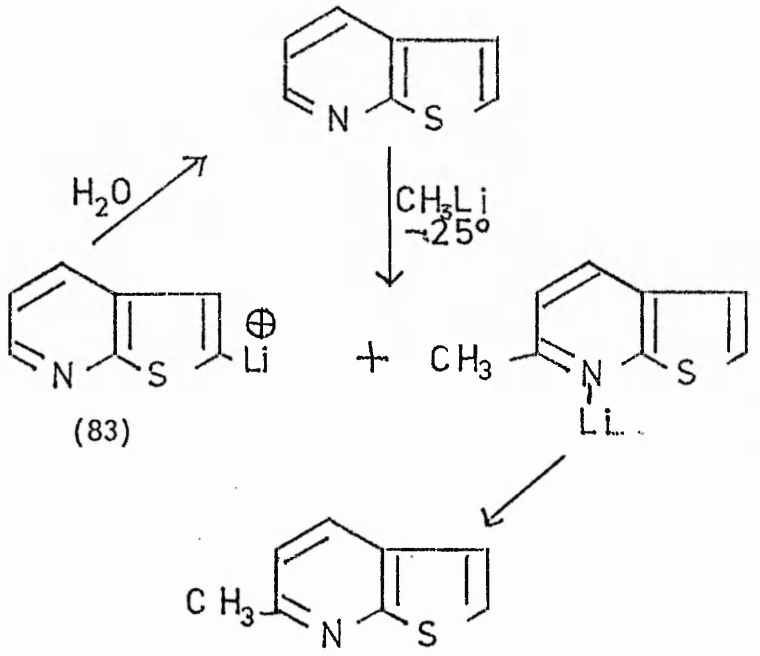
Similarly, nitration (with mixed acid) of the -[2,3-b]- and -[3,2-b]- systems resulted in the formation of the 3-nitro derivatives.[122] However, for thieno[2,3-b]pyridine-N-oxide (82) it was found that the pyridine ring was more reactive towards electrophiles than the thiophen ring;[123] moreover, the orientation in nitration of this molecule depended on the reagent, as illustrated below:-



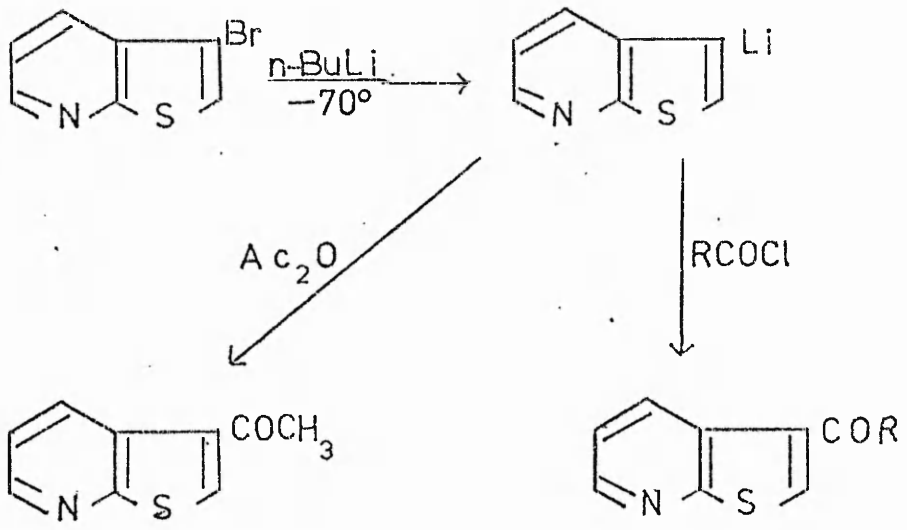
(82)

(2) Nucleophilic substitution

Treatment of thieno[2,3-b]pyridine with n-butyl lithium at 25-30°, or with methyl lithium at -25° yielded the corresponding 6-butyl and 6-methyl derivatives respectively,[81] in low yield; starting material was also recovered. This could well have arisen from hydrolysis (during the work-up procedure) of 2-lithiothieno[2,3-b]pyridine (83) formed in a competing reaction:-

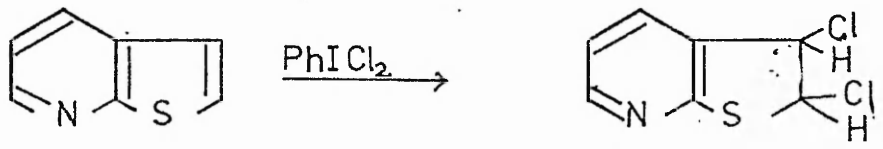


At a lower temperature (-70°) addition to the azomethine bond is apparently unimportant, since Klemm[83] obtained a good yield (66%) of thieno[2,3-b]pyridine-2-aldehyde by formylation of the lithium derivative. Lithium derivatives are also readily available by halogen-metal interchange at low temperature,[124] and have been used in typical reactions as illustrated below:-



(3) Oxidation

In thienopyridines the possibility exists of oxidation at nitrogen (to the N-oxide) or a sulphur (to the sulphone or sulphoxide). Peracids selectively oxidise the nitrogen atom in thieno[2,3-b][121] and [3,2-b][125] pyridines. Preparation of sulphones and sulphoxides is less readily achieved. The sulphones of thieno[2,3-b] and [3,2-b] pyridine were prepared by reaction of the parent heterocycles with sodium hypochlorite and dilute hydrochloric acid.[126] Treatment of thieno[2,3-b]pyridine with iodobenzene dichloride, led to a low yield of the oxidation-addition product (84).[121]



(84)

Vigorous oxidation of a thienopyridine results in the destruction of the thiophen ring.

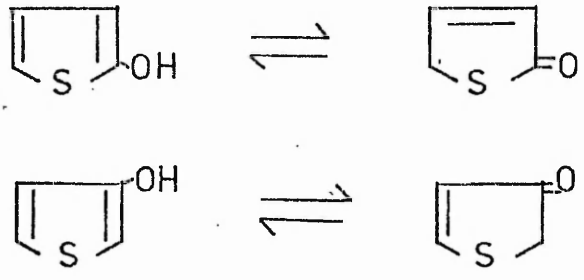
Reduction

In contrast to quinolines and isoquinolines, thienopyridines are apparently resistant to reduction by tin-hydrochloric acid, since the parent systems are obtainable by reductive de-halogenation of the chloro-derivatives. Quaternary salts are reduced to N-alkyl-4,5,6,7-tetrahydrothienopyridines by sodium borohydride.[127,128,129]

Hydroxy compounds

Few hydroxy thienopyridines have been described. A major point of interest is the extent to which the compounds exist as the hydroxy- or keto-tautomer. Derivatives in which the hydroxy group is attached to the pyridine ring would be expected to resemble their quinoline analogues; 2- and 4-hydroxyquinolines exist almost exclusively in the keto form, whereas 3-hydroxyquinoline is extensively enolized. A parallel trend has been observed in the thienopyridines; thus, 5-methylthieno[3,2-b]pyridin-7(4H)one (50) is formulated as existing in the keto form, whereas the infra-red data for 5-hydroxythieno [2,3-b]pyridine[123] implies no contribution from the keto tautomer.

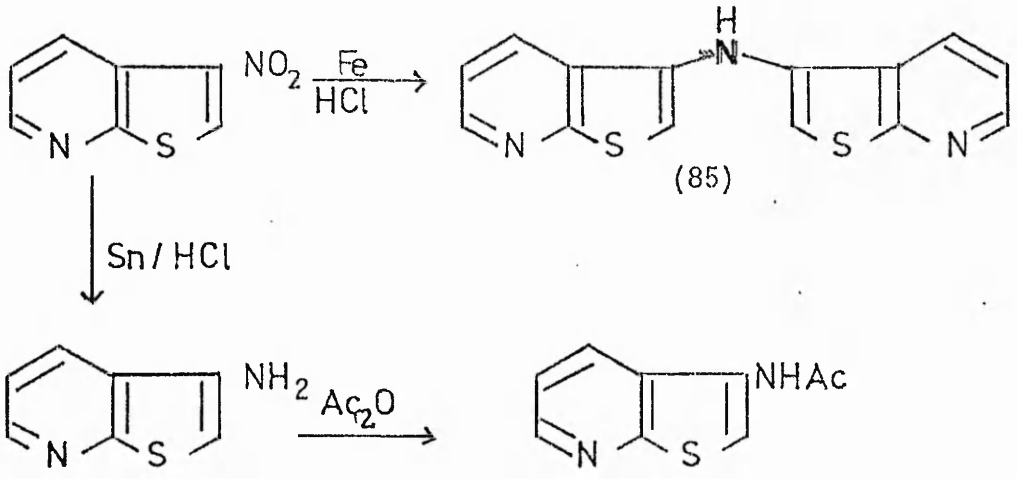
Since hydroxythiophens exist to some extent in the keto form, as illustrated below, the genuinely phenolic properties of the hydroxy



groups on the benzene rings of the isosteric systems might not be reproduced in thienopyridines. However, no chemical or spectroscopic evidence for the keto form in 3-hydroxythieno[3,2-b]pyridine was found.[101]

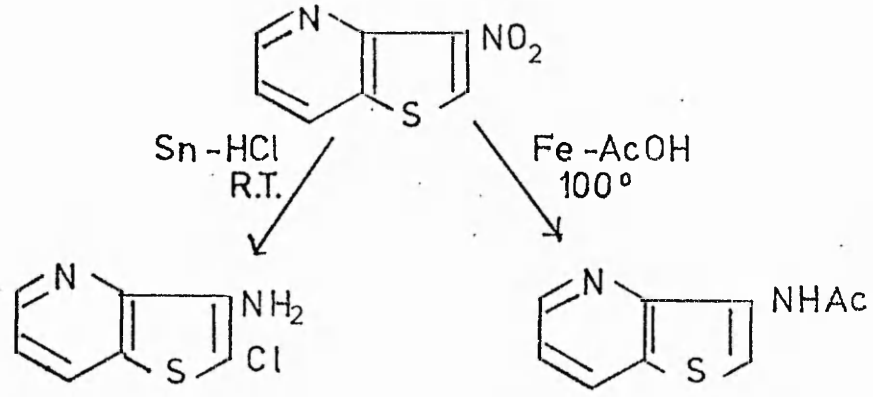
Amino thieno pyridines

The amino derivatives known behave unexceptionally. As is the case with simple aminothiophens, compounds in which a primary amino group is attached directly to the thiophen ring are unstable as the free base. Klemm[119] found that treatment of 3-nitrothieno[2,3-b] pyridine with tin-hydrochloric acid gave the desired 3-amino derivative, but iron-hydrochloric acid gave only the secondary amine (85).



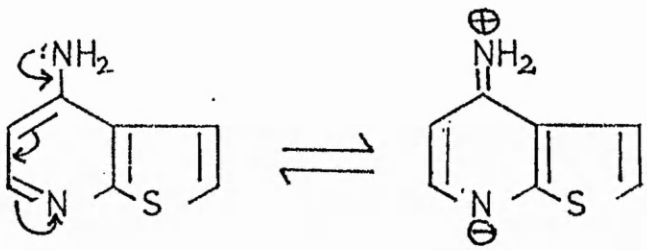
(85)

Metal-acid reduction of 3-nitrothieno[3,2-b]pyridine followed a different pattern. In this case, tin-hydrochloric acid gave 3-amino-2-chlorothieno[3,2-b]pyridine (86). The acetylamine was produced directly by reaction with iron-acetic acid.

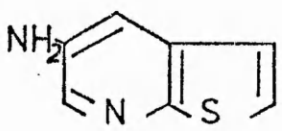


(86)

Nitro groups attached to the pyridine ring are reduced without complication. Both 4- and 5-nitro thieno[2,3-b]pyridine-N-oxide gave the amines on treatment with either tin-hydrochloric acid, or iron-acetic acid, the N-oxide group also being removed during the reaction. Klemm[123] prepared 5-aminothieno[2,3-b]pyridine from the 5-acetyl compound, via the oxime, by Beckmann rearrangement and hydrolysis. The 5-amino derivative readily formed Schiff's bases with a variety of aldehydes, whereas the 4-amino derivative failed to react with aldehydes under similar and more forcing conditions. The difference in reactivity was ascribed to the decreased nucleophilicity of the 4-amino derivative, owing to its position relative to the ring nitrogen.

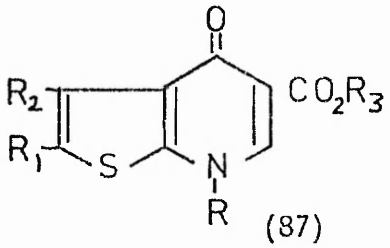


not possible in:



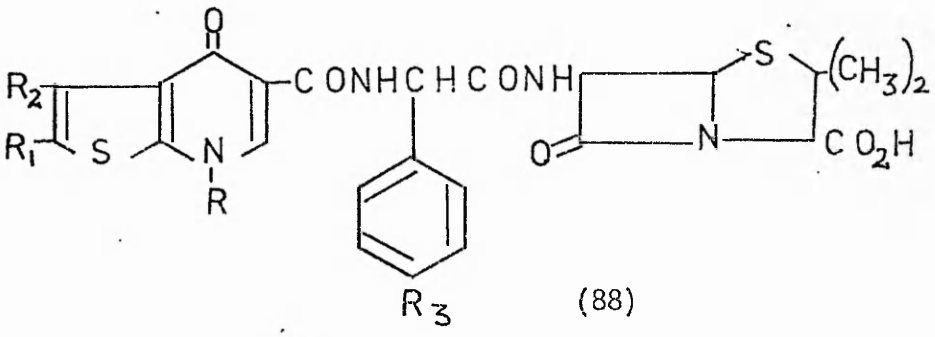
1.13 Biological activity and other uses

Recently, considerable interest has been shown in thieno[2,3-b] pyridine derivatives, but no description of any use for thieno[3,2-b] and [3,4-b]pyridines has appeared in the literature up to the present time. Compounds of the type (87) prepared by the general route previously described (page 30) are the subject of numerous recent publications.[90,130,131,132,133,134,135,136]

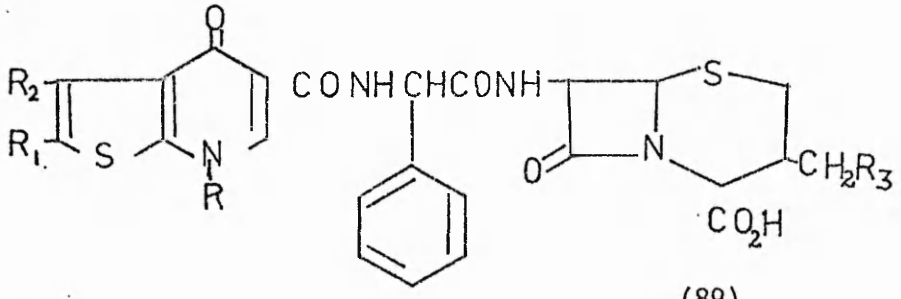


(87)

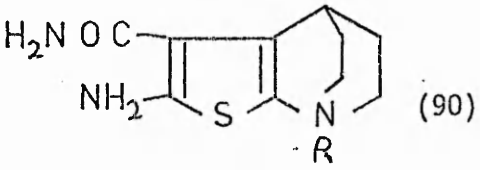
Comparatively simple structures of this basic type (87, where R = H; R_1 = I, Me, OMe; R_3 = H; R_2 = Et) have been found to be active against Staphylococcus aurens S25[130] and Pseudomonas aerugmosa,[90] and are useful as plant fungicides.[132] More elaborately substituted variants of structure (87) have been prepared (eg. R_1 = alkyl, R_3 = $R_4R_5NZR_6$, R_4R_5 = alkyl, R_6 = OH, Cl, Z = alkylene) and have been shown to possess antibacterial activity against Gram positive and Gram negative bacteria.[133] The complex structures (88), (89)[137] and (90)[139] have been patented and are claimed to be effective bacteriocides:-



(88)

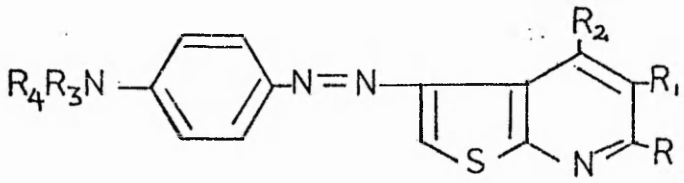


(89)



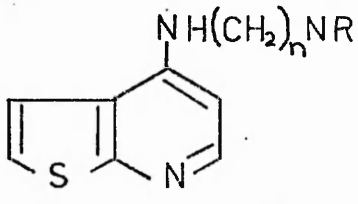
(90)

Compounds of the type (91) have been used as azo dyes to dye polyester fibre.[138]



(91)

Of pharmacological interest are compounds of the type (92) since these are isosteres of the 4-dialkylaminoalkylaminoquinoline anti-malarial drugs. They are reported to have high activity against Plasmodium gallinaceum in the salivary glands of the mosquito.[125]



(92)

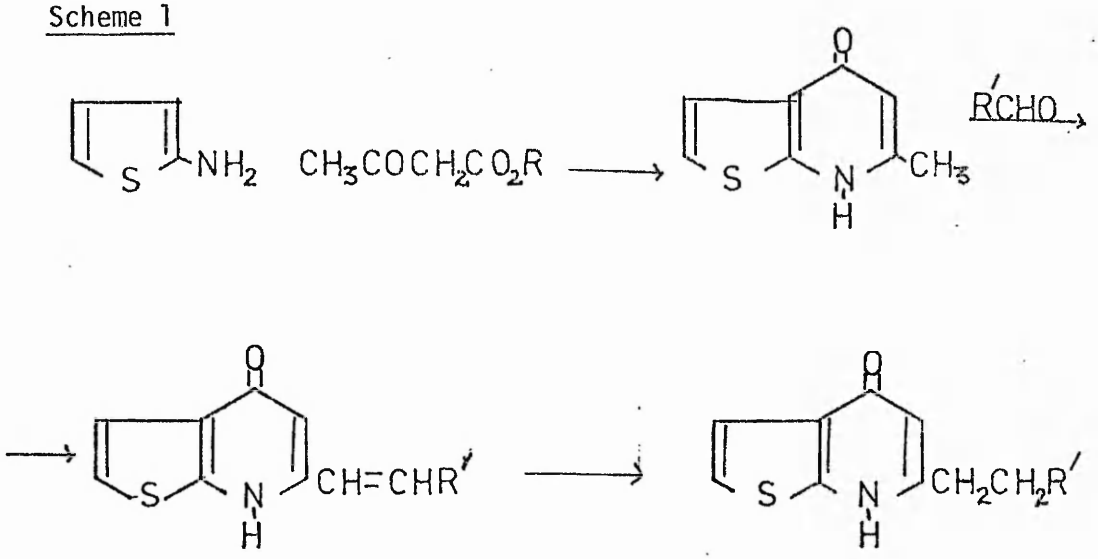
Chapter Two

DISCUSSION

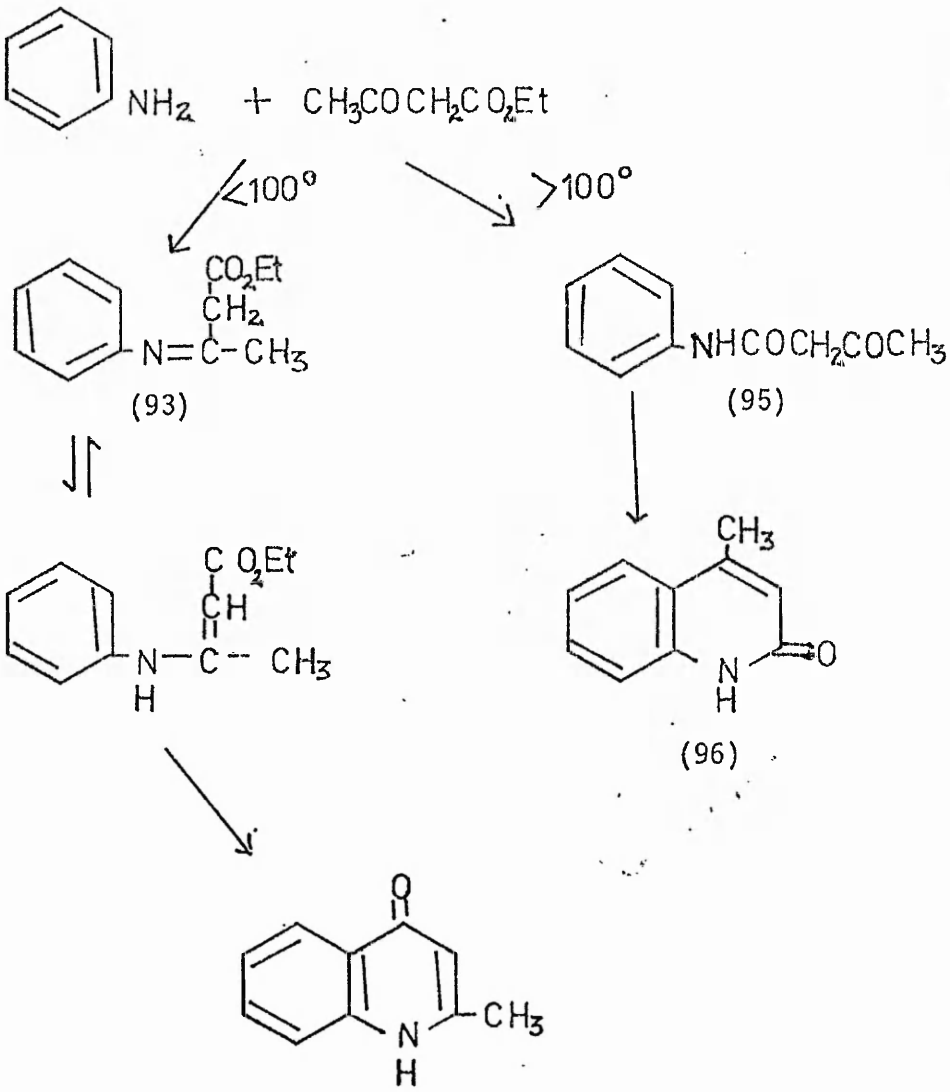
Section I

Scheme 1 shows the first reaction plan evisaged for the preparation of thienopyridine analogues of quinoline alkaloids such as galipine (17).

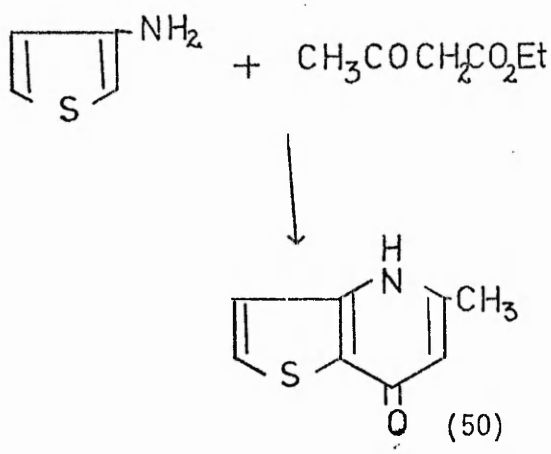
Scheme 1



The synthesis of quinolines by cyclisation of the condensation products of anilines and β-keto esters is well known. The condensation may take two alternative courses; at low temperatures the enamine (93) is produced, cyclisation then producing the 4-quinolone (94) (the Conrad-Limpach Synthesis), whilst at higher temperatures the amide (95) is formed and this, in turn, leads to the 2-quinolone (96) (the Knorr Synthesis).


NH2 + CH3COCH2CO2Et
<100°
>100°
CO2Et
CH2
N=C-CH3
(93)
NHCOCH2COCH3
(95)
CH3
O
N
H
(96)
C O2Et
CH
N-C-CH3
H
O
N
H
CH3
(94)

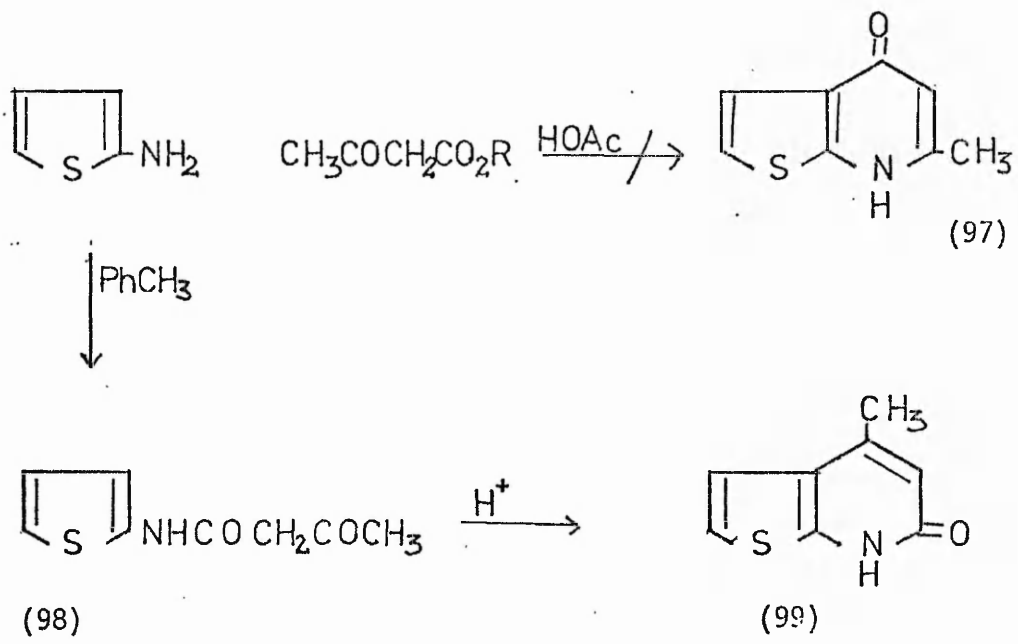
The proposed reaction sequence seemed reasonable in view of the fact that Abramenko[88] had reported that 3-aminothiophen and ethyl acetoacetate, when boiled together under reflux in glacial acetic acid yielded 5-methylthieno[3,2-b]pyridin-7(4H)one (50).



(50)

The preparation of the required aminothiophen presented considerable difficulties. Nitration of thiophen with mixed acid following the procedure of Babasinian[140] gave a mixture of 2-nitrothiophen containing up to 40% of the 3-nitro isomer. Similar results were obtained when the nitration was carried out in glacial acetic acid. The isomers were readily separated by preparative scale gas liquid chromatography, but this was clearly not practicable for large scale work. Repeated recrystallisation of the crude reaction mixture from light petroleum resulted in a product enriched in the 2-isomer,[141] but did not provide isomer-free material. Reduction with tin and concentrated hydrochloric acid, according to the method of Steinkopf,[142] gave the 2-aminothiophen tin double salt, with some of the corresponding 3-isomer as impurity, in good yield. Basification of the tin double salt in a nitrogen atmosphere resulted in very poor returns of the 2-aminothiophen; a considerable practical problem, which may account for the low yield, was the difficulty encountered in separating the organic extracts from the thick emulsions formed by the precipitated tin salts.

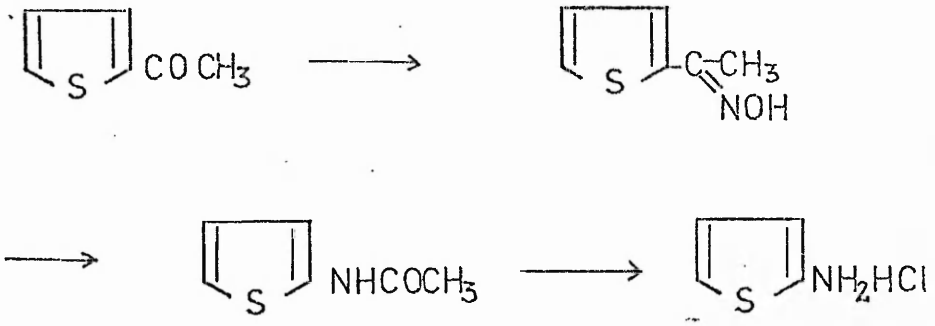
Following the procedure described by Abramenko, the 2-aminothiophen and ethyl acetoacetate were boiled together in glacial acetic acid solution. However, only polymeric material was obtained and none of the desired 6-methylthieno[2,3-b]pyridin-4(7H)one (97) could be isolated. Changing the solvent from acetic acid to toluene considerably reduced the amount of polymeric material produced, and gave a yellow compound, N-(2-thienyl)-3-keto-butanamide (98) isomeric with the desired intermediate. This was readily cyclised, with concentrated sulphuric acid to 4-methylthieno[2,3-b]pyridin-6(1H)one (99).



This result is what one would have expected, and it must be stated that the course of the reaction described by Abramenko is decidedly unusual. When 2-aminothiophen and methyl acetoacetate were mixed together and set aside at room temperature, in the dark, and under a nitrogen atmosphere for several days, again only polymeric material was produced. This was probably due to the instability of the 2-aminothiophen.

Because the yield of aminothiophen obtained by the route described above was so poor an alternative preparation (by the scheme outlined below) was attempted:-

Scheme 2:

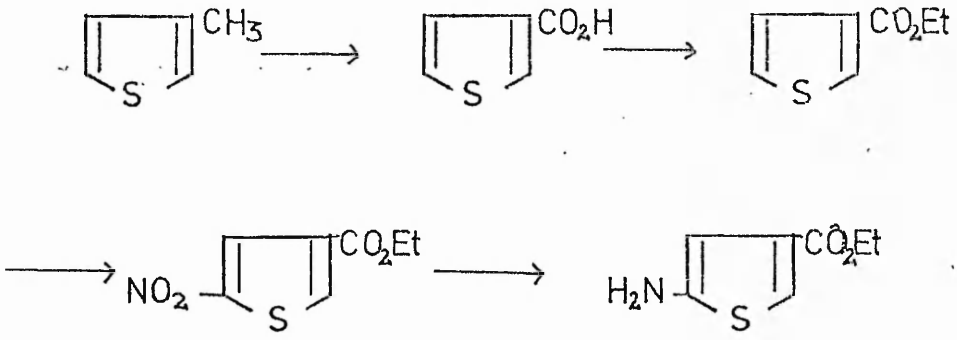


Treatment of 2-acetylthiophen with hydroxylamine gave methyl-2-thienyl ketoxime[170] in high yield. Unfortunately, the Beckmann rearrangement of the oxime (using phosphorus pentachloride, as described in the literature[143]) gave consistently poor yields. The desired 2-acetylaminothiophen was readily prepared, however, in considerably improved yield over that previously reported,[144] by the reductive acetylation of 2-nitrothiophen with reduced iron powder, glacial acetic acid and acetic anhydride. Treatment of the crude acetylamino compound with concentrated hydrochloric acid failed to give the required amine hydrochloride. It was found that the 2-acetylamino compound could be purified very satisfactorily by vacuum sublimation, but even very pure amide gave a polymeric material on attempted acid hydrolysis.

A problem already mentioned is that nitration of thiophen gives a mixture of isomers. It was decided to attempt to prepare isomer free-nitrothiophens to discover if the unsatisfactory results described above could be improved by use of pure materials. In the first approach thiophen-2-carboxylic acid was nitrated with fuming nitric acid, according to the procedure of Rinkes.[145] Unfortunately, the separation of the 4- and 5-nitrothiophen-2-carboxylic acids produced

proved to be very difficult. No real success was experienced with fractional crystallisation of the free acids or their barium salts,[145] or with column chromatography. Similar lack of success was observed with the mixed nitro esters, obtained by nitration of ethyl thiophen-2-carboxylate with either mixed acid or fuming nitric acid in acetic acid.

Another line of attack was then pursued, illustrated in scheme 3:-



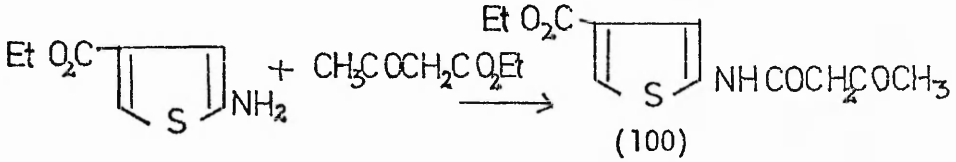
Scheme 3

This had two probable advantages. Firstly, the nitration of thiophen-3-carboxylates gives the 5-nitro derivatives exclusively.[146] Secondly, the amine finally produced carries an electron withdrawing substituent, and would thus be expected to be reasonably stable. Hydrolysis and decarboxylation at some appropriate stage in the alkaloid analogue synthesis would then lead to compounds of the desired type.

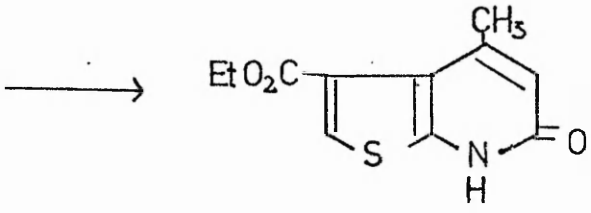
Thiophen-3-carboxylic acid was prepared by the oxidation of 3-methylthiophen with aqueous sodium dichromate solution by heating at 180^{0} in an autoclave for six hours. Treatment of the acid with thionylchloride gave the acid chloride, which, when refluxed with ethanol gave ethyl-thiophen-3-carboxylate in high yield. Nitration of this ester, using mixed acid, gave ethyl-5-nitrothiophen-3-carboxylate exclusively. Nitration of thiophen-3-carboxylic acid itself with mixed acid also led exclusively to the 5-nitro derivative.

Two different methods for the reduction of 5-nitrothiophen-3-carboxylic acid or its ethyl ester to the corresponding amine were investigated. Stannous chloride and concentrated hydrochloric acid gave the amine in low yields, but the second method (granulated zinc and ethanol saturated with hydrogen chloride gas)[147] gave a yield which, although not high (46%), was acceptable in view of the availability of the starting material.

As was the case with the unsubstituted amine, treatment with ethyl acetoacetate in acetic acid, at reflux or at room temperature, led only to polymeric products. Similar results to those described previously were noted when the two reactants were heated together in boiling toluene; the N-(4-ethoxycarbonyl-2-thienyl)-3-keto-butanamide (100) that was formed yielded 3-ethoxycarbonyl-4-methylthieno[2,3-b]pyridin-6(7H)one (101) on cyclisation with concentrated sulphuric acid:-



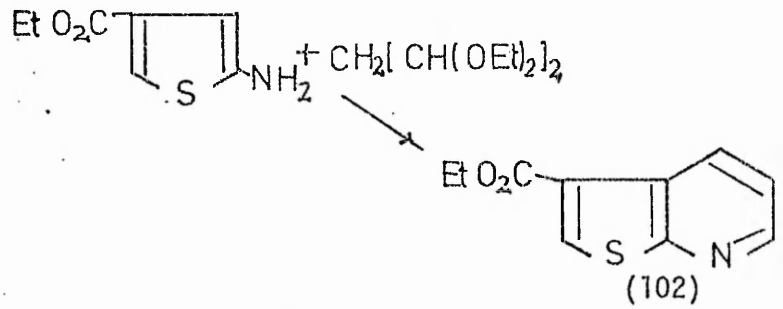
(100)



(101)

The spectroscopic and analytical data for the new compounds described were in good agreement with those expected.

Treatment of 5-amino-3-ethoxycarbonyl-thiophen with malondialdehydetetraethylacetal, following the general procedure described for the preparation of the parent thienopyridine,[81] gave 3-ethoxycarbonyl-thieno[2,3-b]pyridine in good yield (102).



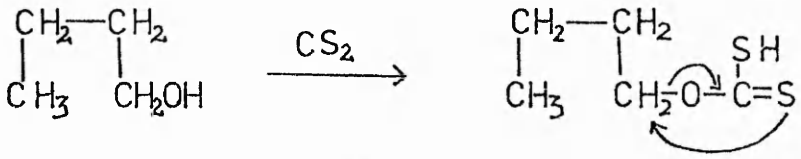
(102)

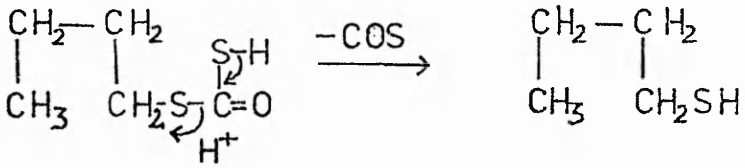
Since the general approach discussed above was not progressing towards the preparation of the desired thienopyridine derivatives, alternative routes involving vapour phase techniques for the synthesis of thienopyridines were investigated: these are described in the next section.

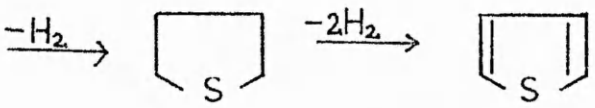
Section II

Attempted preparation of thienopyridines by vapour phase reactions

A widely used industrial preparation of thiophens involves the vapour phase ring closure of butane, pentane, isopentane or their unsaturated counterparts with a sulphur source such as hydrogen sulphide. More recently, Webster and coworkers[148] have shown that carbon disulphide will react with a wide variety of starting materials in the vapour phase at temperatures greater than 350°, in the presence of suitable catalysts (for example, chromium-aluminium oxide promoted with potassium carbonate [Gridler G41 catalyst]) to form thiophens. The yields are frequently greatly in excess of those obtained with other sulphur sources. For example, n-butanol and carbon disulphide react together over G41 catalyst at 500° to give a 48% yield of thiophen:-







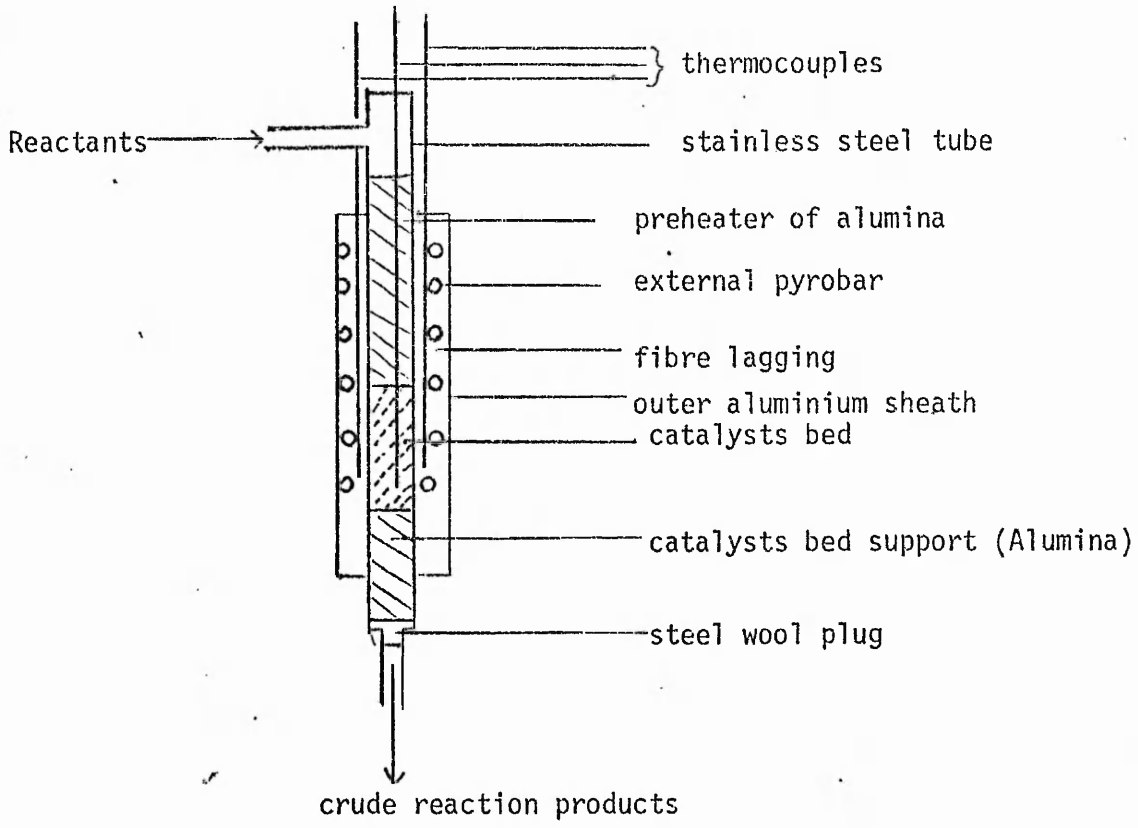
In similar reactions carbon disulphide has been applied to the synthesis of benzo-thiophens. In a typical case 2-methylbenzyl alcohol and carbon disulphide yield dihydrobenzo[c]thiophen.[149]

In the past, several attempts have been made to prepare thienopyridines by vapour phase reactions of alkyl and vinyl pyridines with hydrogen sulphide (see chapter 1, p.37) generally adapting the method of Moore and Greensfelder [150] for benzothiophens, but the results have always been poor. There have been no reports of the use of carbon disulphide in vapour phase catalytic reactions with alkyl or vinyl pyridines; an investigation of this potential thienopyridine synthesis was therefore undertaken.

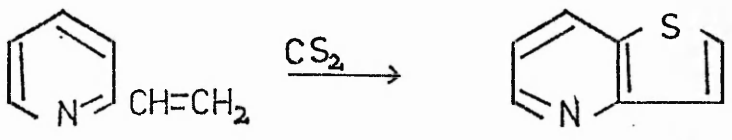
Apparatus

The reactor used for this work was made from a 32" length of 1" diameter stainless steel tube and was heated electrically by an external pyrobar surrounding the reactor. Both the reactor and heater were surrounded with fibre lagging and an outer aluminium sheath. Temperature control was effected electronically by an Ether controller type 1298B using two external and one internal thermocouple. The crude reaction products were condensed by a double surfaced condenser and collected in a receiver, cooled by solid carbon dioxide-acetone. The essential features of the reactor are shown in the accompanying diagram.

Diagram of vapour phase reactor:



Initially, a solution of 2-vinylpyridine and carbon disulphide was pumped into the reactor packed with activated alumina at a temperature of 500-520^{o} in the hope of achieving the following reaction:-



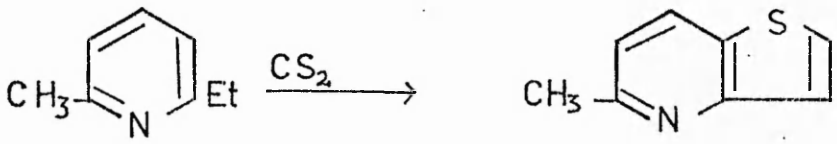
The resulting mixture contained only a small proportion of thieno [3,2-b]pyridine. Also identified in the residue were 2-methyl- and 2-ethylpyridine together with unreacted starting material. Similarly,

reaction over G41 catalyst at 500° resulted in a low yield of thieno [3,2-b] pyridine.

For reference spectra for this work, 4,6-dimethylthieno[2,3-b] pyridine[83] and thieno[2,3-b]pyridine[81] were prepared by the methods described by Klemm.

In the next series of experiments the reaction between 4-vinyl-pyridine and carbon disulphide at 500° over alumina was investigated. In all cases less than 1% thieno[2,3-c]pyridine was detected in the crude condensate; much unreacted starting material, and 4-methyl and 4-ethylpyridines were also present. At a lower temperature (300°) over G41 catalyst, and over alumina no significant conversions were observed.

In the next set of experiments 5-ethyl-2-methyl-pyridine was employed as feedstock. It was hoped that the presence of an electron donating group might facilitate the ring closure reaction; further, the probable product, 5-methylthieno[3,2-b]pyridine would have been a useful starting material for elaboration into alkaloid analogues:-

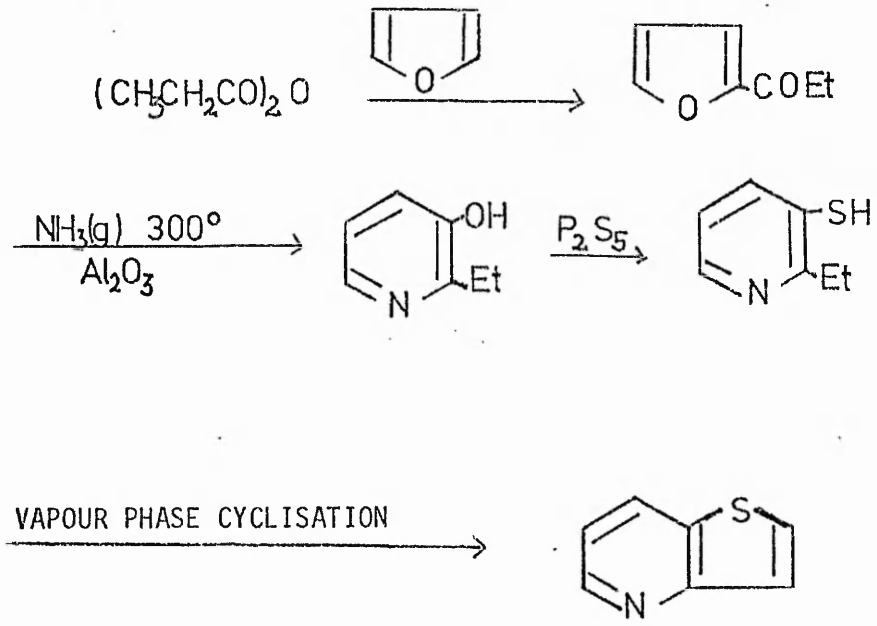


Once again, however, no significant formation of the thienopyridine took place.

The lack of success in the reactions using carbon disulphide as a sulphur source, described above, parallel the poor results reported for the reactions of vinylpyridines with hydrogen sulphide. It appears that a single-step process from a suitably substituted pyridine and a sulphur source is not a viable preparative route to thieno-pyridines, in contrast to the successful syntheses of thiophens and

benzothiophens by analogous processes.

In view of the lack of success in the reactions described above, another approach was considered, in which the substrate for vapour phase cyclisation already contained the necessary sulphur atom. The sequence outlined in scheme 5 was proposed:-



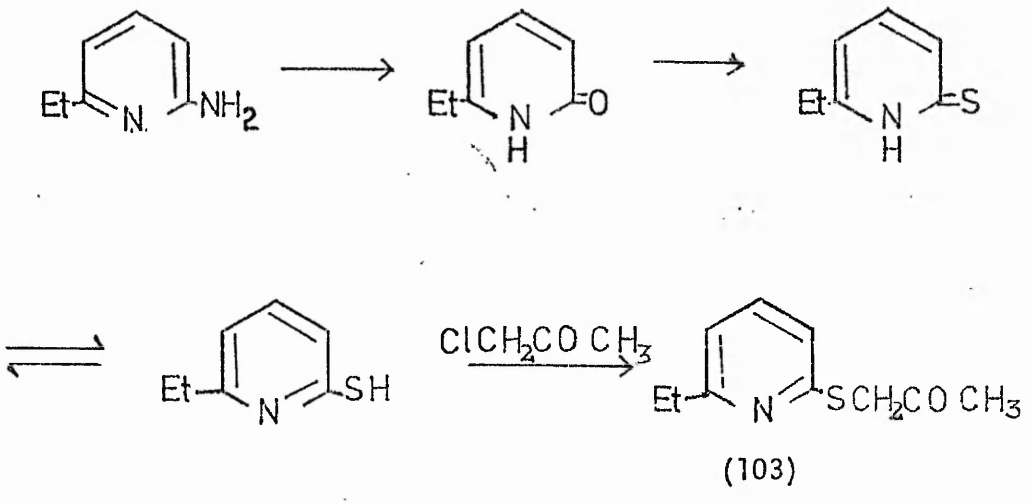
Scheme 5

The conversion of 2-propionylfuran into 2-ethyl-3-hydroxypyridine is an established process,[151] but the scale and convenience of the literature method are limited by the fact that the reaction is carried out in a sealed tube. It was hoped that the same result could be achieved in the vapour phase reactor, since this technique is very suitable for the production of large quantities of material. In the event, the yields of hydroxypyridine were very low (although some product was formed); since the main attraction of the proposed route was the possibility of large-scale working, the project was abandoned.

Section III

Scheme 6 illustrates another approach to the synthesis of a thienopyridine that was investigated; it also involved formation of the thiophen ring. Since 2-amino-6-ethylpyridine was commercially available, it was used as the starting material to investigate the viability of the reaction sequence.

Scheme 6

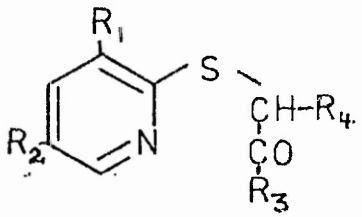


Following the procedure described by Adnams and Schrecker,[152] the amino compound was readily converted by nitrous acid into the corresponding pyridone, which then reacted smoothly with phosphorous pentasulphide to give 6-ethylpyridin-2-thiol[153] in good yield. Reaction of the sodium thiolate with chloroacetone, gave 5-(6-ethyl-2-pyridyl) mercaptoacetone (103) without complication. Several methods were

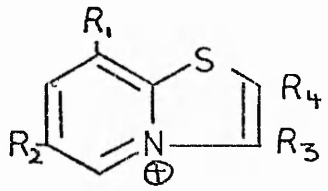
attempted to induce ring closure of compound (103). These included heating it with polyphosphoric acid at 150-160°, with polyphoric acid-phosphorus pentoxide at 180°, with phosphorus pentoxide in boiling chloroform or xylene, and with phosphoryl chloride in pyridine. In no case was there any evidence of any change.

However, when 5-(6-ethyl-2-pyridyl)-mercaptoacetone was dissolved in concentrated sulphuric acid and the solution was heated on the steambath, the desired cyclisation did occur to give a low yield of 7-ethyl-3-methylthieno[2,3-b]pyridine (104), characterised as its picrate.

A reasonable explanation for the low yield of thienopyridine is that a competing reaction is taking place. Bradsher and Lohr[154,155] showed that pyridyl sulphides of general type (105) having a carbonyl function beta to the sulphur atom are cyclised in concentrated sulphuric acid to afford good yields of thiazolo[3,2-a]-pyridinium salts (106):-



(105)

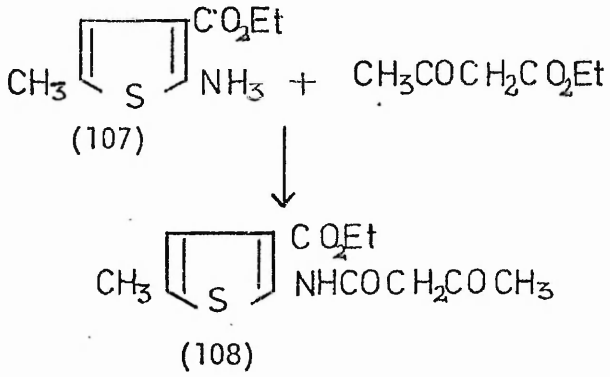


(106)

Section IV

Owing to the difficulties previously discussed in the preparation of amino thiophens by initial nitration of thiophen followed by reduction of the nitro compounds, alternative synthetic routes to amino thiophens involving the direct synthesis of the compounds from suitable precursors were pursued.

Initially, 2-amino-3-ethoxycarbonyl-5-methylthiophen (107) was prepared (from ethyl cyanoacetate, sulphur and propionaldehyde) according to the procedure of Gewald,[156] to investigate further the reaction of ethyl acetoacetate and amino thiophens. The compound (107) and the ester were heated together in boiling toluene; N-(3-ethoxycarbonyl-5-methyl-2-thienyl)-3-ketobutanamide (108) was isolated as the only product from the reaction:-

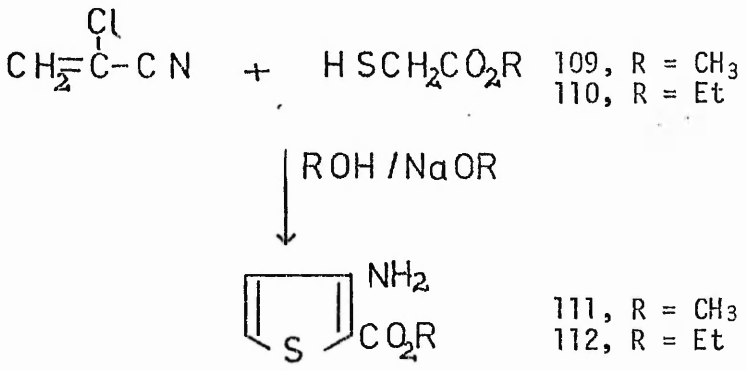


An attempt to cyclise (108) with sodium hydride in dimethyl formamide solution resulted in the formation of a dark polymeric substance from which no identifiable product was obtained.

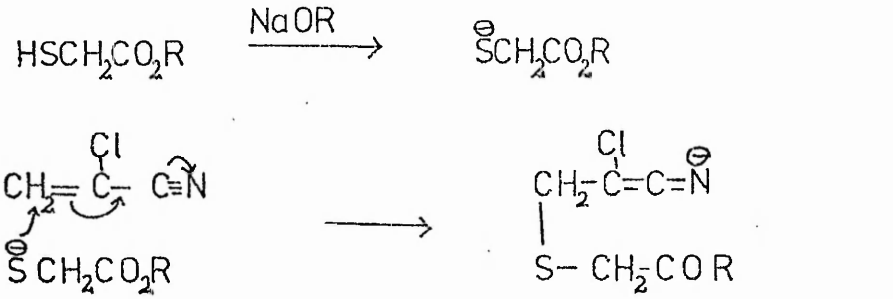
At this time a new and convenient synthesis of 2-substituted 3-amino thiophens was developed in these laboratories,[157] and it was decided that further work should proceed with these compounds, since they are potential starting materials for the otherwise rather inaccessible thieno[3,2-b] and -[3,4-b] pyridine systems.

Synthesis of 3-amino- and 3-hydroxy-2-substituted thiophens by the base induced condensations of methyl thioglycolate with 2,3-dihalogenopropionitrite and 2,3-dihalogenopropionate esters, respectively, had previously been published by Fiesselmann.[158] The new method[157] developed here replaces the 2,3-dihalogenopropionitrile with 2-chloroacrylonitrile, a cheap, commercially available material.

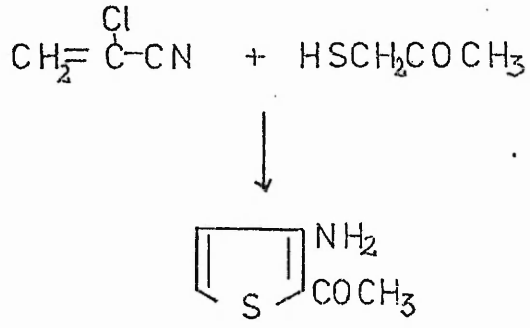
The new approach is illustrated by the use of compounds (109) and (110), which led to good yields of the thiophen derviatives (111) and (112) respectively.



The reaction sequence leading to the thiophen ring is thought to involve Michael addition of the thioglycolate anion to the 2-chloroacrylonitrile, followed by a cyclisation of the Thorpe or Dieckmann type and elimination of hydrogen chloride:-



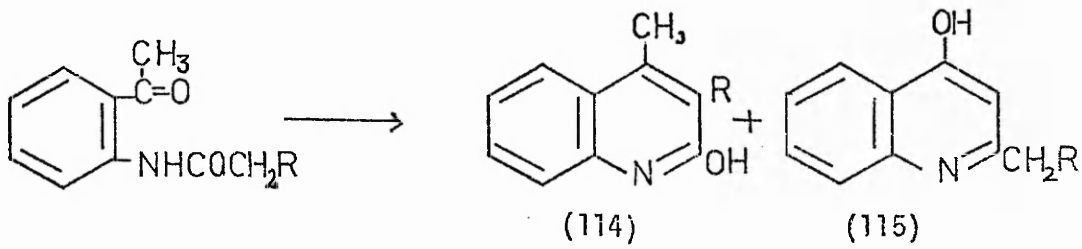
By a similar route, using mercaptoacetone[175] and 2-chloroacrylonitrile, 3-amino-2-acetylthiophen (113)[176] was also prepared in a good yield:-



(113)

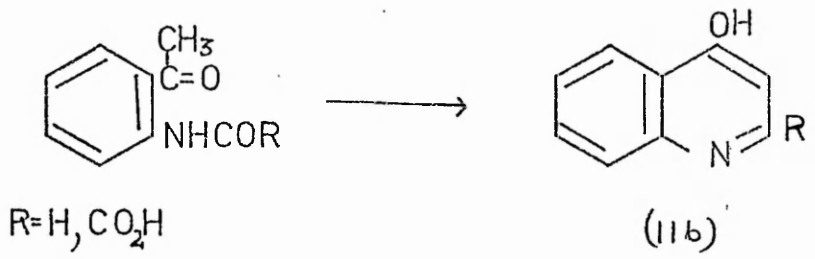
3-Amino-2-methoxycarbonylthiophen (111) and 3-amino-2-ethoxycarbonylthiophen (112) were stable yellow crystalline compounds, whereas 3-amino-2-acetyl thiophen (113) was an oil. Alkaline hydrolysis of 3-amino-2-methoxycarbonylthiophen gave 3-amino-thiophen-2-carboxylic acid as a white, low melting solid. It was found that this substance was considerably less stable than the corresponding esters and had a shelf life of only a few days before discolouration and decomposition occurred.

Several alternative approaches to thienopyridines from 3-amino-2-acetyl or 2-methoxycarbonylthiophen were explored. In the first approach, reactions analogous to those used in the Camps syntheses of hydroxyquinolines were examined. The syntheses of hydroxyquinolines from orthoacyl aminophenyl ketones was developed by Camps,[159,160] whose name is generally associated with the reaction:



(114) (115)

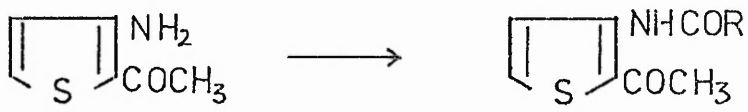
Aqueous alcoholic sodium hydroxide is the preferred condensing agent and usually a mixture of products is obtained. The ratio of (114) to (115) is dependant on the nature of the group R,[161] but with formyl and oxalylaminoacetophenones only products corresponding to (116) are obtained.[161]



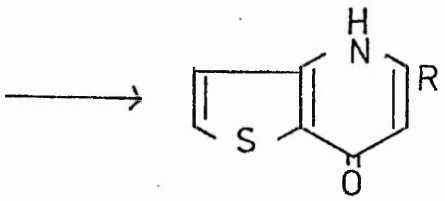
R=H, CO_2H (116)

Owing to the previous inaccessibility of 3-amino-2-acetylthiophen, no report of the application of a Camps type synthesis to thienopyridines has appeared in the literature. Scheme 7 illustrates the proposed reaction scheme for the preparation of 5-substituted-thieno[3,2-b] pyridines by application of the Camps syntheses of hydroxyquinolines:-

Scheme 7



(117)



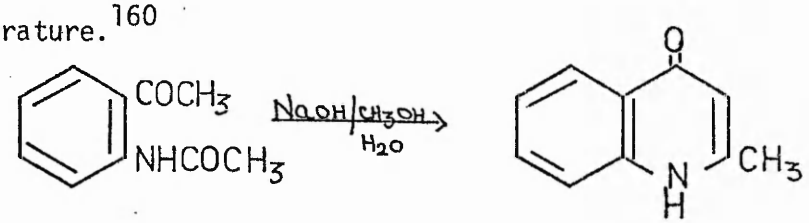
3-Formylamino-2-acetylthiophen (117, R = H) was readily prepared by heating the amine in formic acid- similarly 3-acetylamino-2-acetyl-thiophen (117, R = CH_3) was obtained by treatment of the amine with

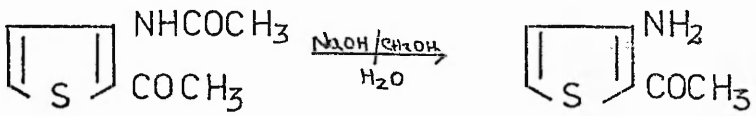
acetic anhydride in glacial acetic acid. 3-Ethyloxaloamino-2-acetylthiophen (117, R = $COOC_2H_5$) was obtained by boiling the amino compound and diethyl oxalate together in the presence of glacial acetic acid.

Attempts to cyclise the compounds (117, R = H, CH_3) was aqueous alcoholic sodium hydroxide were unfortunately unsuccessful. In both cases hydrolysis to the amino compound (113) occurred; there was no evidence of cyclisation when 3-ethyloxaloylamino-2-acetylthiophen was treated in a similar manner, hydrolysis to the acid (118) occurred, but again, this did not cyclise to the desired thienopyridone.

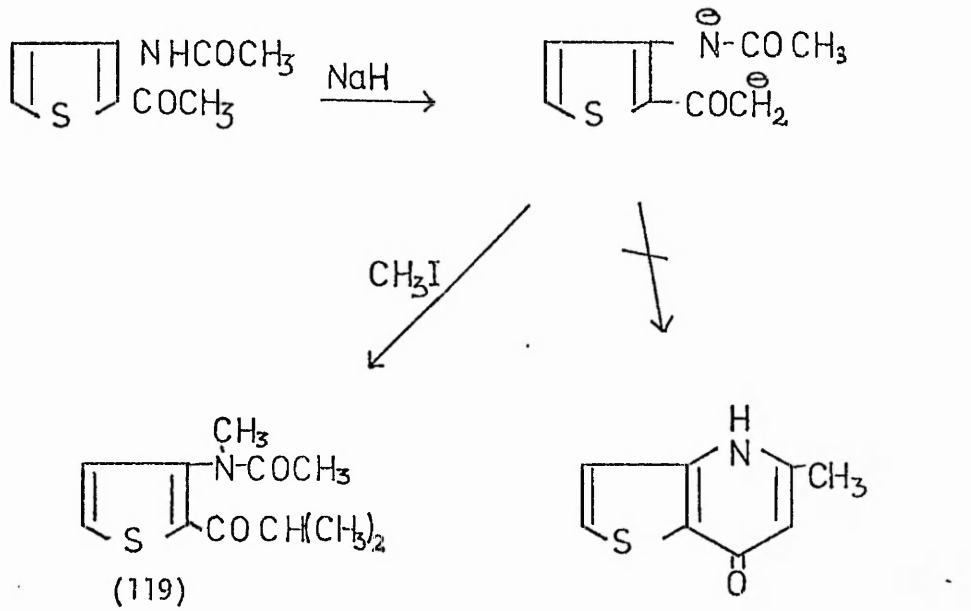
(118)

In order to familiarise himself with a successful reaction of this type the author treated 2-acetylaminoacetophenone with sodium hydroxide in aqueous methanol; the expected product 2-methylquinolin-4(1H)one was obtained in good yield (71%), as previously described in the literature.[160]





An attempt to cyclise 3-acetylamino-2-acetylthiophen with sodium hydride in dimethylformamide solution was likewise unsuccessful; in this case the starting material was recovered unchanged. The failure of the ring closure was shown to be almost certainly due to the facile formation of the anion arising by deprotonation of the amide nitrogen, rendering the group resistant to nucleophilic attack. When the amide (in dimethylformamide) was treated with sodium hydride followed by iodomethane the isolated product (119) was that arising by methylation at both carbon and nitrogen:



(119)

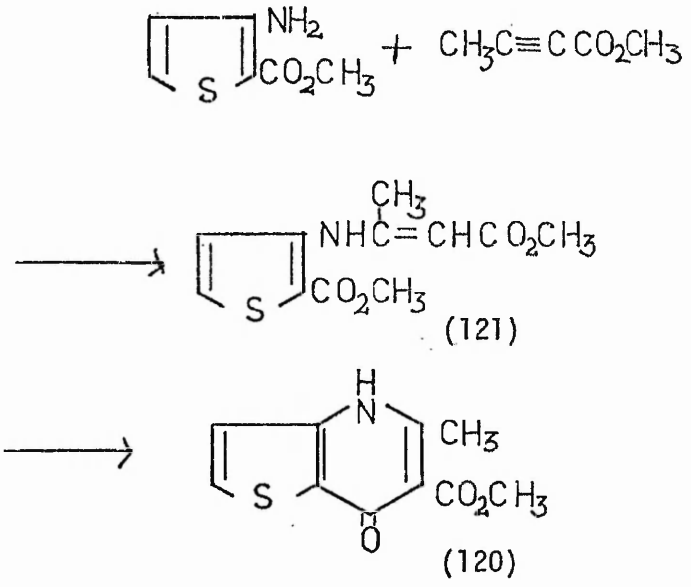
Finally, an attempt to cyclise 3-acetylamino-2-acetylthiophen, by treatment with methanolic ammonia,[179] was also made but this too failed to bring about the desired reaction.

The Friedlander synthesis[162] has previously been used successfully by Gronowitz[96] for the preparations of thienopyridines. The Friedlander synthesis of quinolines is typified by the following equation:-

An attempt to induce the analogous reaction between 3-amino-2-acetylthiophen and acetophenone under the usual conditions (ie. by boiling the reactants together under reflux in benzene in the presence of a catalytic quantity of alkali), failed to achieve the desired result.

The lack of success in attempts to adapt the Camps and Friedlander syntheses to the desired thienopyridines prompted the author to explore a different approach, summarised in Scheme 8.

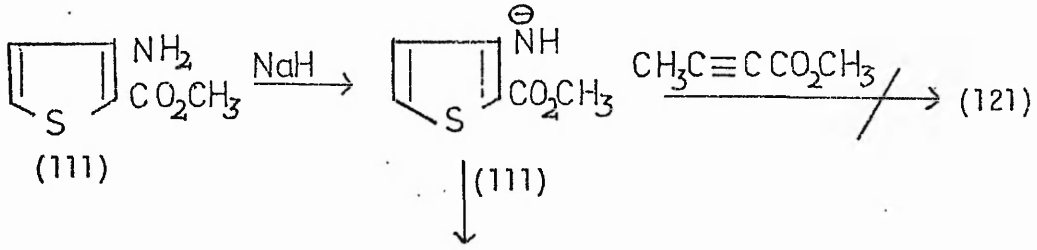
Scheme 8:



It was then expected that hydrolysis of (120) followed by decarboxyation would lead to a suitable precursor for the quinoline alkaloid analogues.

Methyl tetrolate was prepared from ethyl acetoacetate according to the method of McKillop.[163] However, the amino compound and methyltetrolate could not be induced to react when boiled together under reflux for extended periods in methanol, in toluene, in xylene or in glacial acetic acid. Even when boiled together neat for three days the two compounds failed to undergo the desired Michael addition. In an attempt to prepare a more reactive species from the amine it was

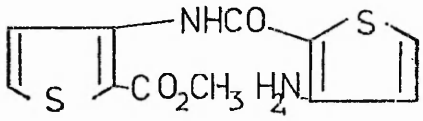
treated with sodium hydride in dimethylformamide in the presence of methyl tetrolate. A reaction did then occur, producing the condensation product (122) rather than the desired Michael adduct (121):



(111)

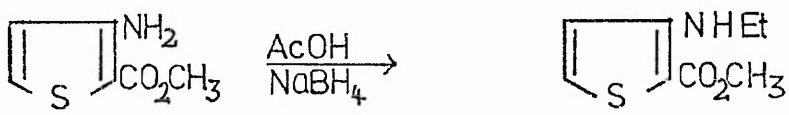
(111)

(121)



(122)

It seemed that the failure of the Michael addition of the amine (111) might be due to the low nucleophilicity of the amino group; accordingly it was converted into N-alkyl derivatives, which might be expected to be more powerful nucleophiles. In the first instance, 3-ethylamino-2-methoxycarbonylthiophen (123) was prepared from the amino compound by treatment with sodium borohydride in glacial acetic acid, following the procedure of Gribble and Lord:[164]

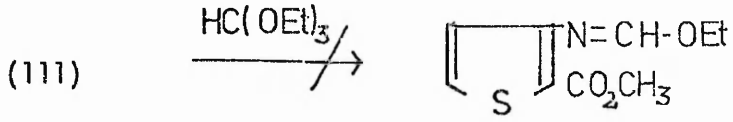


(111)

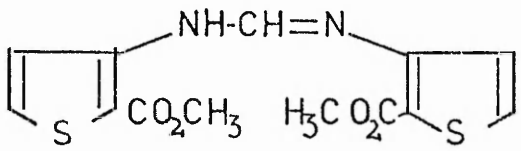
(123)

Secondly, an attempt was made to apply the method of Crochet[165] to the preparation of the N-methyl analogue. This involves reaction of the

primary amine with triethylorthoformate to give the imidate, which is then reduced with sodium borohydride to the corresponding N-methyl compound. With 3-amino-2-methoxycarbonylthiophen, however, the intermediate (124) was not formed, the reaction product was identified as 3-(2-methoxycarbonyl-3-amino-thienyl)methyleneamino-2-methoxy-carbonylthiophen (125):-

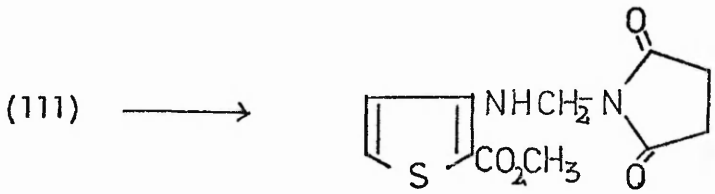


(124)

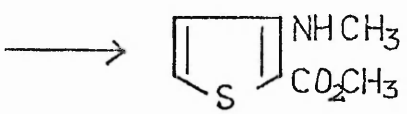


(125)

3-Methylamino-2-methoxycarbonylthiophen (127) was eventually prepared by the reaction of the primary amine with succinimide and aqueous formaldehyde, to give the intermediate 3-N-succinimidomethyleneamino-2-methoxycarbonylthiophen (126), followed by reduction with sodium borohydride in dimethylsulphoxide:-



(126)



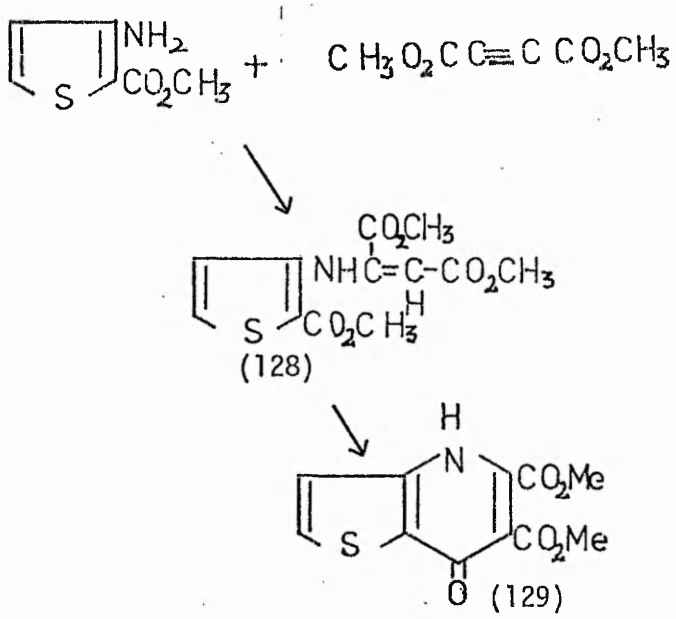
This procedure was recently described by Kadin.[166]

Unfortunately, repeated attempts to react the methylamino (127) and ethylamino (123) compounds with methyl tetrolate in a wide range of solvents and under various conditions failed to give the desired reaction. In all cases only unchanged starting materials were recovered.

For biological testing several derivatives of both 3-amino-2-methoxycarbonyl and -2-ethoxy-carbonylthiophen were prepared; these included the acetyl-, the formyl- and the 3-p-toluenesulphonyl-derivatives.

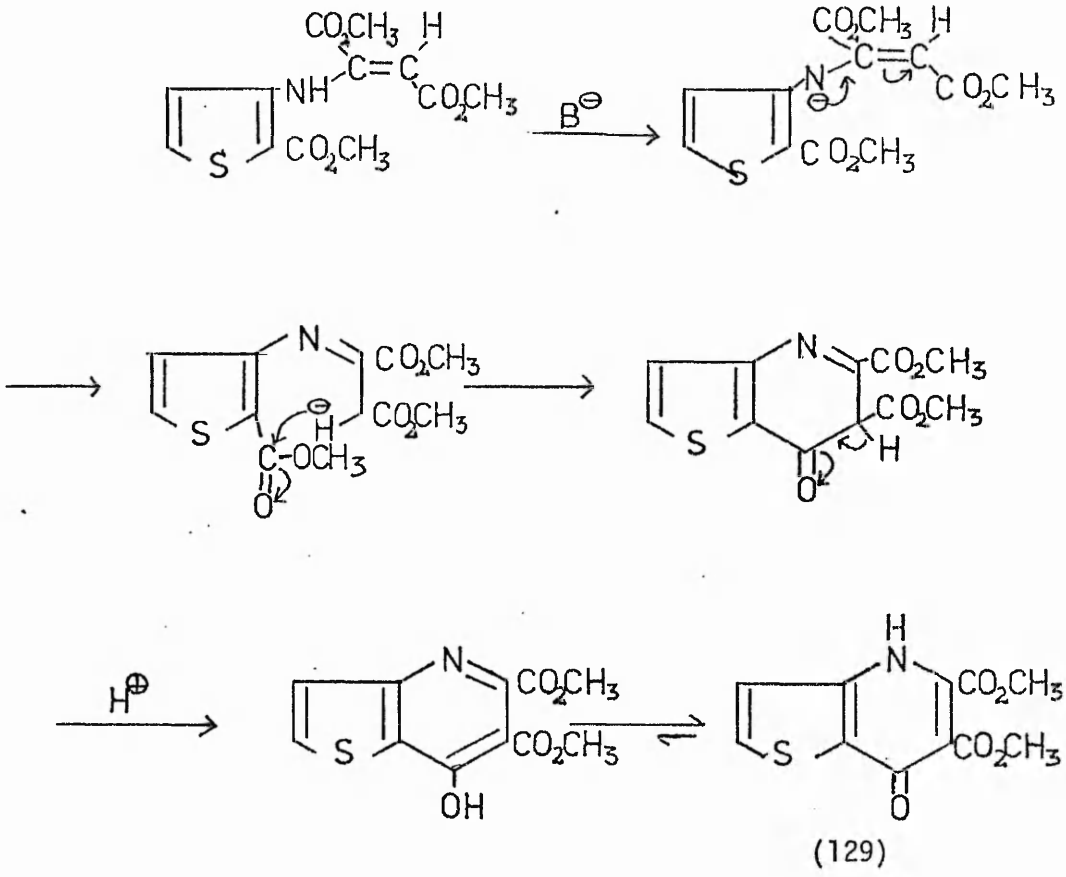
An alternative approach to thienopyridine syntheses, involving the 3-amino-2-methoxycarbonylthiophen-dimethyl acetylenedicarboxylate adduct (128) was then examined, as illustrated in Scheme 9.

Scheme 9



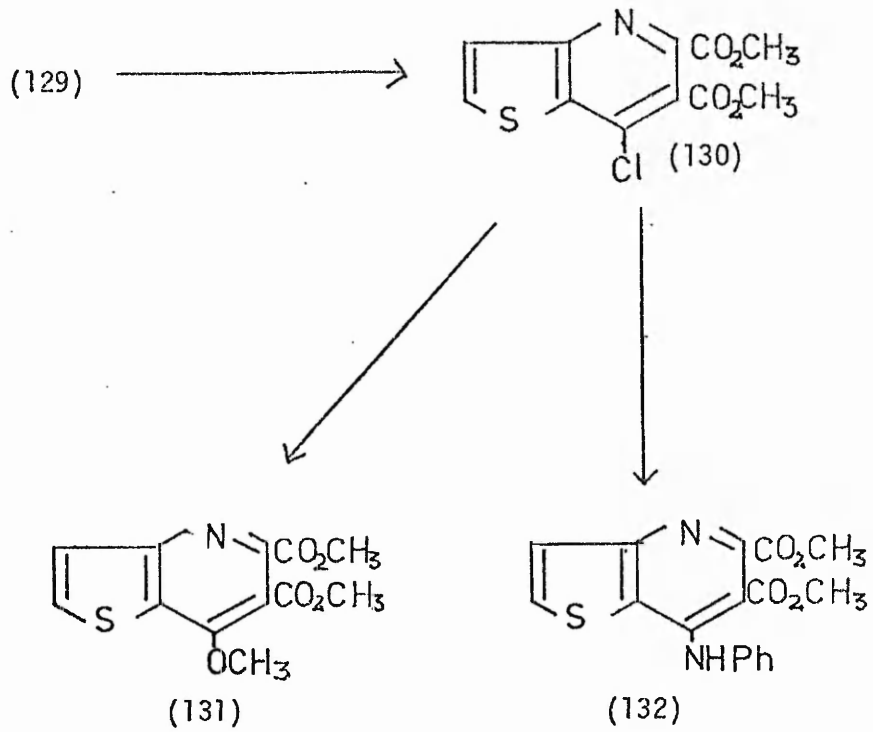
There have been two recent reports[94,167] (both involving 2-amino-thiophens) of the preparation and cyclisation of thienylamine-dimethyl acetylenedicarboxylate adducts. Initially the Michael adduct (128) was obtained by heating the starting materials together in boiling toluene, but yields were low and column chromatography was necessary

to separate the adduct from the numerous by-products. Later it was found that high yields of substantially pure (128) were obtained if the reaction was carried out at room temperature and in glacial acetic acid as solvent. Considerable evidence has accumulated that such adducts have the fumarate configuration[168] and the above example appears to be no exception; in particular the nmr signal of the lone alkenic proton of (128) (at τ 4.55) lies in the region characteristic of the vinyl resonance of such arylamino-fumarates. The Michael adduct, in dimethylformamide, was rapidly and efficiently cyclised on treatment with sodium hydride to give 5,6-bismethoxycarbonylthieno [3,2-b]pyridin-7(4H)one (129). The proposed mechanism for these cyclisations[94] is shown below:-



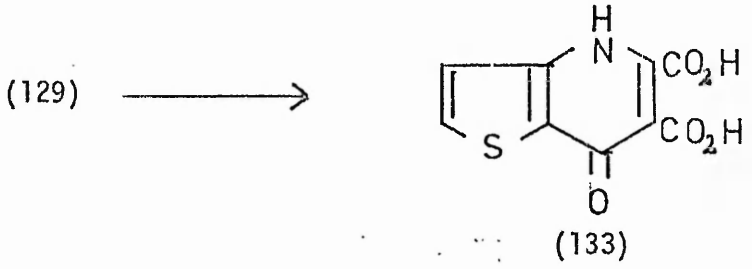
(129)

The chemistry of the thienopyridone (129) has much in common with that of the comparable 4-quinolones. Thus, reaction of (129) with phosphoryl chloride gave 7-choro-5,6-bismethoxycarbonylthieno[3,2-b] pyridine (130); treatment of the latter with sodium methoxide in methanol gave the corresponding 7-methoxy compound (131). Similarly, prolonged heating of the chloro compound (130) with aniline yielded the 7-(N-phenylamino) compound (132):-

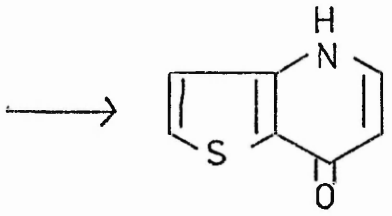


Although nitration of (129) (with mixed acid) led to the 3-nitro derivative,[180] an attempt to brominate (129) with bromine in glacial acetic acid solution at room temperature failed to give the corresponding 3-bromo compound.

Alkaline hydrolysis of the diester (129) gave thieno[3,2-b]pyridin-7(4H)one-5,6-dicarboxylic acid (133), which, when heated to above its melting point was readily decarboxylated; from the residue thieno [3,2-b]pyridin-7(4H)one (134) was obtained:-



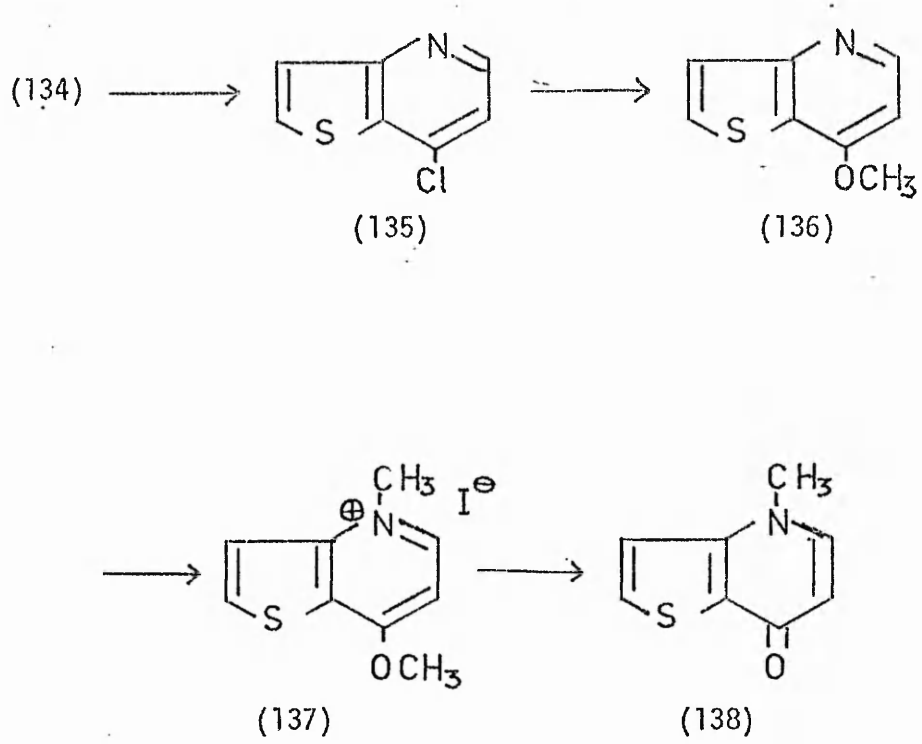
(133)



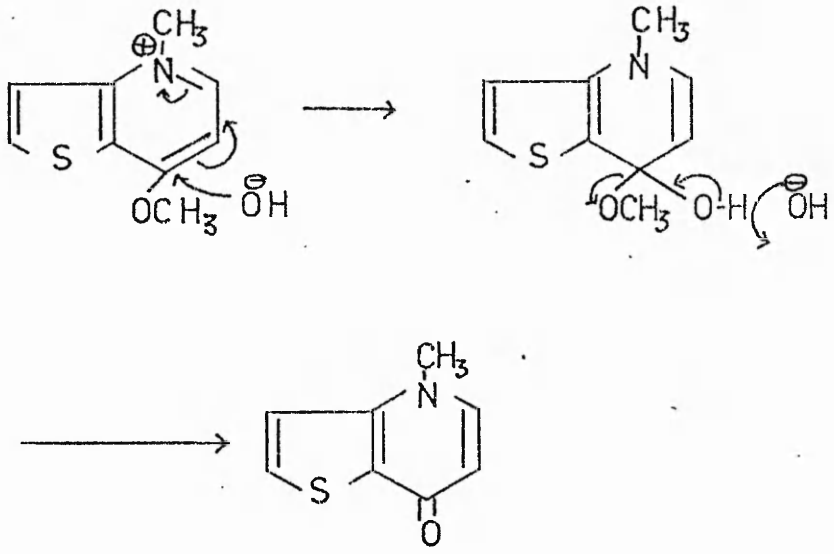
(134)

Once (134) was available, it was clear that thieno[3,2-b]pyridine analogues of the quinoline alkaloids echinopsine (22) and echinorine (24) could readily be prepared, by the reactions outlined in Scheme 10.

Scheme 10

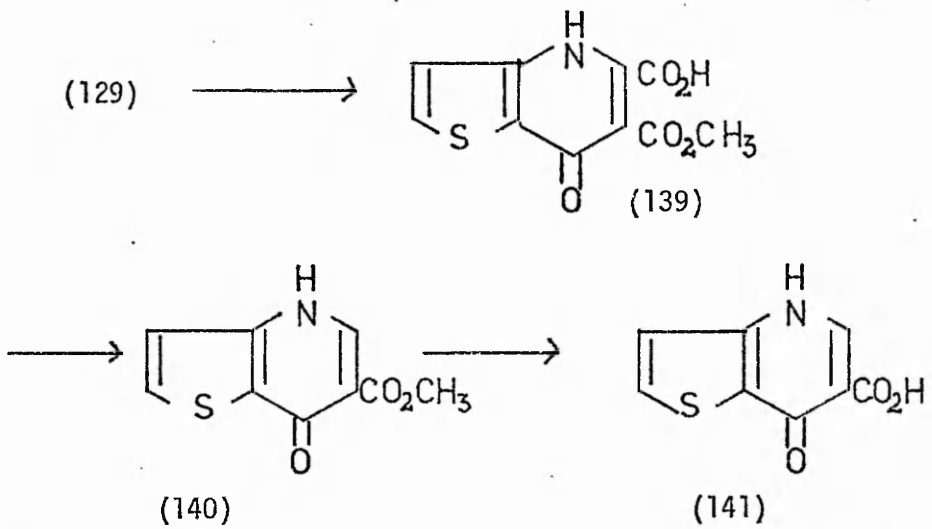


Thus, treatment of (134) with phosphoryl chloride gave 7-chlorothieno [3,4-b]pyridine (135), which, when reacted with sodium methoxide in methanol solution gave the corresponding 7-methoxy compound (136). An ethereal solution of (136) was treated with iodomethane, yielding, 4-methyl-7-methoxythieno[3,2-b]pyridinium iodide (137). This compound is the thieno[3,2-b]pyridine analogue of the alkaloid echinorine (24). By a reaction analogous to that reported for the conversion of echinorine into echinopsine (see chapter one, page 14), (137) on treatment with aqueous alkali gave 4-methylthieno[3,2-b]pyridin-7-one, the thieno[3,2-b]pyridine analogue of echinopsine (22). This facile reaction involves nucleophilic attack on the activated thienopyridinium system:-



In a recent publication by Biere and Seelen,[94] it was reported that treatment of 5,6-bismethoxycarbonylthieno[2,3-b]pyridin-4(7H)one (60) with alkali under controlled conditions resulted in the preferential hydrolysis of the ester group on the carbon atom α to the nitrogen atom. To investigate the possibility of obtaining a thieno[3,2-b] pyridine with a functionalgroup available at C-6 only, the procedure of Biere and Seelen was applied to compound (129) (Scheme 11):-

Scheme 11

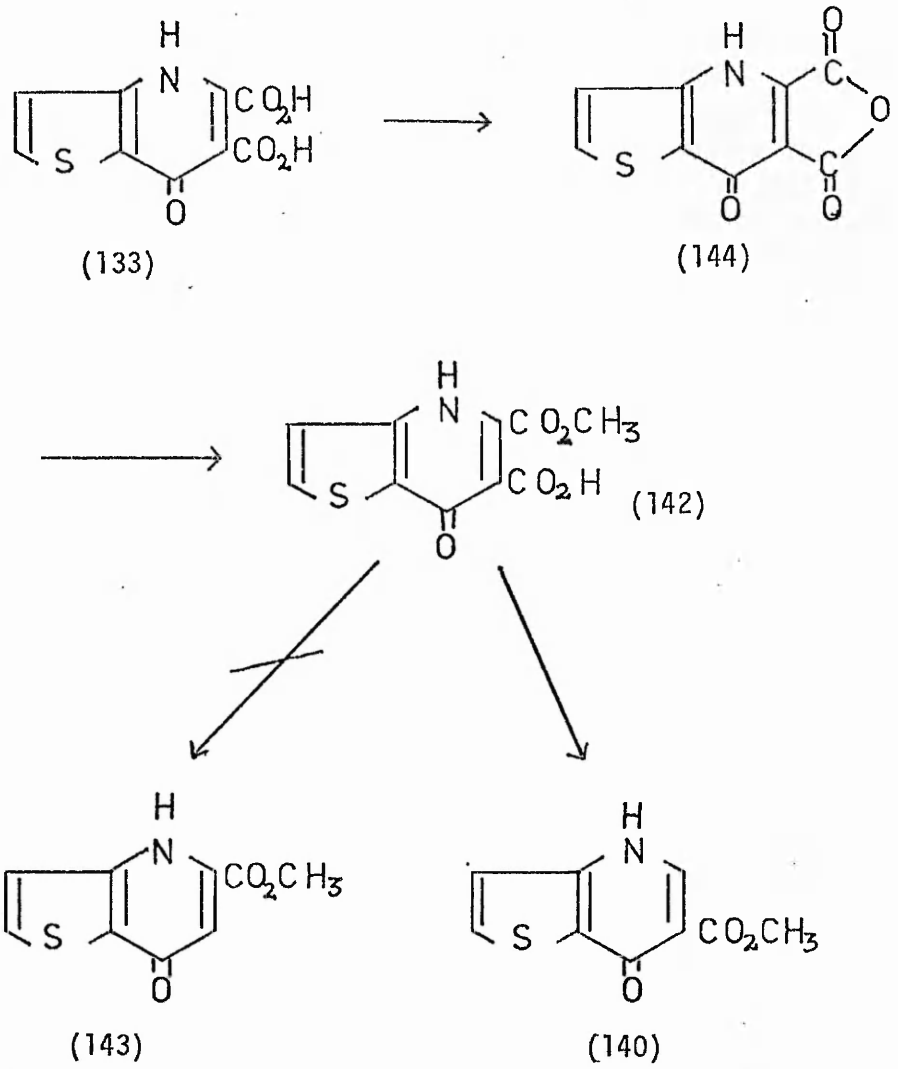


Treatment of (129) with aqueous alkali under the conditions described by Biere and Seelen resulted in the selective hydrolysis to give exclusively 6-methoxycarbonylthieno[3,2-b]pyridin-7(4H)one-5-carboxylic acid (139). Thermal decarboxylation of (139) then led to 6-methoxycarbonylthieno[3,2-b]pyridin-7(4H)one (140). The structure of (139) was deduced by analogy with the work of Biere and Seelen; in particular the nmr signal for the methyl ester group (in dimethyl sulphoxide) at τ 6.24 is at the same position as that reported for 5-methoxycarbonylthieno[2,3-b]pyridin-4(7H)one-6-carboxylic acid. Similarly, the structure of the ester (140) was confirmed since the proton on the pyridine ring of the decarboxylation product gave a signal at τ 1.15, in the region (τ 1.07-1.42) reported[169] for comparable 4-quinolone-3-carboxylic acids and esters; the isomeric 4-quinolone-2-carboxylic acids and esters give absorptions at considerably higher fields (eg. τ 3.08-3.28).[170]

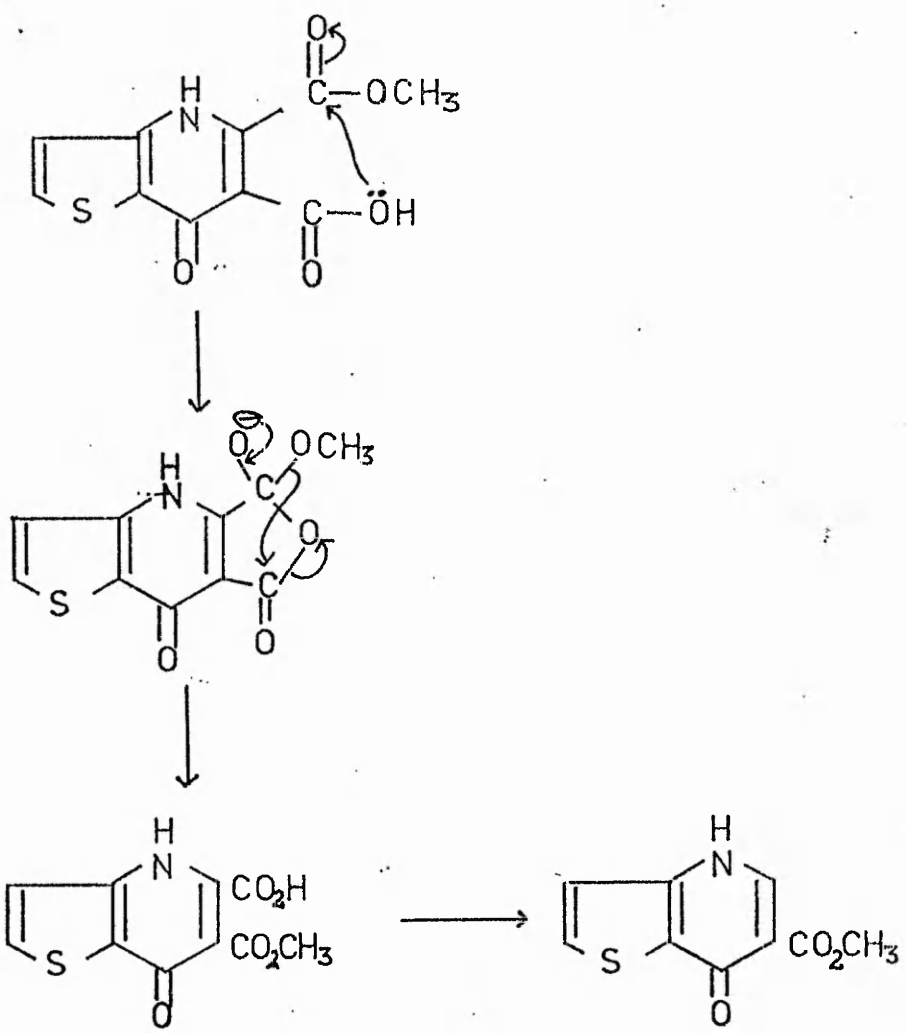
Isolation of the pure ester (140) from the decarboxylation product was rather difficult, so, on some occasions the crude decarboxylation product was saponified and the acid (141) was obtained.

It was envisaged at this stage that preparation of the isomeric half ester (142), followed by thermal decarboxylation would be a convenient route to the preparation of a thieno[3,2-b]pyridin-7(4H)one with a substituent attached to C-5 (143). This would be a suitable starting material for the preparation of quinoline alkaloid analogues of the type previously illustrated in chapter two, which carry a substituent α- to the nitrogen atom. The reaction sequence shown in scheme 12 was now investigated as a route to the desired compound (143):-

Scheme 12:

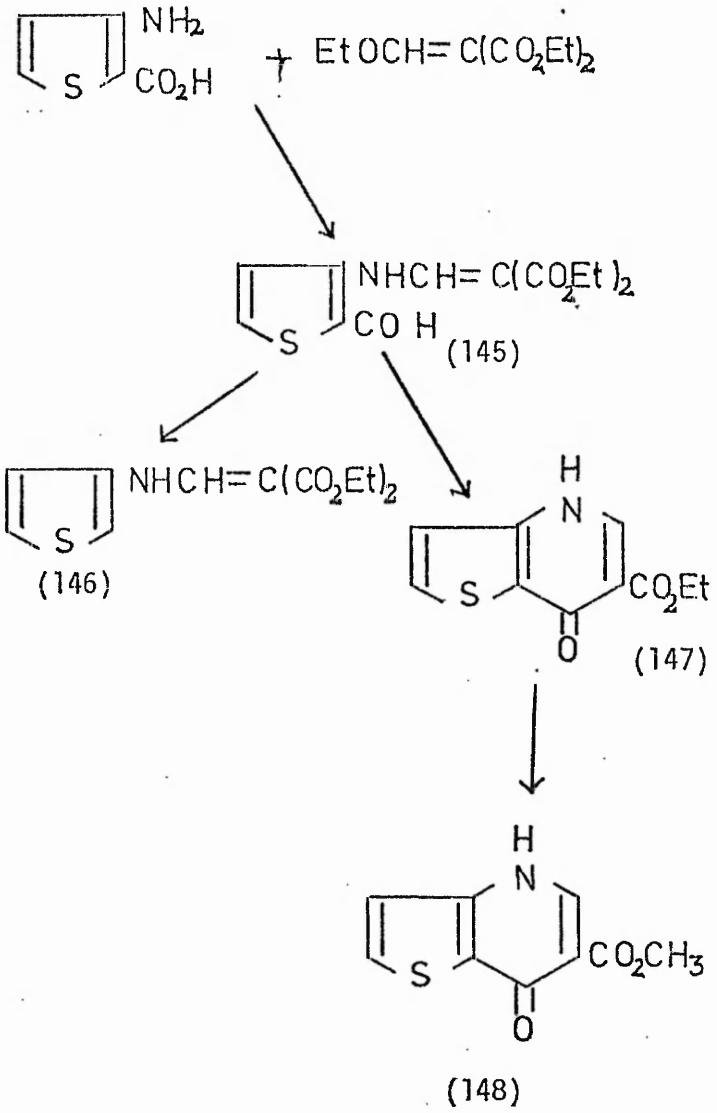


Treatment of the diacid (133) with acetic anhydride gave thieno [3,2-b] pyridin-7(4H)one-5,6-dicarboxylic anhydride (144) in excellent yield. This, when boiled with methanol gave exclusively the half ester, 5-methoxycarbonylthieno[3,2-b]pyridin-7(4H)one-6-carboxylic acid (142). Surprisingly, thermal decarboxylation of (142) did not give the expected product (143) but yielded instead a product shown conclusively to be the isomeric 6-methoxycarbonylthieno[3,2-b] pyridin-7(4H)one (140). The material had identical nmr and ir spectra, and its mixed melting point showed no depression with the substance prepared by the route of Biere and Seelen. A possible mechanism for this isomerisation is shown below:-



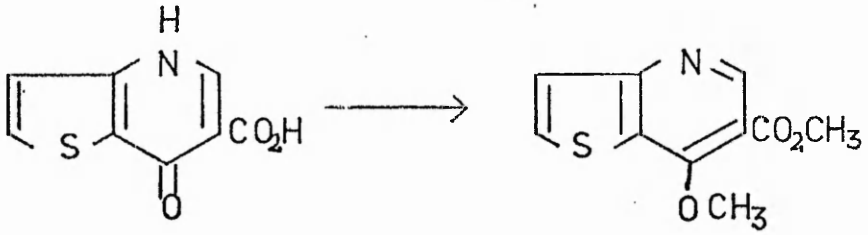
The structure of (140), the common decarboxylation product, was further confirmed beyond reasonable doubt by an unambiguous synthesis by the route shown in scheme 13:-

Scheme 13



By the reaction of 3-aminothiophen-2-carboxylic acid with diethyl ethoxymethylenemalonate in boiling toluene, 3-(2,2-bisethoxycarbonyl-vinylamino)-thiophen-2-carboxylic acid (145) was obtained. This compound was found to be very readily decarboxylated [to give ethyl α-ethoxycarbonyl-β-(N-3-thienyl)amino acrylate[82] (146)] when heated. Treatment of (145) with polyphosphoric acid ester brought about cyclisation to give 6-ethoxycarbonylthieno[3,2-b]pyridin-7(4H)one (147). Transesterification of (147) by prolonged heating in boiling methanol, containing a catalytic quantity of p-toluenesulphonic acid, gave unambiguously, 6-methoxycarbonylthieno[3,2-b]pyridin-7(4H)one (140).

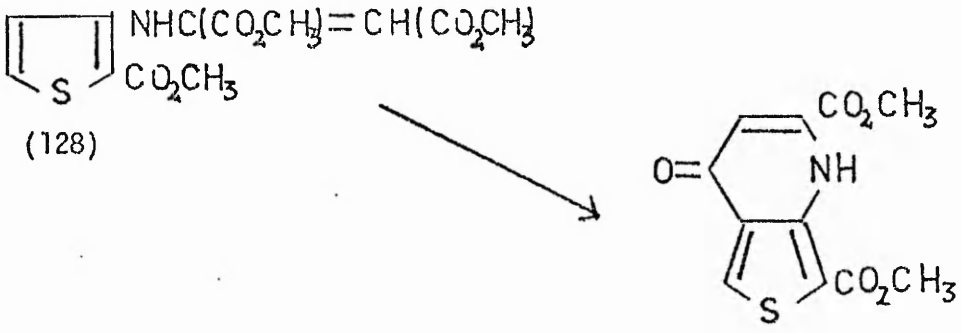
6-Methoxycarbonyl-7-methoxythieno[3,2-b]pyridine (148) was prepared from (141) by initial reaction with phosphorous pentachloride, followed by boiling under reflux in methanol.



(148)

Section V

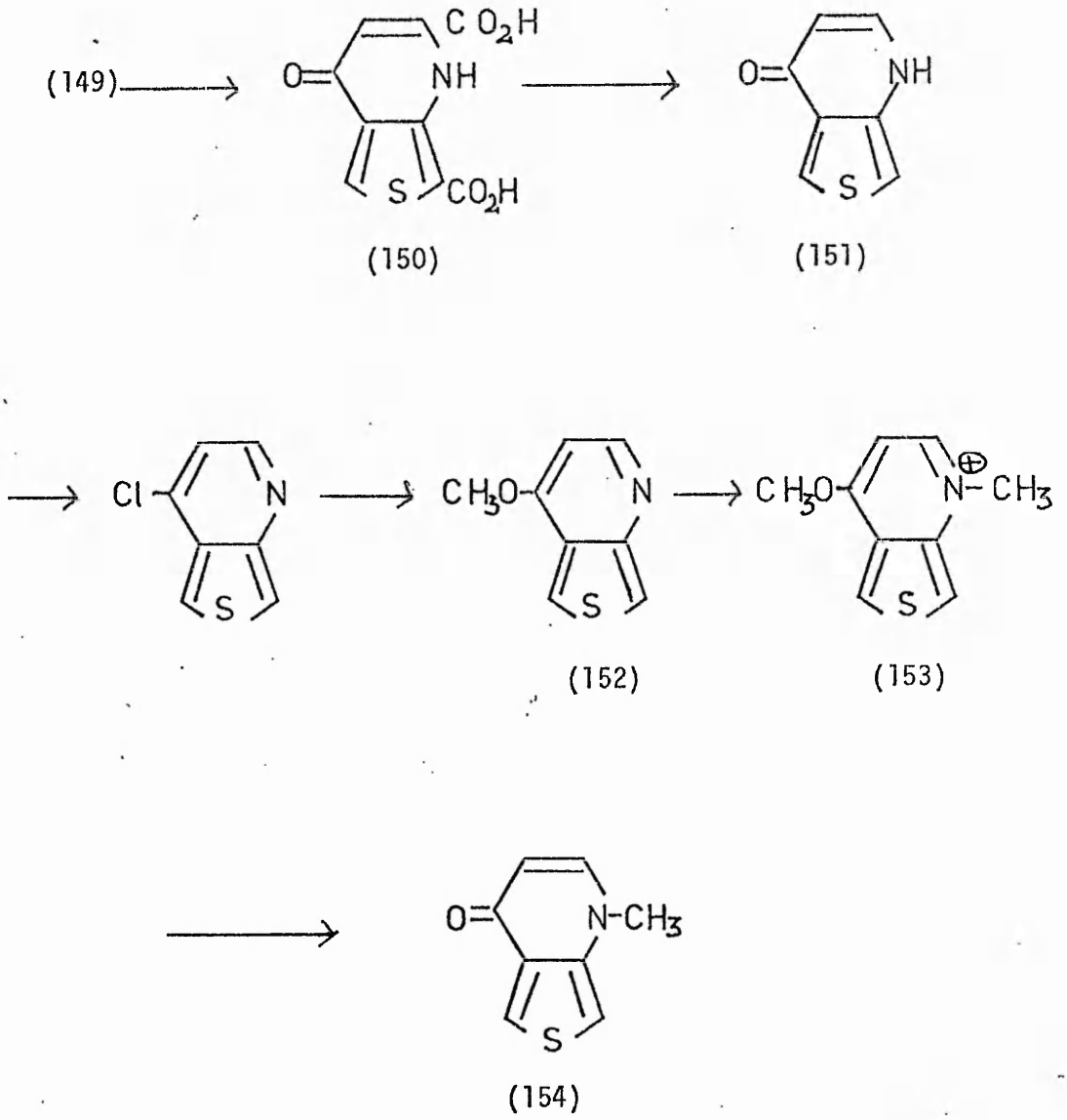
Following the successful cyclisation of the Michael adduct (128) to afford the thieno[3,2-b]pyridines reported above, it was decided to attempt to induce ring closure on the vacant position at C-4 on the thiophen ring, to prepare a 3,5-disubstituted thieno[3,4-b]pyridine. No report of this type of synthesis of these inaccessible compounds has previously appeared in the literature:-



(128) (149)

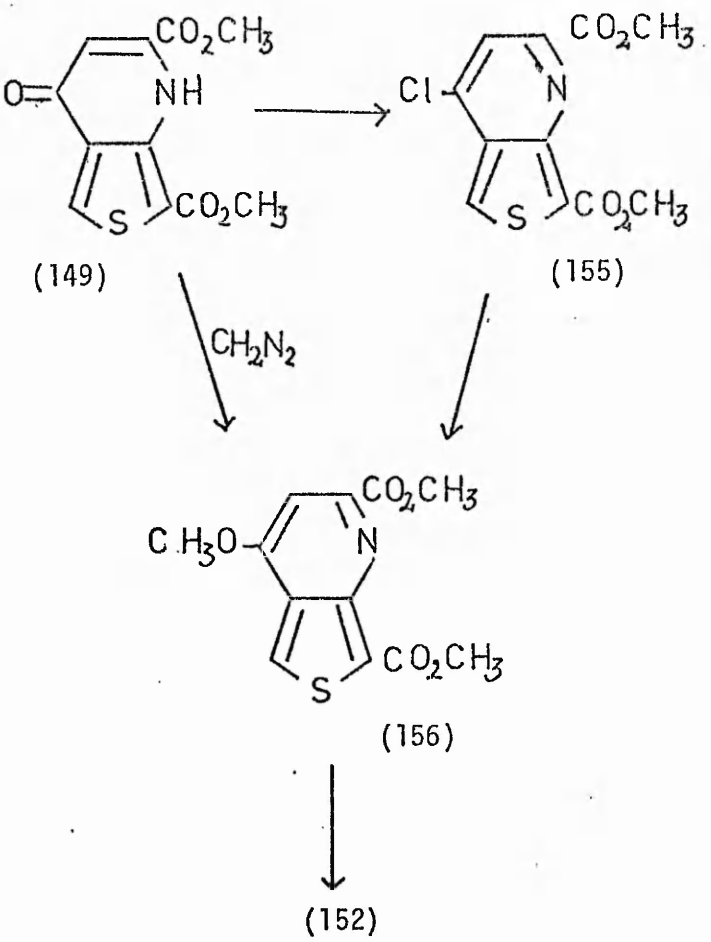
Repeated attempts to induce the desired cyclisation by prolonged heating of the Michael adduct in boiling tetrahydronaphthalene and in diphenyl ether failed; in all cases only polymeric residues were obtained, from which no identifiable product was isolated. However, when (128) was heated in triethyleneglycol dimethyl ether (triglyme) the desired cyclisation did occur, to give 3,5-bismethoxycarbonyl-thieno[3,4-b]pyridin-7(4H)one (149) in excellent yield. At this stage it was assumed that a parallel reaction sequence to those previously described for the thieno[3,2-b]pyridines, would lead to the thieno [3,4-b]pyridine analogues of the alkaloids echinopsine and echinorine. Scheme 14 below illustrates the proposed reaction sequence to the desired compounds (153) and (154).

Scheme 14


(149)
C O2H
O
NH
S
CO2H
(150)
O
NH
S
(151)
Cl
N
S
CH3O
N
S
(152)
CH3O
N-CH3
S
(153)
O
N-CH3
S
(154)

Alkaline hydrolysis of the diester (149) gave thieno[3,4-b]pyridin-7(4H)one-3,5-dicarboxylic acid (150) without difficulty. Attempted thermal decarboxylation of this diacid, by the procedure used successfully previously for the decarboxylation of thieno[3,2-b]pyridin-7(4H)one-5,6-dicarboxylic acid (133) failed however, yielding an intractable material. The probable reason for the failure in this instance was the very high melting point of the diacid (150). An alternative preparation of (152) by the route illustrated in Scheme 15, shown below, was attempted in the hope that the methoxy compound (157) would melt at a lower temperature and thus would be more readily thermally decarboxylated:-

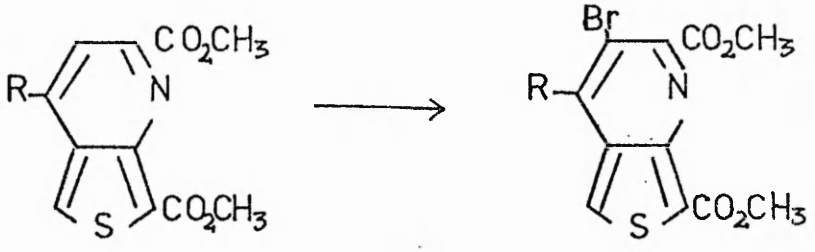
Scheme 15


CO2CH3
O
NH
S
CO2CH3
(149)
Cl
N
CO2CH3
S
CO2CH3
(155)
CH2N2
CH3O
N
CO2CH3
S
CO2CH3
(156)
(152)

Reaction of (149) with phosphoryl chloride gave the corresponding 7-chloro compound (155), and treatment of the latter with sodium methoxide in methanol yielded 7-methoxy-3,5-bismethoxycarbonylthieno [3,4-b]pyridine (156). An alternative synthesis of (156) was also investigated; it was found that reaction of the pyridone (149) with diazomethane in dichloromethane-methanol solution gave the 7-methoxy compound directly. Alkaline hydrolysis of (156) then led to 7-methoxy-thieno[3,4-b]pyridine-3,5-dicarboxylic acid (157). Unfortunately, thermal decarboxylation of (157) was no more successful than that of the corresponding pyridone (150). Due to lack of time, conventional decarboxylation reactions were not pursued with compounds (150) and (157), although preliminary results were encouraging.

A point of interest concerning all the compounds obtained in the thieno[3,4-b]pyridine series is that they exhibit very strong green fluorescence in alkaline solution.

Bromination of compounds (149) and (156) with bromine in glacial acetic acid solution gave 6-bromo-2,5-bismethoxycarbonylthieno[3,4-b]pyridin-7(4H)one (158) and 6-bromo-7-methoxy-3,5-bismethoxycarbonyl-thieno[3,4-b]pyridine (159) respectively:-



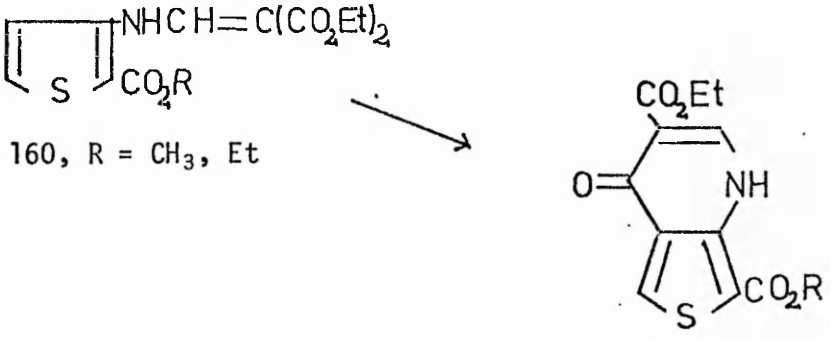
149, R = OH, =O
156, R = OCH_3

158, R = OH, =O
159, R = OCH_3

The location of the bromine at C-6 was confirmed by comparison of the nmr spectra of the above compounds with those of 2,6-disubstituted thieno[3,4-b]pyridine (see later). The site of entry of the bromine in these reactions is somewhat unexpected, as electrophilic substitution in thienopyridines normally occurs preferentially on the vacant carbon atoms of the thiophen ring (in the above case at C-1). A reasonable explanation for the observed result is that one can ascribe high reactivity at C-6 in the pyridine rings of the above compounds, as these are ortho to a phenolic hydroxyl and alkoxyl function.

The syntheses of compounds of the type (150) have been described earlier in this thesis (eg. 160, R = H (145)) in connection with the unambiguous synthesis of 6-methoxycarbonylthieno[3,2-b]pyridin-7(4H)-one (140). A further use of these intermediates for the preparation of thieno[3,4-b]pyridines was now examined, as illustrated in Scheme 16 below:-

Scheme 16



160, R = CH_3, Et

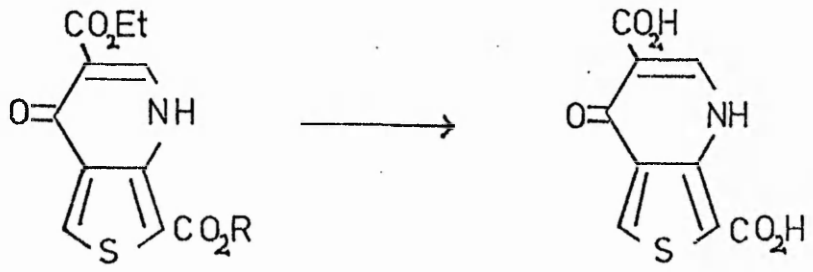
161, R = CH_3, Et

Interestingly, treatment of (160, R = CH_3, C_2H_5) with polyphosphate ester resulted in cyclisation to give 6-ethoxycarbonyl-3-methoxy (or ethoxy)-carbonylthieno[3,4-b]pyridin-7(4H)ones (161).

Attempts to selectively hydrolyse the ester group on the thiophen ring of the enamine 3-[2,2-bisethoxycarbonylvinylamino]-2-methoxycarbonylthiophen (160, R = CH), to give (145) failed; only polymeric material was obtained.

Compound (161) failed to undergo bromination under identical conditions to those described previously for the bromination of (149) and (156); presumably, the failure was due to the fact that the vacant position in the pyridine ring is now meta to the phenol function.

Alkaline hydrolysis of the diesters (161) gave thieno[3,4-b]pyridin-7(4H)one-3,6-dicarboxylic acid (162):-



(161) (162)

Unfortunately, due to lack of time, further development of these compounds towards the preparation of quinoline alkaloid analogues could not be attempted.

Chapter Three

EXPERIMENTAL

GENERAL

Infra-red spectra were recorded using either a Perkin Elmer 137 NaCl, or a Perkin Elmer 137G grating spectrophotometer, both calibrated with polystyrene film.

Proton magnetic resonance spectra were recorded on a JEOL JNM C-60 HL 60 MHz spectrophotometer with tetramethylsilane as the internal standard in the solvents indicated.

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

Micro analyses for C, H, N were determined by the Microanalysis Unit, University of Nottingham; by Butterworths Microanalytical Consultancy Limited, Teddington, Middlesex; or by the analytical section of Imperial Chemical Industries Limited, Alderley Edge, Macclesfield.

Thin layer chromatography was carried out using pre-spread plates (5 x 20 cm; Polygram SIL/GUV$_{254}$ and Polygram ALOX N/UV$_{254}$ from Camlab, Cambridge). Column chromatography was carried out using Fison silica gel MFC (80-200 mesh) and Fison alumina (100-250 mesh).

Ether or dichloromethane solutions obtained when compounds were extracted from aqueous phases were dried over magnesium sulphate and evaporated under reduced pressure.

Light petroleum refers to the fraction b.p. 60-80^{o}.

2-Nitrothiophen

Attempts to prepare this compound by the method of Babasinian[140] gave a mixture which was shown by NMR to consist of the 2-nitro isomer containing up to 40% of the 3-nitro compound. Repeated recrystallisation from light petroleum gave a material greatly enriched in the 2-isomer, but isomer free 2-nitrothiophen could not be obtained.

An analytically pure smaple of 2-nitrothiophen was obtained by separation of the isomers by preparative scale gas-liquid chromatography on a Pye Unicam series 10 chromatograph (with a 15' polyethylene glycol adipate column at a temperature of 206^{o} and a column pressure of 3216 sq m of nitrogen).

2-Aminothiophen tin double salt

This compound was prepared in 68% yield by the reduction of nitrothiophen with tin and concentrated hydrochloric acid according to the method of Steinkopf.[142]

2-Aminothiophen

This was prepared (5-12% yield) from the 2-aminothiophen tin double salt by treatment with 2M sodium hydroxide solution, under nitrogen, followed the procedure described by Abramenko.[88]

Thiophen-2-carboxylic acid

This acid was prepared in good yield (>70%) by hypobromite oxidation of 2-acetylthiophen, according to the method of Hartough.[171] In the later stages of the work the acid was donated by Croda Limited.

Attempted reaction of 2-aminothiophen with ethyl acetoacetate

Ethyl acetoacetate (0.5 g) was added to 2-aminothiophen (0.5 g) dissolved in glacial acetic acid (5 ml) under nitrogen. The solution was boiled under reflux for 1.5 h, under nitrogen. Evaporation of the solution under reduced pressure gave a black polymeric material, from which none of the desired 6-methylthieno[2,3-b]pyridin-4(7H)one (97) could be obtained.

N-(2-Thienyl)-3-keto-butanamide (98)

2-Aminothiophen tin double salt (50 g) was placed in a 500 ml round bottom flask, under nitrogen. Aqueous 10% sodium hydroxide solution (100 ml) was added, and the resulting slurry was extracted several times with toluene. The toluene extracts were combined, dried ($MgSO_4$), filtered and ethyl acetoacetate (15 ml) was added to the solution, which was then boiled under reflux for 4 h, under nitrogen, under a Dean and Stark apparatus. The solution was then cooled in the refrigerator overnight, when the product crystallised out. It was filtered off and recrystallised from toluene to give N-(2-thienyl)-3-keto-butanamide (1.2 g, 12%) mp. 134-6^{o} as pale yellow needles. (Found: C, 52.4; H, 5.0; N, 7.3. $C_8H_9NO_2S$ requires C, 52.5; H, 4.9; N, 7.6%.)

$\tau(CDCl_3)$: 3.2 (m, 3x Ar-H), 6.38 (s, $-CH_2-$)
7.7 (s, $COCH_3$).

Cyclisation of N-(2-thienyl)-3-keto-butanamide

The keto-amide (0.3 g) obtained above was dissolved in concentrated sulphuric acid (1 ml) and the resulting solution was kept at room temperature for 15 min. The solution was then added dropwise to ice (10 g) then the mixture was repeatedly extracted with dichloromethane. Evaporation of the combined dichloromethane extracts gave a white residue.

Crystallisation from methanol gave 4-methyl-thieno[2,3-b]pyridin-6-(1H)one (99) (0.12 g, 44%) as a white solid, mp. 226-228°. (Found: C, 58.0; H, 3.9; N, 7.9. C_8H_7NOS requires C, 58.1; H, 4.2; N, 8.4%.)
τ[$(CD_3)_2SO$] 1.90 (d, H-2, J = 6 Hz), 2.5 (d, H-3, J = 6 Hz)
3.3 (s, H-5), 7.7 (s, Ar-$C\underline{H}_3$).

Methyl-2-thienylketoxime

To a solution of hydroxylamine hydrochloride (30 g) in water (100 ml), aqueous 10% sodium hydroxide (140 ml) and 2-acetylthiophen (20 g) were added followed by sufficient methanol to give a clear solution, which was then boiled under reflux for 1 h. The cooled solution was set aside for several hours when methyl-2-thienylketoxime crystallised out. The product (21 g, 91%) mp. 81-83° (lit.[170] 81-83°) was filtered off and dried in a vacuum desiccator.

2-Acetylaminothiophen

Method A: By Beckmann rearrangement. cf. Williams[143]

Methyl-2-thienylketoxime (20 g) was dissolved in dry ether (200 ml) and the solution was cooled to 0° C. Phosphorus pentachloride (30 g) was added in portions (1 g) to the above, such that the temperature did not exceed 2° C. The resulting mixture was stirred for 30 min, then water (50 ml) was added, dropwise, with external cooling, so that the temperature did not exceed 20° C. 2M Sodium hydroxide solution was then added until the aqueous phase had pH 5. The ether layer was decanted off, and the aqueous solution was extracted again with ether. The combined ether extracts were dried ($MgSO_4$) and evaporated. The residue thus obtained was crystallised from benzene to give 2-acetylaminothiophen (2.5 g, 12%) mp. 153-154° (lit[143] 153-154°).
$\tau(CDCl_3)$ 3.3 (m, 3x Ar-$\underline{H}$), 7.95 (s, $CO\underline{CH}_3$).

Method B: By reductive acetylation. cf. Klemm et al[144]

A stirred mixture of 2-nitrothiophen (containing ca. 40% 3-nitro isomer) (24 g), reduced iron powder (45 g), glacial acetic acid (700 ml) and acetic anhydride (100 ml) was heated to 80°. The solution was maintained at this temperature for 24 h, then cooled and poured into ice cold water (2 l). The resulting mixture was filtered and the filtrate was evaporated under reduced pressure to one-third its original volume, then extracted repeatedly with ether. The combined (ether) extracts were dried ($MgSO_4$) and evaporated. The dark residue obtained was purified by vacuum sublimation, yielding acetylaminothiophen as white needles (18 g, 69%) mp. 154-155°.

Attempted hydrolysis of 2-acetylaminothiophen

2-Acetylaminothiophen (2 g) was dissolved in concentrated hydrochloric acid (25 ml) and the solution was heated on a steam bath for 1 h, treated with decolourizing carbon, then evaporated under reduced pressure. The product was very dark, and apparently polymeric, and none of the desired 2-aminothiophen hydrochloride was obtained.

Nitration of thiophen-2-carboxylic acid

Attempts to prepare 5-nitrothiophen-2-carboxylic acid by nitration of the acid with fuming nitric acid in glacial acetic acid according to the method of Rinkes,[145] gave a mixture of the 4- and 5-nitro isomers. Attempts to separate these by repeated recrystallisation from various solvents, by column chromatography or by the preferential solubilities of their barium salts, all failed to give isomerically pure 5-nitrothiophen-2-carboxylic acid.

Similarly, nitration with mixed acids resulted in mixed isomers.

Ethyl thiophen-2-carboxylate

This compound was prepared (in 60% yield) as a pale yellow oil, from the acid by reaction with thionyl chloride, then treatment of the resulting acid chloride with ethanol, according to the method of Hartought.[171]

Ethyl 5-nitrothiophen-2-carboxylate

The preparation of this compound was attempted by nitration of ethyl thiophen-2-carboxylate using the procedures described for the nitration of thiophen-2-carboxylic acid. Similarly, mixed isomers were obtained, attempts to separate these to give isomerically pure ethyl-5-nitrothiophen-2-carboxylate were unsuccessful.

Thiophen-3-carboxylic acid

A mixture of 3-methyl thiophen (1.17 kg) and aqueous sodium dichromate solution (3.57 kg in 9 l water) was placed in an 18 l capacity autoclave. The autoclave was sealed and pressure-tested with nitrogen to 500 psi. The solution was stirred and heated at 180° for 6 h, then allowed to cool overnight. The crude reaction mixture was filtered, and the pH of the filtrate was adjusted to 1 by the addition of concentrated hydrochloric acid, when the crude thiophen-3-carboxylic acid precipitated from solution. The solid was filtered off, washed repeatedly with cold water and crystallised from water to give thiophen-3-carboxylic acid (520 g, 40%) as a white solid mp. 136-139° (lit[172,181] 137-139°).

Ethyl thiophen-3-carboxylate

Thionyl chloride (200 ml) was added dropwise to thiophen-3-carboxylic acid (60 g). After the initial vigorous reaction had subsided, the solution was boiled under reflux for 2 h. The excess of

thionyl chloride was removed by distillation, and the residue was distilled at atmospheric pressure to give the acid chloride, bp. 208-210°. The acid chloride was dissolved in ethanol (500 ml) and the resulting solution was boiled under reflux for 3 h. When cool, water (500 ml) was added and the aqueous solution was repeatedly extracted with ether. The ether extracts were combined, washed with 4M sodium hydroxide solution, water, and saturated sodium chloride solution, then dried ($MgSO_4$), filtered and evaporated. The crude product was distilled at atmospheric pressure to yield ethyl thiophen-3-carboxylate[146] (31 g, 81%) as a pale yellow oil, bp. 212-214°.

$\tau(CDCl_3)$ 2.0 and 2.6 (m, 3x Ar-H)

5.8 (q, CH_2CH_3, J = 5 Hz)

8.8 (t, CH_2CH_3, J = 5 Hz)

5-Nitrothiophen-3-carboxylic acid[146]

Thiophen-3-carboxylic acid (6.4 g) was added in small portions to an ice cold mixture of concentrated sulphuric acid (10 ml) and concentrated nitric acid (20 ml). The resulting solution was stirred at 0° for 2 h, then poured onto ice cold water (200 ml). The solid obtained was filtered off; crystallisation from methanol gave 5-nitrothiophen-3-carboxylic acid (4.2 g, 50%) as pale yellow needles mp. 144-5° (lit[146] 144-5°).

$\tau(CDCl_3)$: 1.2 and 1.6 (both s, Ar-H)

Ethyl 5-nitrothiophen-3-carboxylate

Ethyl thiophen-3-carboxylate (100 g) was added carefully in small portions to an ice cold mixture of concentrated nitric (250 ml) and sulphuric (150 ml) acids. The solution was stirred for 3 h at 0° then poured carefully onto ice cold water (1 ℓ). The crude product was isolated with ether and crystallised from light petroleum to provide

the ester (78 g, 56%) as pale yellow needles, mp. 41-43° (lit[146] 44-46°).

τ($CDCl_3$): 1.9 (s, 2x Ar-H), 5.6 (q, CH_2CH_3, J = 6 Hz)
8.7 (t, CH_2CH_3, J = 6 Hz).

2-Amino-4-ethoxycarbonylthiophen

Method A

To a solution of stannous chloride (30 g) in concentrated hydrochloric acid (50 ml) the foregoing ester (10 g) was added in small portions. The solution was stirred vigorously, when an exothermic reaction occurred and the temperature rapidly rose to 80°. The mixture was then cooled in an ice bath, and stirred for 4 h. The pH of the solution was adjusted to pH 10 by the addition of 4M sodium hydroxide solution and then repeatedly extracted with ether. The combined ether extracts were washed with brine, dried ($MgSO_4$) then evaporated to yield 2-amino-4-ethoxycarbonylthiophen (1.6 g, 19%) as a pale orange oil.

Method B[147]

A solution of ethyl 5-nitrothiophen-3-carboxylate (5 g) in ethanol (50 ml) was cooled to 0° and saturated with hydrogen chloride gas. The gas stream was maintained while granulated zinc (12 g) was added in small portions. The mixture was then stirred for 30 min, poured into water (200 ml) and made basic (pH 10) with 4M sodium hydroxide solution. The product was isolated with ether as before to give an improved yield (1.9 g, 46%) of the crude amino-compound, which was used without further purification in the next reaction.

3-Ethoxycarbonyl-4-methylthieno[2,3-b]pyridin-6(7H)one (101)

Ethyl acetoacetate (5 ml) was added to a solution of 5-amino-2-ethoxycarbonylthiophen (1.9 g) in toluene (5 ml) and the whole was boiled under reflux under a Dean and Stark apparatus for 4 h. The solution was cooled in the refrigerator overnight, when crystallisation occurred. The solid obtained was filtered off and recrystallised from toluene to give N-(4-ethoxycarbonyl-2-thienyl)-3-keto-butanamide (100) (0.9 g, 30%), mp. 155-156°. (Found: C, 51.4; H, 5.1; N, 5.3. $C_{11}H_{13}O_4NS$ requires C, 51.7; H, 5.1; N, 5.4%.)

$\tau(CDCl_3)$ 1.90 and 2.10 (s, 2x Ar-H), 5.6 (q, CH_2CH_3, J = 6 Hz)
6.38 (s, $-CH_2-$), 7.7 (s, $COCH_3$)
8.75 (t, CH_2CH_3, J = 6 Hz)

The foregoing amide (0.6 g) was added to concentrated sulphuric acid (1 ml), the solution was kept at room temperature for 10 min then poured into ice-cold water (20 ml) and repeatedly extracted with dichloromethane. The organic solutions were combined, dried ($MgSO_4$) and evaporated to furnish a white solid. Crystallisation from ethanol gave 3-ethoxycarbonyl-4-methylthieno[2,3-b]pyridin-6(7H)one (101) (0.4 g, 67%) as white platelets, mp. 239-244°. (Found: C, 55.3; H, 4.4; N, 5.4. $C_{11}H_{11}NO_3S$ requires C, 55.6; H, 4.6; N, 5.9%.)

$\tau[(CD_3)_2SO]$ 1.85 (s, H-2), 1.60 (s, H-5)
5.40 (q, CH_2CH_3), 7.1 (s, $ArCH_3$)
8.45 (t, CH_2CH_3).

3-Ethoxycarbonylthieno[2,3-b]pyridine (102)

To a solution of ethyl 5-nitrothiophen-3-carboyxlate (20 g) in concentrated hydrochloric acid (200 ml), granular tin (25 g) was added in five gram portions; during the addition the solution was stirred vigorously and maintained at 30° by cooling in an ice-salt bath. After the addition of the tin was completed, ethanol (70 ml) and

anhydrous zinc chloride (6 g) were added and the resulting mixture was heated to 85°. To the hot solution, malondialdehydetetraethyl acetal (17 g) in ethanol (20 ml) was added. After 1 h at 85° the mixture was cooled, poured into water (100 ml) and neutralised with aqueous ammonia (d = 0.88). The resulting slurry was filtered, the solid was washed repeatedly with dilute ammonia solution and the filtrate and washings were combined and repeatedly extracted with dichloromethane to yield 3-ethoxycarbonylthieno[2,3-b]pyridine[126] (2.1 g, 9%) as a pale yellow oil.

$\tau(CDCl_3)$ 1.5 and 2.8 (both m, 4x Ar-H)

5.8 (q, $-C\underline{H}_2CH_3$, J = 6 Hz)

8.65 (t, $-CH_2C\underline{H}_3$, J = 6 Hz).

Investigation of the vapour phase reaction between 2-vinylpyridine and carbon disulphide

The vapour phase reactor (see section II) was packed with activated alumina (600 ml) and heated to a temperature of 500-520°. A solution of 2-vinylpyridine (25 g) in carbon disulphide (240 ml) was pumped into the reactor at a rate of 60 ml/h. After 4 h the product obtained was evaporated under reduced pressure and the residue was distilled under vacuum to give a clear yellow oil (bp. 80-120°/10 mm Hg). Tlc investigation of the product (alumina/ethylacetate) showed it to be a mixture of several components. With the aid of standard nmr spectra, the presence of 2-vinyl-, 2-methyl- and 2-ethylpyridine was demonstrated.

The distillation pot residue was chromatographed on alumina (100 g) with cyclohexane as eluant. The initial fractions were combined and evaporated under reduced pressure to give traces of a clear yellow oil. The nmr spectrum of this was consistent with that reported for thieno[3,2-b]pyridine.[173]

$\tau(CDCl_3)$: 2.38, 2.49, 1.36, 2.88, 1.92 (Ar-H)

The estimated yield of thienopyridine obtained in this run was less than 1%.

The above procedure was repeated using activated alumina at 350° and G41 catalyst at 500° and at 350° with the same pumping rate as before. In no case was a significant conversion of vinylpyridine into thienopyridine observed. The highest estimated yield was 4% (G41 catalyst at 500°). No attempt to identify the other reaction products was made.

Investigation of the vapour phase reaction between 4-vinylpyridine and carbon disulphide

The reaction was carried out under identical conditions to those described for 2-vinylpyridine over alumina at 500°. The crude reaction product (freed of carbon disulphide) was distilled under reduced pressure to give a low boiling (bp. 30-40°/2 mm Hg) and a high boiling fraction (bp. 100-130°/2 mm Hg). NMR analysis of the lower boiling fraction indicated the presence of 4-vinyl-, 4-methyl- and 4-ethylpyridine. The distillate from the higher boiling fractions was chromatographed on alumina (100 g) with cyclohexane-benzene as eluant, to give thieno[2,3-c]pyridine as a semi-solid, in a yield of less than 1%. The picrate was prepared and had mp. 185-6° (lit[124] 185-6°). The procedure was repeated using activated alumina at 350°, and G41 catalyst at 500°. In neither case was significant conversion into thienopyridine observed.

4,6-Dimethylthieno[2,3-b]pyridine

This compound was prepared in 42% yield from the reaction of 2-aminothiophen tin double salt and acetylacetone according to the method of Klemm.[83] The picrate had mp. 191-4° (lit[83] 191-2°).

Thieno[2,3-b]pyridine

This compound was prepared in 12% yield from the reaction of 2-aminothiophen tin double salt and malondialdehydebisdimethylacetal according to the method of Klemm.[81] The picrate had mp. 170-2° (lit[81] 170-2°).

Vapour phase reaction between 5-ethyl-2-methylpyridine and carbon disulphide

The vapour phase reactor was packed with G41 catalyst (100 ml), and a pre-heated section was packed with alumina (500 ml) (see page 58) and heated to 500°. A solution of 5-ethyl-2-methylpyridine (40 g) in carbon disulphide (400 ml) was pumped into the reactor at a rate of 50 ml/h. After 4 h the product was collected and distilled under reduced pressure (after removal of carbon disulphide); the bulk of the material had bp. 55-70°/10 mm Hg. By nmr analysis the distillate was shown to consist of 5-ethyl-2-methyl-, 2-methyl-5-vinyl- and 2,5-dimethylpyridines. The pot residue consisted of a tar from which no pure substance was obtained.

2-Propionylfuran

This compound was prepared from propionic anhydride, furan and ortho phosphoric acid in 46% yield, following the procedure described by Gruber.[151]

Attempt to prepare 3-hydroxy-2-ethylpyridine by the vapour phase reaction of 2-propionylfuran and ammonia

The vapour phase reactor was packed with activated alumina (600 ml) and heated to 300°. Ammonia gas was pumped into the reactor at a rate of 0.7 ℓ/min and 2-propionylfuran at a rate of 4.5 g/h. After 6 h the product from the reactor was collected and dissolved in chloroform (100 ml). The chloroform solution was extracted several times with aqueous 2M hydrochloric acid, the acidic solution was neutralised with concentrated ammonia solution (d = 0.88), then repeatedly extracted with ether. The combined ether extracts were dried ($MgSO_4$) and evaporated. The residue was crystallised from light petroleum to give 3-hydroxy-2-ethylpyridine (0.8 g, 3%), mp. 131-2°

(lit[151] 134-6°).

τ($CDCl_3$): 2.45, 2.9, 3.6 (all m, 3x Ar-H)

7.55 (q, CH_2CH_3, J = 7.5 Hz)

8.9 (t, CH_2CH_3, J = 7.5 Hz).

6-Ethylpyridin-2(1H)-one

A solution of 2-amino-6-ethylpyridine (122 g) in concentrated sulphuric acid (110 ml) and water (830 ml) was cooled in an ice-salt bath to 0°. A solution of sodium nitrite (74 g) in water (140 ml) was then added dropwise at such a rate that the temperature of the resulting solution did not exceed 5°. After the addition was completed, the solution was stirred for 1 h, then heated to 90° for 10 min, cooled, and neutralised by the addition of anhydrous potassium carbonate (205 g). The aqueous solution was then evaporated under reduced pressure and the residue was repeatedly extracted with boiling benzene (6 x 100 ml). The combined benzene extracts were evaporated under reduced pressure to one-third of the original volume, then cooled in ice when yellow crystals of 6-ethylpyridin-2(1H)-one were obtained. The product (106 g, 86%) was filtered off and dried in a vacuum desiccator. It had mp. 96-98° (lit[174] 96-8°).

τ($CDCl_3$): 2.65 and 3.75 (m, 3x Ar-H)

7.35 (q, CH_2CH_3, J = 6 Hz)

8.75 (t, CH_2CH_3, J = 6 Hz).

6-Ethylpyridin-2-thiol

6-Ethylpyridin-2(1H)-one (50 g), finely powdered, was placed in a 250 ml round bottom flask. Powdered phosphorous pentasulphide (100 g) was added, and the flask was shaken to give a homogeneous mixture, which was then heated gently to 90-95°. The mixture melted and the temperature rose rapidly to 210°. The dark-orange residue obtained on

cooling was dissolved in boiling water (200 ml) and the cooled aqueous solution was repeatedly extracted with chloroform. The combined chloroform extracts were dried ($MgSO_4$) and evaporated to give 6-ethylpyridin-2-thiol (46 g, 93%), mp. 124-6° (lit[153] 125-6°).

τ($CDCl_3$): 2.65 and 3.4 (m, 3x Ar-H)
7.2 (q, CH_2CH_3, J = 6 Hz)
8.8 (t, CH_2CH_3, J = 6 Hz).

S-(6-Ethyl-2-pyridyl)mercaptoacetone (103)

A solution of 6-ethylpyridin-2-thiol (8 g) in aqueous 20% sodium hydroxide solution (100 ml) was cooled in an ice-salt bath to 0°. Chloroacetone (8 ml) was added dropwise with stirring, at such a rate that the temperature did not exceed 5°. After the addition was completed, the solution was stirred at room temperature for 3 h, then extracted with ether (4x). The ether extracts were combined, dried ($MgSO_4$) and evaporated to give a residue, which was distilled to provide S-(6-ethyl-2-pyridyl)mercaptoacetone (4.2 g, 38%) as a yellow oil, bp. 103-5°/0.3 mm Hg.

τ($CDCl_3$): 2.9 (m, 3x Ar-H), 6.1 (s, S-CH_2-)
7.35 (q, CH_2CH_3, J = 6 Hz), 7.8 (s, $COCH_3$)
8.85 (t, CH_2CH_3, J = 6 Hz).

Attempts to cyclise S-(6-ethyl-2-pyridyl)mercaptoacetone to 7-ethyl-3-methylthieno[2,3-b]pyridine (104)

A The above compound (1 g) was added to polyphosphoric acid (5 g) and the solution was heated in an oil bath to 150-60°. After 6 h, TLC and nmr investigations showed that no reaction had occurred, and, when the reaction was worked up, starting material was recovered.

B The above compound (1 g) was added to phosphorous pentoxide (5 g) in chloroform (30 ml) and the resulting solution was boiled under reflux for 4 h. Tlc and nmr investigation showed that no reaction had occurred.

C To stirred polyphosphoric acid (4 g), phosphorous pentoxide (2 g) was added. The above compound (1 g) was added to the 'super' polyphosphoric acid solution and the resulting mixture was heated in an oil bath at 180° for 6 h. When cooled, the mixture was added in portions to cold water (20 ml), the solution was neutralised with 4M sodium hydroxide solution and repeatedly extracted with chloroform. The chloroform solution contained only the unreacted mercaptoacetone derivative (0.8 g).

D Similarly, treatment of S-(6-ethyl-2-pyridyl) mercaptoacetone with boiling phosphoryl chloride-pyridine and with phosphorous pentoxide-xylene both failed to induce the desired cyclisation.

E S-(6-ethyl-2-pyridyl)mercaptoacetone (2.6 g) was dissolved in concentrated sulphuric acid (30 ml) and the solution was set aside at room temperature for 48 h, then heated on a steam bath until the starting material was no longer detectable by tlc. The solution was cooled and added dropwise to ice-cold water (100 ml). The aqueous solution was neutralised with 4M sodium hydroxide solution, then repeatedly extracted with dichloromethane. The combined extracts were washed with water, with brine, then dried ($MgSO_4$) and evaporated to yield an oil. This was distilled in vacuo to provide 7-ethyl-3-methylthieno[2,3-b]pyridine (104) (0.8 g, 34%), bp. 100-102°/0.4 mm Hg.

$\tau(CDCl_3)$: 3.40 (m, 3x Ar-H)

7.66 (m, superimposed q and s, CH_2CH_3 and Ar-CH_3)

8.9 (t, CH_2CH_3)

The picrate was prepared in ether and after crystallisation from ethanol had mp. 137-8°. (Found: C, 46.8; H, 3.4; N, 13.2. $C_{16}H_{14}N_4O_7S$ requires C, 47.1; H, 3.3; N, 13.8%.)

2-Amino-3-ethoxycarbonyl-5-methylthiophen (107)[157]

A mixture of ethyl cyanoacetate (11.6 g), finely powdered sulphur (6.2 g) and dimethylformamide (30 ml) was stirred at room temperature, and triethylamine (15 ml) was added dropwise. The solution was cooled to 0° in ice-salt, and propionaldehyde (22 g) was added dropwise at such a rate that the temperature of the solution remained below 5°. After the addition was complete the solution was stirred for 3 h at room temperature, then poured into water (50 ml), and extracted repeatedly with ether. The combined extracts were washed with water, with brine, and dried ($MgSO_4$), then evaporated to give a dark viscous oil. This was distilled under reduced pressure to give 2-amino-3-ethoxycarbonylthiophen as an oil, bp. 108-110°/0.3 mm Hg, which solidified on cooling.

Crystallisation from light petroleum afforded the amino compound (7.0 g, 37%) with mp. 45-47° (lit[157] 45-46°).

$\tau(CDCl_3)$: 3.5 (s, Ar-H), 5.85 (q, CH_2CH_3, J = 7 Hz)
7.85 (s, CH_3), 8.8 (t, CH_2CH_3, J = 7 Hz).

Reaction of 2-amino-3-ethoxycarbonyl-5-methylthiophen with methyl acetoacetate

A solution of 2-amino-3-ethoxycarbonyl-5-methylthiophen (1 g) and methyl acetoacetate (1 g) in toluene (5 ml) was boiled under reflux for 24 h. The solution was then evaporated under reduced pressure to give an oil, which was dissolved in ether. The ether solution was treated with decolourizing carbon, filtered and cooled, when N-(3-ethoxycarbonyl-5-methyl-2-thienyl)-3-ketobutanamide (108) (0.6 g, 83%)

was obtained as yellow needles, mp. 76-78°. The analytical sample was crystallised from light petroleum and had mp. 77-78°. (Found: C, 53.7; H, 4.8; N, 5.1. $C_{12}H_{13}NO_4S$ requires C, 54.0; H, 4.9; N, 5.2%.)

$\tau(CDCl_3)$: 3.5 (s, Ar-H), 5.85 (q, CH_2CH_3, J = 7 Hz)
6.35 (s, $COCH_2CO$-), 7.5 (s, $COCH_3$)
7.85 (s, CH_3), 8.8 (t, CH_2CH_3, J = 7 Hz).

Attempted cyclisation of N-(3-ethoxycarbonyl-5-methyl-2-thienyl)-3-ketobutanamide

The ketoamide (1 g) was dissolved in anhydrous dimethylformamide (5 ml) and sodium hydride (80% dispersion in oil, 0.4 g) was added. The resulting solution was heated on a steam bath for 30 min, cooled, diluted with water (20 ml) and extracted with ether to give a dark polymeric substance (0.6 g). Repeated attempts to obtain an identifiable compound from the residue failed.

3-Amino-2-methoxycarbonylthiophen[158] (111)

Methyl thioglycolate (53 g) was added to sodium methoxide (from 26 g sodium) in methanol (500 ml), then 2-chloroacrylonitrile (44 g) in methanol (50 ml) was added dropwise to the solution, the temperature being maintained at 25° by external cooling. After the addition was completed, the solution was stirred at room temperature for 1 h, then concentrated, in vacuum, to about one-third its original volume, diluted with water (400 ml) and extracted repeatedly to give 3-amino-2-methoxycarbonylthiophen (111), as a pale yellow oil, which solidified on standing. It was crystallised from light petroleum and formed yellow platelets (53 g, 68%), mp. 63-64° (lit[158] 64-65°). (Found: C, 45.8; H, 4.3; N, 8.6. Calculated for $C_6H_7NO_2S$: C, 45.8; H, 4.4; N, 8.9%.)

$\tau(CDCl_3)$: 2.46 (d, H-5, J = 6 Hz)

2.92 (d, H-4, J = 6 Hz)

6.2 (s, $COOCH_3$).

ν_{max} (KBr): 3800, 3960 cm^{-1} (NH_2), 1680, 1710 cm^{-1} (C = O)

Similarly, using the procedure described above, but starting from ethyl mercaptoacetate (24 g), 3-amino-2-ethoxycarbonylthiophen (112) (21.7 g, 64%) was obtained as a pale yellow oil.[158]

$\tau(CDCl_3)$: 2.85 (d, H-4, J = 6 Hz), 1.9 (d, H-5, J = 6 Hz)

5.8 (q, $COOCH_2CH_3$), 8.76 (t, $COOCH_2CH_3$).

ν_{max}: 3800, 3960 cm^{-1} (NH_2), 1680, 1710 cm^{-1} (C = O)

3-Amino-2-acetylthiophen (113)[176]

Mercaptoacetone[175] (18 g) was added in portions to an ice-cold solution of sodium methoxide (from 9.3 g sodium) in methanol (200 ml). A solution of 2-chloroacrylonitrile (17.6 g) in methanol (100 ml) was then added dropwise with stirring, at such a rate that the temperature did not exceed 4^o. After the addition was completed the solution was stirred at room temperature for 2 h, then evaporated under reduced pressure, to approximately one-third of its original volume, diluted with water (200 ml) and repeatedly extracted with ether. The combined ether extracts were dried ($MgSO_4$) and evaporated, to give a dark-brown oil. Distillation afforded the aminoketone (bp. 82-84^o/0.33 mm Hg) which solidified on cooling. The solid was recrystallised from light petroleum to give 3-amino-2-acetylthiophen (18.2 g, 65%) mp. 82-83^o (lit[176] 89-90^o). (Found: C, 50.3; H, 5.0; N, 9.8. Calculated for C_6H_7ONS: C, 50.0; H, 4.9; N, 9.9%.)

$\tau(CDCl_3)$: 2.82 (d, H-5, J = 6 Hz)

3.5 (d, H-4, J = 6 Hz)

7.65 (s, $COCH_3$)

ν_{max} (KBr): 3450, 3200 cm^{-1} (NH_2), 1600 cm^{-1} (C = O)

3-Aminothiophen-2-carboxylic acid[177]

A solution of 3-amino-2-methoxycarbonylthiophen (10 g) in 2M-sodium hydroxide solution (100 ml) was boiled under reflux for 2 h, then cooled and poured into water (200 ml). Careful acidification with concentrated hydrochloric acid precipitated the crude acid. The acid was extracted into warm chloroform, the extracts were dried ($MgSO_4$) and evaporated to give a white residue. Crystallisation from ether-acetone solution gave 3-aminothiophen-2-carboxylic acid (7.6 g, 84%) as white crystals, mp. 79-80° (with effervescence), (lit[177] mp. 80° with decomposition).

$\tau(CDCl_3)$: 2.2 (d, H-5, J = 6 Hz), 3.0 (d, H-4, J = 6 Hz)

ν_{max} (KBr): 3860, 3900 cm^{-1} (NH_2), 3100 cm^{-1} (COOH).

3-Formylamino-2-acetylthiophen (117, R = H)

A solution of 3-amino-2-acetylthiophen (1 g) in formic acid (10 ml) was boiled under reflux for 30 min. When cool, the solution was diluted with water (30 ml). Prolonged cooling of the solution gave 3-formylamino-2-acetylthiophen (0.7 g, 83%) as white needles, mp. 114-116°. (Found: C, 49.1; H, 4.0; N, 8.2. $C_7H_7O_2NS$ requires C, 49.7; H, 4.1; N, 8.2%.)

$\tau(CDCl_3)$: 1.85 (d, H-5, J = 6 Hz)

2.6 (d, H-4, J = 6 Hz)

7.55 (s, OCH)

ν_{max} (KBr): 1610 and 1680 cm^{-1} (C =O), 3490 cm^{-1} (NH)

3-Acetylamino-2-acetylthiophen[178] (117, R = CH_3)

A solution of 3-amino-2-acetylthiophen (5 g) in glacial acetic acid (8 ml) and acetic anhydride (8 ml) was heated on a steam bath for 2 h. When cool the solution was poured into ice-cold water (100 ml). The solid obtained was filtered off and recrystallised from water to

give 3-acetylamino-2-acetylthiophen (5.6 g, 86%), mp. 109-110° (lit[178] 112-13°). (Found: C, 52.4; H, 4.9; N, 7.6. Calculated for $C_8H_9NO_2S$: C, 52.5; H, 4.9; N, 7.6%.)

$\tau(CDCl_3)$: 1.85 (d, H-5, J = 6 Hz), 2.6 (d, (H-4, J = 6 Hz)
7.55 (s, $-OC\underline{H}_3$), 7.8 (s, $-OC\underline{H}_3$)

ν_{max}: 1610 and 1700 cm^{-1} (C = O)

3-Ethyloxaloylamino-2-acetylthiophen (117, R = $COOC_2H_5$)

3-Amino-2-acetylthiophen (1.4 g), diethyl oxalate (1.7 g) and a catalytic amount of glacial acetic acid were boiled together under reflux for 4 h. When cool, the solution was diluted with dichloromethane (30 ml), washed with 2M hydrochloric acid, water, saturated sodium hydrogen carbonate solution, water and finally with brine. The solution was dried ($MgSO_4$) and evaporated to yield a dark oily material. This was dissolved in acetone, the solution was treated with decolourizing charcoal, filtered and evaporated; on tituration with light petroleum the oil solidified. Crystallisation from ether-methanol gave 3-ethyloxaloylamino-2-acetylthiophen (117, R = $COOC_2H_5$) (0.6 g, 24%) as white blades, mp. 114-6°. (Found: C, 49.9; H, 4.6; N, 5.8. $C_{10}H_{11}NO_4S$ requires C, 49.9; H, 4.6; N, 5.8%.)

$\tau(CDCl_3)$: 1.90 (d, H-5, J = 5 Hz), 2.55 (d, H-4, J = 5 Hz)
5.66 (q, $C\underline{H}_2CH_3$), 7.55 (s, $COC\underline{H}_3$)
8.6 (t, $CH_2C\underline{H}_3$)

ν_{max} (KBr): 1700, 1640, 1570 cm^{-1} (C = O)

Attempted cyclisation of 3-ethyloxaloylamino-2-acetylthiophen

The above compound (1 g) and sodium hydroxide (0.2 g) in water (30 ml)-ethanol (7 ml) were boiled under reflux for 4 h. When cool, the solution was extracted with dichloromethane to give a material (0.2 g) which, on crystallisation from light petroleum, yielded 3-amino-

2-acetylthiophen (mp. and mixed mp. 82-4°). The original aqueous solution was acidified with 2M hydrochloric acid, the resulting white precipitate was filtered off, dried and recrystallised from ethanol, when it had mp. 194-6°. The product (0.4 g) was shown to be 3-oxaloylamino-2-acetylthiophen (118). (Found: C, 45.1; H, 3.2, N, 6.5. $C_8H_7O_4NS$ requires C, 45.1; H, 3.3; N, 6.6%.)

τ[$(CD_3)_2SO$]: 2.05 (d, H-5, J = 5 Hz), 2.55 (d, H-4, J = 5 Hz)
4.05 (broad s, -NH), 7.55 (s, $COCH_3$)

2-Methylquinolin-4(1H)one[160]

2-Acetylaminoacetophenone (1.9 g) and sodium hydroxide (0.57 g) in methanol (11 ml) and water (60 ml) were boiled together under reflux for 3 h. The solution was set aside overnight, when crystallisation occurred. The product was filtered off and recrystallised from methanol to give 2-methylquinolin-4(1H)one (1.2 g, 71%), mp. 225-7° (lit[160] 225-6°).

Attempted cyclisation of 3-formylamino-2-acetylthiophen

A solution of 3-formylamino-2-acetylthiophen (0.5 g) in 10% aqueous sodium hydroxide (10 ml) was boiled under reflux for 2 h (2-3 ml methanol was added to give a clear solution). The solution was cooled and extracted with dichloromethane. Thus, an oil was obtained, which, on cooling and tituration with light petroleum, solidified. The solid (0.2 g) was crystallised from light petroleum and was identified (mp., mixed mp. and nmr spectrum) as 3-amino-2-acetylthiophen.

When treated with alcoholic ammonia solution, in the manner described for the 3-acetylamino-compound (page 111), 3-formylamino-2-acetylthiophen was unchanged.

Attempted cyclisations of 3-acetylamino-2-acetylthiophen

Method A[159]

A solution of 3-acetylamino-2-acetylthiophen (2 g) and sodium hydride (0.51 g) in methanol (11 ml) and water (60 ml) was boiled under reflux for 3 h. The solution was left to stand at room temperature overnight. The aqueous solution was repeatedly extracted with dichloromethane. The combined extracts were dried ($MgSO_4$) and evaporated to give an oil which solidified on cooling. Crystallisation from light petroleum gave a solid (0.9 g). Its mp. (83-4°), mixed mp. and nmr spectrum showed it to be 3-amino-2-acetylthiophen.

Method B

A solution of 3-acetylamino-2-acetylthiophen (1 g) in dimethylformamide (10 ml) was stirred at room temperature and sodium hydride (80% dispersion in oil, 0.5 g) was added. The solution was kept at room temperature for 30 min, then heated on a steam bath for 30 min. When cool, the solution was poured into water (100 ml). The solid which precipitated was filtered off, and crystallised from methanol to give a material (0.8 g) mp. 109-110°, shown (mixed mp., nmr spectrum) to be unreacted 3-acetylamino-2-acetylthiophen.

The following experiment was carried out to demonstrate that the failure of the ring closure reaction was not due to non-formation of a suitable anion:

The acetylamino compound (1 g) in dimethylformamide (10 ml) was treated with sodium hydride (80% dispersion in oil, 0.5 g) as above, then iodomethane (4 ml) was added. The solution was maintained at room temperature for 30 min then poured into water and the product was isolated with ether as an oil. This was distilled (bp. 112-14°/0.1 mm Hg); the distillate solidified on cooling, and was crystallised from cyclohexane - light petroleum to provide a solid, mp. 66-8° (0.46 g, 42%) identified as 3-N-methyl-N-acetyl-2-(2-methylpropionyl)thiophen

(119). (Found: C, 58.5; H, 6.4; N, 6.0. $C_{11}H_{15}NO_2S$ requires C, 58.6; H, 6.6; N, 6.2%.)

$\tau(CDCl_3)$: 2.41 (d, H-5, J = 6 Hz), 3.05 (d, H-4, J = 6 Hz)
6.81 (s, $-OC\underline{H}_3$), 7.55 (s, O-C<u>H</u>-)
8.15 (s, $-NC\underline{H}_3$), 8.75 and 8.85 (both s, 2 x $C\underline{H}_3$)

ν_{max} (KBr): 2790 cm^{-1} ($N-CH_3$)

Method C

A solution of 3-acetylamino-2-acetylthiophen (0.5 g) in methanol (10 ml) was added dropwise to a stirred solution of methanol saturated with ammonia gas. The solution was stirred for 4 h after the addition, then evaporated to dryness. The residue was crystallised from methanol to give a solid identified (mp., mixed mp., nmr spectrum) as unchanged starting material.

The experiment was repeated in a modified form, the solution being boiled under reflux for 4 h. However, only unchanged starting material was recovered.

Attempts to react 3-amino-2-acetylthiophen with acetophenone

A 3-Amino-2-acetylthiophen (1 g) and acetophenone (1 g) were dissolved in benzene (10 ml), one drop of 4M sodium hydroxide was added and the mixture was boiled under reflux for 7 h. Tlc of the resulting solution indicated that no reaction had occurred.

B 3-Amino-2-acetylthiophen (1 g) and acetophenone (1 g) were boiled together under reflux for 3 days. Tlc of the resulting mixture showed the no significant reaction had taken place.

Methyl tetrolate[163]

A solution of ethyl acetoacetate (65 g) in methanol (100 ml) was treated with hydrazine hydrate (100 g) in methanol (50 ml). The resulting solution was cooled in an ice-bath, when 5-methyl-2-pyrazoline-5-one (40g, 80%), mp. 218-20° (lit[163] 218-20°), crystallised out. The product (15 g) was dissolved in glacial acetic acid (60 ml), the solution was cooled and a solution of bromine (32 g) in glacial acetic acid (20 ml) was added, dropwise. After the addition was completed, the solution was stirred at room temperature for 1 h, then poured into water (500 ml) when 4,4-dibromo-5-methyl-2-pyrazolin-5-one (15 g, 61%), mp. 130-132° (lit[163] 130-131°), was obtained.

This compound was added in portions to an ice-cold solution of sodium hydroxide (10 g) in water (300 ml). After the addition the solution was stirred for 3 h at room temperature, then acidified with concentrated hydrochloric acid. The aqueous solution was repeatedly extracted with ether to give tetrolic acid, as a dark coloured oil. It was dried in a vacuum desiccator, over concentrated sulphuric acid for 8 days to produce a solid, which on crystallisation from light petroleum gave the acid (3.1 g, 66%), mp. 72-73° (lit[163] 72-74°).

The acid was dissolved in methanol (40 ml) and boiled under reflux in the presence of concentrated sulphuric acid (1 ml) for 6 h. The solution was diluted with water and extracted repeatedly with ether to yield methyl tetrolate (2.6 g, 70%) as an oil.

$\tau(CDCl_3)$: 6.2 (s, $COOC\underline{H}_3$), 8.05 (s, $\underline{CH}_3C$-)

Attempts to react methyl tetrolate with 3-amino-2-methoxycarbonyl-thiophen

The amino compound and methyl tetrolate failed to react when boiled together under reflux for extended periods in methanol; in toluene; in xylene or in glacial acetic acid. Even in the absence of

solvent no reaction was observed after 3 days at 100°.

The amino compound (0.5 g) in dimethylformamide (10 ml) was treated with sodium hydride (80% dispersion in oil, 0.1 g). Methyl tetrolate (0.5 g) was added dropwise to the solution, which was then heated on a steam bath for 6 h, then poured into water (20 ml). The aqueous solution was repeatedly extracted with ether; the combined extracts were dried ($MgSO_4$), cooled and treated with hydrogen chloride gas. The white precipitate was filtered off, and recrystallised from methanol. Thus was obtained the hydrochloride of N-(3-amino-2-thenoyl)-3-amino-2-methoxycarbonylthiophen (122) (0.3 g, 70%) as a white solid, mp. 201-3°. (Found: C, 51.6; H, 4.2; N, 10.7. $C_{11}H_{11}O_3N_2Cl$ requires C, 51.9; H, 4.3; N, 11.0%.)

τ[$(CD_3)_2SO$]: 1.7 (d, J = 5 Hz), 2.18 (d, J = 5 Hz)
3.22 (d, J = 5 Hz), 2.45 (d, J = 5 Hz)
6.10 (s, $COOCH_3$), 7.25 (broad s, NH_2)

3-Ethylamino-2-methoxycarbonylthiophen (123)

To a stirred solution of 3-amino-2-methoxycarbonylthiophen (1 g) in glacial acetic acid (10 ml), sodium borohydride (2.4 g) was added, in small portions. The temperature was maintained below 25° by external cooling (ice-salt). The solution was stirred for 4.5 h at room temperature (by which time no starting material was detected by tlc [ethylacetate/alumina], then poured into ice-cold water (50 ml). The aqueous solution was repeatedly extracted with ether; the combined extracts were dried ($MgSO_4$) and evaporated to yield 3-ethylamino-2-methoxycarbonylthiophen (1.0 g, 83%) as a pale yellow oil. (Found: C, 51.6; H, 5.8; N, 7.4. $C_8H_{11}O_2NS$ requires C, 51.8; H, 5.9; N, 7.6%.)

τ($CDCl_3$): 2.65 (d, H-5, J = 6 Hz), 3.35 (d, H-4, J = 6 Hz)
6.21 (s, $COOCH_3$), 6.75 (q, $NHCH_2CH_3$)
8.85 (t, $NHCH_2CH_3$), 4.10 (broad s, NH)

ν_{max} 1720, 1680 cm^{-1} (C = O)

Attempts to prepare 3-methylamino-2-methoxycarbonylthiophen (after the method of Crochet[165])

A stirred solution of 3-amino-2-methoxycarbonylthiophen (7.8 g) in triethyl orthoformate (40 ml) was boiled under reflux for 5 h. The excess of the reagent was removed under reduced pressure to give an oil, which, when cooled and titurated with petroleum ether (bp. 80-100°), solidified. Crystallisation of the solid from methylated spirits gave a pale yellow crystalline solid (4.2 g) mp. 114-7°. The analytical sample (from methylated spirits) had mp. 120-1°. This substance was identified as 3-(2-methoxycarbonyl-3-amino thienyl)methyleneamino-2-methoxycarbonylthiophen (125). (Found: C, 47.9; H, 3.7; N, 8.5. $C_{13}H_{12}N_2O_4S_2$ requires C, 48.1; H, 3.7; N, 8.5%.)

$\tau(CDCl_3)$: 1.7, 3.28 (both d), 2.5 (m)

6.1 (s, 2 x $COOCH_3$)

ν_{max} (KBr): 1720, 1680 cm^{-1} (C = O)

3-Methylamino-2-methoxycarbonthiophen (127)

A solution of 3-amino-2-methoxycarbonylthiophen (7.8 g), succinimide (6 g) and 37% aqueous formaldehyde (5 ml) in ethanol (60 ml) was boiled under reflux for 4 h. Prolonged cooling in ice gave a white crystalline substance. This was filtered off and recrystallised from ethanol to give 3-aminomethyl succinimide-2-methoxycarbonylthiophen (126) (12.6 g, 94%) as white crystals, mp. 208-210°. (Found: C, 48.9; H, 4.5; N, 10.2. $C_{11}H_{12}N_2O_4S$ requires C, 49.2; H, 4.47; N, 10.4%.)

$\tau(CDCl_3)$: 2.46 (d, H-5, J = 6 Hz), 2.90 (d, H-4, J = 6 Hz)

6.10 (s, $COOCH_3$), 7.25 (s, 2 x CH_2)

4.9 (d, $NHCH_2$, J = 9 Hz)

To a stirred solution of the above product (2 g) in dimethyl-sulphoxide (5 ml), sodium borohydride (3 g) was added in small portions over a 5 min period. When the exothermic reaction had subsided, the

solution was heated on a steam bath for 20 min, cooled, then poured into water (20 ml). The product was isolated with ether to yield 3-methylamino-2-methoxycarbonylthiophen (1.0 g, 83%) as a pale yellow oil. (Found: C, 49.1; H, 5.2; N, 8.1. $C_7H_9NO_2S$ requires C, 49.1; H, 5.3; N, 8.2%.)

$\tau(CDCl_3)$: 2.65 (d, H-5, J = 6 Hz), 3.4 (d, H-4, J = 6 Hz)
6.2 (s, $COOC\underline{H}_3$), 7.05 (s, $-NC\underline{H}_3$)

Repeated attempts to react the N-methyl and N-ethyl compounds with methyl tetrolate in a wide range of solvents and under various conditions failed to give the desired product.

In all cases only unchanged starting materials were recovered.

3-Formylamino-2-methoxycarbonylthiophen

A solution of 3-amino-2-methoxycarbonylthiophen (1 g) in formic acid (10 ml) was boiled under reflux for 30 min. When cool, the solution was diluted with ice-cold water (20 ml); prolonged cooling in ice-salt gave 3-N-formylamino-2-methoxycarbonylthiophen (0.84 g, 85%) as a white crystalline material, mp. 89-90°. (Found: C, 45.3; H, 3.8; N, 7.4. $C_7H_7NO_3S$ requires C, 45.5; H, 3.8; N, 7.6%.)

$\tau(CDCl_3)$: 2.62 (d, H-5, J = 6 Hz)
3.35 (d, H-4, J = 6 Hz)
6.20 (s, $COOC\underline{H}_3$)

3-Acetylamino-2-ethoxycarbonylthiophen

A solution of 3-amino-2-ethoxycarbonylthiophen (1.5 g) in glacial acetic acid (2 ml) and acetic anhydride (2 ml) was heated on a steam bath for 1 h. The hot solution was poured into water (20 ml), when the crude product precipitated. It was filtered off and recrystallised from light petroleum-ether to give 3-acetylamino-2-ethoxycarbonylthiophen (1.7 g, 91%) as white platelets, mp. 77-9°. (Found: C, 50.7; H, 5.0;

N, 6.3. $C_9H_{11}O_3NS$ requires C, 50.7; H, 5.16; N, 6.6%.)

$\tau(CDCl_3)$: 1.94 (d, H-5, J = 6 Hz), 2.64 (d, H-4, J = 6 Hz)
5.74 (q, $COOC\underline{H}_2CH_3$), 7.82 (s, $-COC\underline{H}_3$)
8.70 (t, $COOCH_2C\underline{H}_3$)

3-Acetylamino-2-methoxycarbonylthiophen

A solution of 3-amino-2-methoxycarbonylthiophen (2 g) in glacial acetic acid (3 ml) and acetic anhydride (3 ml) was heated on a steam bath for 1 h. The hot solution was poured into water (30 ml) and the white solid that separated was filtered off. Recrystallisation from methanol gave 3-acetylamino-2-methoxycarbonylthiophen (2.1 g, 84%) as white needles, mp. 102-3° (lit[178] 100-101°).

$\tau(CDCl_3)$: 1.80 (d, H-5, J = 6 Hz), 2.48 (d, H-4, J = 6 Hz)
6.10 (s, $COOC\underline{H}_3$), 7.84 (s, $NHCOC\underline{H}_3$)

3-p-toluenesulphonylamino-2-methoxycarbonylthiophen

3-Amino-2-methoxycarbonylthiophen (1.5 g) was added to a solution of p-toluenesulphonylchloride (2.1 g) in pyridine (10 ml) and the mixture was heated on a steam bath for 30 min. The cooled solution was poured into an excess of 4M hydrochloric acid, and the precipitate was filtered off; crystallisation from methanol gave the tosyl derivative (1.8 g, 76%) as white platelets, mp. 140-141°. (Found: C, 50.5; H, 4.3; N, 4.7. $C_{13}H_{13}O_4S_2N$ requires C, 50.2; H, 4.2; N, 4.5%.)

E-Dimethyl 2-N-(2-methoxycarbonyl-3-thienyl)-but-2-endioate (128)

A solution of 3-amino-2-methoxycarbonylthiophen (30 g) and dimethyl acetylenedicarboxylate (30 g) in glacial acetic acid (150 ml) was set aside at room temperature for 5 days. The solution was poured into water (500 ml) and repeatedly extracted with ether. The combined extracts were washed successively with 4M hydrochloric acid (3x),

water (3x), saturated sodium hydrogen carbonate solution, water and brine, dried ($MgSO_4$) and evaporated to yield a yellow residue. Crystallisation from cyclohexane (400 ml) containing acetone (25 ml) gave the Michael adduct - E-dimethyl 2-N-(2-methoxycarbonyl-3-thienyl)-but-2-endioate (37 g, 65%) as yellow blades, mp. 88-91°. For analysis a sample was crystallised from cyclohexane and had mp. 93-4°. (Found: C, 48.1; H, 4.5; N, 4.4. $C_{12}H_{13}O_6NS$ requires C, 48.2; H, 4.3; N, 4.7%.)

$\tau(CDCl_3)$: 2.65 (d, H-5, J = 6 Hz)
3.55 (d, H-4, J = 6 Hz)
4.55 (s, =C-H)
6.10, 6.20, 6.25 (all s, 3 x OCH_3)

ν_{max} (KBr): 1740, 1680, 1610, 1565 cm^{-1} (C = O)

5,6-Bismethoxycarbonylthieno[3,2-b]pyridin-7(4H)-one (129)

The foregoing Michael adduct (31.5 g) was dissolved in anhydrous dimethylformamide (180 ml) and sodium hydride (80% dispersion in oil, 4.3 g) was added in small portions. A vigorous exothermic reaction occurred; when the reaction had subsided and the temperature began to fall, the solution was heated on a steam bath for 30 min. The solution was cooled, poured into water (400 ml) and extracted with ether; the extracts yielded only a very small quantity of neutral material.

The aqueous solution was freed of ether by warming on a steam bath, cooled and nearly saturated with sodium chloride, then acidified with concentrated hydrochloric acid to give a white precipitate. This was filtered off, washed with water and crystallised from acetone to give 5,6-bismethoxycarbonylthieno[3,2-b]pyridin-7-(4H)-one (19.3 g, 68%) as white crystals, mp. 168-73°. The analytical sample was recrystallised from acetone-methanol and had mp. 176-8°. (Found: C, 49.0; H, 3.2; N, 4.9. $C_{11}H_9NO_5S$ requires C, 49.4; H, 3.4; N, 5.2%.)

τ[$(CD_3)_2SO$]: 1.85 (d, H-2, J = 6 Hz), 2.60 (d, H-3, J = 6 Hz)

6.8 (s, -OO$\underline{CH_3}$), 6.25 (s, -OO$\underline{CH_3}$)

ν_{max} (KBr): 1740, 1680 cm^{-1} (C = O)

7-Chloro-5,6-bismethoxycarbonylthieno[3,2-b]pyridine (130)

A mixture of 5,6-bismethoxycarbonylthieno[3,2-b]pyridin-7(4H)one (6 g) and phosphoryl chloride (30 ml) was boiled under reflux for 4.5 h. The excess of reagent was removed by distillation under reduced pressure and the residue was treated with water (100 ml) then saturated sodium hydrogen carbonate solution until neutral. The product was isolated with ether and crystallisation from light petroleum gave 7-chloro-5,6-bismethoxycarbonylthieno[3,2-b]pyridine (5.5 g, 86%) as white needles, mp. 103-5°. (Found: C, 46.5; H, 2.7; N, 4.6. $C_{11}H_8ClNO_4S$ requires C, 46.2; H, 2.8; N, 4.9%.)

$\tau(CDCl_3)$: 1.81 (d, H-2, J = 6 Hz)

2.1 (d, H-3, J = 6 Hz)

5.9 (s, OO$\underline{CH_3}$)

ν_{max} (KBr): 1720 cm^{-1} (C = O)

7-Methoxy-5,6-bismethoxycarbonylthieno[3,2-b]pyridine (131)

7-Chloro-5,6-bismethoxycarbonylthieno[3,2-b]pyridine (1 g) was added in small portions to a stirred solution of sodium methoxide (from 0.2 g sodium) in methanol (10 ml). After the addition was complete, the solution was boiled under reflux for 20 min, cooled and poured into water (50 ml). The product was isolated with dichloromethane to yield 7-methoxy-5,6-bismethoxycarbonylthieno[3,2-b]pyridine (0.8 g, 81%) as a solid. A sample for analysis was crystallised from acetone-light petroleum and had mp. 163-4°. (Found: C, 51.6; H, 4.0; N, 5.0. $C_{12}H_{11}NO_5S$ requires C, 51.2; H, 3.9; N, 5.0%.)

$\tau(CDCl_3)$: 2.06 (d, H-2, J = 5.2 Hz)

2.28 (d, H-3, J = 5.2 Hz)

5.67 (s, $OC\underline{H}_3$)

5.96 and 5.99 (both s, 2 x $COOC\underline{H}_3$)

ν_{max} (KBr): 1720 cm^{-1} (C = O).

7-(N-phenylamino)-5,6-bismethoxycarbonylthieno[3,2-b]pyridine (132)

A solution of 7-chloro-5,6-bismethoxycarbonylthieno[3,2-b] pyridine (1 g) and aniline (1 g) in toluene (10 ml) was boiled under reflux for 30 h. The mixture was cooled and diluted with ether (200 ml); the ethereal solution was washed with water and 2M hydrochloric acid, dried ($MgSO_4$) and evaporated to give unreacted chloro-compound (600 mg). Basification of the acid washings yielded an impure solid, which, on crystallisation from acetone-light petroleum yielded 7-(N-phenylamino)-5,6-bismethoxycarbonylthieno[3,2-b]pyridine (100 mg) as colourless needles, mp. 173-5°. (Found: C, 59.8; H, 4.1; N, 8.0. $C_{17}H_{14}N_2O_4S$ requires C, 59.6; H, 4.1; N, 8.2%.)

$\tau(CDCl_3)$: -0.05 (broad s, N-$\underline{H}$)

2.5 (m, 7 x Ar-$\underline{H}$)

6.01 and 6.10 (s, 2 x $OOC\underline{H}_3$)

Attempt to brominate 5,6-bismethoxycarbonylthieno[3,2-b]pyridin-7(4H)one

To a stirred solution of 5,6-bismethoxycarbonythieno[3,2-b] pyridin-7(4H)one (0.5 g) in glacial acetic acid (5 ml), a solution of bromine (0.6 g) in glacial acetic acid (5 ml) was added dropwise. After the addition was complete, the solution was stirred at room temperature for 1 h, then poured into water (20 ml). The solid obtained was filtered off and recrystallised from methanol, and was identified as unchanged starting material (mp., mixed mp. and nmr spectrum).

Thieno[3,2-b]pyridin-7(4H)one-5,6-dicarboxylic acid (133)

A solution of 5,6-bismethoxycarbonylthieno[3,2-b]pyridin-7(4H)one (10 g) in 10% aqueous sodium hydroxide solution (70 ml) was boiled under reflux for 3 h. The solution was cooled, diluted with water (200 ml) and acidified with 4M hydrochloric acid, precipitating the crude product. This was filtered off, washed repeatedly with water and recrystallised from a mixture of methanol (500 ml) and 4M hydrochloric acid (20 ml) to yield thieno[3,2-b]pyridin-7(4H)one-5,6-dicarboxylic acid (6.5 g, 83%) as a white solid, mp. 268-70°. Found: C, 45.3; H, 5.8; N, 2.2. $C_9H_5NO_5S$ requires C, 45.2; H, 5.8; N, 2.1%.)

τ[$(CD_3)_2SO$]: 1.60 (d, H-2, J = 6 Hz)

2.46 (d, H-3, J = 6 Hz)

Thieno[3,2-b]pyridin-7(4H)one (134)

Thieno[3,2-b]pyridin-7(4H)one-5,6-dicarboxylic acid (1 g) was intimately mixed with powdered glass in a boiling tube and heated in a Woods metal bath at 280-90° for 10-12 min; after which time the vigorous evolution of carbon dioxide had ceased. The cooled, dark residue was dissolved in boiling water (20 ml), the solution was treated with decolourizing carbon, filtered and evaporated to give a white residue. Crystallisation of this from ethanol gave thieno[3,2-b]pyridin-7(4H)one (0.47 g, 61%) as white needles, mp. 98-100°. (Found: C, 55.6; H, 3.2; N, 9.2. C H NOS requires C, 55.6; H, 3.3; N, 9.2%.)

$\tau(D_2O)$: 1.78 (d, H-2, J = 5.2 Hz)

2.55 (d, H-3, J = 5.2 Hz)

1.60 (d, H-5, J = 7.5 Hz)

3.05 (d, H-6, J = 7.5 Hz)

7-Chlorothieno[3,2-b]pyridine (135)

A solution of thieno[3,2-b]pyridin-7(4H)one (1.1 g) in phosphoryl chloride (6 ml) was boiled under reflux for 4.5 h. The solution was evaporated under reduced pressure, and the residue was treated with cold water (20 ml) then neutralised with saturated sodium hydrogen carbonate solution. The product was isolated with ether and crystallisation from light petroleum gave 7-chlorothieno[3,2-b]pyridine (0.51 g, 41%) as colourless prisms, mp. 45-6°. (Found: C, 48.9; H, 2.6; N, 7.7. C_7H_4NSCl requires C, 49.4; H, 2.9; N, 8.9%.)

$\tau(CDCl_3)$: 2.13 (d, H-2, J = 5.3 Hz)
2.40 (d, H-3, J = 5.3 Hz)
1.35 (d, H-5, J = 5.3 Hz)
2.7 (d, H-6, J = 5.3 Hz)

The methiodide formed yellow needles from methanol and mp. 275-7°. (Found: C, 30.8; H, 2.2; N, 4.8. C_8H_7NSClI requires C, 30.9; H, 2.3; N, 4.5%.)

7-Methoxythieno[3,2-b]pyridine (136)

7-Chlorothieno[3,2-b]pyridine (1.12 g) was dissolved in a solution of sodium methoxide (from 0.2 g sodium) in methanol (15 ml), and the mixture was boiled under reflux for 6 h. The cooled solution was diluted with water (30 ml) and repeatedly extracted with dichloromethane to give 7-methoxythieno[3,2-b]pyridine (0.74 g, 69%) as a pale yellow oil.

$\tau(CDCl_3)$: 0.9 (d, H-5, J = 6 Hz), 2.13 (d, H-2, J = 6 Hz)
2.40 (d, H-3, J = 6 Hz), 3.15 (d, H-6, J = 6 Hz)
5.90 (s, OCH_3)

The picrate had mp. 210-11° when recrystallised from methanol. (Found: C, 42.6; H, 2.5; N, 13.9. $C_{14}H_{10}N_4O_8S$ requires C, 42.6; H, 2.5; N, 14.2%.)

4-Methyl-7-methoxythieno[3,2-b]pyridinium iodide (137)

A solution of 7-methoxythieno[3,2-b]pyridine (2.1 g) in methanol (1 ml) was treated with a solution of iodomethane (3 ml) in methanol (2 ml), and set aside at room temperature for 1 h. The crystalline product obtained was filtered off and recrystallised from methanol to give the methiodide (2.6 g, 67%) as yellow needles, mp. 153-4°. (Found: C, 35.0; H, 3.2; N, 4.3. $C_9H_{10}NOSI$ requires C, 35.3; H, 3.3; N, 4.6%.)

τ[$(CD_3)_2SO$]: 0.62 (d, H-5, J = 7 Hz), 1.02 (d, H-2, J = 6 Hz)
1.75 (d, H-3, J = 6 Hz), 2.10 (d, H-6, J = 7 Hz)
5.45 (s, OCH_3), 6.55 (s, $\overset{+}{N}$-CH_3)

4-Methylthieno[3,2-b]pyridin-7-one (138)

A solution of the foregoing methiodide (2.0 g) in 4M-sodium hydroxide solution (5 ml) was warmed on a steam bath to give a clear solution, then stirred at room temperature. The white solid which precipitated was filtered off, dissolved in warm chloroform, and the solution was dried ($MgSO_4$) and evaporated. The residue was crystallised from acetone-ether to give 4-methylthieno[3,2-b]pyridin-7-one (0.91 g, 84%) as white needles, mp. 98-100°. (Found: C, 58.3; H, 4.1; N, 8.3. C_8H_7NOS requires C, 58.2; H, 4.2; N, 8.5%.)

τ($CDCl_3$): 2.28 (d, H-2, J = 6 Hz), 2.55 (d, H-5, J = 7 Hz)
2.90 (d, H-3, J = 6 Hz), 3.81 (d, H-6, J = 7 Hz)
6.15 (s, N-CH_3)

6-Methoxycarbonylthieno[3,2-b]pyridin-7(4H)one-5-carboxylic acid (139)

To a stirred solution of 5,6-bismethoxycarbonylthieno[3,2-b]pyridin-7(4H)one (6.1 g) in water (90 ml), sodium hydroxide (0.95 g) was added, in one lot, and the solution was maintained at 60° for 8 hr. Acidification, with concentrated hydrochloric acid, of the solution when cool gave a white precipitate; this was filtered off, washed

repeatedly with water then recrystallised from methanol-dilute hydrochloric acid to give 6-methoxycarbonylthieno[3,2-b]pyridin-7(4H)one-5-carboxylic acid (3.8 g, 66%) as a white solid, mp. 163-6°. (Found: C, 46.9; H, 2.6; N, 4.8. $C_{10}H_7NO_5S$ requires C, 47.7; H, 2.7; N, 5.5%.)

τ[$(CD_3)_2SO$]: 1.90 (d, H-2, J = 6 Hz)

2.37 (d, H-3, J = 6 Hz)

6.24 (s, $COOCH_3$)

ν_{max} (KBr): 1730, 1605 cm^{-1} (C = O)

6-Methoxycarbonylthieno[3,2-b]pyridin-7(4H)one (140)

Method A

6-Methoxycarbonylthieno[3,2-b]pyridin-7(4H)one-5-carboxylic acid (0.5 g) was placed in a boiling tube and heated in a Woods metal bath at 230-40° until evolution of carbon dioxide ceased. The dark residue obtained was dissolved in cold 2M sodium hydroxide solution (25 ml); the solution was treated with decolourizing carbon, filtered and acidified. The product was isolated with dichloromethane and recrystallised from methanol to give 6-methoxycarbonylthieno[3,2-b]pyridin-7(4H)one (0.28 g, 68%) as a white solid, mp. 238-42°. (Found: C, 51.3; H, 3.2; N, 6.6. $C_9H_7NO_3S$ requires C, 51.7; H, 3.3; N, 6.7%.)

τ[$(CD_3)_2SO$]: 1.15 (s, H-5), 1.65 (d, H-2, J = 6 Hz)

2.43 (d, H-3, J = 6 Hz), 6.13 (s, CO_2CH_3)

ν_{max}: 1720 and 1615 cm^{-1} (C = O)

Method B, via thieno[3,2-b]pyridin-7(4H)one-6-carboxylic acid (141)

6-Methoxycarbonylthieno[3,2-b]pyridin-7(4H)one-5-carboxylic acid (0.5 g) was placed in a boiling tube and heated in a Woods metal bath at 230-40°, until evolution of carbon dioxide ceased. The dark residue obtained was dissolved in 2M sodium hydroxide solution (10 ml) and boiled under reflux for 1 h. The cooled solution was poured into

water (30 ml) and acidified with concentrated hydrochloric acid when the product precipitated out. It was filtered off, washed with water and crystallised from methanol and aqueous hydrochloric acid to give thieno[3,2-b]pyridin-7(4H)one-6-carboxylic acid (0.21 g, 52%), mp. 252-255° - with effervescence. (Found: C, 49.6; H, 2.6; N, 6.9. $C_8H_5NO_3S$ requires C, 49.2; H, 2.6; N, 7.2%.)

τ[$(CD_3)_2SO$]: 1.15 (s, H-5), 1.65 (d, H-2, J = 6 Hz)
2.43 (d, H-3)

A solution of thieno[3,2-b]pyridin-7(4H)one-6-carboxylic acid (2 g) in thionylchloride (30 ml) was boiled under reflux for 5 h. The excess of reagent was removed by distillation in methanol (30 ml) and boiled under reflux for 2h. The resulting solution was treated with decolourizing carbon, filtered and evaporated to give a residue which was crystallised from methanol to give 6-methoxycarbonylthieno[3,2-b]pyridin-7(4H)one (1.4 g, 68%) as a white solid, mp. 238-42° (identical to that obtained by method A).

Thieno[3,2-b]pyridin-7(4H)one-5,6-dicarboxylic anhydride (144)

A solution of thieno[3,2-b]pyridin-7(4H)one-5,6-dicarboxylic acid (17 g) in acetic anhydride (200 ml) was boiled under reflux for 4 h. The hot solution was filtered, and the filtrate was cooled in an ice-salt bath, when the product crystallised out. It was filtered off and washed repeatedly with ether, then recrystallised from acetone to give thieno[3,2-b]pyridin-7(4H)one-5,6-dicarboxylic anhydride (12.8 g, 80%) as white needles, mp. 184-6°. (Found: C, 48.9; H, 1.4; N, 5.6. $C_9H_3NO_4S$ requires C, 48.9; H, 1.35; N, 6.3%.)

τ[$(CD_3)_2SO$]: 1.37 (d, H-2, J = 6 Hz)
2.25 (d, H-3, J = 6 Hz)

ν_{max} (KBr): 1860, 1780 cm^{-1} (cyclic anhydride, C=O)

5-Methoxycarbonylthieno[3,2-b]pyridin-7(4H)one-6-carboxylic acid (142)

A solution of the acid anhydride (8 g) in methanol (100 ml) was boiled under reflux for 3 h, then evaporated under reduced pressure to yield a white residue. Crystallisation of this from methanol yielded 5-methoxycarbonylthieno[3,2-b]pyridin-7(4H)one-6-carboxylic acid (7.5 g, 82%) as white needles, mp. 225-7°. (Found: C, 47.3; H, 2.7; N, 5.5. $C_{10}H_7NO_5S$ requires C, 47.4; H, 2.8; N, 5.5%.)

τ[$(CD_3)_2SO$]: 1.28 (d, H-2, J = 6 Hz)

2.20 (d, H-3, J = 6 Hz)

5.85 (s, $COOCH_3$)

ν_{max} (KBr): 1750 and 1680 cm^{-1} (ester and acid C=O, resp.)

Decarboxylation of this half ester (0.5 g) by the procedure described for its isomer (139) gave 6-methoxycarbonylthieno[3,2-b]pyridin-7(4H)one (140) (0.31 g, 75%), identical (C, H, N analyses, mixed mp's, NMR and ir spectra) with the substance (139) obtained previously by decarboxylation of 6-methoxycarbonylthieno[3,2-b]pyridin-7(4H)one-5-carboxylic acid.

3-[2,2-Bisethoxycarbonylvinylamino]-thiophen-2-carboxylic acid (145)

A solution of 3-aminothiophen-2-carboxylic acid (8 g) and diethyl ethoxy methylenemalonate (9 g) in toluene (100 ml) was maintained at 70° for 6 h. The solution was evaporated under reduced pressure to give a dark oil; on cooling and tituration with light petroleum, a solid was obtained. This was dissolved in boiling cyclohexane (100 ml), the solution was treated with decolourising carbon, filtered and evaporated to half its original volume. On cooling 3-[2,2-bisethoxycarbonylvinylamino]-thiophen-2-carboxylic acid (7.0 g, 41%) was obtained as pale brown crystals, mp. 98-101°. The analytical sample* was recrystallised from cyclohexane-acetone solution as white needles, and

had mp. 101-2°. (Found: C, 47.2; H, 5.2; N, 4.1. $C_{13}H_{15}NO_6S$ requires C, 47.1; H, 5.3; N, 4.1%.)

$\tau(CDCl_3)$: 1.70 (d, NHC<u>H</u>, J = 15 Hz)

2.55 (d, H-5, J = 6 Hz)

2.91 (d, H-4, J = 6 Hz)

5.75 (2 superim. q, $COOC\underline{H}_2$)

8.71 (2 superim. t, $COOCH_2C\underline{H}_3$)

ν_{max} (KBr): 3200 cm^{-1} (COOH)

1760, 1680, 1610 cm^{-1} (C=O)

* The analytical sample, when dried under vacuum at 60°, was found to suffer decarboxylation, to give ethyl ethoxycarbonyl-β-(N-3-thienyl) aminoacrylate (146), mp. 77-8° (lit[182] mp. 74-5°). (Found: C, 53.2; H, 5.4; N, 5.0. Calculated for $C_{12}H_{15}NO_4S$: C, 53.2; H, 5.6; N, 5.2%.)

$\tau(CDCl_3)$: 1.40 (d, NHC<u>H</u>, J = 15 Hz)

2.65 (m, 3 x Ar-H)

5.62 (2 superim. q, $CO_2C\underline{H}_2$)

8.61 (2 superim. t, $COOCH_2C\underline{H}_3$)

Unambiguous synthesis of 6-methoxycarbonylthieno[3,2-b]pyridin-7(4H)one

1 6-Ethoxycarbonylthieno[3,2-b]pyridin-7(4H)one

A stirred solution of 3-[2,2-bisethoxycarbonylvinylamino]-thiophen-2-carboxylic acid (2 g) in polyphosphate ester* (30 g) was heated at 120-130° for 30 min. The solution, when cool, was poured into water (200 ml) and the product isolated by repeated extractions with dichloromethane. The residue obtained was crystallised from ethanol to give 6-ethoxycarbonylthieno[3,2-b]pyridin-7(4H)one (0.7 g, 40%) as a white solid, mp. 240-44°.(Found: C, 53.3; H, 4.0; N, 6.3. $C_{10}H_9O_3NS$ requires C, 53.8; H, 4.0; N, 6.3%.)

τ[$(CD_3)_2SO$]: 1.55 (s, H-5)
2.10 (d, H-2, J = 6 Hz)
2.78 (d, H-3, J = 6 Hz)
5.88 (q, $OC\underline{H}_2CH_3$)
8.8 (t, $OCH_2C\underline{H}_3$)

2 6-Methoxycarbonylthieno[3,2-b]pyridin-7(4H)one (140)

A solution of 6-ethoxycarbonylthieno[3,2-b]pyridin-7(4H)one (0.9 g) in methanol (20 ml) was boiled under reflux for 5 h in the presence of a catalytic quantity of p-toluenesulphonic acid. The solution was cooled in the refrigerator overnight to give 6-methoxycarbonylthieno[3,2-b]pyridin-7(4H)one (0.51 g, 61%) as a white solid, mp. 238-41°. (Identical nmr and mixed mp. with the sample obtained earlier, page 127).

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* *Polyphosphate ester*

The polyphosphate ester was prepared from phosphorous pentoxide and diethyl ether by the method of Pollmann and Schramm.[182]

6-Methoxycarbonyl-7-methoxythieno[3,2-b]pyridine (148)

Thieno[3,2-b]pyridin-7(4H)one-6-carboxylic acid (1.6 g) mixed with phosphorous pentachloride (3 g), was heated in an oil bath at 170° for 30 min. When cool, the resulting solid was dissolved in chloroform (30 ml) and methanol (50 ml) and the solution was boiled under reflux for 2 h. The cooled solution was filtered, poured into water (100 ml) and repeatedly extracted with dichloromethane, to give a residue, which was crystallised from methanol, affording 6-methoxycarbonyl-7-methoxythieno[3,2-b]pyridine (0.6 g, 32%) as a white solid, mp. 223-5°. The analytical sample was crystallised from methanol and had mp. 225-7°. (Found: C, 53.3; H, 3.8; N, 6.0. $C_{10}H_9NO_3S$ requires C, 53.8; H, 4.0; N, 6.3%.)

$\tau(CDCl_3)$: 1.65 (s, H-5), 2.25 (d, H-2, J = 6 Hz)
2.85 (d, H-3, J = 6 Hz)
6.15 (s, $COOCH_3$), 6.3 (s, OCH_3)

ν_{max}(KBr): 1610 and 1680 cm^{-1} (C=O)

Thermal cyclisation of E-dimethyl-2-N-(2-methoxycarbonyl-3-thienyl)-but-2-endioate

Repeated attempts to induce a thermal cyclisation of the Michael adduct by prolonged boiling under reflux in tetrahydronaphthalene and in diphenyl ether failed to give the desired reaction. In both cases, black polymeric residues were obtained, from which no identifiable substance was isolated. Eventually, it was found that triglyme was a suitable solvent for this thermal cyclisation. A solution of the Michael adduct (5 g) in triglyme (triethyleneglycol dimethyl ether) (25 ml) was boiled under reflux for 1 h, the solution was cooled in an ice-salt bath, the product was filtered off and washed with ether. On crystallisation from methanol (after treatment with decolourising carbon) 3,5-bismethoxycarbonyl thieno[3,4-b]pyridin-7(4H)one (149)

(3.2 g, 72%) was obtained as yellow needles, showing a brilliant green fluorescence in solution, mp. 176-8°. (Found: C, 49.5; H, 3.4; N, 5.0. $C_{11}H_9NO_5S$ requires C, 49.4; H, 3.3; N, 5.2%.)

τ[$(CD_3)_2SO$]: 1.48 (s, H-1), 3.30 (s, H-6)

5.98, 5.90 (both s, $COOCH_3$)

ν_{max} (KBr): 3340 cm^{-1} (NH)

1730, 1640 and 1685 cm^{-1} (C=O)

Thieno[3,4-b]pyridin-7(4H)one-3,5-dicarboxylic acid (150)

A solution of 3,5-bismethoxycarbonylthieno[3,4-b]pyridin-7(4H)one (2 g) in 10% aqueous potassium hydroxide (35 ml) was boiled under reflux for 2 h. The solution was cooled, then poured into water (100 ml) and acidified with concentrated hydrochloric acid, when the crude product precipitated from solution. It was filtered off, washed repeatedly with water and recrystallised from methanol (150 ml) containing 2M-hydrochloric acid (120 ml) to give thieno[3,4-b]pyridin-7(4H)one-3,5-dicarboxylic acid (1.6 g, 83%) as yellow plates, mp. >300°. (Found: C, 45.2; H, 2.0; N, 5.5. $C_9H_5NO_5S$ requires C, 45.2; H, 2.1; N 5.8%.)

τ[$(CD_3)_2SO$]: 1.35 (s, H-1), 3.65 (s, H-6)

Attempted thermal decarboxylation of the above diacid by the procedure described previously (page 124) resulted in a polymeric material, which was found to be insoluble in a wide range of solvents. No identifiable product was obtained from the residue.

7-Chloro-3,5-bismethoxycarbonylthieno[3,4-b]pyridine (155)

A solution of 3,5-bismethoxycarbonylthieno[3,4-b]pyridin-7(4H)one (2 g) in freshly distilled phosphoryl chloride (15 ml) was boiled under reflux for 6 h. The excess of reagent was removed by evaporation under reduced pressure and the residue was added carefully to water (100 ml). The aqueous solution was neutralised with saturated sodium hydrogen carbonate solution, then extracted with dichloromethane, to yield a residue, which, on crystallisation from methanol, provided 7-chloro-3,5-bismethoxycarbonylthieno[3,4-b]pyridine (1.1 g, 52%) as yellow needles, mp. 180-4°. (Found: C, 45.7; H, 2.7; N, 4.5. $C_{11}H_8NO_4SCl$ requires C, 46.2; H, 2.8; N, 4.9%.)

τ[$(CD_3)_2SO$]: 1.25 (s, H-1), 2.15 (s, H-6)

6.05 and 6.15 (both s, $COOCH_3$)

ν_{max} (KBr): 1730 and 1685 cm^{-1} (C=O)

7-Methoxy-3,5-bismethoxycarbonylthieno[3,4-b]pyridine (156)

(i) From 7-chloro-3,5-bismethoxycarbonylthieno[3,4-b]pyridine

The chloro compound (1.3 g) was added to a solution of sodium methoxide (from 0.2 g sodium) in methanol (10 ml). The solution was boiled under reflux for 4 h, cooled, and poured into water (40 ml). The product was isolated with dichloromethane to give a residue, crystallisation of which from methanol afforded 7-methoxy-3,5-bismethoxycarbonylthieno[3,4-b]pyridine (0.76 g, 59%) as yellow plates, mp. 196-8°. (Found: C, 51.0; H, 3.7; N, 4.7. $C_{12}H_{11}O_5NS$ requires C, 51.2; H, 3.9; N, 4.9%.)

$\tau(CDCl_3)$: 1.38 (s, H-1), 3.44 (s, H-6)

5.95 (s, OCH_3), 6.05 and 6.15 (both s, $COOCH_3$)

(ii) From 3,5-bismethoxycarbonylthieno[3,4-b]pyridin-7(4H)one

To a stirred ice-cold solution of the pyridone (2 g) in dichloromethane (50 ml) and methanol (15 ml) a solution of diazomethane* in ether was added dropwise. When the addition was complete, the solution was stirred at room temperature for 2 h, then evaporated under reduced pressure. Crystallisation of the residue from methanol afforded 7-methoxy-3,5-bismethoxycarbonylthieno 3,4-b pyridine (1.8 g, 85%), mp. 196-8° [identical to that obtained by procedure (i)].

7-Methoxythieno[3,4-b]pyridine-3,5-dicarboxylic acid (157)

A solution of 3,5-bismethoxycarbonyl-7-methoxythieno[3,2-b] pyridine (1 g) in 10%) aqueous potassium hydroxide solution (10 ml) was boiled under reflux for 1 h, then cooled and poured into water (50 ml). The aqueous solution was acidified with concentrated hydrochloric acid and the crude product was filtered off and recrystallised from methanol-dilute hydrochloric acid solution to give 7-methoxythieno[3,4-b]pyridine-3,5-dicarboxylic acid (0.8 g, 76%) as a yellow solid, mp. 208-10°. (Found: C, 47.3; H, 2.6; N, 4.6. $C_{10}H_7NO_5S$ requires C, 47.4; H, 2.8; N, 5.5%.)

τ[$(CD_3)_2SO$]: 1.45 (s, H-1), 3.6 (s, H-6)

5.95 (s, $OC\underline{H}_3$)

Attempted thermal decarboxylation of this diacid by the procedure previously used successfully for thieno[3,2-b]pyridin-7(4H)one-5,6-dicarboxylic acid gave a black polymeric residue from which no identifiable substance was isolated.

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* *The diazomethane was prepared from nitrosomethylamine (10 g) and sodium hydroxide solution.*[179]

6-Bromo-3,5-bismethoxycarbonylthieno[3,4-b]pyridin-7(4H)one (158)

To a stirred solution of 3,5-bismethoxycarbonylthieno[3,4-b]pyridin-7(4H)one (0.5 g) in glacial acetic acid (5 ml) at room temperature, a solution of bromine (0.4 g) in glacial acetic acid (5 ml) was added dropwise. After the addition was complete, the solution was stirred for 15 min, when a solid precipitated. This was filtered off, washed with cold water and recrystallised from methanol to give 6-bromo-3,5-bismethoxycarbonylthieno[3,4-b]pyridin-7(4H)one (0.46 g, 66%) as yellow needles, mp. 207-8°. (Found: C, 37.9; H, 2.1; N, 3.7. $C_{11}H_8NO_5SBr$ requires C, 38.1; H, 2.3; N, 4.0%.)

$\tau(CDCl_3)$: 1.55 (s, H-1)

5.95 and 6.1 (both s, 2 x $COOCH_3$)

ν_{max} (KBr): 3340 cm^{-1} (NH)

1610, 1670 and 1710 cm^{-1} (C=O)

6-Bromo-7-methoxy-3,5-bismethoxycarbonylthieno[3,4-b]pyridine (159)

To a stirred solution of 7-methoxy-3,5-bismethoxycarbonylthieno[3,4-b]pyridine (0.4 g) in glacial acetic acid (5 ml) at room temperature, a solution of bromine (0.3 g) in glacial acetic acid (2 ml) was added dropwise. After the addition was complete, the solution was stirred for 15 min, when the product precipitated. It was filtered off, washed with cold water and crystallised from methanol to give 6-bromo-7-methoxy-3,5-bismethoxycarbonylthieno[3,4-b]pyridine (0.4 g, 78%) as yellow needles, mp. 214-16°. (Found: C, 40.0; H, 2.6; N, 3.7. $C_{12}H_{10}BrNO_5S$ requires C, 40.0; H, 2.8; N, 3.9%.)

$\tau(CDCl_3)$: 1.45 (s, H-1), 5.95 (s, OCH_3)

6.1 and 6.15 (both s, $COOCH_3$)

ν_{max} (KBr): 1730, 1710 and 1620 cm^{-1} (C=O)

3-[2,2-bisethoxycarbonylvinylamino]-2-methoxycarbonylthiophen (160, R = CH_3)

A solution of 3-amino-2-methoxycarbonylthiophen (3 g) and diethyl ethoxymethylenemalonate (3 g) in toluene (10 ml) was boiled under reflux for 3 h. Evaporation under reduced pressure yielded a yellow residue which, on crystallisation from light petroleum-benzene, gave 3-[2,2-bisethoxycarbonylvinylamino]-2-methoxycarbonylthiophen (4.1 g, 68%) as yellow needles, mp. 68-70°. (Found: C, 51.0; H, 5.3; N, 4.1. $C_{14}H_{17}NO_6S$ requires C, 51.4; H, 5.2; N, 4.3%.)

$\tau(CDCl_3)$: 1.70 (d, NHCH, J = 15 Hz)
2.55 (d, H-5, J = 6 Hz)
2.91 (s, H-4, J = 6 Hz)
5.75 (2 superim. q, $-CO_2CH_2CH_3$)
6.10 (s, $COOCH_3$)
8.71 (2 superim. t, $CO_2CH_2CH_3$)

ν_{max} (KBr): 1685, 1610, 1760 cm^{-1} (C=O)

3-[2,2-bisethoxycarbonylvinylamino]-2-ethoxycarbonylthiophen (160, R = C_2H_5)

A solution of 3-amino-2-ethoxycarbonylthiophen (3 g) and diethyl ethoxymethylenemalonate (3 g) in toluene (10 ml) was boiled under reflux for 2 h. The solution was evaporated under reduced pressure to give a yellow oil; this, on cooling and tituration with light petroleum, solidified. Crystallisation from benzene gave 3-[2,2-bisethoxycarbonylvinylamino]-2-ethoxycarbonylthiophen (4.6g, 77%) as yellow needles, mp. 111-13°. (Found: C, 52.5; H, 5.7; N, 4.1. $C_{15}H_{19}NO_6S$ requires C, 52.8; H, 5.57; N, 4.1%.)

$\tau(CDCl_3)$: 1.70 (d, NHCH, J = 15 Hz)
2.50 (d, H-5, J = 6 Hz)
2.91 (d, H-4, J = 6 Hz)

5.7 (3 superim. q, $COOCH_2CH_3$)

8.7 (3 superim. t, $COOCH_2CH_3$)

ν_{max} (KBr): 1760, 1680, 1610 cm^{-1} (C=O)

Attempted selective hydrolysis of 3[2,2-bisethoxycarbonylvinylamino]-2-methoxycarbonylthiophen to 3[2,2;bisethoxycarbonylvinylamino]-thiophen-2-carboxylic acid

A stirred solution of 3[2,2-bisethoxycarbonylvinylamino]-2-methoxycarbonylthiophen (0.4 g) and sodium hydroxide (0.1 g) in water (4 ml) was heated at 60° for 2 h. The cooled solution was acidified with 2M-hydrochloric acid, then repeatedly extracted with dichloromethane. From the extracts a polymeric substance was obtained and attempts to obtain an identifiable substance from the residue failed.

6-Ethoxycarbonyl-3-methoxycarbonylthieno[3,4-b]pyridin-7(4H)one (161, R = CH_3)

A stirred solution of 3-[2,2-bisethoxycarbonylvinylamino]-2-methoxycarbonylthiophen (2 g) in polyphosphate ester (30 g) was heated for 30 min at 120-130°. The cooled solution was poured into water (100 ml), and repeatedly extracted with dichloromethane to give a yellow residue. This, on crystallisation from methanol, gave 6-ethoxycarbonyl-3-methoxycarbonylthieno[3,4-b]pyridin-7(4H)one (1.4 g, 81%) as yellow needles, mp. 210-14°. (Found: C, 49.1; H, 3.9; N, 5.4. $C_{12}H_{11}NO_5S$ requires C, 51.2; H, 3.9; N, 5.0%.)

$\tau[(CD_3)_2SO]$: 1.05 (s, H-1)

1.35 (d, H-5, J = 6.5 Hz)

5.95 (s, $COOCH_3$)

5.65 (q, $COOCH_2CH_3$, J = 7 Hz)

8.70 (t, $COOCH_2CH_3$, J = 7 Hz)

ν_{max} (KBr): 3340 cm^{-1} (NH)

1730, 1680 cm^{-1} (C=O)

3,6-Bisethoxycarbonylthieno[3,4-b]pyridin-7(4H)one (161, R = C_2H_5)

Following the procedure described above, using 3[2,2-bisethoxycarbonylvinylamino -2-ethoxycarbonylthiophen (2 g), 3,6-bisethoxycarbonylthieno[3,4-b]pyridin-7(4H)one (1.06 g, 61%) was obtained as yellow needles, mp. 228-30°. (Found: C, 52.6; H, 4.2; N, 4.6. $C_{13}H_{13}O_5NS$ requires C, 52.8; H, 4.4; N, 4.7%.)

τ[$(CD_3)_2SO$]: 1.39 (s, H-1)

1.64 (d, H-5, J = 6.5 Hz)

5.75 (superim. q, 2 x $COOCH_2CH_3$)

8.75 (superim. t, 2 x $COOCH_2CH_3$)

ν_{max} (KBr): 3340 cm^{-1} (NH)

1730, 1680 cm^{-1} (C=O)

Attempted bromination of 3,6-bisethoxycarbonylthieno[3,4-b]pyridin-7(4H)one

To a solution of the pyridone (0.5 g) in glacial acetic acid (10 ml), a solution a bromine (0.5 g) was added dropwise. The solution was stirred at room temperature for 1 h, then poured into water. The solid was filtered off, washed with water and recrystallised from ethanol; it proved to be unreacted starting material.

Thieno[3,4-b]pyridin-7(4H)one-3,6-dicarboxylic acid (162)

A solution of 3,6-bisethoxycarbonylthieno[3,4-b]pyridin-7(4H)one (0.5 g) in 10% aqueous potassium hydroxide (10 ml) was boiled under reflux for 1 h. The cooled solution was poured into water (20 ml) and acidified with concentrated hydrochloric acid, precipitating the crude product. The precipitate was filtered off and crystallised from methanol to give thieno[3,4-b]pyridine-7(4H)one-3,6-dicarboxylic acid (0.3 g, 76%) as a yellow solid, mp. >300°. (Found: C, 45.2; H, 2.2, N, 5.3. C_9H_5NOS requires C, 45.2; H, 2.1; N, 5.8%.)

τ[$(CD_3)_2SO$]: 1.35 (s, H-1)

1.54 (d, H-5, J = 6.5 Hz)

0.5 (broad d, NH)

ν_{max} (KBr): 3000 cm^{-1} (v. broad H-bonded OH)

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