PYRROLO[2-3-b]PYRIDINES OF POTENTIAL CHEMOTHERAPEUTIC VALUE

BY

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SUMMARY

The methods available for the synthesis of pyrrolopyridines and the biological activity of the pyrrolo[2,3-b]pyridines are reviewed briefly.

The reasons for the synthesis of pyrrolo[2,3-b]pyridines from a pyrrole precursor are discussed and the possible routes from the available starting materials outlined. The synthesis of pyrrolo[2,3-b]pyridines was approached by two main routes.

The attempted syntheses of pyrrolo[2,3-b]pyridines from 3-substitued 2-aminopyrroles are discussed and a possible explanation of the failure of these reactions is postulated.

The preparation of a series of 2-amino-4-cyanopyrroles and their reaction with 1,3-dicarbonyl reagents to give pyrrolo[2,3-b]pyridines is discussed. The two-stage synthesis of pyrrolo[2,3-b]pyridin-4(7H)-ones from 2-amino-4-cyanopyrroles and diethyl ethoxymethylenemalonate is discussed. The preferred orientation of products obtained from the reaction between 2-amino-4-cyanopyrroles and unsymmetrical dicarbonyl reagents is discussed in terms of a reaction mechanism. The chemistry of the pyrrolo[2,3-b]pyridines is discussed.

^{13}C nuclear magnetic resonance spectroscopy 1H-pyrrolo-[2,3-b]pyridine is discussed and the chemical shifts are rationalised in terms of electron density calculations. The ^{13}C chemical shifts of 1H-pyrrolo[3,2-b]pyridine and 1H-pyrrolo[3,2-c]pyridine are compared with those of 1H-pyrrolo-[2,3-b]pyridine. The ^{13}C chemical shifts of a series of

pyrrolo[2,3-b]pyridine derivatives are recorded, and a comparison of the chemical shift data with available data for methyl-substituted pyridines was made. The comparison of data established the product of the reaction between an aminopyrrole and 4,4-dimethoxybutan-2-one to be a 6-methylpyrrolo[2,3-b]pyridine and not a 4-methylpyrrolo[2,3-b]pyridine.

The mass spectra of most of the compounds prepared in this work are recorded and possible fragmentation pathways are postulated.

The author would like to thank Professor D. G. Wibberley for his help and encouragement during the course of this work. Grateful thanks are also extended to Dr. W. J. Irwin and Dr. C. H. Schwalbe for their work on the molecular orbital calculations, and to Dr. M. F. G. Stevens, Dr. A. Z. Britten and the postgraduates (1972-1975) for useful discussion.

The author also acknowledges the technical assistance of Mr. P. R. Lowe, Mr. M. J. Horton and Mr. E. Hartland.

To my wife and

parents

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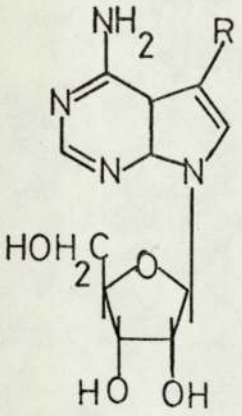
INTRODUCTION

THE PYRROLOPYRIDINES

The rationale for the design of structural analogues of a normal metabolite is that such compounds may interfere in the utilisation or function of the metabolite. A compound which is effective in this respect may be called an antimetabolite. The search for an antimetabolite successful in the chemotherapy of a bacterial, viral or tumour growth has been based mainly on aza and deaza analogues of the purines and pyrimidines. The discovery of the nucleosides Sangivamycin (1), Toyacamycin (2), and Tubercidin (3), and their biological activity,[1,2,3,4] has stimulated further research into the synthesis and properties of deaza analogues of the purines. The known inhibitory effects of purine, pyrimidine and nucleoside



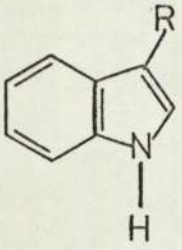
(1) R=$CONH_2$

(2) R=CN

(3) R=H

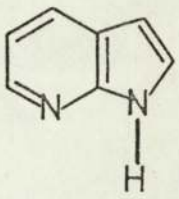
analogues have been reviewed recently[5].

It is well known that indole (4) and tryptophan (5) are essential metabolites[6] for the growth of bacterial cells and 5-hydroxytryptophan has an important function in the cardiovascular system[7] and in mental activity[8]. It is of little surprise, therefore, that the pyrrolo pyridines have received increasing attention over the last two decades. The pyrrolopyridines have been the



(4) R=H

(5) R=$CH_2CH(NH_2)COOH$



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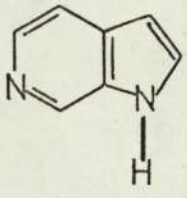

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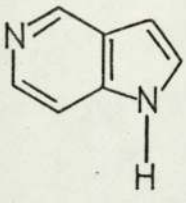

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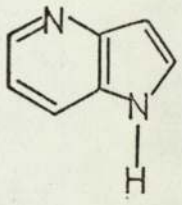


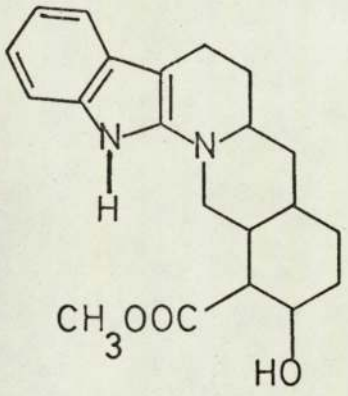
(9)

subject of previous reviews[9,10,11] in which the "azaindole" nomenclature was preferred. The Ring Index[12], Chemical Abstracts and I.U.P.A.C. conventions require that the pyrrolopyridine nomenclature be used and this has been adopted for the present work. The four parent heterocycles are named: 1H-pyrrolo[2,3-b]pyridine (6), 1H-pyrrolo[2,3-c]pyridine (7), 1H-pyrrolo[3,2-c]pyridine (8) and 1H-pyrrolo[3,2-b]pyridine (9). Willette[9] gives an exhaustive presentation of the synthetic methods available for pyrrolopyridines; these have been mainly adapted from the earlier indole syntheses but also included in the review are several novel routes. These ring systems (6), (7), (8), and (9), almost without exception, are derived from an available pyridine

starting material with fusion of the pyrrole ring using drastic conditions which severely restrict the synthesis of pyrrolopyridines with labile functional groups.

METHODS OF SYNTHESIS

Most pyrrolopyridines are synthetic products, but some, like Yohimbine (10), Harmine (11), and 1H-pyrrolo[2,3-b]pyridine (6), found in the lepidine fraction of coal tar[13], are known to exist as free bases in nature.



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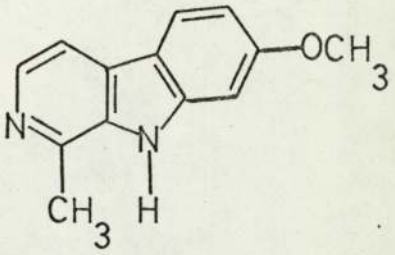

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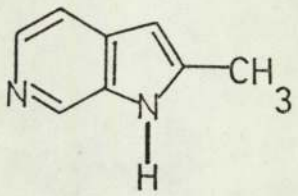

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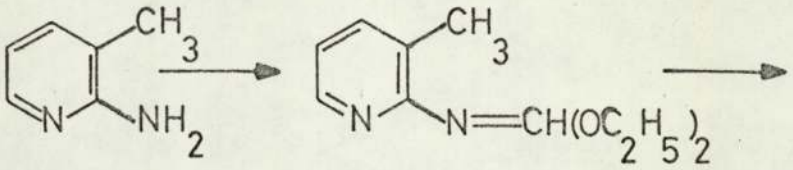
(a) The Madelung Synthesis

The Madelung synthesis of indoles[14] was the first method successfully applied to the pyrrolopyridine ring system and it has survived, with various modifications, as one of the most versatile and most frequently used methods. This involves a cyclisation of an ortho-acylamino picoline under basic conditions, and was first recorded for the 1H-pyrrolo[2,3-c]pyridines by Koenigs and Fulde in 1927[15]. The cyclisation of 3-acetamido-4-methylpyridine

with sodium ethoxide gave a yield of 23% for the 2-methyl pyrrolo[2,3-b]pyridine (12). Since then the method has been applied to the 1H-pyrrolo[2,3-b]pyridines, 1H-pyrrolo [3,2-c]pyridines, and 1H-pyrrolo[3,2-b]pyridines[16,17] in various ways and has yielded the parent heterocycle in these systems. The parent 1H-pyrrolo[2,3-c]pyridine (7) has proved impossible to make due to the instability of the corresponding 3-formamido-4-methlypyridine. A significant improvement in the Madelung reaction involved the use of sodium anilide and potassium formate (as condensing reagent) for the cyclisation of 2-formamido-3-methylpyridine to 1H-pyrrolo[2,3-b]pyridine (6) in 51% yield[18] while other pyrrolopyridines were made in lower yields[19]. Contradictory results have been published regarding this method for the other pyrrolopyridines[20,21,22,23]. A further improvement was made by Lorenz et al.,[24] involving the use of mineral oil as a high boiling solvent in the preparation of 1H-pyrrolo[2,3-b]pyridine (6) on a 3molar scale. They also investigated the use of a new base, sodium N-methylanilide and the formamidine derivative (15) rather than a formamidopyridine (see scheme 1). This modification was successfully applied to the 1H-pyrrolo [3,2-c]pyridines and 1H-pyrrolo[3,2-b]pyridines[24].

SCHEME 1



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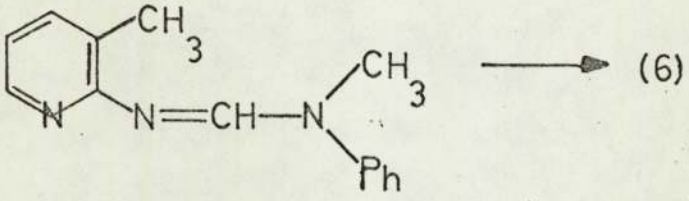


(15)

(b) The Fischer Indole Synthesis.

The Fischer Indole synthesis has not yielded so far any parent pyrrolopyridine, however, this is not surprising for two reasons:

(i) There is a decreased nucleophilicity of the ring carbon atoms in pyridine with respect to benzene.

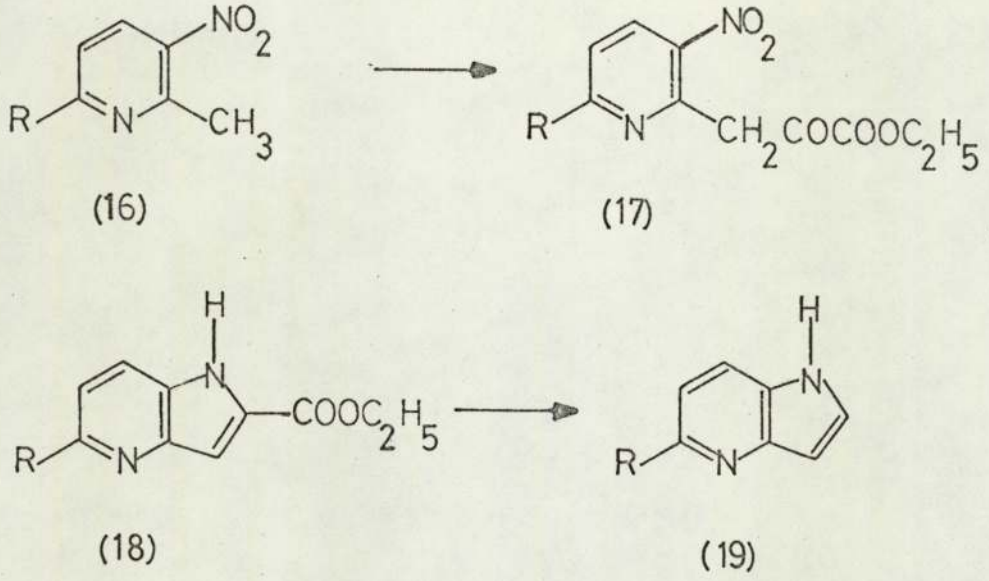
(ii) Under normal acid or Lewis acid catalysis the ring nitrogen of pyridine could be expected to carry the positive charge, and hence increase the electron acceptor property of that atom. Thus the conditions for cyclisation of pyridylhydrazones were expected to be more vigorous than that for arylhydrazones[25], this was later proved to be the case for various condensing reagents[26]. The Fischer reaction has, however, proved useful in preparing several 2,3-disubstituted pyrrolopyridines from cyclohexanone[27,28]

3-methylbutan-2-one[30,31], desoxybenzoin[29,32], cyclopentanone and α-tetralone[33], and indan-1-one[31]. Thermal indolisation of pyridylhydrazones has been successful in certain pyrrolo[2,3-b]pyridines[32,33] and has been extended to the other three systems. The main disadvantage of this procedure is that it yields pyrrolopyridines substituted in the pyrrole ring and the pyridylhydrazones are mainly unstable. However, the lack of protonation of the pyridine ring undoubtedly increases the yield of the pyrrolopyridine, as does an electron donor substituent at C-5 or C-6 in the pyridine ring. Electron acceptor substituents have been shown by Yakhontov[34] to hinder the reaction by deactivation of C-3 in the pyridine ring.

(c) The Reissert Synthesis.

The Reissert synthesis has been applied with limited success in the preparation of pyrrolopyridines. It was based on the synthesis of indoles by the reductive cyclisation of ortho-nitrophenylpyruvates . Initial work by Badger and Rao[35], and Herz and Murty[21] was unsuccessful at the first stage of synthesis - the base-catalysed condensation of ethyl oxalate and an ortho-nitropicoline. However, Frydman et al.[36,37] have reported the successful conversion of 3-nitro-2-picolines (16) and 3-nitro-4-picolines into the corresponding 1H-pyrrolo[3,2-b]pyridine (19) and 1H-pyrrolo[2,3-c]pyridines in good yield (see scheme 2). The Reissert synthesis has recently provided a convenient route to the parent 1H-pyrrolo[2,3-c]pyridine[38], and 1H-pyrrolo[3,2-b]pyridine[39].

SCHEME 2



(16) (17)

(18) (19)

R = alkoxy, benzyloxy

This method has not been applicable to the pyrrolo [2,3-b] pyridines or pyrrolo [3,2-c] pyridines.

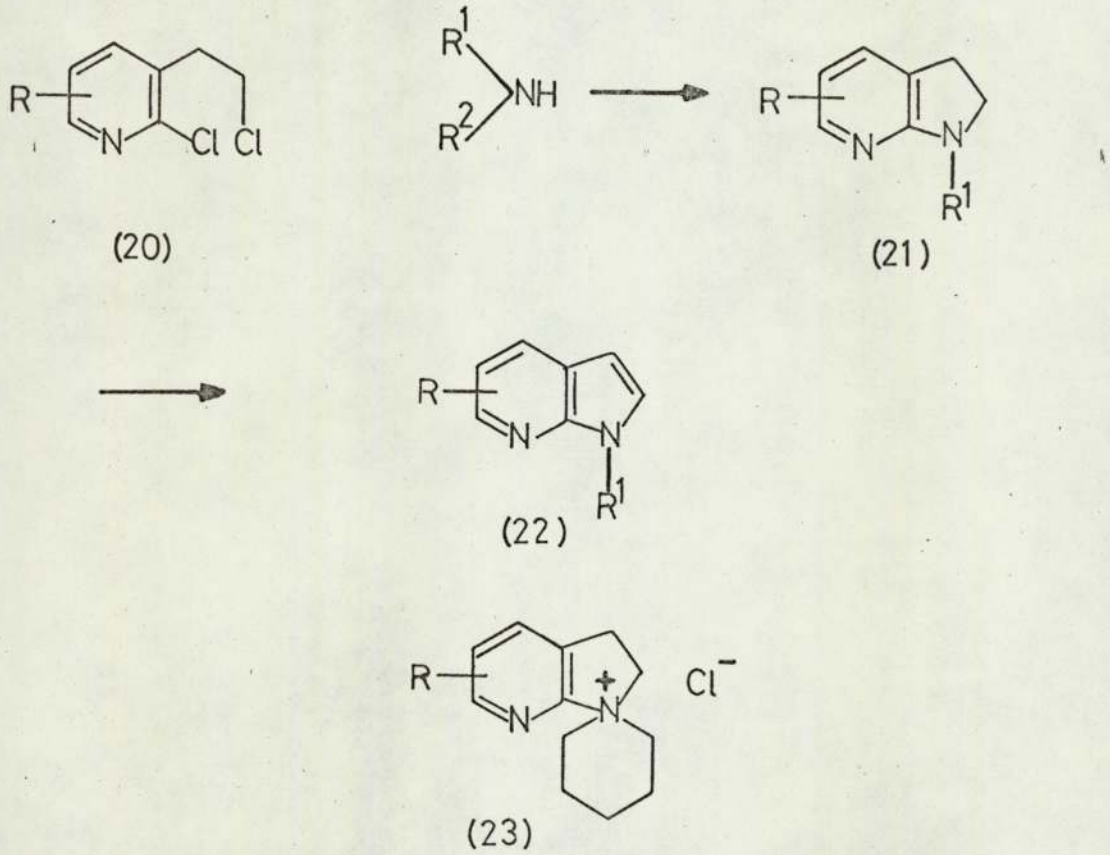
(d) The Photochemical Ring Contraction Synthesis.

This rather lengthy method is of value because it gives consistent results and leads to all four parent heterocycles. The reaction was developed by Sus and Moller for the synthesis of indoles and pyrrolo [2,3-b] pyridines[40] and they later extended the method to the other pyrrolopyridine systems[41,42]. The reaction consists of a photochemical ring contraction of an appropiate 3-diazonium-4-hydroxy naphthyridine by means of ultra-violet irradiation to yield the pyrrolopyridine-3-carboxylic acid.

(e) The Yakhontov-Rubtsov Synthesis.

A general method for the synthesis of pyrrolo[2,3-b] pyridines and pyrrolo[3,2-c]pyridines has been developed by Yakhontov and Rubtsov et al.[43]. The method consists of a novel cyclisation of 3-2'-chloroethylpyridines (20) with a 2-, or 4-chloro group and a primary or secondary amine to yield a 2,3-dihydropyrrolopyridine derivative (21) which is then dehydrogenated to the pyrrolopyridine (22) (see scheme 3). The pyrrole ring closure is accompanied by N-dealkylation and the alkyl halide thus formed reacts with excess amine to give a tertiary amine. Pyrrolidine and piperidine have been used and this resulted in the formation of a spiro compound (23) which was unable to split off alkyl halide[44].

SCHEME 3



The factors affecting this reaction are:

(i) The basicity of the secondary amine[41,43], secondary aliphatic amines are more reactive than N-alkyl arylamines.

(ii) Increased reactivity of secondary amines leads to dehydrohalogenation of the 3-2'-chloroethyl group and yields 3-vinylpyridines[41,44].

(iii) N-alkyl arylamines are slow to react but give excellent yields of N-aryl-2,3-dihydropyrrolopyridines[45].

(iv) A substituent group in the pyridine ring can affect the loss of the 2-chloro group.

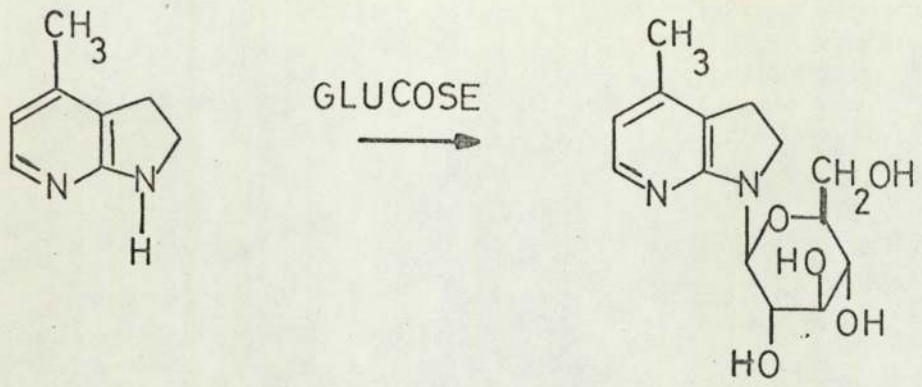
(v) Increase in length of the alkyl group in N-alkyl arylamines can decrease the yields[41,43].

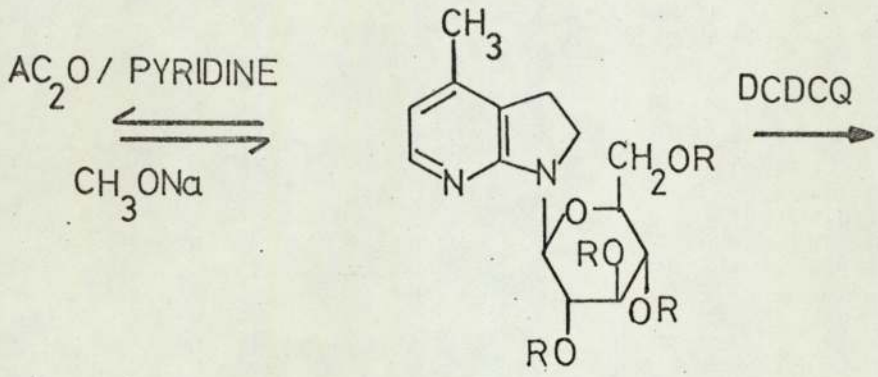
(vi) Ease of formation and cleavage of the C-N bond in the intermediate ions is such that benzyl > alkyl > aryl.

(vii) The reaction is favoured by a p-substituted electron donor group on the N-arylamine while a p-substituted electron acceptor group impedes the rection[46].

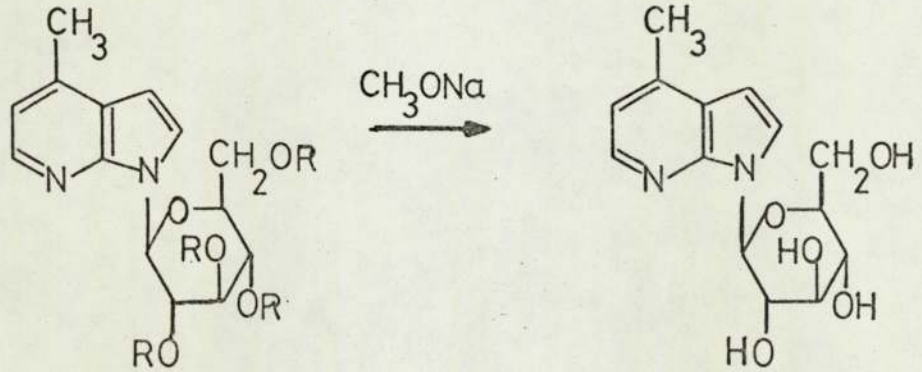
The final step in the rection, the dehydrogenation, was helped if in (21) R=6-methoxy-[47] and the best conditions were found to be sodium in liquid ammonia or chloranil in refluxing xylene. The rections were smooth and gave good yields of pyrrolopyridines[45,46, 47, 48, 49, 50]. The limitations of the route lie in the availability of the chloroethylpyridines and the adaptation to the other pyrrolopyridines. The parent 1H-pyrrolo[2,3-b]pyridine (6) can be made by this method when dibenzylamine is used, (scheme 3 R=Cl, R^1=R^2=benzyl). The N-benzyl derivative is reduced by palladium/charcoal[51] which also removes the 6-chloro group.

SCHEME 4





R= ACETYL



This route has led to the first synthesis of an N-substituted pyrrolo[2,3-b]pyridine with a glucose moiety (see scheme 4). This potential route to a purine nucleoside analogue makes this route one of the most significant contributions to pyrrolopyridine chemistry[52]. The reaction was repeated recently with ribose in place of glucose[53].

A number of other approaches have been made and can be found in the reviews of Willette[9] and Yakhontov[10]. There have, however, been some more recent syntheses.

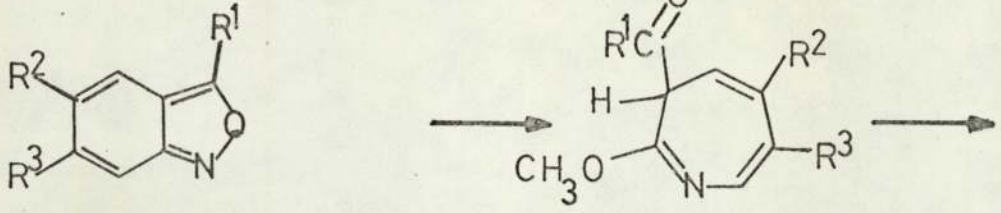
NEW SYNTHESES OF PYRROLO[2,3-b]PYRIDINES.

(a) A new synthetic method involving the photochemical transformation of anthranils in the presence of a primary amine was discovered by Ogata et al.[54]. The resulting 2-amino-3-acyl-3H-azepine (30) undergoes a facile rearrangement and contracts to a pyrrolo[2,3-b]pyridine (31) in a good yield (see scheme 5). The rearrangement of (30) to (31) is thought to proceed through the intermediates (33) and (34).

(b) The Bischler Reaction.

Although widely used in the synthesis of indoles[55,56] this route has had few applications in the pyrrolopyridine field. Bernstein et al.[57] and Herbert and Wibberley[58] were able to cyclise 2,6-diaminopyridine with benzoin and anisoin respectively. More recently this reaction has been extended using various α-hydroxy ketones leading to pyrrolo[2,3-b]pyridines with alkyl and aryl groups in the pyrrole ring[59]. The reactions gave moderate yields and

SCHEME 5



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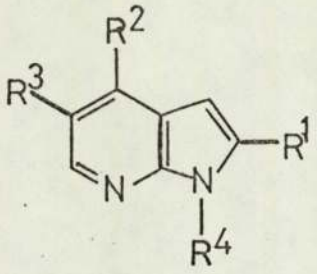

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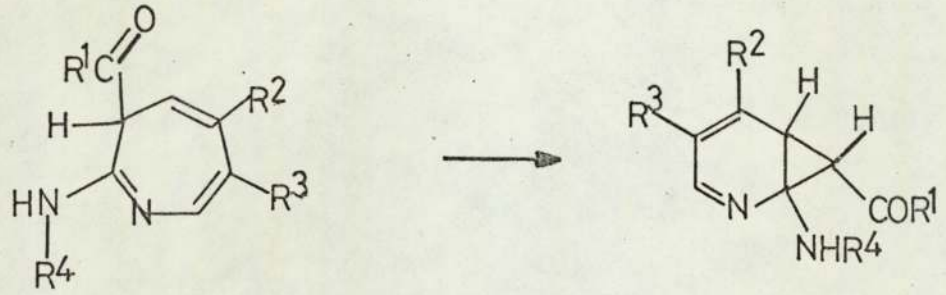

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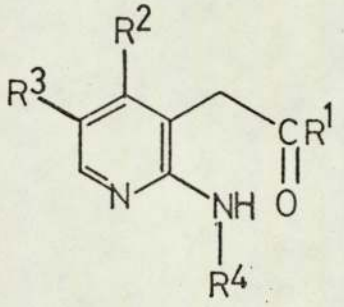
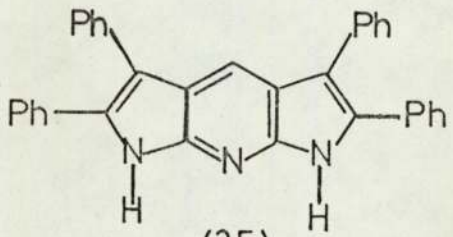


(34) (31)

lead to the novel dipyrrolopyridine system (35). The reaction did not proceed with hydroxyacetaldehyde but α-halogenoketones, which may be expected to give imidazo [1,2-a] pyridines by ring closure onto the pyridine ring nitrogen, gave a fairly good yield of pyrrolopyridine. In a two-step Bischler reaction 2,6-diaminopyridine and benzoin (2 moles) gave the tetraphenyl dipyrrolopyridine (35) (R=phenyl)



(35)

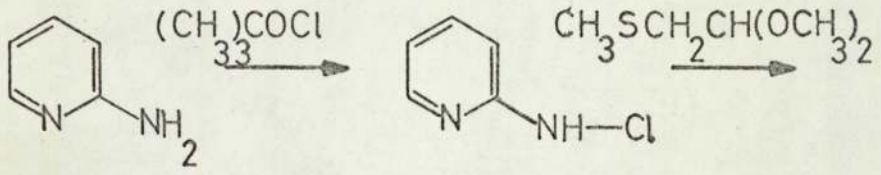
(c) Use Of β-Carbonyl Sulphides.

Following their work on the specific ortho-alkylation of heterocyclic amines Gassman et al.[60] derived a new method for the synthesis of indoles and pyrrolo [2,3-b] pyridines. The specific ortho-alkylation of 2-amino pyridine (36) with an alkyl side chain containing a masked β-carbonyl group leads to a condensation of that group with the 2-amino group. Despite the lengthy process a fairly good yield was obtained overall (see scheme 6).

(d) The Madelung Synthesis.

A further modification to the Madelung synthesis was made recently by Goméz-Revilla[61]. This route, although involving harsh cyclisation conditions, had been the best method for pyrrolo [2,3-b] pyridines[24] with alkyl and aryl substituents, but even then with the disadvantage that no 2-alkyl pyrrolopyridines may be made[58]. The parent

SCHEME 6



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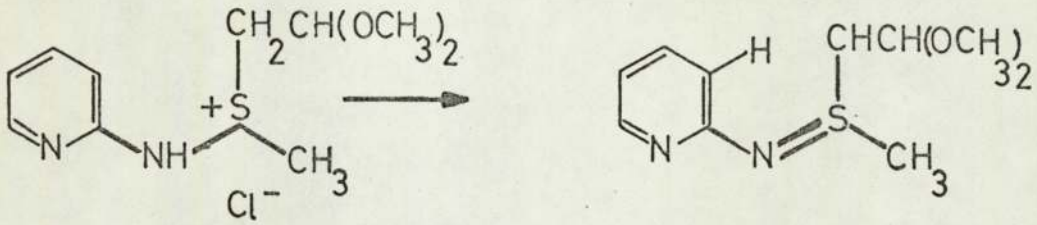

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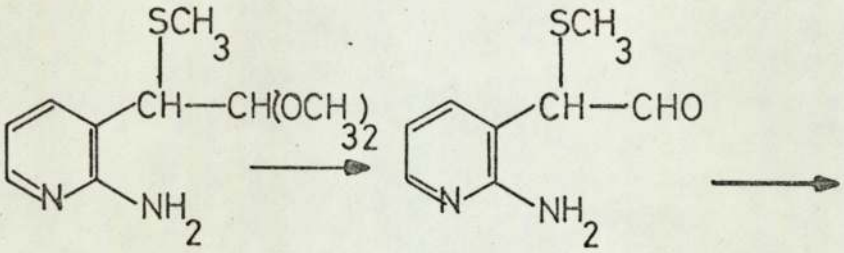

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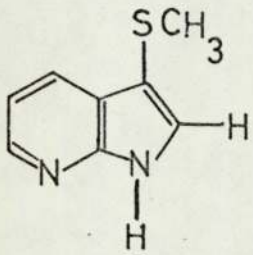
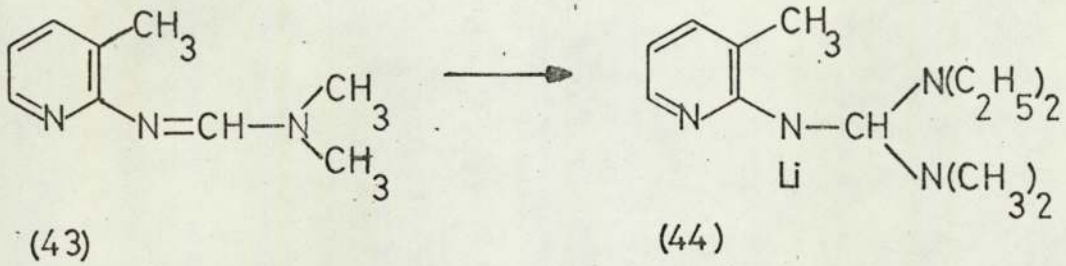


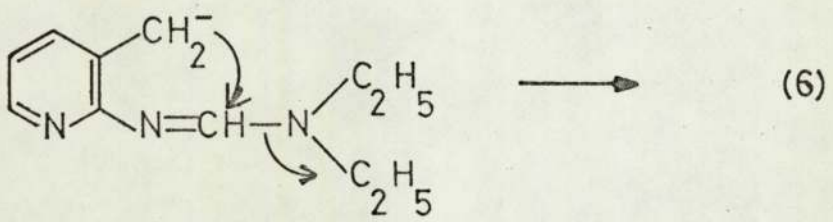
(42)

1H-pyrrolo[2,3-b]pyridine was made under mild basic conditions using lithium diethylamide, a stronger base, thus lowering the thermal contribution for proton abstraction from the 3-methylpyridine group (see scheme 7). The intra-molecular nucleophilic attack on the amidine intermediate would involve less steric hinderance than the N-methylaniline derivative and also there is no possibility of π-electron overlap along the CH:N(Me)·Ph linkage to provide an electronic barrier to carbanion attack. These new reaction conditions enabled some pyrrolopyridines to be prepared with a labile functional group at C-5 of the pyridine ring (46).

SCHEME 7



(43) (44)



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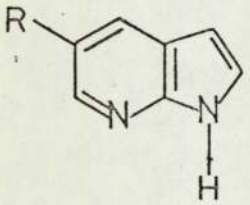
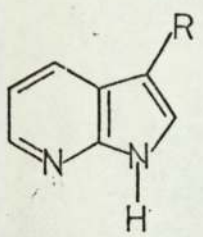


(46) R=Cl,OH

BIOLOGICAL ACTIVITY OF PYRROLO [2,3-b] PYRIDINES

The interest in pyrrolopyridines, stimulated by their potential use as an aza-analogue of indole derivatives led to the synthesis[62] of 1H-pyrrolo[2,3-b] pyridine-3-acetic (47), 1H-pyrrolo[2,3-b]pyridine-3-ethanamine (48) and α-amino-1H-pyrrolo[2,3-b]pyridine-3-propanoic acid (49). The latter derivative is more commonly named using the azaindole nomenclature and is called 7-azatryptophan. Its significant antimetabolite properties have been widely studied in Escherica coli[63], Bacillis subtilis[64], Pseudomonas acidovorans[65], Staphylococcus aureus[66], and also in the cell cultures of rat liver[67], carrots and tobacco[68].



(47) R=CH_2COOH

(48) R=$CH_2CH_2NH_2$

(49) R=$CH_2CH(NH_2)COOH$

The biosynthesis of 7-azatryptophan from 1H-pyrrolo [2,3-b]pyridine (6) and serine in phosphate buffer has been reported[69], however, the usefulness of 7-azatryptophan remains within the scope of the laboratory experiments. Reports of some biological data appear in the review by Willette[9], there have, however, been more recent publications. In a series of patents the sedative effects of 1H-pyrrolo[2,3-b]pyridine-3-amidoximes[70], 1H-pyrrolo[2,3-b] pyridine-3-alkylpiperazines[71], and 1-acyl-pyrrolo[2,3-b]pyridine-3-acetic acid derivatives[72] are described.

The sedative effect has been accompanied by various analgesic, antidepressive, anticonvulsive and hypotensive actions. Pyrrolopyridines have also been tested as anthelmintic[73], antimalarial[74] and antileukaemic[75] agents with limited success.

DISCUSSION

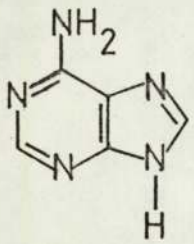
(A) Aims and Objectives

The aim of this work was directed at the synthesis of a 1H-pyrrolo[2,3-b]pyridine bearing a close structural resemblance to the purine bases adenine (50) and guanine (51) The working hypothesis for such a resemblance was that for potential antimetabolite activity the ring system should contain:-

(i) A nitrogen atom available for H-bonding at N-1 of purine.

(ii) A nitrogen atom bound to a sugar or false sugar moiety at N-9 of purine

(iii) A carbon-6 substituent capable of H-bonding with a pyrimidine base.



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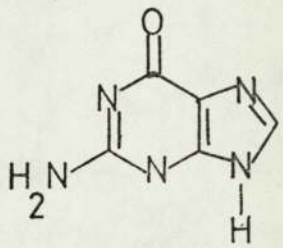


(51)

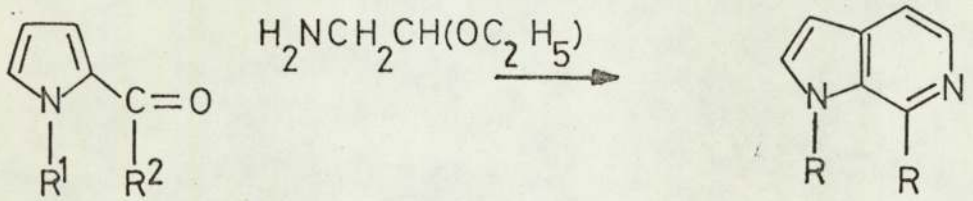
Two approaches to this objective were considered. Firstly the substitution of the parent 1H-pyrrolo[2,3-b]pyridine (6) and secondly the preparation of a substituted pyrrolopyridine from a suitably substituted starting material. The proven inertness[9,10] of the pyrrolopyridine ring system to electrophiles in all positions except C-3 of the pyrrole ring has precluded the synthesis of pyrrolopyridines with a functional group in the pyridine ring from the parent (6). No nucleophilic substitution of the parent molecule is known but 6-chloro-4-methylpyrrolo[2,3-b]pyridine has been converted to the 6-iodo-4-methylpyrrolo[2,3-b]pyridine under drastic conditions[76].

The fusion of a π-electron deficient and a π-electron excessive ring gives a pyrrolopyridine ring system in which there has been a redistribution of effective charges. The comparison between indole (4) and 1H-pyrrolo[2,3-b]pyridine (6) has been made by the theoretical calculation of electron density throughout the molecule using the simple Huckel-Molecular Orbital (HMO) treatment[77,78,79]. The results show that the C-3 pyrrole carbon is the preferential site for electrophilic attack in both indole and the pyrrolopyridines. The increased electron density of C-4 and C-6 by comparison with C-2 and C-4 of pyridine was expected to account for the difficulty in nucleophilic substitution [80].

The second approach is dependent on the availability of a suitably substituted starting material and the protection of labile functional groups during the lengthy and drastic procedures involved in the synthesis of pyrrolopyridines. The methods outlined in the introduction were examined critically and it was concluded that the pyrrolopyridine syntheses, based on the earlier indole preparations, were difficult and unwieldy for the type of synthetic work envisaged. Despite the drawbacks of this approach it was considered to be a better prospect than the direct substitution of the parent heterocycle.

The conventional methods of synthesis of 1H-pyrrolo[2,3-b]pyridines discussed in the introduction have all started from an available pyridine precursor and build on the pyrrole ring. These methods have been the subject of modifications in the past so a new alternative to the problem was seen in a novel synthetic route to the pyrrolo[2,3-b]pyridines which used a pyrrole precursor in the preparation of the ring system.

The use of a pyrrole starting material, although novel to the 1H-pyrrolo 2,3-b pyridine, has had limited success in the past for the synthesis for 1H-pyrrolo[2,3-c]pyridines (53), 1H-pyrrolo[3,2-b]pyridines (55) and 1H-pyrrolo[3,2-c]pyridines (57) when 2-acylpyrroles (52)[81,82], 3-amino-pyrroles (54)[83] and cis-3-(pyrrol-2-yl)acrylic acid (56)[84] were used.



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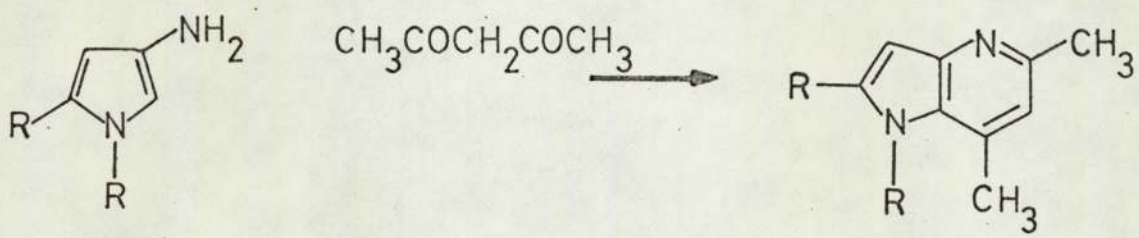

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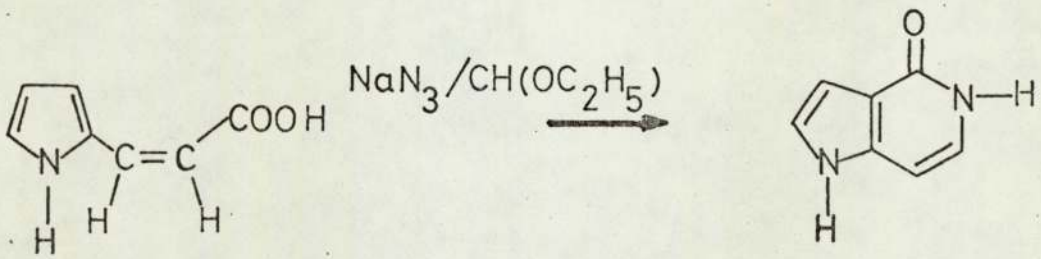
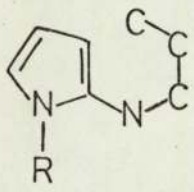
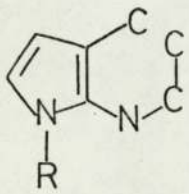


(56) (57)

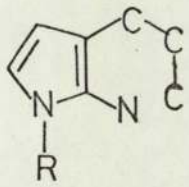
The fusion of a pyridine ring onto a pyrrole precurser was considered to be an attractive prospect in pyrrolo[2,3-b] pyridines since an essential step in any such route must be the electrophilic attack on C-3 of the pyrrole ring, a reaction expected to be enhanced by the π-excessive character of pyrrole. Starting from suitably substituted pyrroles the most common skeletons from which a pyrrolo[2,3-b]pyridine may be theoretically derived are:-



Type 1



Type 2



Type 3

Several fused pyridine heterocycles have been prepared, based on the earlier quinoline syntheses, and modifications to these methods were hoped to provide the new route to pyrrolo[2,3-b]pyridines from a pyrrole starting material.

Ring-closure reactions of Type 1 will require an amino-pyrrole with a free C-3 position and preferably a blocking group on the nitrogen if formation of a pyrrolo[1,2-a] pyrimidine is to be avoided. The analagous quinoline syntheses are the Skraup Synthesis, the Doebner-von Miller Synthesis, the Combes Synthesis, the Knorr Synthesis and Conrad-Limpach Synthesis[85]. Reactions of Type 2 require a pyrrole starting material with a carbon substituent in position C-3 of the nucleus. The common functional groups in the analagous Friedlander and Niementowski Quinoline Syntheses are aldehydes, ketones, carboxylic acids and their esters. The presence of a blocking group at the

pyrrole nitrogen atom may be required to prevent pyrrolo[1,2-a] imidazole formation in this type of reaction. Examples of the Type 3 ring-closure are few and comparatively unimportant in the quinoline series, and are limited to the intramolecular reductive cyclisation of ortho-nitrocinnamic acids and their esters.

(B) The Available Pyrrole Starting Materials

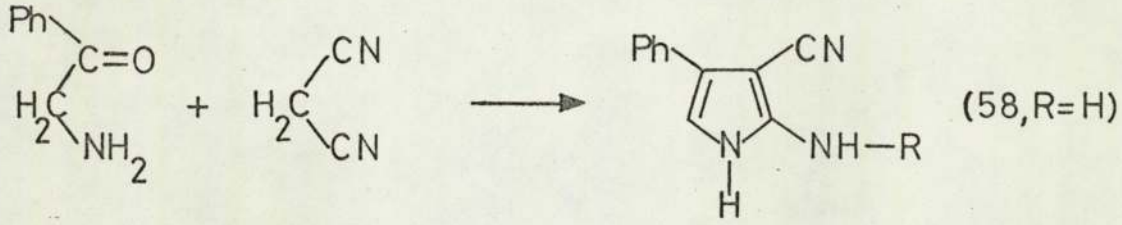
Very few simple 2-aminopyrroles are known and they are generally unstable compounds, however, an electron withdrawing substituent does confer some stability. The known 2-aminopyrroles have been prepared from 2-nitro- or 2-nitrosopyrroles by catalytic reduction[86,87] and from 5-pyrrole-carboxylic acid azides[88]. A convenient synthesis of 2-nitropyrrole has been reported[89] but 2-aminopyrrole itself is unknown, 2-aminopyrroles bearing a 3-cyano- [90,91] and 3-methoxycarbonyl- [92,93] substituents are available for a Type 2 ring-closure and the preliminary investigation began with these readily prepared pyrroles.

(C) Attempted Preparation of Pyrrolopyridines by a Type 2 Ring-Closure

(I) From 2-amino-3-cyano-4-phenylpyrrole

The one-step synthesis of an aminopyrrole from an ω-aminoketone and malononitrile under basic conditions yields a solid aminopyrrole which rapidly deteriorates in air. This reaction was repeated using ω-aminoacetophenone to yield 2-amino-3-cyano-4-phenylpyrrole (58).

Attempts to extend this reaction[94], which proceeds smoothly in ethanolic sodium hydroxide, were limited to the preparation of 2-amino-3,4-diphenylpyrrole from benzyl cyanide and ω-aminoacetophenone. The aminopyrrole (58) was prepared and acylated by an appropriate acyl chloride or acyl anhydride to give the stable derivatives (59)-(62). It was hoped to use the aminopyrrole (58) or an acyl derivative in a Type 2 ring-closure based on the known cyclisation of ortho-acylaminonitriles in the benzene and cyclohexene systems[95].

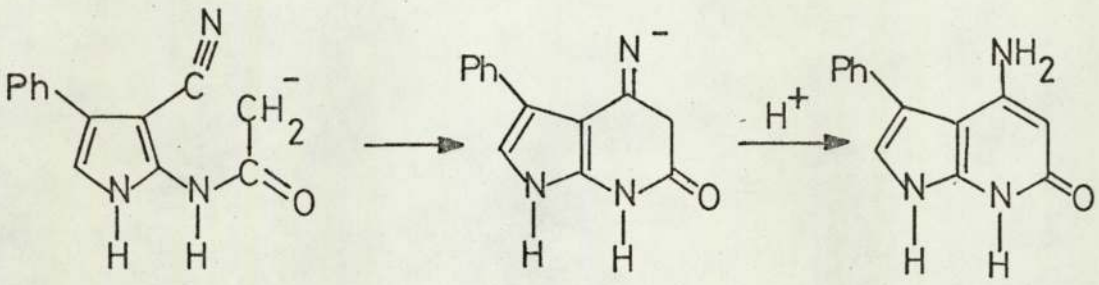


(58, R=H)

(59) R = $COCH_3$ (60) R = $COCH_2Ph$

(61) R = $COCH_2Cl$ (62) R = $COCH_2CH_3$

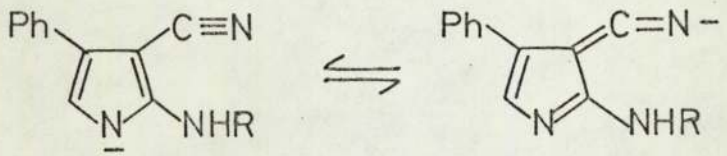
The reaction was expected to take the form of a base catalysed nucleophilic attack by a carbanion on the carbon centre of the 3-cyano- group.



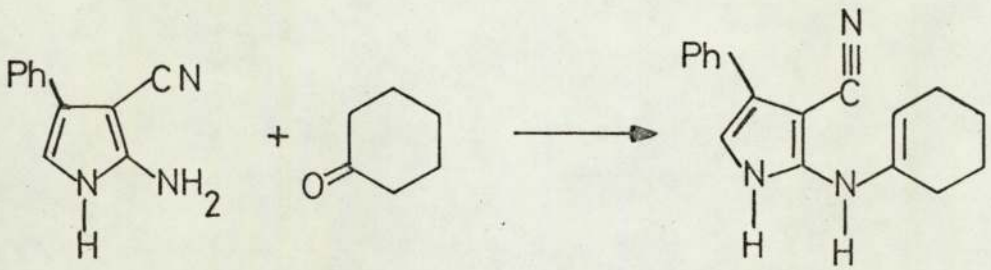
(63) (64)

The reaction was unsuccessful with the use of pyridine, sodium methoxide, sodamide in liquid paraffin and sodium in liquid ammonia. The starting material was recovered

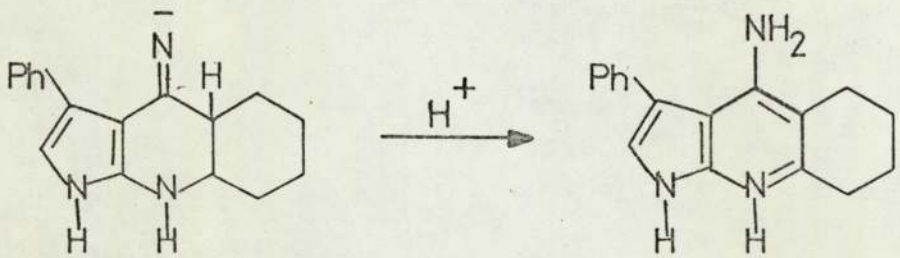
intact from each reaction indicating that the initial high energy step of carbanion formation did not occur. Under basic conditions the pyrrolyl anion was anticipated to form preferentially. This anion can delocalise in the manner shown and contribute to the stability of the nitrile.



Several workers[96,97,98,99] have prepared fused pyridine ring systems by reacting an ortho-aminonitrile with a cyclic ketone such as cyclohexanone or cyclopentanone. Attempts to utilise this reaction for a pyrrolopyridine synthesis however, failed using similar conditions. The reaction presumably would have proceeded by a Schiffs-base formation followed by a Lewis-acid catalysed intra-molecular cyclisation of the enaminonitrile (65).



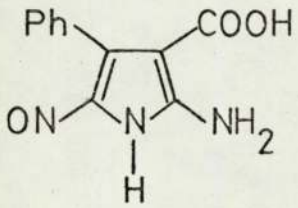
(65)



(66) (67)

The failure of the reaction to provide the 4-aminopyrrolopyridine (67) was attributed to the lack of reactivity of the nitrile group. Evidence of enamine formation was found by heating equimolar quantities of cyclohexanone and the aminopyrrole (58) in benzene under Dean-Stark conditions. Water formation was observed but the solution darkened considerably, due to the instability of the aminopyrrole, and the enamine was not isolated.

Hydrolysis of the 3-cyanopyrrole (59) to the corresponding pyrrole-3-carboxylic acid was attempted. The reasoning for this was based on the known Friedlander and Niementowski reactions and the expected easier condensation of a reactive methylene group with a pyrrole-3-carboxylic acid or ester. The nitrile (59) proved very stable to hydrolysis and the amide was formed only under strong acid conditions. The nitriles (59) and (62) were hydrolysed with concentrated sulphuric acid at room temperature after 2 hours. An excess of sodium nitrite solution was then added to an ice cooled solution of the amides and the reaction worked up in the method used by Bouveault[100]. The products of these reactions were identical and shown to be a 5-nitrosopyrrole (68).



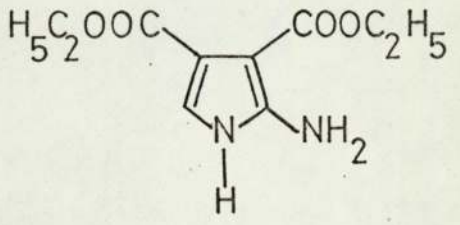
(68)

The infra-red spectra showed the usual carboxylic acid characteristics, (C=O) absorption at 1730 cm^{-1} and (OH) broad

absorption at 3400 cm^{-1}. The Liebermans nitrosamine test was found to be negative indicating a 2-nitrosaminopyrrole had not been formed. Mass spectral and microanalytical data indicated the product had a molecular weight of 231 and the molecular formula $C_{11}H_9N_3O_3$. The 5-H pyrrole proton was not observed in the nuclear magnetic spectrum. Formation of the nitrosopyrrole (68) was presumably due to the high susceptibility of the pyrrole nucleus to electrophilic substitution.

(II) From 2-amino-3-ethoxycarbonylpyrroles

Dialkyl 2-aminopyrrole-3,4-dicarboxylates have been prepared recently in good yields[92,93] and the method of Gewald[93] was used to provide the diethyl 2-aminopyrrole-3,4-dicarboxylate (69).



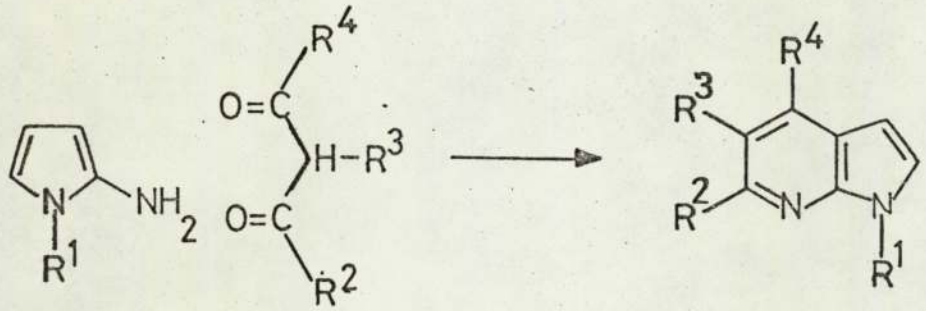
(69)

Several attempts to convert the aminopyrrole (69) to a pyrrolopyridine under basic conditions with reagents containing an active methylene group failed and the starting material was recovered. The preparation of some 1,8-naphthyridines under similar conditions was found to be difficult[101] with very reactive methylene compounds such as diethyl malonate. In this case the recovery of the starting material was attributed to the delocalisation of charge in the pyrrolyl anion.

There was no evidence of hydrolysis of the pyrrole diester or reaction between the 2-amino- group and the carbonyl site of the reactive methylene compound.

(D) Preparation of Pyrrolopyridines by a Type 1 Ring-Closure

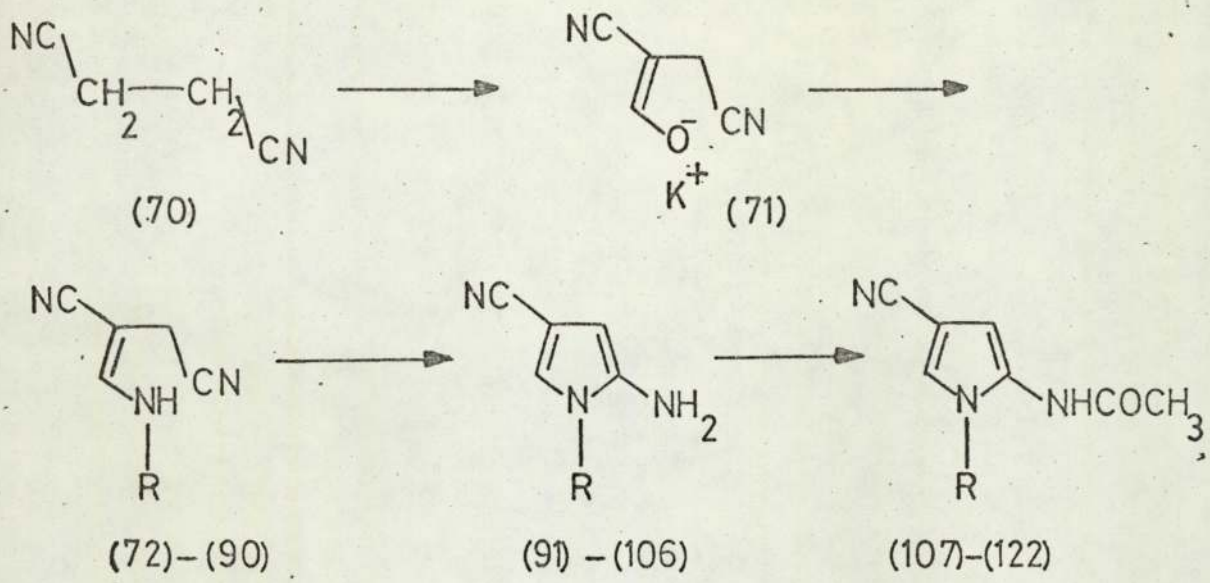
The preparation of pyrrolopyridines from an aminopyrrole and a reagent providing three carbon atoms for completion of a pyridine ring in a Type 1 ring-closure was envisaged. The general route shown in scheme 8 was based on the analagous syntheses in the quinoline series. A suitable starting material should have a blocking group on the pyrrole nitrogen to prevent the known pyrrolo[1,2-a] pyrimidine formation by 2-aminopyrroles and 1,3-dicarbonyl reagents[102].



SCHEME 8

The route to 2-amino-4-cyanopyrroles reported by Grob and Ankli[103,104] in 1950 was adapted and extended to give a variety of N-substituted 2-amino-4-cyanopyrroles which were considered to be good prospective starting materials. The preparation of the aminopyrroles (see scheme 9) involved a 3-step reaction in which succinonitrile (70) was condensed with ethyl formate in the presence of potassium tert.-pentoxide. The potassioformyl derivative thus

SCHEME 9



(72), (91), (107) R = cyclohexyl-

(73), (92), (108) R = phenyl-

(74), (93), (109) R = benzyl-

(75), (94), (110) R = phenethyl-

(76), (95), (111) R = o-tolyl-

(77), (96), (112) R = m-tolyl-

(78), (97), (113) R = p-tolyl-

(79), (98), (114) R = o-methoxyphenyl-

(80), (99), (115) R = m-methoxyphenyl-

(81), (100), (116) R = p-methoxyphenyl-

(82), (101), (117) R = o-chlorophenyl-

(83), (102), (118) R = m-chlorophenyl-

(84), (103), (119) R = p-chlorophenyl-

(85), (104), (120) R = m-nitrophenyl-

(86), (105), (121) R = p-nitrophenyl-

(87), (106), (122) R = p-ethoxycarbonylphenyl-

(88) R = o-methoxycarbonylphenyl-

(89) R = o-acetophenyl-

(90) R = o-hydroxyphenyl-

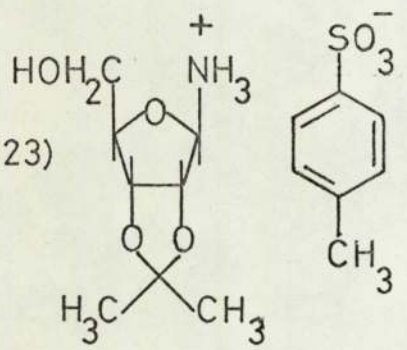
formed was reacted with a primary amine to yield an aminomethylenesuccinonitrile (72)-(90). The aminomethylene-succinonitriles were readily cyclised to the corresponding aminopyrroles (91)-(106) in ethanolic potassium ethoxide or triethylamine. As the aminopyrroles had the same molecular formula and, therefore, the same analytical values as the aminomethylenesuccinonitriles the amines were further characterised by the preparation of their acetyl derivatives (107)-(122). The aminopyrroles (91)-(106) were ultimately used in the successful preparation of pyrrolopyridines from a variety of cyclising reagents (see section E).

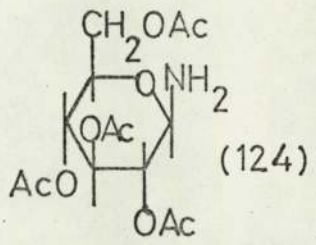
(I) Preparation of aminomethylenesuccinonitriles (72)-(90)

The potassioformyl derivative of succinonitrile (71) was prepared by the method of Grob and Ankli[103] with only minor modifications. The salt was then caused to react with various primary amines to investigate the scope of the reaction in terms of chemical reactivity and with the long term view to provide a wide range of compounds for biological testing. The aminomethylenesuccinonitriles were prepared in good yields from cyclohexylamine, benzylamine, 2-phenyl-ethylamine, and variously substituted anilines. There was no obvious differences in the yields despite the wide variation in pK_a values of the amines used (range 1.02-10.64). However, ortho-nitroaniline (pK_a -0.3) failed to provide the desired product and was recovered from the reaction mixture. No aminomethylenesuccinonitriles were obtained when 2-hydroxyethylamine, urethane, hydrazines, amides or aminopyridines were used. Attempts to prepare ribosyl or glucosyl derivatives by reaction of the amino sugars and the potassioformyl derivative of succinonitrile (71) also failed.

The protected derivatives (123) and (124) did not afford the required aminomethlenesuccinonitriles either. This failure was attributed to the lack of strong nucleophilic character in the amino sugars and the stabilisation of the salt (123) in acid solution.

(123)



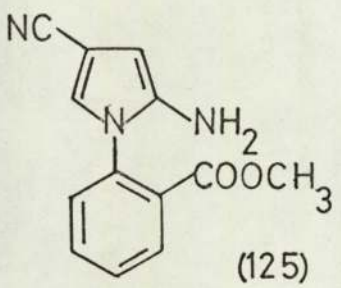


(124)

The free base of the salt (123) was prepared by the method of Shaw et al.[105] but the amine still failed to react under the conditions found successful for the other aminomethylenesuccinonitriles. Despite the failure to prepare a ribosylamino or glucosylamino derivative the successful preparation of a benzylamino derivative was interesting due to the possibility of debenzylation at a later stage. The infra-red spectra of the aminomethylenesuccinonitriles showed two nitrile absorptions in the range 2150-2300 cm^{-1} but the peak at the higher wavenumber was of much lower intensity. The nuclear magnetic resonance spectra in deuteriochloroform were characterised by the typical vinyl proton (ca τ3.2) and the coupling with the adjacent proton of the amino group (-NH-CH=). This coupling gave rise to a doublet with a large coupling constant of 8-12 Hz which on addition of deuterium oxide collapsed to a singlet.

(II) Preparation of 2-amino-4-cyanopyrroles and their acetyl derivatives

The cyclisation of the aminomethylenesuccinonitriles proceeded smoothly in ethanolic potassium ethoxide to give excellent yields of the corresponding 2-amino-4-cyanopyrroles The nitroanilinomethylenesuccinonitriles (85) and (86), however, gave a deep brown solution with potassium ethoxide solution but were cyclised in a satisfactory manner on treatment with triethylamine under reflux for three hours. The two ortho-substituted derivatives (88) and (89) when treated with potassium ethoxide yielded the pyrrolo[1,2-a] quinazolines (127) and (128) presumably via the aminopyrroles (125) and (126) which were not isolated. The cyclisation of ortho-chlorophenylaminomethylenesuccinonitrile (82) in potassium ethoxide gave the 2-aminopyrrole (101) and did not proceed further to yield a pyrrolobenzimidazole (129) as may have been expected.



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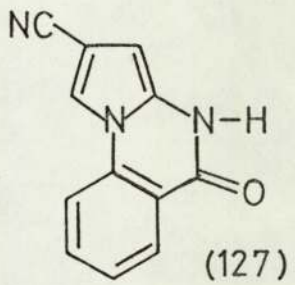

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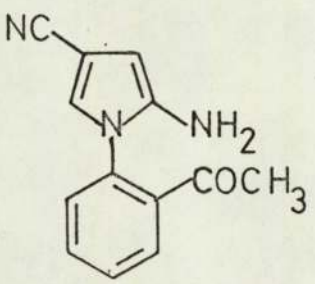
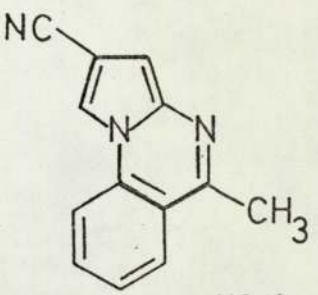
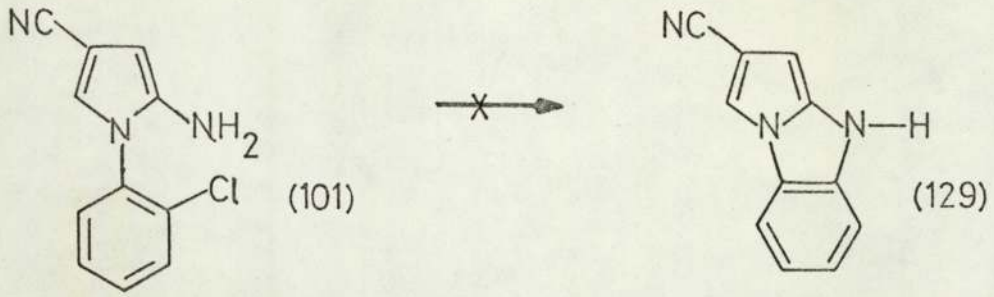


(126)

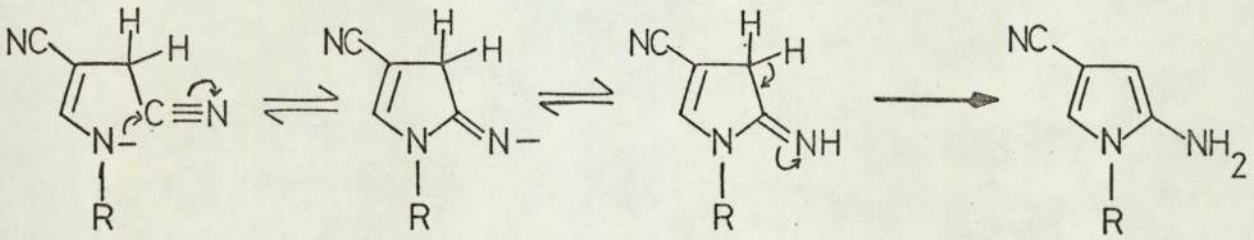


(128)



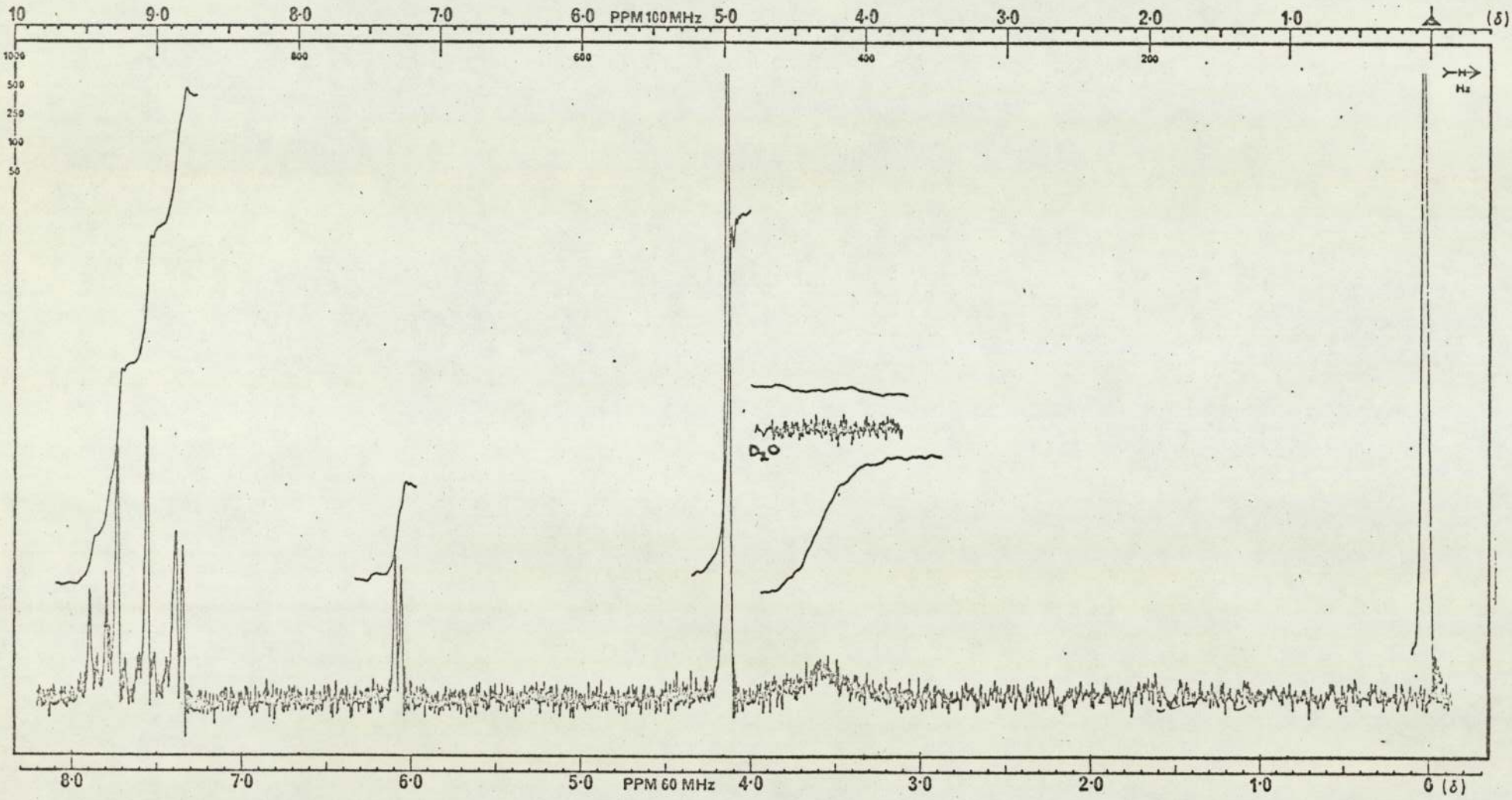
The mechanism of the cyclisation shown in scheme 10 involves the production of the anion of the aminomethylenesuccinonitrile followed by an intramolecular nucleophilic attack on the acetonitrile part of the molecule. The reaction is similar to the Thorpe-Ziegler cyclisation of ortho-aminonitriles[106].

SCHEME 10



The aminopyrroles are true aromatic amines and not imino tautomers, primary amine stretching vibrations are observed in the infra-red spectra in the range 3150-3500 cm^{-1}. The nuclear magnetic resonance spectra also show the typical broad amine peaks at τ5.8-6.8 which integrate for two protons. The 3-H and 5-H protons of the pyrrole nucleus are observed in the aromatic region and show long-range coupling of 2Hz in common with other 2,4 disubstituted pyrroles[107] (J_{2-4}=1.95-2.20 Hz). The lower signal in the spectrum for the 5-H is attributed to the deshielding effect of the adjacent ring nitrogen. The interaction of an aryl substituent on the ring nitrogen is essentially an inductive

^{1}H n.m.r. of 2-amino-4-cyano-1-(p-methoxyphenyl)-pyrrole (100)



effect with no appreciable variation of the ring-current[108] thus the 5-H signal (τ 2.8-3.2) which is lower than in pyrrole (τ 3.32) remains relatively unaltered with the change of aryl substituent. The shielding effect of the ortho-amino group and the lesser deshielding effect of the ortho-cyano group on the 3-H proton gives rise to a signal at τ3.95-4.35 (cf pyrrole 3-H at τ3.78)[107]. The nuclear magnetic resonance spectrum of 2-amino-4-cyano-1-(p-methoxyphenyl) pyrrole (100) is shown on page 35 and is typical of these aminopyrroles.

The long-range coupling of 2,4-disubstituted pyrroles is also present in the 2-acetamido-4-cyanopyrroles which are readily prepared by heating the aminopyrrole in acetic anhydride for several minutes. The acetamidopyrroles are more stable in air and have a higher melting point than the corresponding aminopyrrole. The infra-red spectra of the acetamidopyrroles have a single peak at 3300 cm^{-1} for an amide (NH) stretching vibration, and a carbonyl absorption at 1640-1660 cm^{-1}.

Attempts to reduce the 2-acetamidopyrroles to 2-ethyl aminopyrroles with lithium aluminium hydride or sodium borohydride were not successful, the amides were recovered intact.

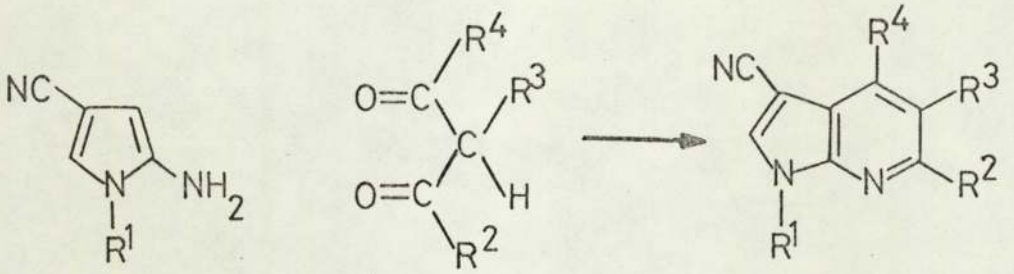
(E) Preparation of Pyrrolopyridines from 2-Amino-4-cyano-pyrroles

Although the Skraup reaction is of universal applicability to the synthesis of quinolines and is useful in the synthesis of other fused pyridine heterocycles this method was not considered here due to the instability of pyrroles in strong acid conditions. However the related Combes synthesis involving a β-diketone, was considered to be a more moderate variation of the type 1 syntheses. The general route is shown in scheme 11.

(I) Preparation of pyrrolopyridines from β-diketones

The aminopyrroles (91)-(106) were each caused to react with pentane-2,4-dione (130) to yield the pyrrolopyridines (136)-(150). These pyrrolopyridines were prepared for biological testing and hence to evaluate the most suitable N-substituent if any. The aminopyrroles (92) and (102) were also reacted with 1-phenylbutan-1,3-dione (131) which afforded the 4-phenylpyrrolopyridines (151) and (152) respectively. A mixture resulted from the reaction of 2-amino-4-cyano-1-cyclohexylpyrrole (91) and 1-phenylbutan-1,3-dione. In a single case the aminopyrrole (91) was reacted with dibenzoylmethane (132) and this yielded the diphenylpyrrolopyridine (153). The reactions involving the symmetrical diketones pentane-2,4-dione (130) and dibenzoylmethane obviously give rise to the symmetrical product and no proof for the orientation of the reaction is neccessary. In the case of 1-phenylbutan-1,3-dione the orientation of the reaction can vary to give two possible products, a 4-methyl-6-phenylpyrrolopyridine or a 4-phenyl

SCHEME 11



(91)-(106) (130) $R^2 = R^4 = Me$, $R^3 = H$; (136)-(150)

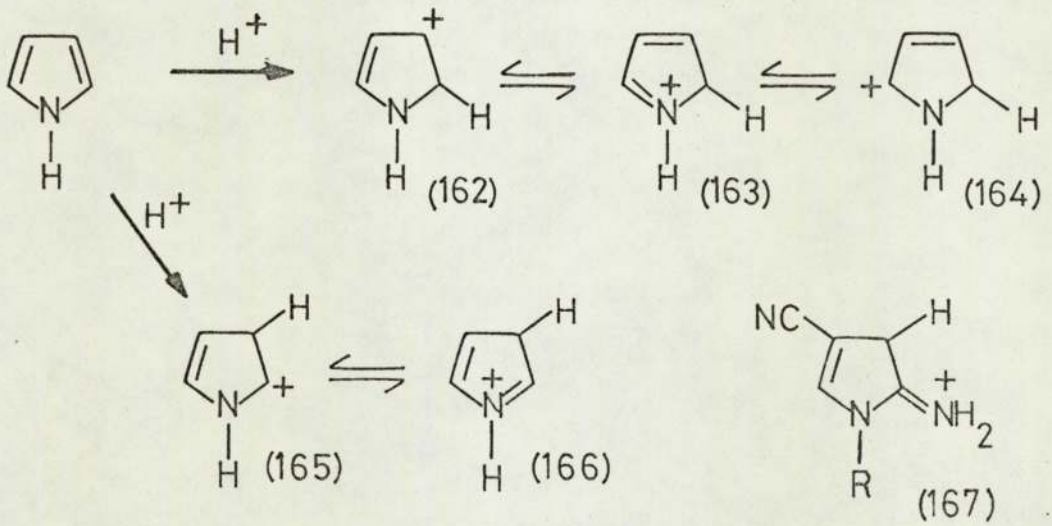
(92),(102) (131) $R^2 = Me$, $R^3 = H$, $R^4 = Ph$; (151),(152)

(91) (132) $R^2 = R^4 = Ph$, $R^3 = H$; (153)

(91),(92), (102) (133) $R^2 = Me$, $R^3 = H$, $R^4 = H$; (154)-(156)

(91),(92), (102),(103) (134) $R^2 = R^3 = R^4 = H$; (157)-(160)

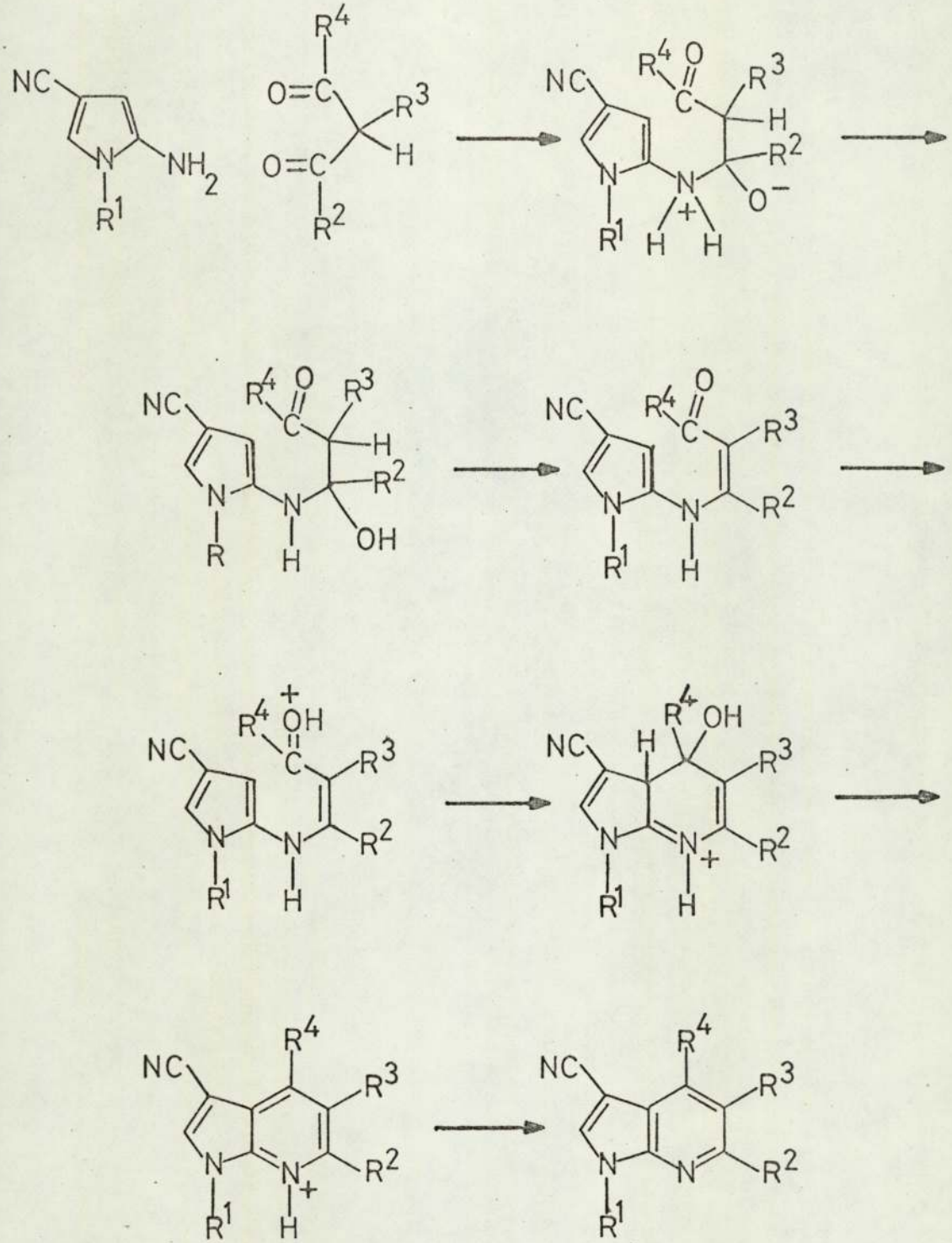
(91) (135) $R^2 = R^4 = NO_2$, $R^3 = H$; (161)



Resonance hybrids of pyrrole

6-methylpyrrolopyridine. The structural proof for the latter orientation was found by comparison of nuclear magnetic resonance spectra. It is not obvious, at first, which carbonyl attacks the pyrrole nucleus and which carbonyl group is attacked by the exocyclic amino group. In the quinoline series the intermediate anil formation is proved by the isolation of that intermediate. In these reactions no intermediates are isolated but a similar reaction mechanism is postulated (see scheme 12). The more difficult and, therefore, the rate determining step will be the electrophilic attack of the pyrrole nucleus. The initial attack, in common with the quinolines[85], naphthyridines[109] and pyrido[2,3-d]pyrimidines[110], will be the nucleophilic attack by the exocyclic amine on the more reactive carbonyl group in the case of unsymmetrical diketones. The lack of intermediate formation is not surprising in view of the ready reaction between pyrroles and electrophiles which is rationalised in terms of the resonance hybrids (162)-(166). The site of preferential attack in pyrrole is the C-2 position, however, in the 2-aminopyrroles attack at the C-3 position is enhanced by the contribution from an extra resonance hybrid (167). The electrophilic attack at C-3 in the 2-amino-4-cyano-1-substituted pyrroles is of course further explained by the initial attack on the carbonyl compound by the exocyclic 2-amino group thus "holding" the side chain in position for the electrophilic attack. Steric hinderance of the C-5 position in these pyrroles by the bulky N-substituents might prevent C-5 substitution if electrophilic attck was the only consideration.

SCHEME 12



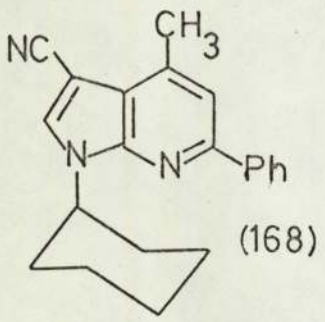
Because of the unambiguous products formed by pentane-2,4-dione , and the desire to produce a wide range of N-substituted pyrrolopyridines for biological testing, these reactions were investigated first. The pyrrolopyridines (136)-(150) were prepared in good yields and the type of N-substituent (R) had no obvious effect on the yields which were in the range 50-80%.

The infra-red spectra of the pyrrolopyridines (136)-(150) showed the nitrile absorption (CN) at 2225-2250 cm^{-1} and other peaks characteristic of the substituent group (R). The detailed infra-red absorptions for individual compounds are listed in the experimental section.

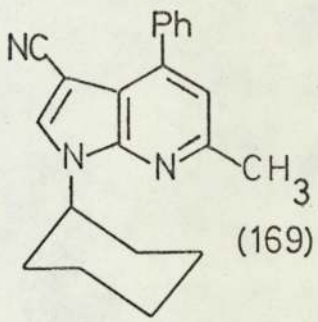
The nuclear magnetic resonance spectra showed the aromatic pyrrolopyridine protons at τ3.15 and τ2.35 (±0.2) the upfield signal was assigned to the proton at C-5 in the pyridine ring and the lower signal to the deshielded C-2 position in the pyrrole ring. The methyl groups were observed at τ7.35 and τ7.45 (±0.2), the lower signal was assigned to the 6-methyl group due to the deshielding effect of the adjacent ring nitrogen atom.

With the unsymmetrical diketone 1-phenylbutan-1,3-dione the orientation of the reaction is controlled by the more reactive carbonyl group. The acetyl group was expected to react with the exocyclic 2-amino group to yield 6-methyl-4-phenylpyrrolopyridines by a mechanism shown in scheme 12 (R^2=Me, R^4=Ph). This was found to be the case for the reaction between the aminopyrroles (92) and (102) with 1-phenylbutan-1,3-dione. The chemical shift for the 6-Me group was observed at τ7.35.

The reaction between 2-amino-4-cyano-1-cyclohexylpyrrole (91) and 1-phenylbutan-1,3-dione gave a mixture of products. The mixture had a sharp melting point and satisfactory analytical values but ^{1}H nuclear magnetic resonance and ^{13}C nuclear magnetic resonance spectra showed the products were the isomeric pyrrolopyridines (168) and (169) in a 40:60 ratio.



(168)



(169)

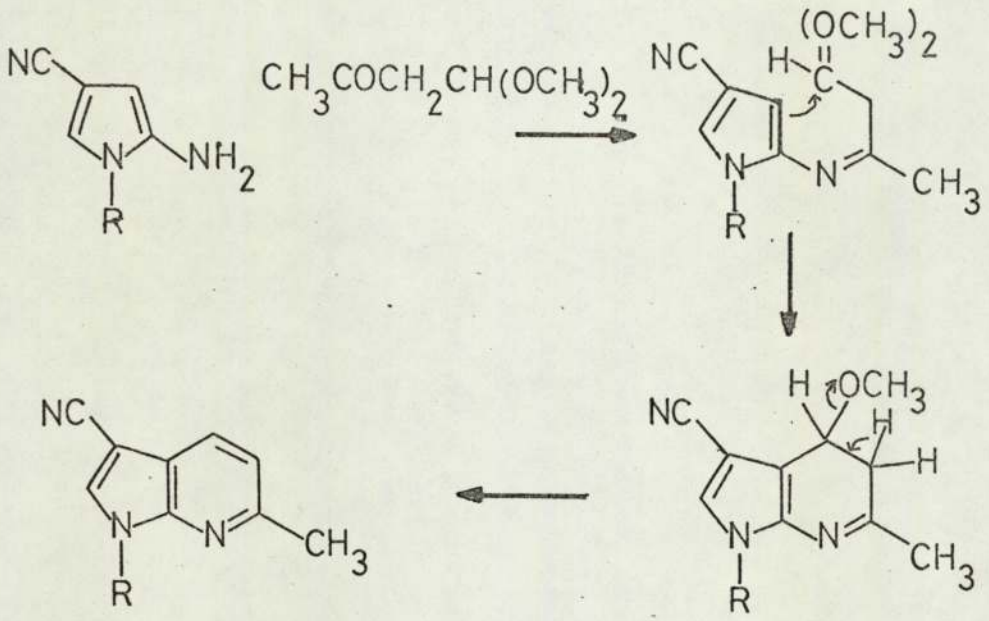
Formation of the isomer (168) in 40% of the total yield raised the possibility of an alternative mechanism competing with the normal one (scheme 12; R^1=cyclohexyl, R^2=Me, R^3=H, R^4=Ph). In other fused pyridine systems[8,108] the 4-phenyl-6-methylpyridine orientation is preferred, with the rate determining step being the Friedl-Crafts acylation of the nucleus by the less reactive benzoyl group. The formation of isomer (168) may be due to this acylation procedure occuring at the pyrrole nucleus under more favourable conditions. The electron donor property of the C-3 position was expected to be enhanced by the inductive effect of the cyclohexyl group.

(II) Preparation of pyrrolopyridines from β-ketoaldehydes

The ketoaldehyde (133) (as the bis-methyl acetal) is an unsymmetrical reagent and can give rise to two possible products, a 4-methylpyrrolopyridine or a 6-methylpyrrolopyridine. Only one isomer was isolated in the reactions with this reagent and these were shown to be the 6-methyl-

pyrrolopyridines (154)-(156). The reaction proceeds presumably via attack of the acetyl group by the exocyclic 2-amino group. This initial anil formation must occur before the bis-methyl acetal is hydrolysed to a formyl group in the acid medium or this would react preferentially with the amine. Hydrolysis of the acetal group to the aldehyde is not essential to the cyclisation and a mechanism is shown in scheme 13 in which cyclisation occurs by elimination of methanol.

SCHEME 13



The formation of 6-methylpyrrolopyridines is consistent with the orientation found in similar reactions involving quinoline[85], naphthyridine[108] and pyrido[2,3-d]pyrimidine[109] syntheses. Structural proof was obtained from ^{1}H nuclear magnetic resonance and ^{13}C nuclear magnetic resonance spectra. The ^{1}H n.m.r. spectra showed a coupling constant of 8 Hz for the doublets arising from the 4-H and 5-H protons. A similar coupling constant is observed in 2,6-lutidine for the J_{3-4} value. The chemical shift of the 6-methyl group

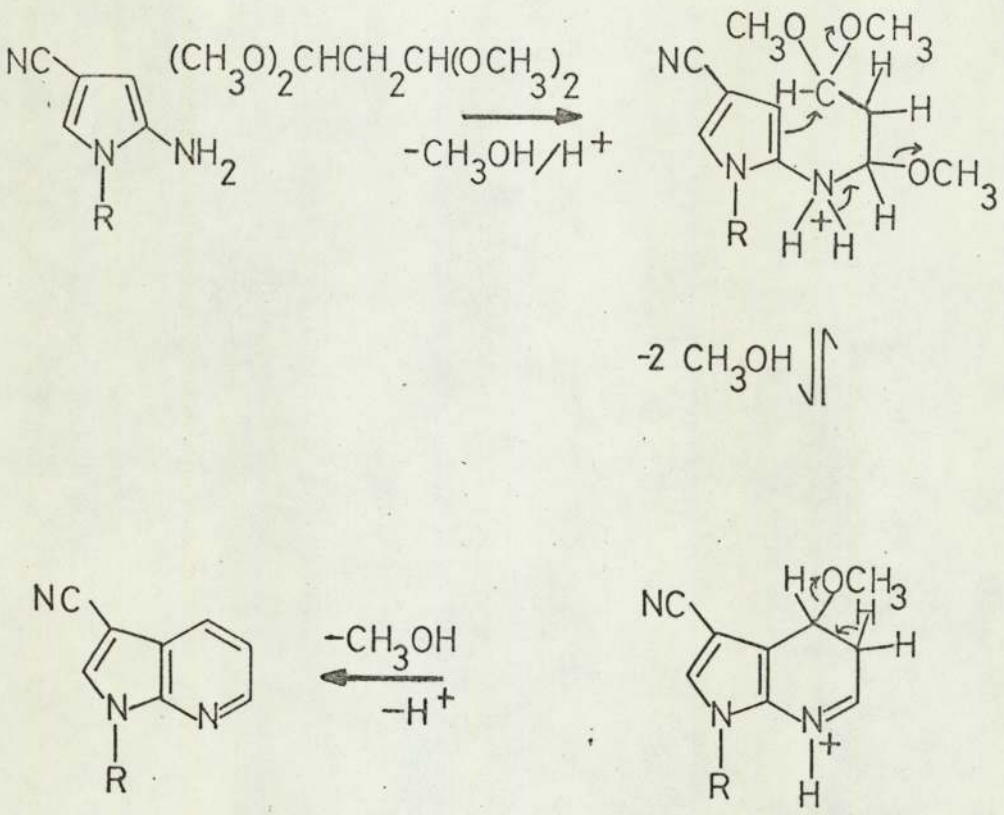
at τ7.35 was similar to that found for the 6-methyl group of 4,6-dimethylpyrrolopyridines prepared earlier. Further evidence was deduced from ^{13}C n.m.r. spectroscopy (see section G).

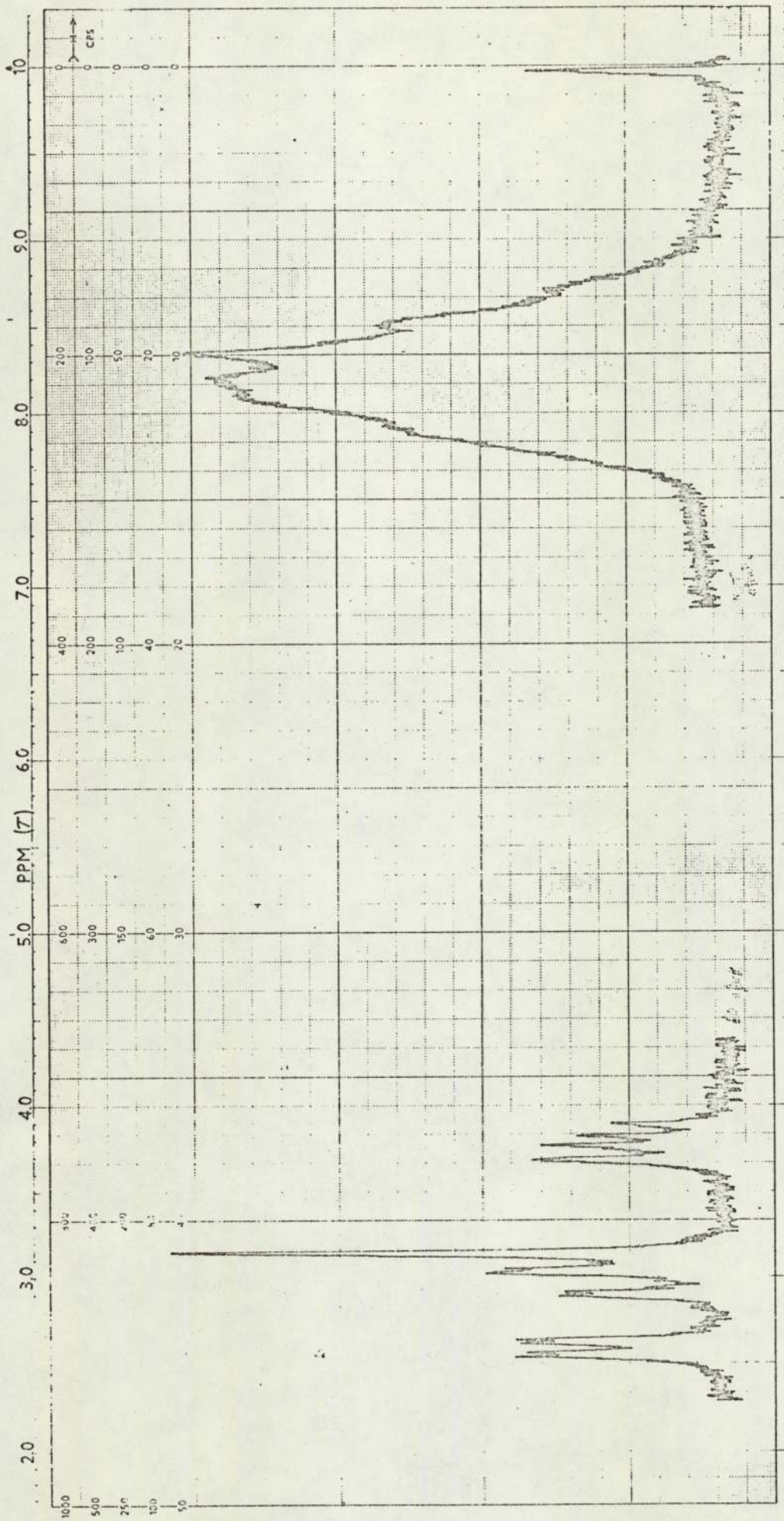
(III) Preparation of pyrrolopyridines from dialdehydes

In reactions closely related to the Combes-like syntheses of pyrrolopyridines [sections E (I) and E (II)] the aminopyrroles (91), (92), (102) and (103) were reacted with 1,1,3,3-tetramethoxypropane (134) to yield the pyrrolopyridines (157)-(160). The sodio derivative of nitromalondialdehyde (135) was reacted with the aminopyrrole (91) to yield the 5-nitropyrrolopyridine (161). These reagents are symmetrical and present no problem for structural proof of the products. The lack of any intermediate formation or bis-anil formation as found in similar reactions in the pyrido[3,2-d]pyrimidines[111] was further confirmation of the ease of electrophilic substitution in pyrroles. Despite the lack of any experimental evidence concerning the mechanism of these reactions it is proposed that the pathway is similar to the previous ones involving dicarbonyl reagents. The proposed mechanism for the reaction involving 1,1,3,3-tetramethoxypropane is shown in scheme 14, and assumes the reaction takes place without hydrolysis of the acetal groups. This may account for the longer reaction time for these compounds than the analagous diketone syntheses.

The dialdehyde reagents give good yields of the pyrrolopyridines (157)-(160) which are unsubstituted in the pyridine ring. The ^{1}H n.m.r. spectra of these compounds have the classical ABX system of three coupling nuclei typical of a 2,3-disubstituted pyridine[112]. The n.m.r. spectra of

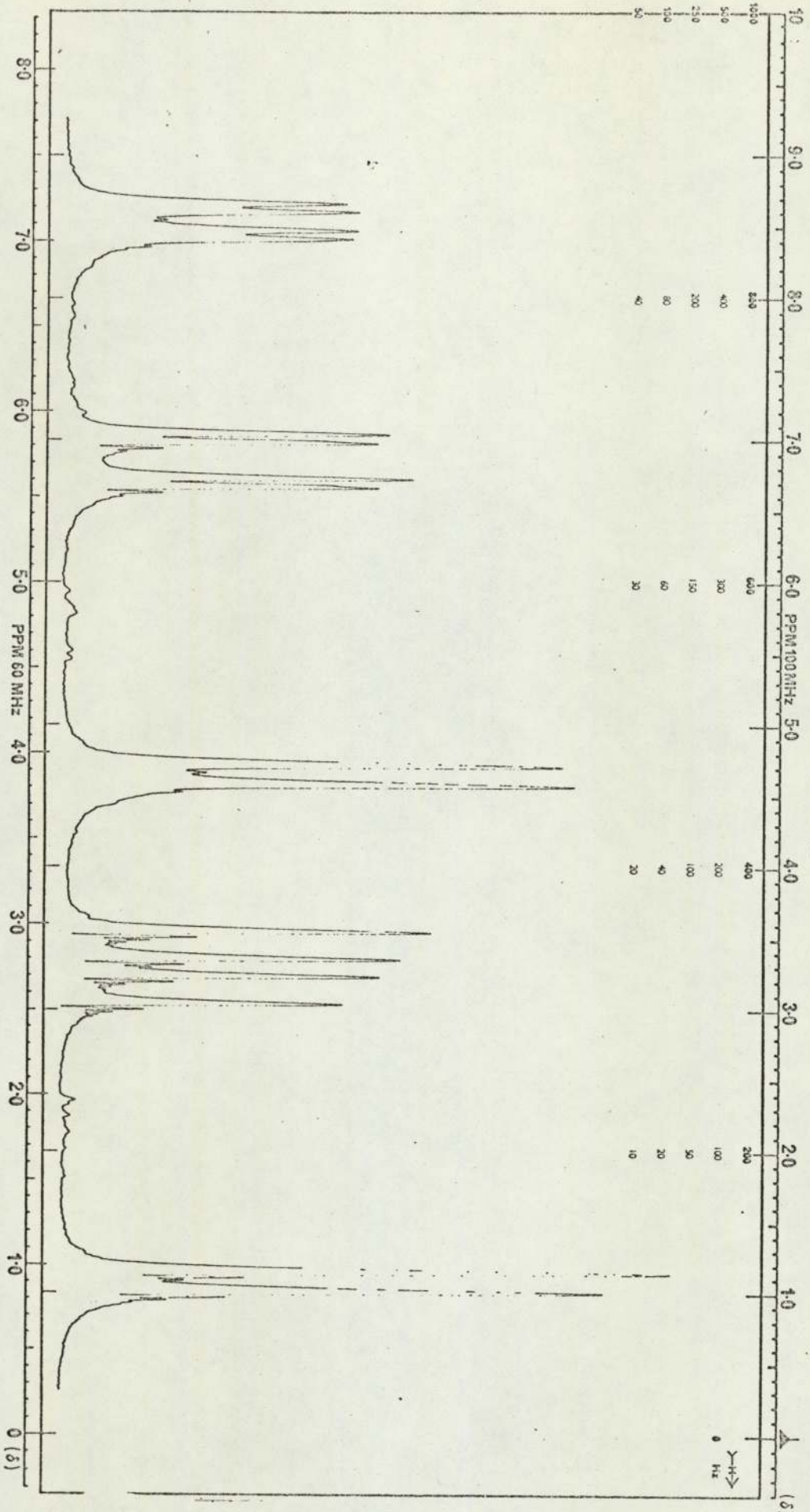
SCHEME 14


NC
(CH3O)2CHCH2CH(OCH3)2
NH2
R
-CH3OH/H+
CH3O
OCH3
H
H-C
H
OCH3
H
H
H
-2 CH3OH
-CH3OH
-H+



^{1}H n.m.r. of 3-cyano-1-cyclohexylpyrrolo[2,3-b]pyridine

^{1}H n.m.r. of 1H-pyrrolo [2,3-b] pyridine (100 mHz)



3-cyano-1-cyclohexylpyrrolo[2,3-b]pyridine (157) is shown on page 46. The 4-H and 6-H protons give rise to the more strongly deshielded AB portion of the spectrum, and consist of two pseudo-AB quartets. The 5-H proton is observed as a quartet, coupling with the 4-H and 6-H protons, and "leans" towards the AB portion of the spectrum. This is also observed in the parent molecule (6) and the expanded 100 MHz spectrum of 1H-pyrrolo[2,3-b]pyridine is shown on page 47 for comparison. The AB, AX, BX coupling constants are of a similar magnitude for the pyrrolopyridines (6) and (157) The effect of the 3-cyano- and 1-cyclohexyl- groups on the pyrrole 2-H proton was found to be a deshielding one of τ0.6 compared with τ1.0 deshielding in 3-cyanopyrrolo[2,3-b] pyridine (170) which was prepared by the method of Verbisar[113]. The 3-cyanopyrrolo[2,3-b]pyridine (170) was of value in the assignment of ^{13}C chemical shifts in the series of pyrrolopyridines, the ^{1}H n.m.r. data of these pyrrolopyridines are shown in Table 1.

The sodio derivative of nitromalondialdehyde was prepared by the method of Morley and Simpson [114] and was found to give the pyrrolopyridine (161) by liberation of the dialdehyde from its sodium salt with glacial acetic acid. No further catalysis was required for the reaction which proceeded in a good yield. In pyrido[2,3-d]pyrimidines[115] a similar reaction has been reported to occur in 1% base solution.

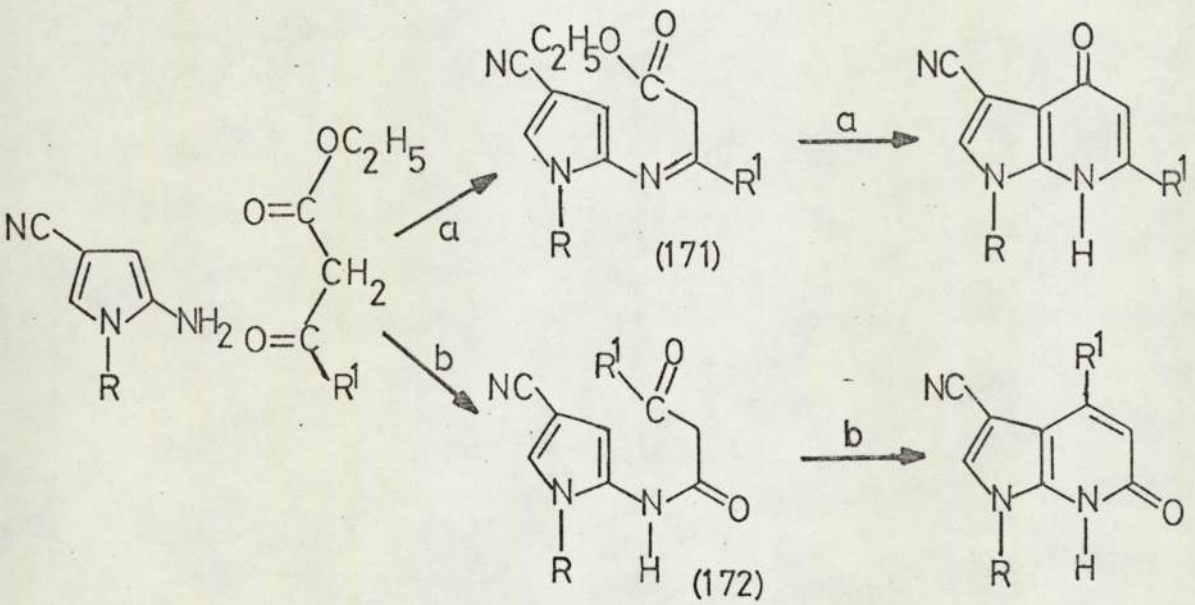
TABLE 1

	chemical shift				coupling const.			substituent group		
No.	C-2	C-4	C-5	C-6	J_{4-5}	J_{4-6}	J_{5-6}	6-Me	4-Me	C_6H_{11}
170	1.50	1.90	2.75	1.55	8.0	--	6.0	--	--	--
161	2.00	1.15	--	0.75	--	1.2	--	--	--	7.7-8.0
157	2.20	1.92	2.81	1.56	8.0	1.2	6.0	--	--	7.6-8.6
154	2.27	2.12	2.92	--	8.0	--	--	7.37	--	7.7-8.6
136	2.35	--	3.25	--	--	--	--	7.35	7.45	7.8-8.8
6	2.58	2.00	2.90	1.63	7.5	2.0	4.5	--	--	--

(IV) The preparation of pyrrolopyridines from β-keto-esters

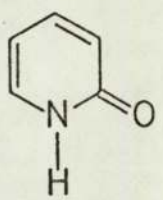
When an aminopyrrole and a β-keto-ester were caused to react the products were found to be pyrrolopyridinones from analytical and mass spectral data. The reactions took place in butan-1-ol under reflux and with acid catalysis. The products formed may be a pyrrolopyridin-4(7H)-one or a pyrrolopyridin-6(7H)-one, depending on the course of the reaction. The two possible pathways are shown in scheme 15.

SCHEME 15

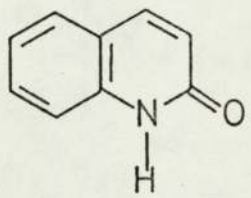


No intermediate of type (171) analagous to a Conrad-Limpach reaction was formed under Dean-Stark conditions and in absence of catalyst. No intermediate of type (172) analagous to a Knorr reaction was found either. The tarry products obtained proved impossible to work up, however, the condensation of the aminopyrrole (91) and ethyl acetoacetate (173), ethyl 2-methylacetoacetate (174) and ethyl benzoyl-acetate (175) gave good yields of the pyrrolopyridin-6(7H)-ones (176)-(178) at the higher temperature and with acid

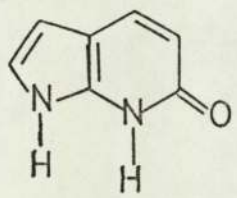
catalysis. These reaction conditions favour the Knorr-type synthesis (pathway b, scheme 15). The elimination of ethanol was expected to take place in preference to water under these conditions which were based on the results of Hauser and Reynolds[116] for similar reactions in the quinoline series. The formation of a pyrrolopyridin-6(7H)-one is also favoured by the ease of electrophilic attack by the acetyl or benzoyl group at the pyrrole nucleus. The lack of any intermediate is not surprising in view of the easier substitution in pyrroles compared with benzene. Direct comparison of the two possible isomeric products was not possible, however, pyrrolopyridin-6(7H)-ones have been prepared previously and the infra-red and ultra-violet data were compared together with data for pyridin-2-one (179) and quinolin-2-one (180)[117,118]. The data for 1H-pyrrolo[2,3-b]pyridin-6(7H)-one (181)[119], 2,3-dihydropyrrolo[2,3-b]pyridin-6(7H)-one (182)[119], and 4-methyl-2,3dihydropyrrolo[2,3-b]pyridin-6(7H)-one (183)[120] are included in Table 2.



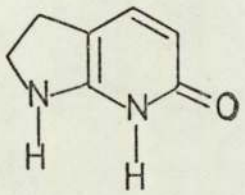
(179)



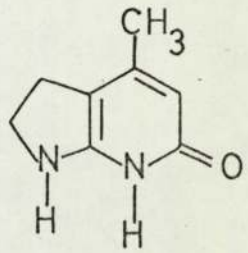
(180)



(181)



(182)



(183)

TABLE 2

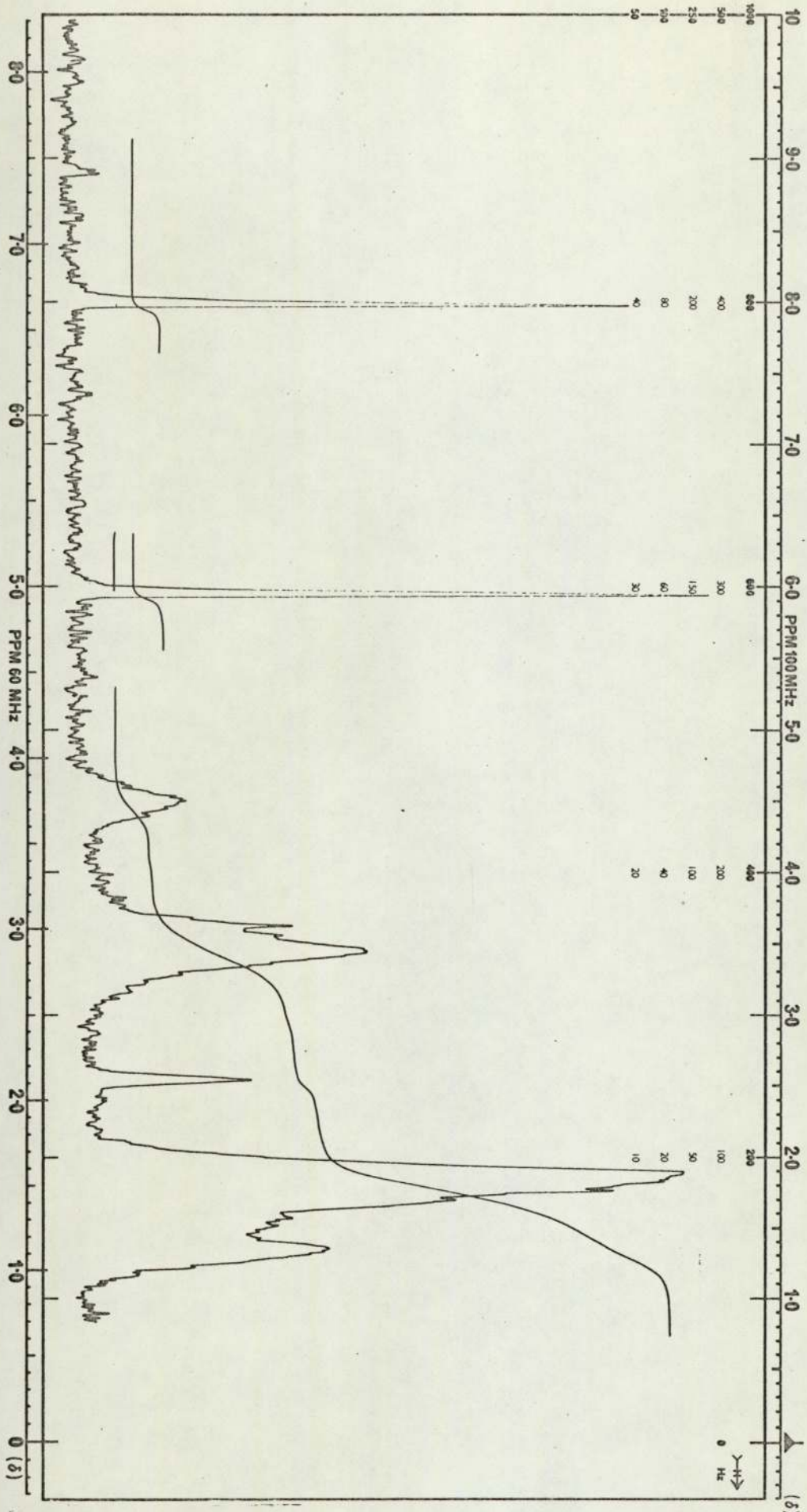
Compound	λmax			ν(NH)	ν(C=O)
176	300,	280,	225 nm.	3150,	1640 cm^{-1}.
177	312,	284,	225 nm.	3150,	1640 cm^{-1}.
178	304,	275,	225 nm.	3125,	1640 cm^{-1}.
179	---,	293,	224 nm.	3180,	1650 cm^{-1}.
180	327,	269,	225 nm.	3386,	1656 cm^{-1}.
181	332,	258,	227 nm.	3400,	1650 cm^{-1}.
182	355,	280,	238 nm.	3350,	1640 cm^{-1}.
183	320,	261,	--- nm.	3300,	1638 cm^{-1}.

Cyclic amide formation was shown to be the preferred tautomeric form in pyrrolo[3,2-b]pyridin-5(4H)-ones prepared from 3-aminopyrroles and ethylacetacetate[121]. The nuclear magnetic resonance spectra of the pyrrolopyridinones showed two peaks in the aromatic region, the lower signal at τ1.7-2.0 was assigned to the pyrrole 2-H proton and the upfield signal at τ3.1-3.4 was assigned to the 5-H proton of the pyridinone ring. The spectrum of 3-cyano-1-cyclohexyl-4-methylpyrrolo[2,3-b]pyridin-6(7H)-one (178) in dimethyl sulphoxide also showed a broad peak at τ5.5 and this was assigned to the 7-H proton.

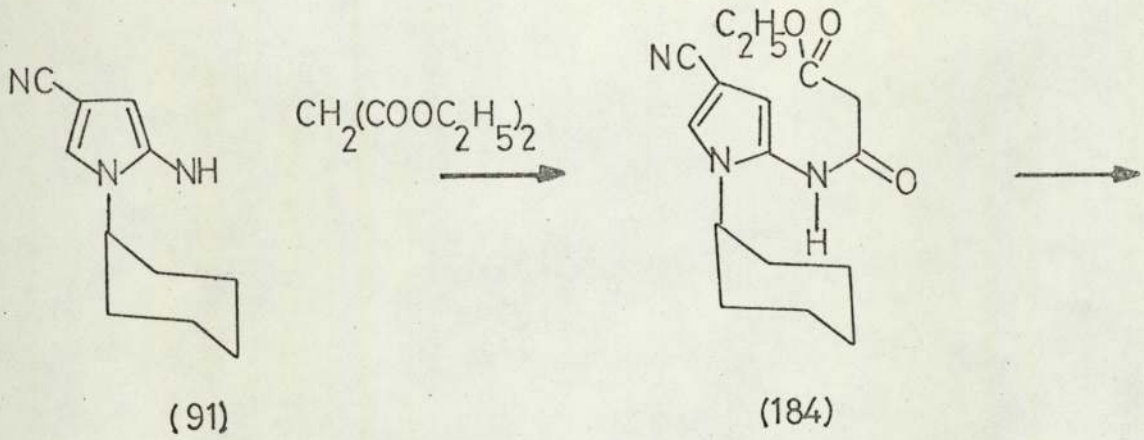
(V) Preparation of pyrrolpyridines from a 1,3-diester

A two stage thermally induced cyclisation in the absence of a catalyst was found to be appropriate for the preparation of 3-cyano-1-cyclohexyl-4-hydroxypyrrolo[2,3-b]pyridin-6(7H)-one (185) from the aminopyrrole (91) and diethyl malonate. The method was adapted from the successful preparation of 1,8-naphthyridinones[122] from 2-aminopyridine and diethyl malonate. In the first stage

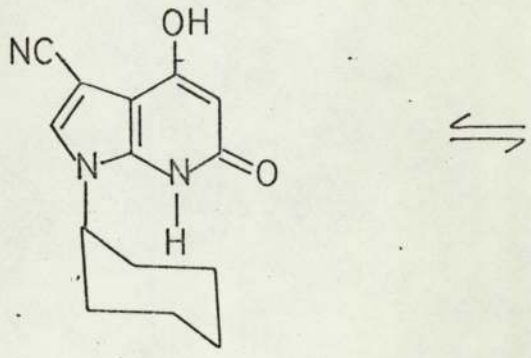
^{1}H n.m.r. of 3-cyano-1-cyclohexyl-4-hydroxypyrrolo 2,3-b pyridin-6(7H)-one (185)



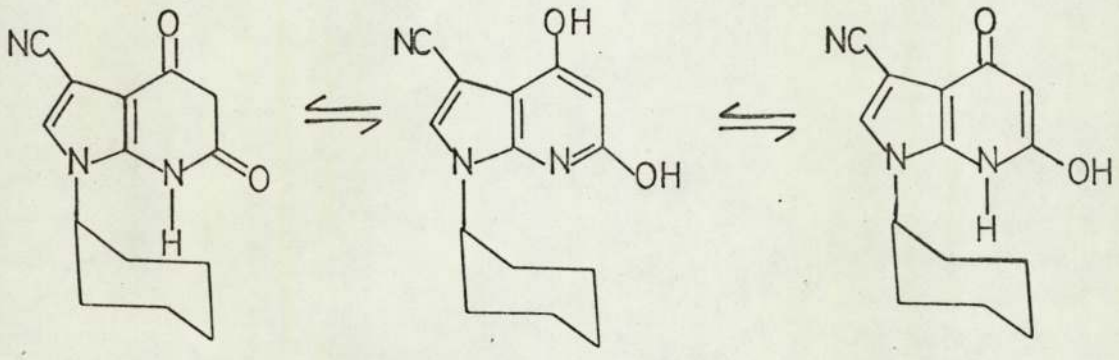
SCHEME 16



(91) (184)



(185)



(186) (187) (188)

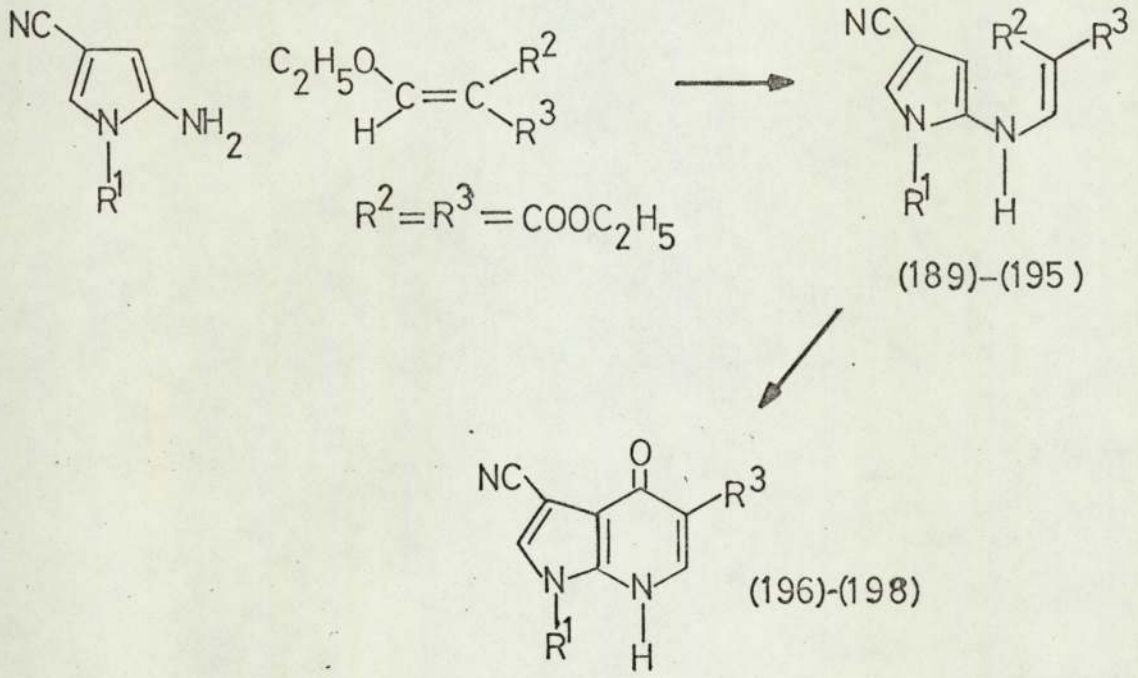
of the reaction the aminopyrrole (91) was heated in diphenyl ether with an excess of diethyl malonate at 140° until the first evolution of ethanol had subsided. It was assumed the ethanol elimination yielded the amide (184) which was converted to the pyrrolopyridinone by heating the mixture under reflux. Diphenyl ether has been found to be effective as a high boiling inert solvent for similar syntheses in the quinoline series[123]. The pyrrolopyridinone (185) can exist in the tautomeric forms (186)-(188) but the preferred tautomer was expected to be (185). The ^{1}H n.m.r spectra of the product showed two singlets in the aromatic region, a broad peak at τ5.4, and a broad singlet at τ 7.5 which were assumed to be the contributions of the NH and OH groups of tautomer (185). The 2-H proton was assigned to the signal at τ2.0 and the 5-H proton to the signal at τ4.1 , the 100 MHz spectrum of (185) in dimethyl sulphoxide is shown on page 53. Evidence of cyclic amide formation as in (185) has been demonstrated in a wide range of heterocycles and 2,4-dihydroxypyridine exists mainly as the 4-hydroxy-pyridin-2-one tautomer[124]. The infra-red spectra of the compound showed absorptions at 3200 cm^{-1}, 2600 cm^{-1} and at 1640 cm^{-1} consistent with there being an amino, carbonyl and hydroxy function. The ultra-violet spectrum had maxima at 280, 260 and 225 nm, resembling the spectra of the pyrrolpyridin-6(7H)-ones prepared from β-keto-esters.

(VI) Preparation of pyrrolopyridines from diethyl ethoxymethylenemalonate

The use of diethyl ethoxymethylenemalonate in the preparation of quinolin-4-ones has been reported[125-127] and similar conditions were found to be successful for the preparation of some pyrrolo[2,3-b]pyridin-4(7H)-ones. The reaction of diethyl ethoxymethylenemalonate and the aminopyrroles (91), (92), (93), (97), (100), (102) and (103) gave the 2,2-diethoxycarbonylvinylaminopyrroles (189)-(195). The reaction took place over six hours in refluxing benzene or ethanol to give almost quantitative yields of the products. The nuclear magnetic resonance spectra of the 2,2-diethoxycarbonylaminopyrroles were characterised by the large coupling constant (12 Hz) for the methine proton, the doublet collapsed to a singlet after addition of deuterium oxide. A large coupling constant for vinylamino protons was observed in the aminomethylenesuccinonitriles (section D(I)) and has been noted in other vinylamino derivatives[128,129]. The two ethyl groups gave rise to the usual triplets and quartets which were virtually superimposed on the spectum although they have different environments, this was observed in the 2,2-diethoxycarbonylvinylamino derivatives of some 1,8-naphthyridines[129]. Cross-ring coupling in the pyrrole nucleus was observed for the 3-H and 5-H protons (J_{3-5}= 2Hz) as in the 2-aminopyrroles and 2-acetamidopyrroles. The n.m.r. spectrum of 2(2',2'-diethoxycarbonylvinylamino)-4-cyano-1-(p-tolyl)pyrrole (192) is shown on page 58 . The infra-red spectra of the vinylaminopyrroles showed a low amine stretching vibration peak at 3150-3200 cm^{-1}, and the ester carbonyl stretching band was observed at 1700-1730 cm^{-1}.

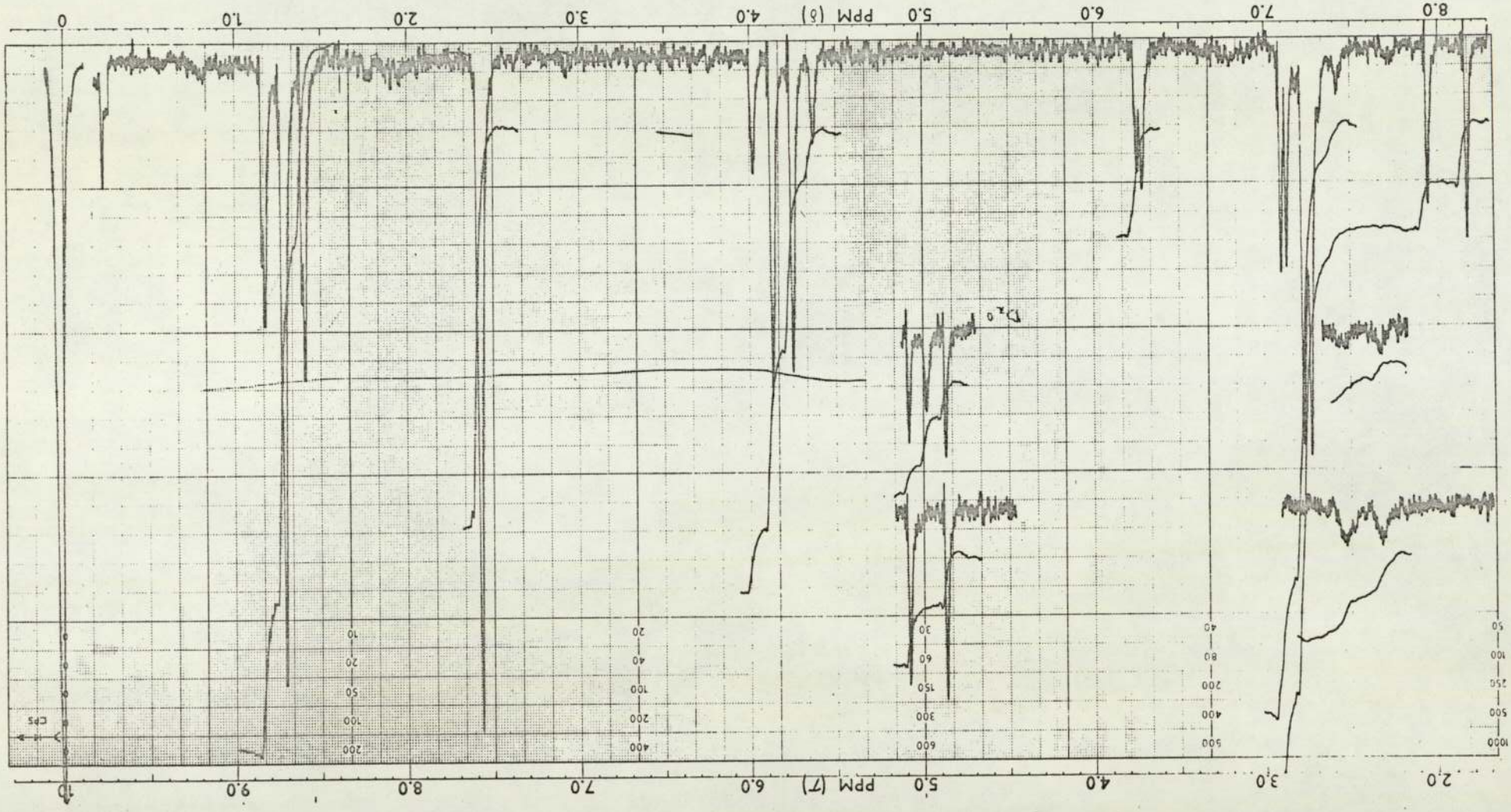
Three of the vinylaminopyrroles were cyclised in refluxing diphenyl ether, and gave the pyrrolopyridin-4(7H)-ones (196), (197) and (198) in moderate yields. The products were isolated by dilution of the cooled solution with petroleum ether. These conditions have been found to be successful in quinoline [126,127] and pyrimido[1,2-a]-1,8-naphthyridines[129]. The general route for pyrrolopyridin-4(7H)-ones is shown in scheme 17 below.

SCHEME 17

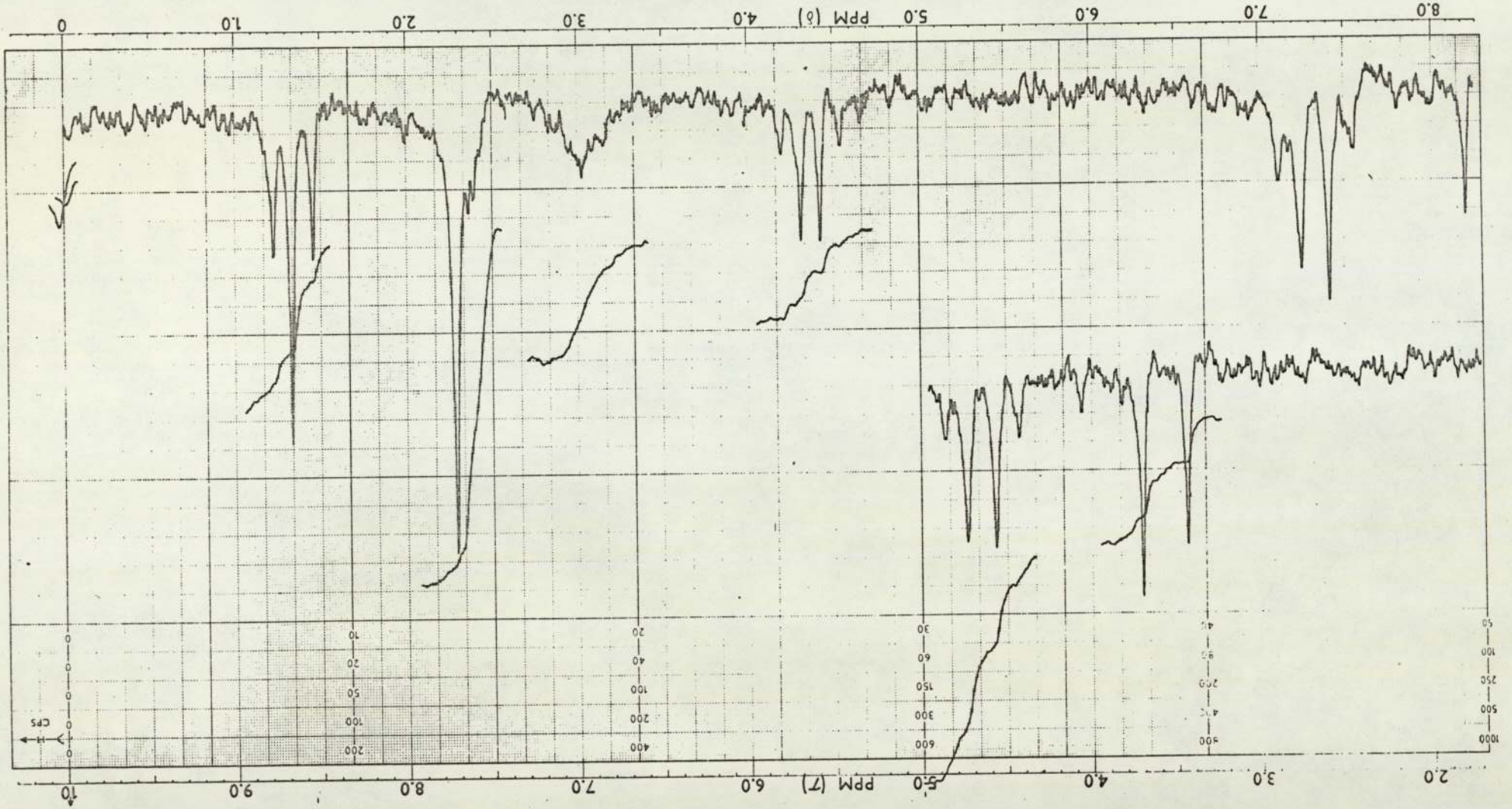


The infra-red spectra of the pyrrolopyridin-4(7H)-ones indicated that the compounds were in the keto-tautomer, the absorptions at 3100-3150 cm^{-1} were attributed to amine stretching vibrations and the pyridone carbonyl absorptions were observed at 1620-1640 cm^{-1}. The ester carbonyl absorptions at 1680-1690 cm^{-1} were considered to be of a low frequency but are explained by the presence of a hybrid structure (199) as a contributing form of the molecule.

^{1}H n.m.r. of 2(2',2'-diethoxycarbonyl)vinylamino-4-cyano-1-(p-tolyl)pyrrole (192)



^{1}H n.m.r. of ethyl 3-cyano-1-(p-tolyl)pyrrolo 2,3-b pyridin-4(7H)-one-5-carboxylate (198)



A nuclear magnetic resonance spectrum of ethyl 3-cyano-1-(p-tolyl)pyrrolo[2,3-b]pyridin-4(7H)-one-5-carboxylate (198) was obtained in dimethyl sulphoxide at 40° and is shown on page 59. Two singlets are observed in the aromatic region apart from the four phenyl protons, the signal at τ1.42 was assigned to the 6-H proton and the singlet at τ1.67 for the 2-H proton. The chemical shift of the 2-H proton at τ1.67 represents a downfield shift of τ1.2 on cyclisation and a similar tendency was observed for the cyclisation of an aminopyrrole and a β-keto-ester.

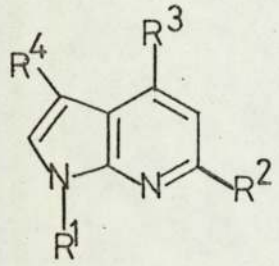
(VII) Chemistry of the pyrrolopyridines

The pyrrolopyridines prepared from the 2-amino-4-cyano-pyrroles contain a nitrile group in the pyrrole ring at C-3 thus blocking the favoured site for electrophilic attack. The next most favoured site is the C-5 position of the pyridine ring. However, attempts to nitrate 3-cyano-1-cyclohexylpyrrolo[2,3-b]pyridine (157) to provide the 3-cyano-1-cylohexyl-5-nitropyrrolo[2,3-b]pyridine (161), previously prepared by an unambiguous route were not successful. The pyrrolopyridine (157) was recovered intact after treatment with concentrated nitric acid/concentrated sulphuric acid mixture for two hours at room temperature. Further attempts to modify the ring system by electrophilic substitution reactions were not considered in view of the stability of the pyrrolopyridines.

Modification of the 3-carbonitrile group was then attempted to furnish pyrrolopyridines more favourably substituted for biological activity. However, it should be noted that the nucleoside antibiotic Toyocamycin (2) has a 3-carbonitrile group in the pyrrole ring. Hydrolysis of the 3-carbonitrile group was attempted under both acidic and basic conditions. It was found that concentrated sulphuric acid at 100° for four hours was neccessary to give the 3-carboxamide. Concentrated hydrochloric acid had previously been found sufficient to hydrolyse 1-acetyl-3-cyanopyrrolo[2,3-b]pyridine to 1H-pyrrolo[2,3-b]pyridine-3-carboxylic acid[130]. The ring system remained unaffected by the drastic hydrolysis conditions showing the remarkable stability of the pyrrolopyridine ring system. The pyrrolo-pyridines (137), (147) and (157) were treated in this way

to give moderate yields of the sparingly soluble pyrrolo-pyridine-3-carboxamides (200)-(202) respectively. The 3-carboxamides were characterised by the absence of nitrile absorptions in the infra-red spectra and presence of (NH) stretching vibrations at 3400 cm^{-1} and 3250 cm^{-1} for a primary amide. The amide carbonyl absorptions were observed at 1640 cm^{-1}.

The hydrolysis of 3-cyano-4,6-dimethyl-1-phenylpyrrolo [2,3-b]pyridine (137) in 10% sodium hydroxide gave a poor yield of the corresponding 3-carboxylic acid (203) after fifteen hours under reflux. The 3-carboxylic acid could not be decarboxylated in a satisfactory manner but evidence for loss of the carboxyl group was seen in the breakdown pathway of the mass-spectrum of the 3-carboxylic acid (203).



(200) R^1 = Ph, R^2 = R^3 = Me
R^4 = $CONH_2$

(201) R^1 = C_6H_{11}, R^2 = R^3 = H
R^4 = $CONH_2$

(202) R^1 = 4'Cl.C_6H_4, R^2 =
R^3 = Me, R^4 = $CONH_2$

(203) R^1 = Ph, R^2 = R^3 = Me
R^4 = COOH

The benzylpyrrolopyridines were expected to yield 1H-pyrrolo[2,3-b]pyridines by a suitable hydrogenation procedure. Attempts to remove the benzyl group with hydrogen/palladium charcoal at atmospheric pressure and at 4 atmospheres were unsuccessful. Attempts to remove the benzyl group from an N-benzylpyrrole have been reported[131]

and found to be difficult under similar conditions. The pyrrolopyridine ring was unaffected by these conditions whereas the parent molecule is known to add one molecule to yield the 2,3-dihydropyrrolopyridine under more stringent comditions. The resistance to reduction in pyrrolopyridines has been noted in the review by Willette[10]. Chemical reduction with lithium aluminium hydride or sodium borohydride was unsuccessful, neither the 1-benzyl nor the 3-carbonitrile group was affected.

The hydrolysis of ethyl 3-cyano-1-cyclohexylpyrrolo[2,3-b] pyridin-4(7H)-one-5-carboxylate (196) in 10% sodium hydroxide gave a poor yield of the 3-cyano-1-cyclohexylpyrrolo[2,3-b] pyridin-4(7H)-one-5-carboxylic acid (204). The acid was isolated from the basic solution by acidifying with 10% hydrochloric acid after six hours.

(F) Carbon-13 Nuclear Magnetic Resonance Spectroscopy

Introduction

To date ^{13}C nuclear magnetic resonance spectroscopy has not been as popular as ^{1}H nuclear magnetic resonance spectroscopy for several reasons. Limitations are placed on the method by the low abundance of the isotope ^{13}C which is 1.11% compared with 99.98% for ^{1}H, and other factors, including the lower magnetogyric ratio and the longer relaxation time of a ^{13}C nucleus, result in a lowered sensitivity of a factor of 6000 compared with a ^{1}H n.m.r. experiment. Since the first n.m.r. observations of ^{13}C nuclei[132,133] the Fourier Transform technique[134] has been developed to give ^{13}C n.m.r. spectroscopy the practical capabilities comparable to ^{1}H n.m.r. spectroscopy.

^{13}C resonances of organic compounds are found over a range of 600 ppm compared with 20 ppm for ^{1}H n.m.r. and are also observed for nuclei not attached to protons (ie. C=O, C=S, C=C=C, C=N, etc.). In aromatic and heteroaromatic compounds the resonance lines are found in the range 100-150 ppm downfield from the internal standard tetramethylsilane (the standard now favoured by most n.m.r. spectroscopists).

The wider separation between resonance lines in a ^{13}C n.m.r. spectra compared to a ^{1}H n.m.r. spectra and the rare probability of having two ^{13}C nuclei of the same chemical shift usually means the spectra are relatively simple. The application of ^{13}C n.m.r. spectroscopy was hoped to prove the orientation of some of the pyrrolopyridines prepared in this work. In particular it was hoped to establish beyond doubt the structure of pyrrolopyridines

prepared by the cyclisation of an aminopyrrole and an unsymmetrical 1,3-dicarbonyl reagent. Although regions in a ^{13}C n.m.r. spectrum can be assigned to a particular kind of carbon atom in terms of sp, sp^2 and sp^3 bonding a full assignment of resonances in a complex molecule is difficult. The useful techniques in the interpretation of ^{13}C n.m.r. spectra involve both experimental procedures and comparison of related spectra[135]. Correlation of ^{13}C chemical shifts and electron densities derived from Molecular Orbital calculations is also possible in hetero-aromatic molecules. An undecoupled ^{13}C n.m.r. spectra is rather complex due to the numerous long range couplings and is not a very useful source of information[136]. Spectra obtained with full proton-noise decoupling give rise to one resonance line for each carbon atom by removal of all ^{13}C-H couplings. This is accomplished by irradiation of the ^{1}H groups with a strong radiofrequency of broad band-width to cover all the protons in the sample. Single frequency off-resonance decoupling is a useful technique in which one-bond C-H couplings are present for all nuclei not at the centre of a low radiofrequency power irradiation. The centre of this irradiation is usually at a frequency of an attached proton, thus giving rise to a singlet for that carbon nucleus. The remaining protonated carbons are observed as multiplets with a reduced coupling constant. The method of selective decoupling is useful if the ^{1}H n.m.r. is known to be first order.

No data concerning ^{13}C n.m.r. spectroscopy had been published for 1H-pyrrolo[2,3-b]pyridine (6) or any of its derivatives prior to the commencement of this work.

An unambiguous assignment of the parent molecule was considered essential in the interpretatation of the chemical shifts of the derivatives. The analysis of the spectrum of 1H-pyrrolo[2,3-b]pyridine (6) was made by the application of experimental techniques, spectral comparison and correlation of chemical shifts with calculated electron densities. The chemical shifts recorded in this work are based on the TMS = 0 convention with positive shifts down-field. Deuteriochloroform has been used as the standard solvent in all experiments to minimise solvent interactions which, however, have been estimated to be small in molecules with no polarisable groups[137]. In the samples recorded the carbon atoms are sufficiently isolated from inter-molecular interactions and consequently the chemical shifts are expected to be controlled by the electronic environment of the molecule. The ^{13}C shieldings are governed by the hybridisation of the carbon atom and the electronegativity of the groups attached. Several workers have attempted to give a theoretical treatment of ^{13}C chemical shifts in three terms[138-142] (equation 1).

$$\sigma = \sigma_d + \sigma_p + \sigma_a \qquad \text{Eq. 1}$$

σ = chemical shift in ppm.

σ_d = the Lamb diamagnetic term resulting from the contribution of circular electron currents in a magnetic field.

σ_p = the paramagnetic term resulting from the magnetic properties of orbitals with angular momentum.

σ_a = the contribution from magnetic screening due to the proximity of an anisotropic group (e.g. Phenyl groups)

The peak area measurements determined for single line resonances in decoupled spectra do not correlate with the number of carbon nuclei present. This is due to variation in spin-lattice relaxation times, bridgehead carbon atoms tend not to relax as fast as protonated carbon atoms. There is also a variation in Nuclear Overhauser Enhancement (NOE) derived from ^{1}H induced relaxation of ^{13}C nuclei in a decoupled spectra.

Interpretation of the ^{13}C n.m.r. of 1H-pyrrolo[2,3-b]pyridine

The chemical shift data for the undecoupled and proton decoupled spectra was obtained directly from the computer output of the Fourier-Transform n.m.r. experiment and is shown on page 85.

The assignment of the chemical shifts are indicated in diagram 1 and are based on the results of the selectively decoupled spectra shown on page 68.

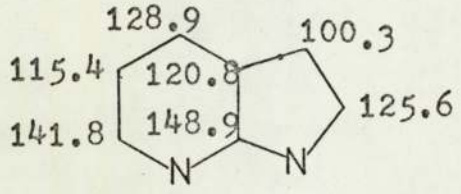
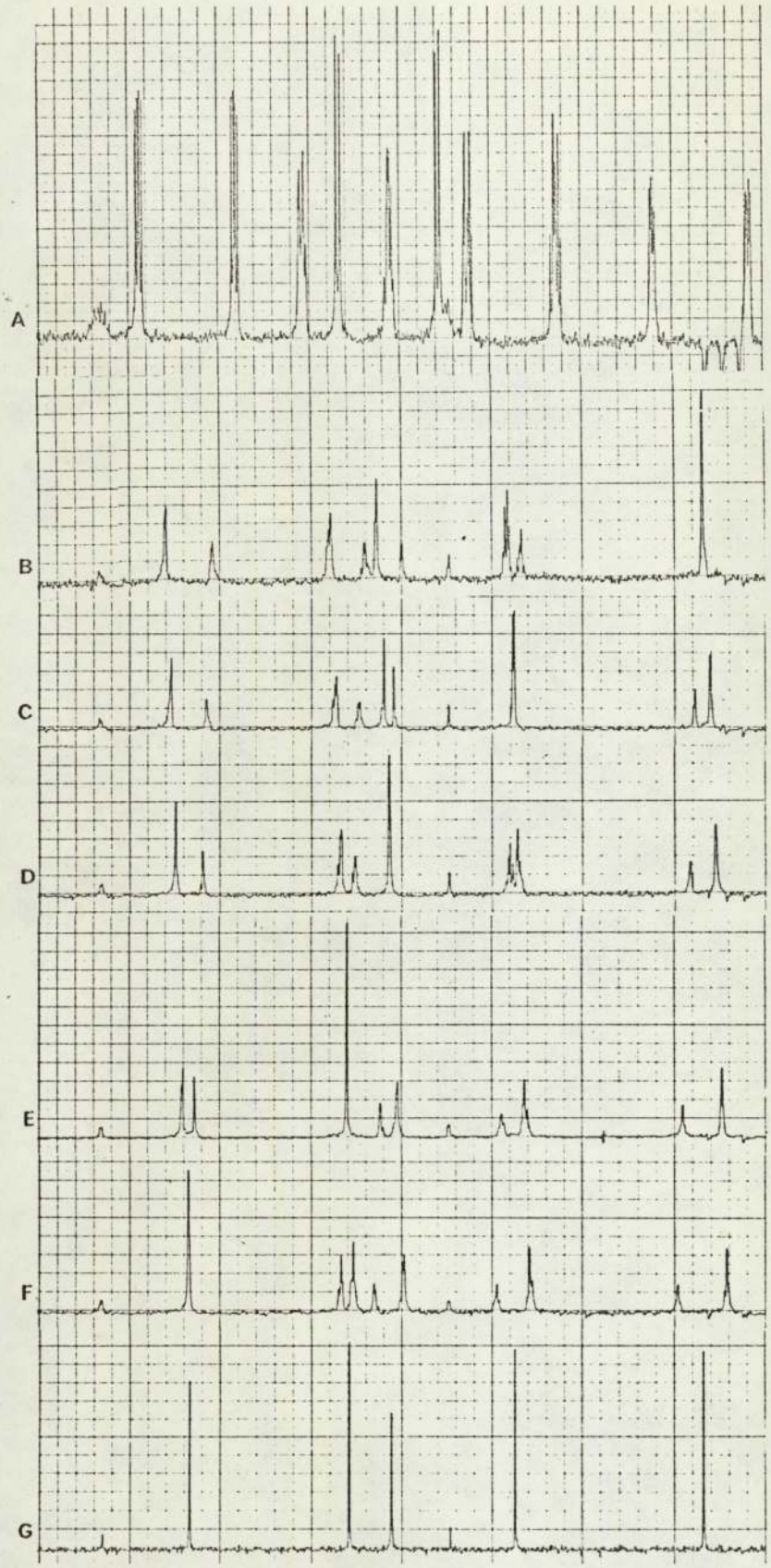


diagram 1

The undecoupled spectrum is shown in part A, and parts B, C, D, E, and F, are the spectra produced by selective single frequency off-resonance decoupling at values for the corresponding ^{1}H chemical shifts. Thus irradiation of the 3-H proton at τ3.69 gives rise to the singlet in spectrum B, irradiation of the 5-H proton at τ3.16 gives rise to the singlet in spectrum C, irradiation of the 2-H proton at



^{13}C Nuclear magnetic resonance spectra of 1H-pyrrolo [2,3-b] pyridine

τ2.8 gives rise to the singlet in spectrum D, irradiation of the 4-H proton at τ2.24 gives rise to the singlet in spectrum E, and irradiation of the 6-H proton at τ1.81 gives rise to the singlet in spectrum F. Spectrum G shows the broadband decoupling on the same scale, the bridgehead carbon atoms are of low intensity. These carbon atoms cannot be assigned as readily, however, the C-8 atom was expected to be strongly deshielded giving rise to the lowest peak in the spectrum. The observed chemical shifts for 1 H-pyrrolo[2,3-b]pyridine (6) were compared with the values reported for the closely related heterocycles indole, pyrrole, pyridine, and quinoline. A further rationalisation of the ^{13}C chemical shifts was made by the molecular orbital calculations of electron density.

Correlation of ^{13}C n.m.r. chemical shifts and electron density

Electron density calculations have been useful in the interpretation of ^{13}C chemical shifts due to the approximate linear relationship found by several workers[143-150]. The varying degrees of success, however, are no doubt due to the errors introduced by the assumptions made in these complex calculations. It should also be noted that electron density is not the sole factor in determining the chemical shift.

Early attempts at correlation between ^{13}C chemical shifts and π-electron density were based on the theory of Karplus and Pople[151]. More recently the comparison of total electron densities and ^{13}C chemical shifts has been made. It was concluded that this latter method[149] was an improvement on π-electron calculations alone, while inclusion of

bond-order terms afforded no further improvement. The total electron density calculations resulted from the CNDO/2 (Complete Neglect of Differential Overlap) molecular orbital method of Pople and Segal[152]. Use of the EHT [153] (Extended Huckel Theory) method is also claimed to give good correlation for ^{13}C chemical shifts and total electron density calculations[150]. The pyrrolopyridines have been subjected to molecular orbital calculations [77-79,154-156] but total electron charges have been neglected and only π-electrons considered. The more refined CNDO/2 and EHT methods were applied to the four parent pyrrolopyridines for this work[157] and the results are shown on pages 71-74.

Linear regression analyses on the paired data sets of ^{13}C chemical shifts and total electron densities by the CNDO/2 and EHT methods were performed. The lines of best fit for the data were found to have the following equations.

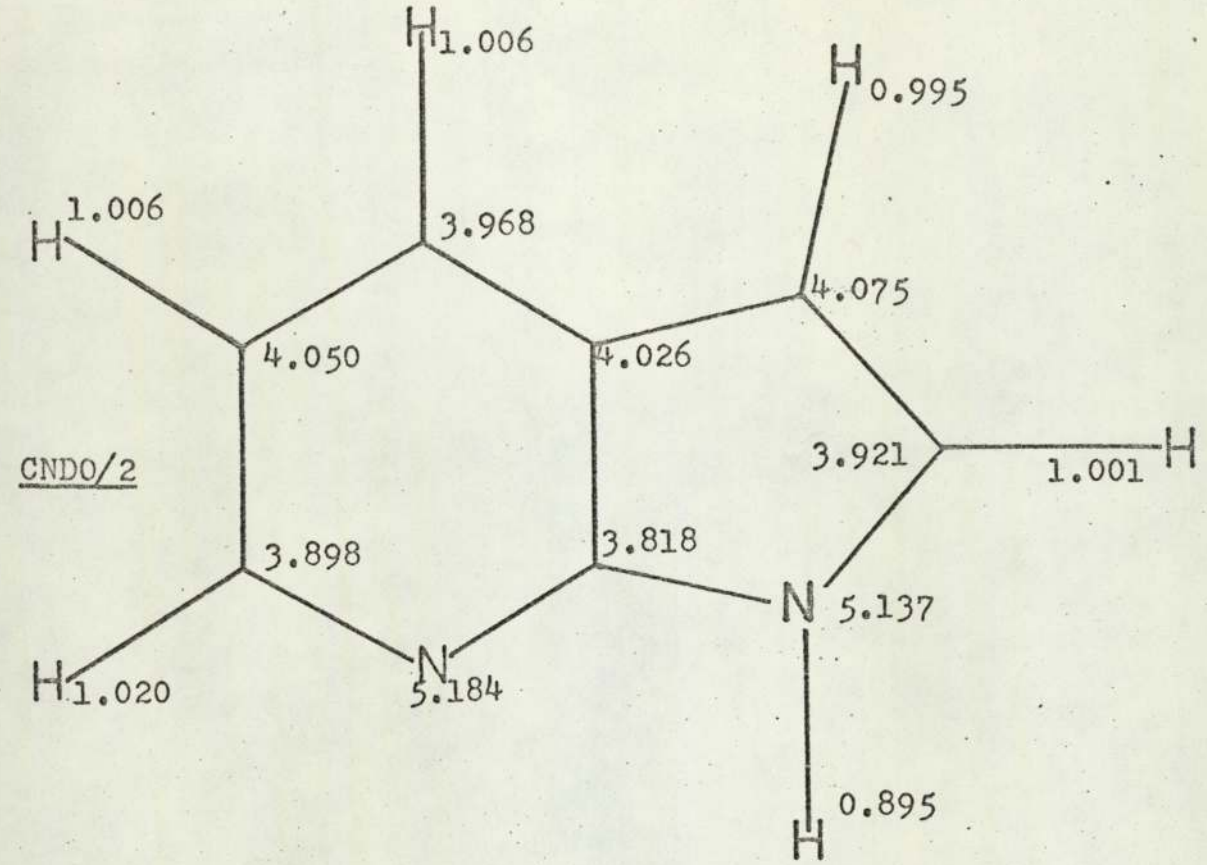
$$\sigma = -(Q_{EHT} \times 47.8) + 301.85 \qquad (r = 0.93) \qquad \text{Eq. 2}$$

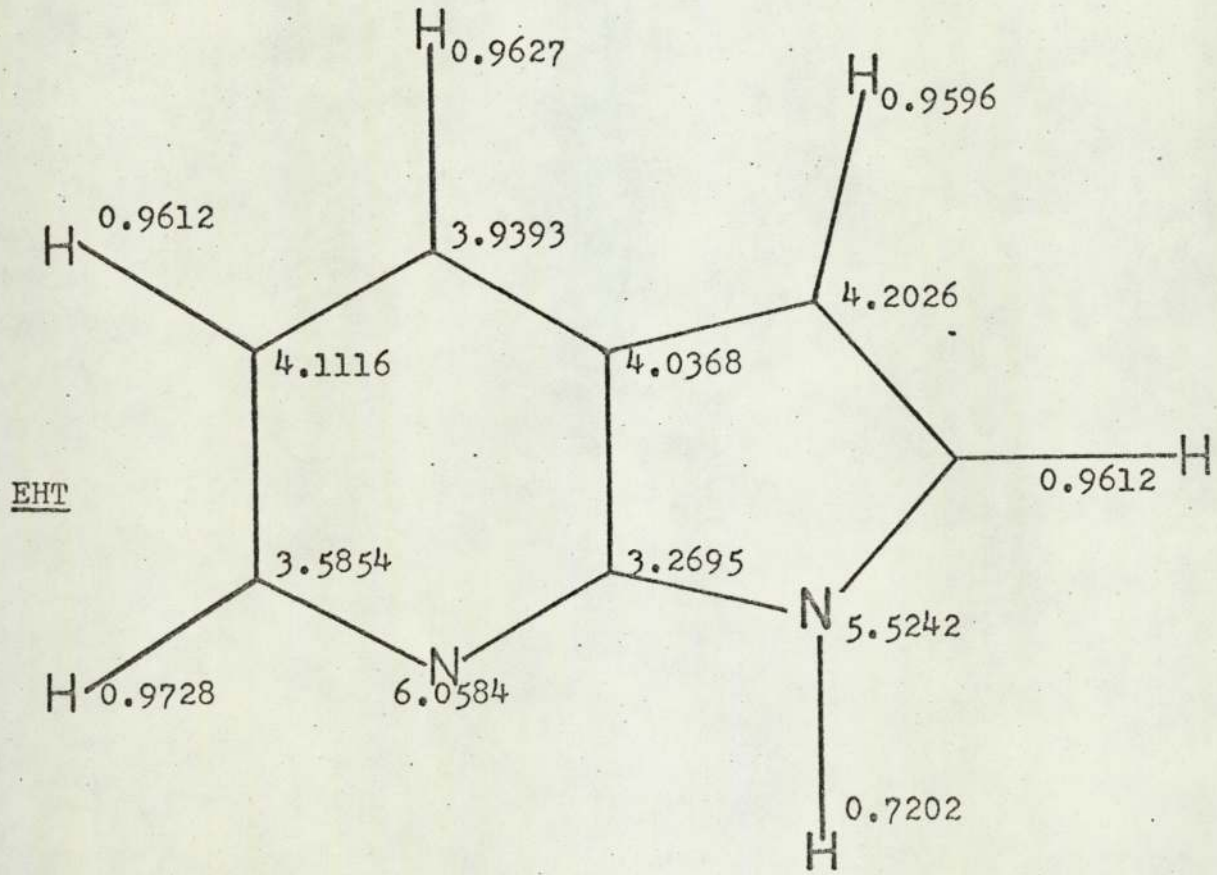
$$\sigma = -(Q_{CNDO/2} \times 165.4) + 781.89 \qquad (r = 0.94) \qquad \text{Eq. 3}$$

σ = ^{13}C chemical shift in ppm; Q = total electron density by the appropiate method;
r = correlation coefficient; (r = 1 for a straight line)

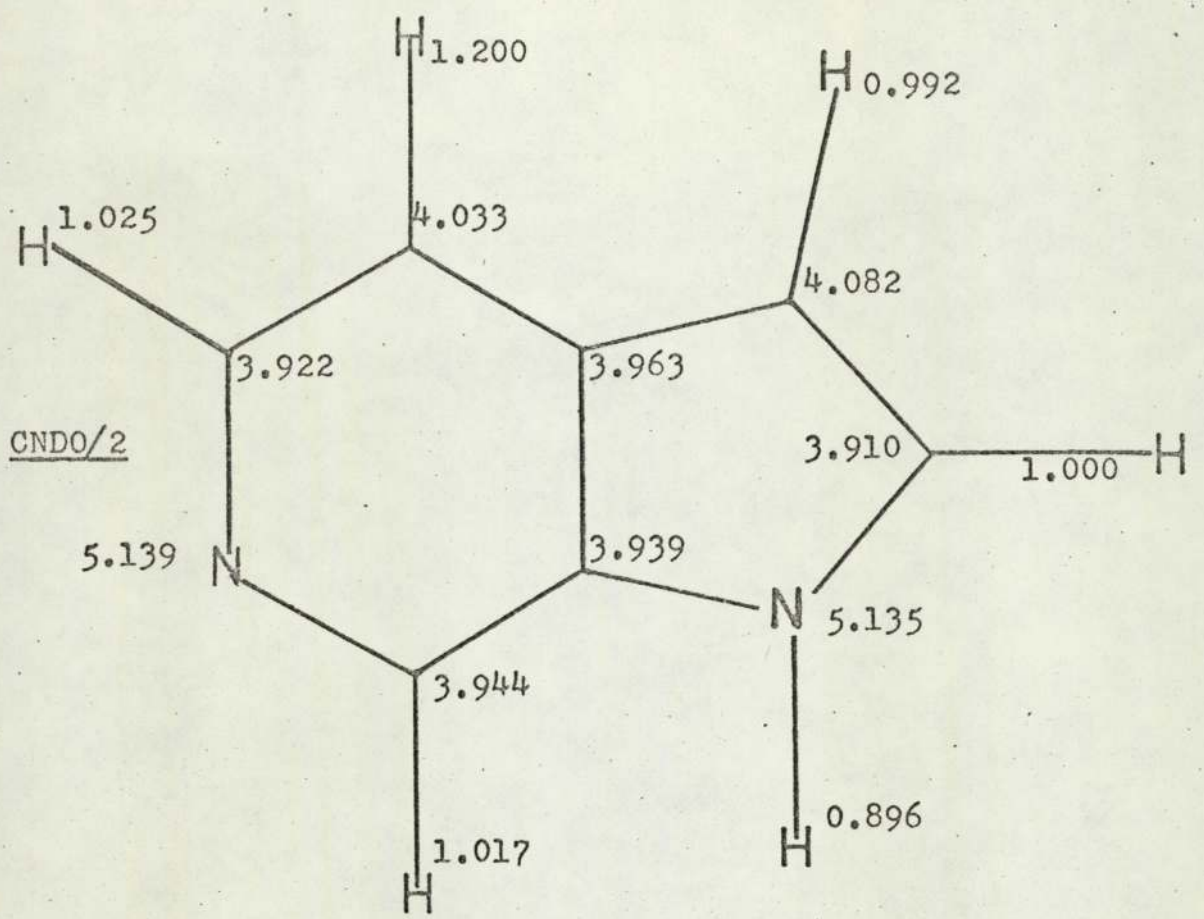
The correlation between ^{13}C chemical shifts and total electron density is seen to be good and the CNDO/2 method to give a somewhat better prediction than the EHT method. The relationship between ^{13}C n.m.r and ^{1}H n.m.r chemical shifts was investigated and the approximate linear relationship between the two was found to be satisfied by the equation 4.

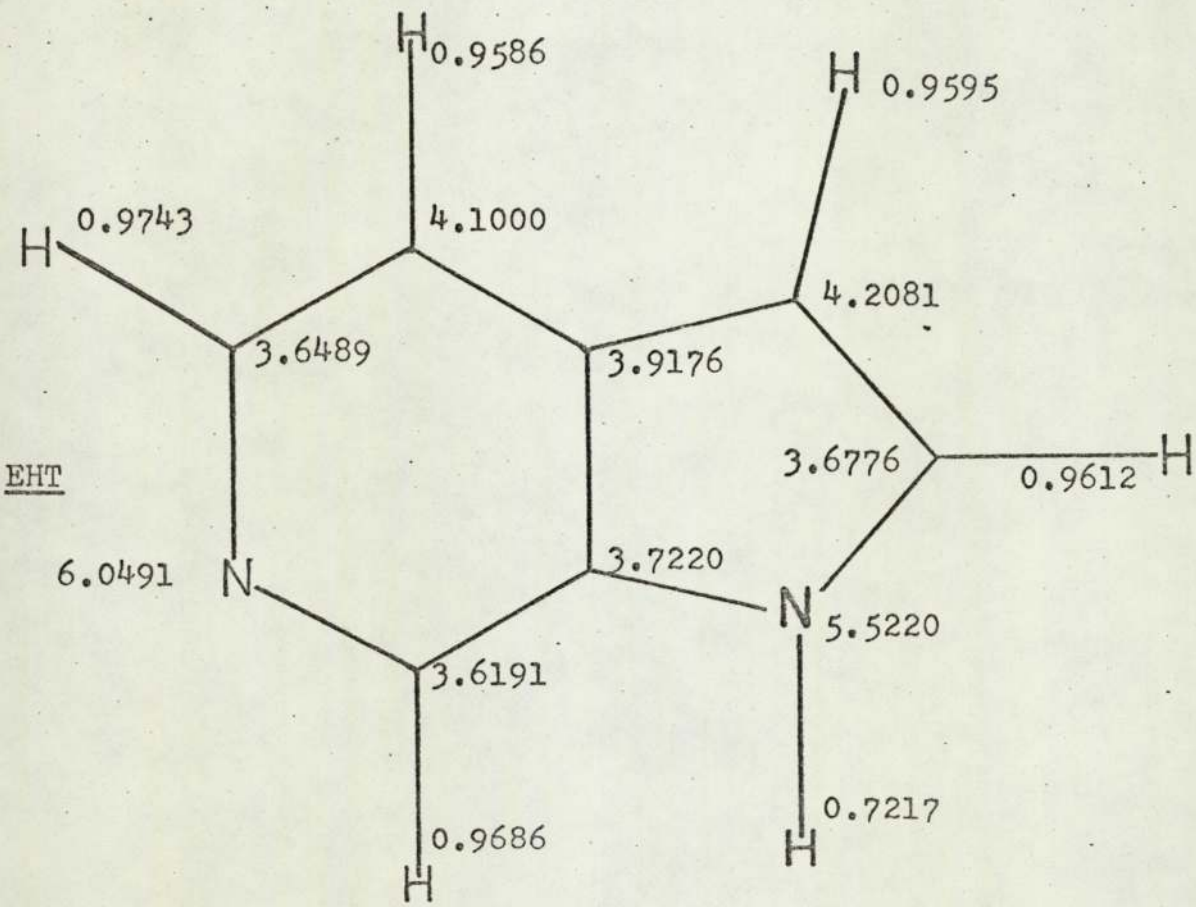
Electron density calculations



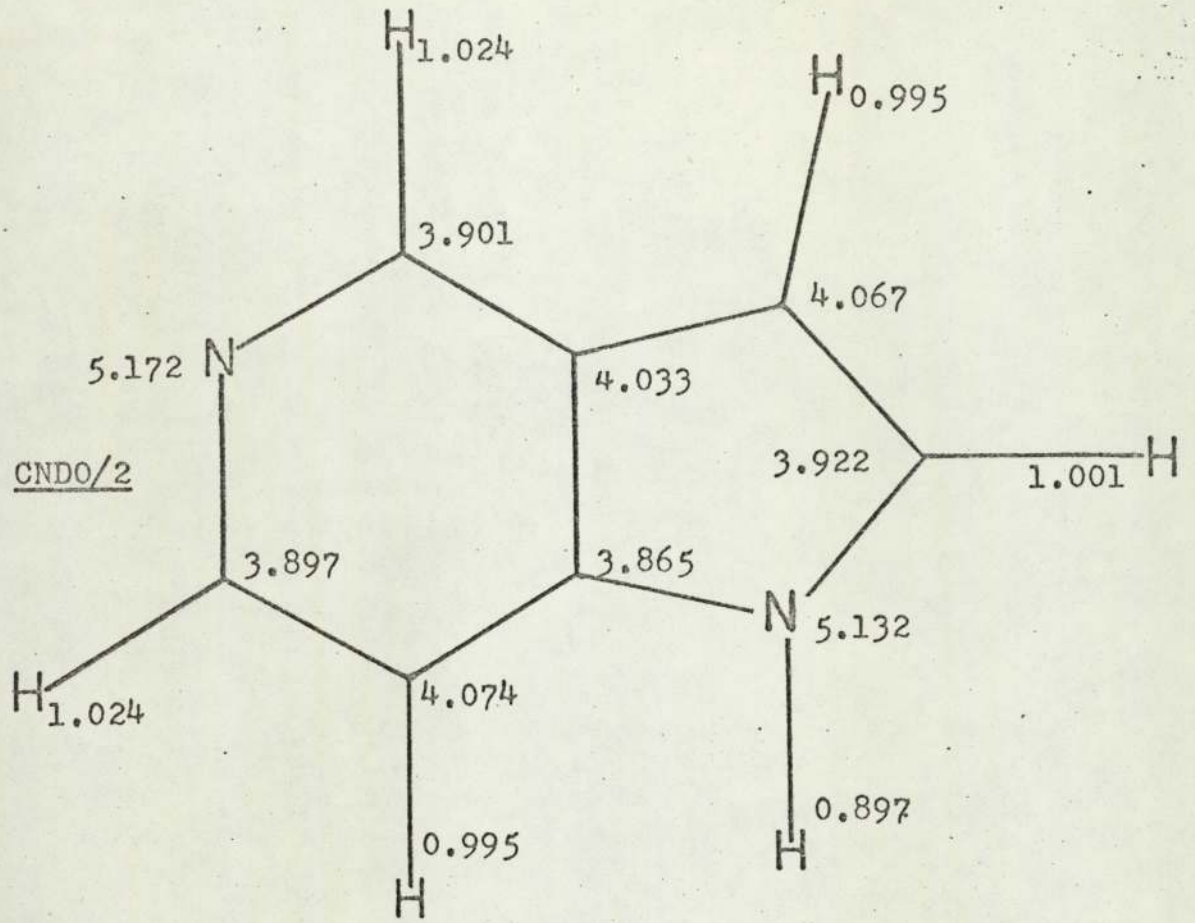


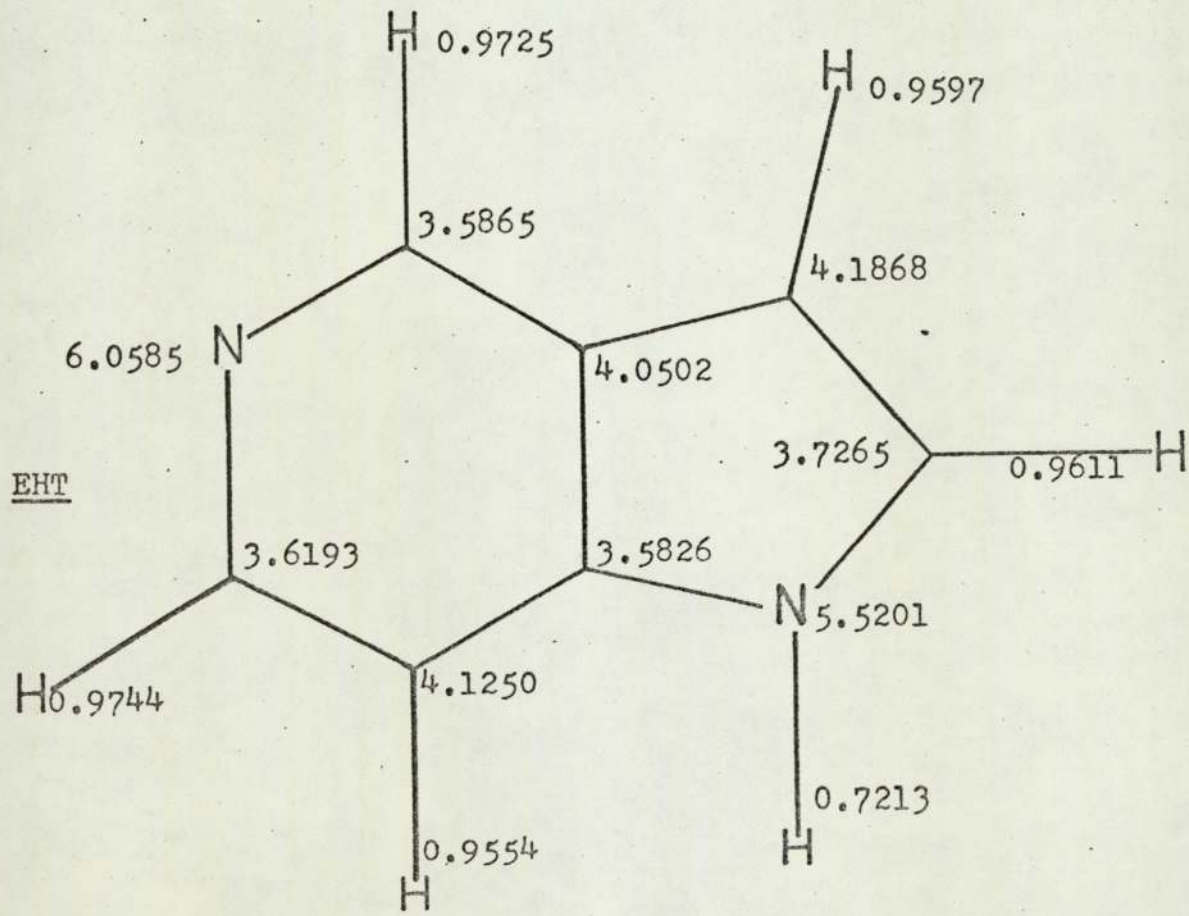
Electron density calculations



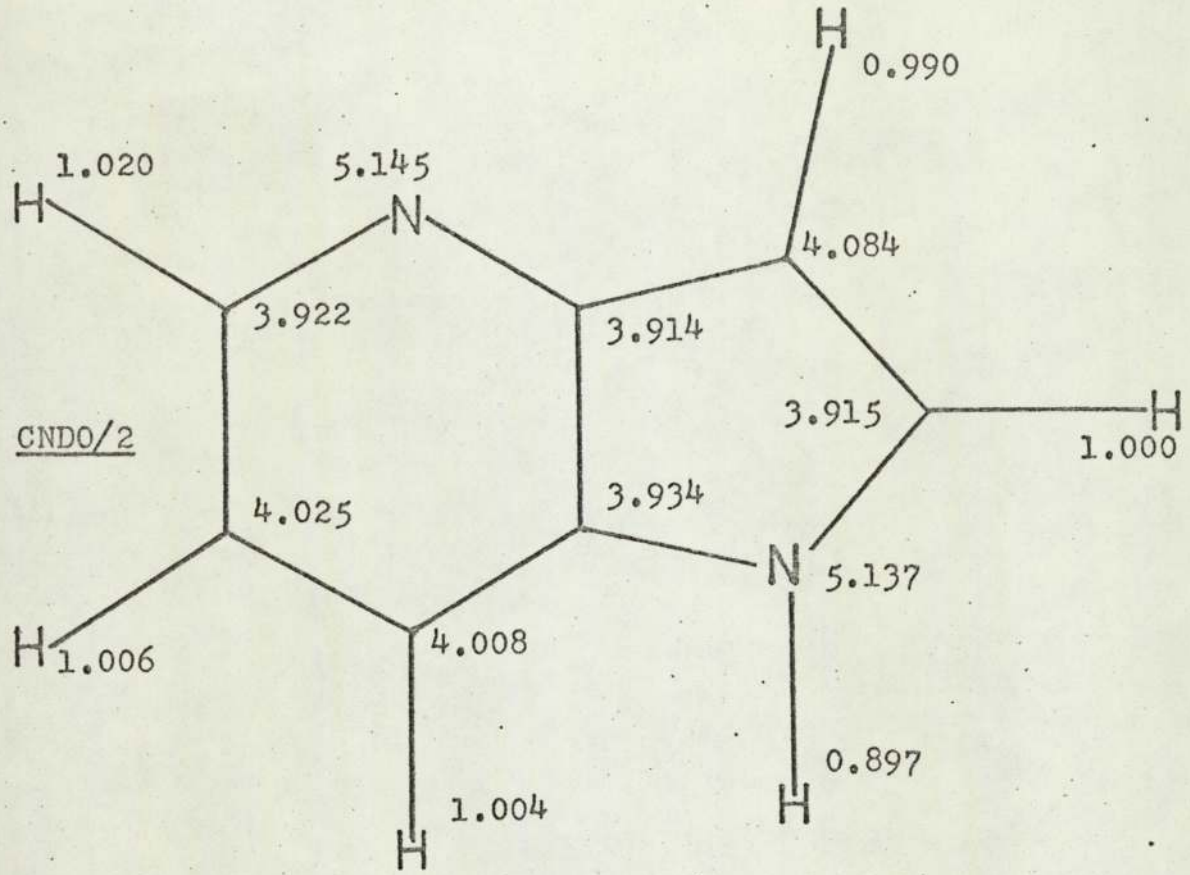


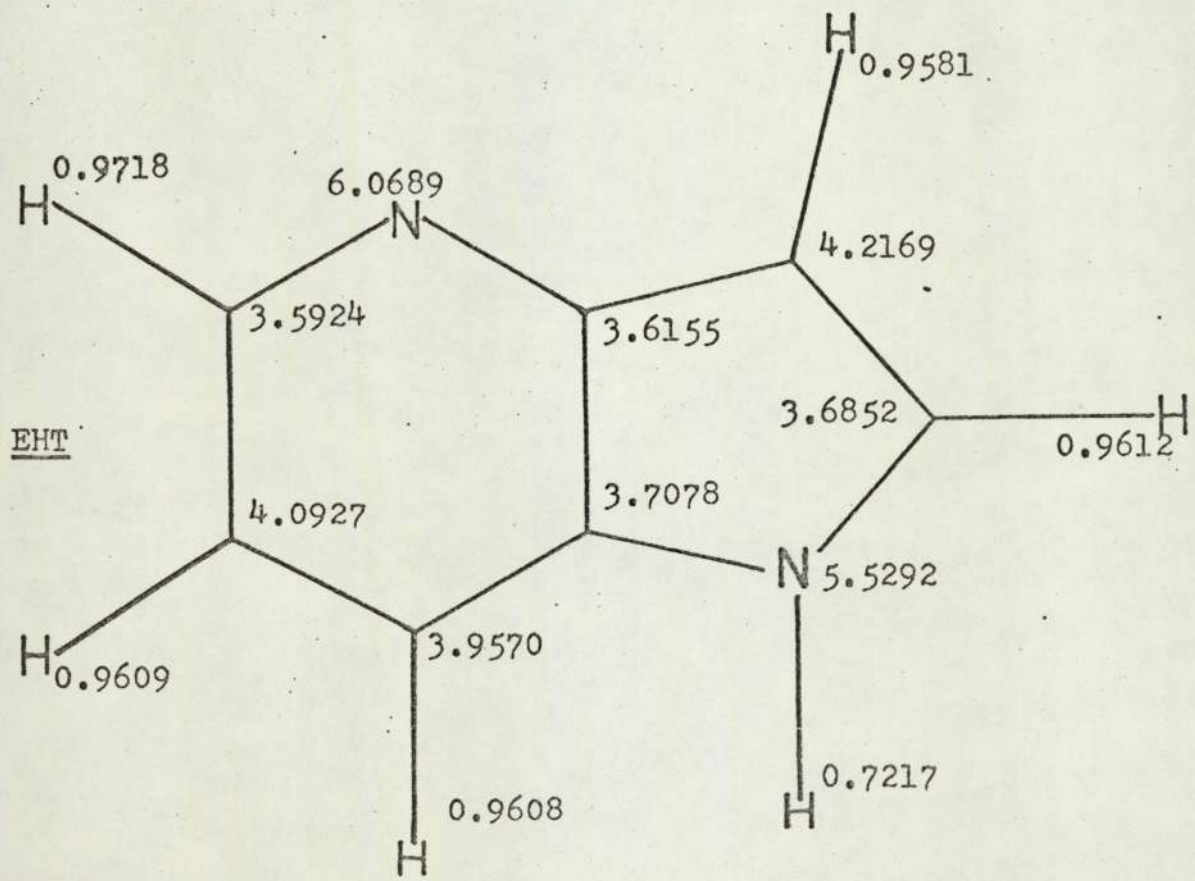
Electron density calculations





Electron density calculations





$$\sigma = (\delta_H \times 20.77) - 31.11 \qquad (r = 0.98) \qquad \text{Eq. 4}$$

A similar relationship has been noted in other systems[158] but is not common to nitrogen heteroaromatic molecules. Approximate linear correlation between ^1H n.m.r. chemical shifts and CNDO/2 calculations of total electron densities have been shown to exist[148,158]. An approximate linear relationship has been noted for ^1H n.m.r. chemical shifts of 1H-pyrrolo[2,3-b]pyridine and π-electron density values calculated by the VESCF method[155].

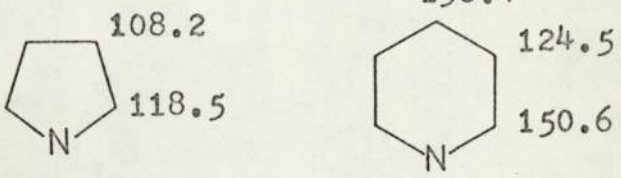
Equations 2, 3, and 4 were used to calculate the expected ^{13}C chemical shift for each carbon atom in 1H-pyrrolo[2,3-b]pyridine and these results are shown in Table 3.

Carbon atom	Observed ^{13}C shift	Calculated ^{13}C chemical shifts by Eq. 2	Eq. 3	Eq. 4
2	125.6	139.8	133.3	121.7
3	100.3	109.4	107.8	102.0
4	128.9	121.4	125.5	132.7
5	115.4	113.5	111.9	114.5
6	141.8	137.6	137.1	141.1
8	148.9	152.1	150.3	-----
9	120.8	117.0	115.9	-----

TABLE 3

The ^{13}C n.m.r. spectra of many heterocyclic compounds have been reported by Grant, Lauterbur, Roberts and Stothers. The chemical shift values for C-2 and C-3 closely resemble those found for indole[159] rather than pyrrole[160], but the C-4, C-5, and C-6 positions have a chemical shift of some 10 ppm upfield than similar positions in pyridine[161],

quinoline[162] and the naphthyridines[163]. The values for pyrrole and pyridine are shown below.



The fusion of a pyrrole and pyridine ring appear to give a system in which the pyrrole properties are maintained but in which the pyridine ring is altered markedly. This has been noted in the chemical properties of the pyrrolopyridines[10]. The ^{13}C n.m.r. spectra of 1H-pyrrolo[3,2-b]pyridine (8) and 1H-pyrrolo[3,2-c]pyridine (9) were determined to see if this trend was common to fused pyrrole and pyridine rings. The results obtained for these compounds were predicted by the CNDO/2 and EHT calculations. The data for the undecoupled and decoupled spectra of (8) and (9) are recorded on pages 86 and 87.

The calculated ^{13}C chemical shifts for 1H-pyrrolo[3,2-b]pyridine (8) are shown in Table 4. Approximate linear correlation was found between the ^{13}C chemical shifts and total electron density and also ^{1}H chemical shifts, the equations for the line of best fit are:-

$$\sigma = -(Q_{EHT} \times 61.22) + 360.85 \qquad (r = 0.96) \quad \text{Eq. 5}$$

$$\sigma = -(Q_{CNDO/2} \times 209.7) + 959.21 \qquad (r = 0.92) \quad \text{Eq. 6}$$

$$\sigma = +(\delta_H \times 20.85) - 35.7 \qquad (r = 0.93) \quad \text{Eq. 7}$$

TABLE 4

Carbon atom	Observed ^{13}C shift	Calculated ^{13}C chemical shifts by Eq. 5	Eq. 6	Eq. 7
2	128.9	135.2	138.3	121.9
3	102.2	102.7	102.9	105.7
5	142.5	140.9	136.8	142.4
6	116.6	114.2	115.2	113.2
7	119.1	118.6	118.8	126.1
8	129.3	133.8	134.3	-----
9	146.3	139.5	138.5	-----

The calculated ^{13}C chemical shifts for 1H-pyrrolo[3,2-c] pyridine (9) are shown in Table 5. Approximate linear correlation was found between the ^{13}C chemical shifts and total electron density and also ^{1}H chemical shifts, the lines of best fit are satisfied by the following equations:-

$$\sigma = -(Q_{EHT} \times 56.4) + 342.69 \qquad (r = 0.94) \qquad \text{Eq. 8}$$

$$\sigma = -(Q_{CNDO/2} \times 167.65) + 790.92 \qquad (r = 0.92) \qquad \text{Eq. 9}$$

$$\sigma = +(\delta_H \times 18.4) - 18.78 \qquad (r = 0.91) \qquad \text{Eq. 10}$$

The results from Tables 4 and 5 show that the trend in the pyrrolopyridines is for the chemical shifts of C-2 and C-3 to resemble those of the analagous positions in indole (cf C-2 125.2 ppm; C-3 102.6 ppm). In the pyridine ring however the values are shifted about 10 ppm from those in similar positions in pyridine, quinoline and isoquinoline. The trends were predicted by the CNDO/2 and EHT methods.

TABLE 5

Carbon atom	Observed ^{13}C shift	Calculated ^{13}C chemical shifts by Eq. 8	Eq. 9	Eq.10
2	126.9	132.5	133.4	116.6
3	101.4	106.5	109.1	104.4
4	142.3	140.4	136.9	146.3
6	138.8	138.5	137.6	133 9
7	107.5	110.0	107.9	116.7
8	140.4	140.6	143.0	-----
9	125.4	114.2	114.8	-----

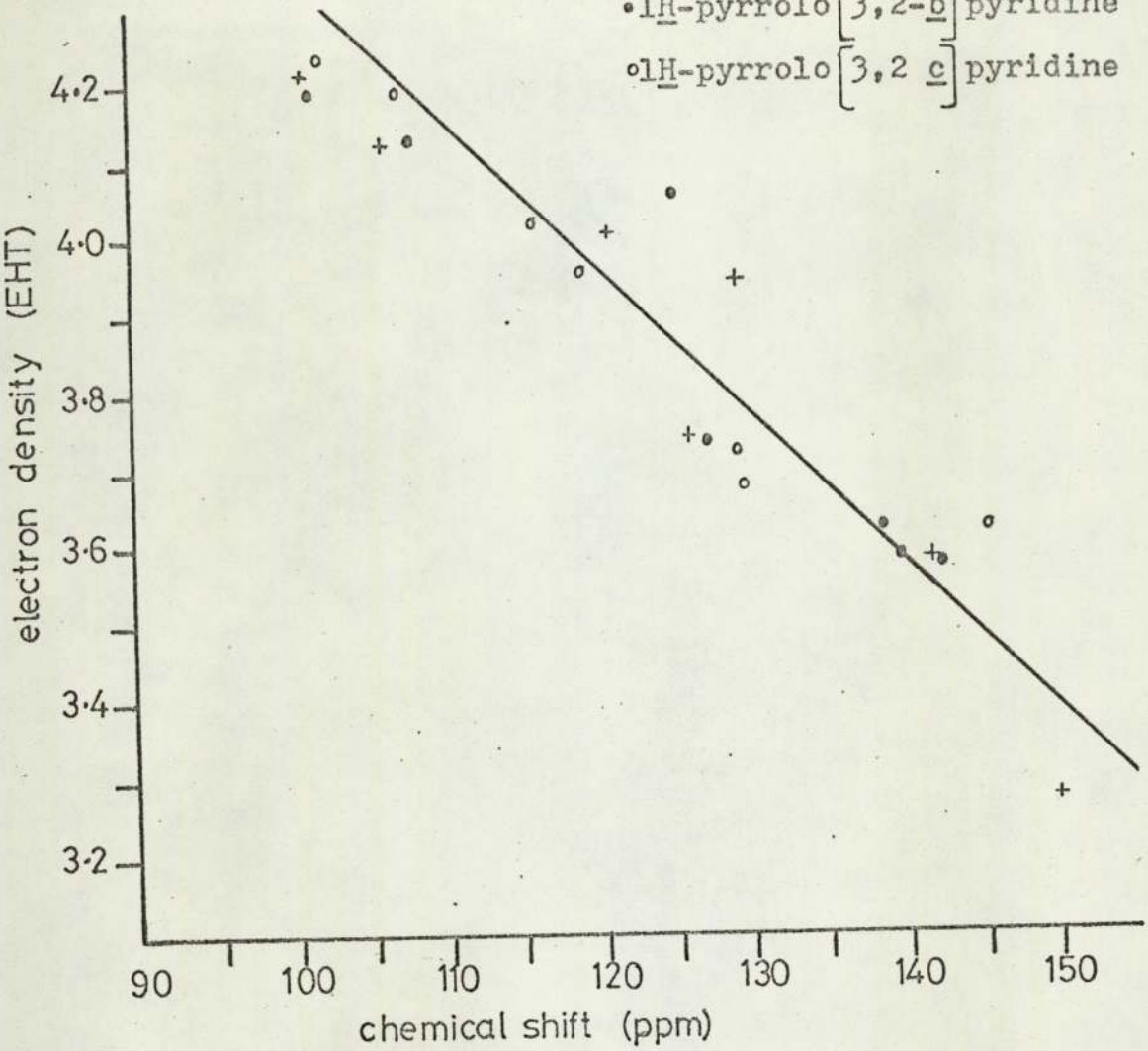
The simple LCAO-MO and VESCF methods gave poor correlation coefficients, however, for the regression analyses of ^{13}C chemical shifts and calculated electron densities. The correlation between the ^{13}C chemical shift and CNDO/2 calculations was shown to be equally as good as the EHT calculations. ^{1}H n.m.r. also gave a good prediction of the ^{13}C chemical shifts, treatment of the ^{1}H and ^{13}C chemical shifts reported for twenty π-deficient and π-excessive heterocycles was found to give an overall correlation coefficient of 0.9 but several data points were seen to deviate from the general trend.

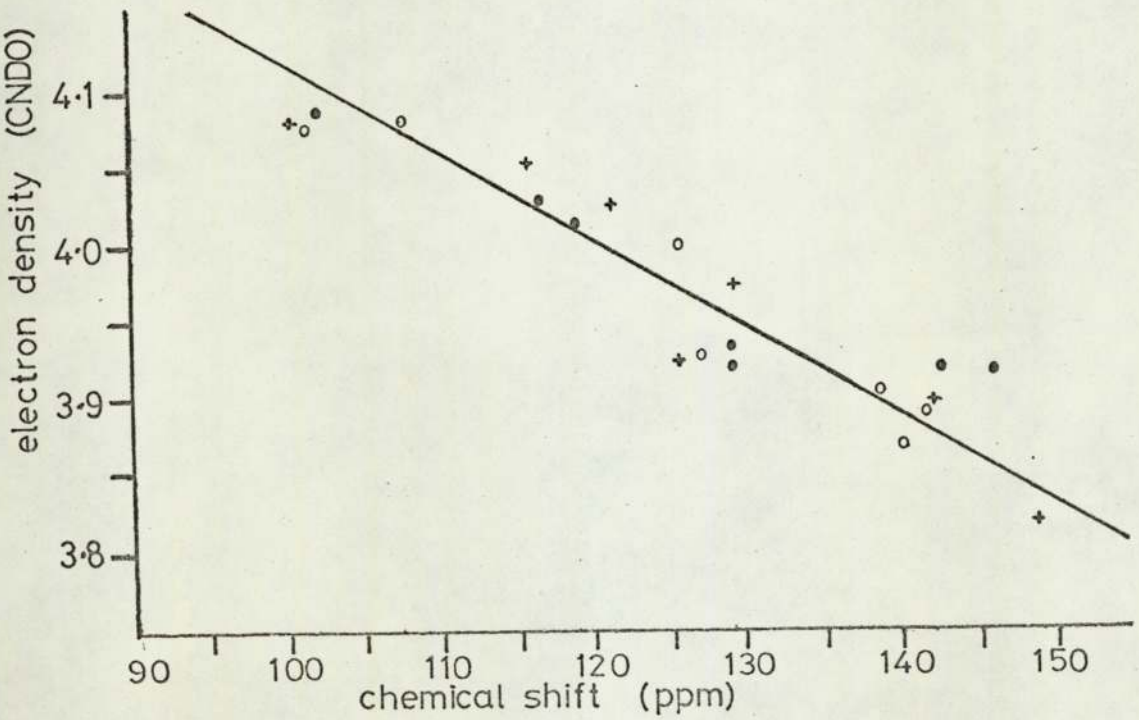
Prediction of the ^{13}C chemical shifts for 1H-pyrrolo[2,3-c]pyridine

The ^{13}C chemical shift data for the three parent pyrrolopyridines (6), (8) and (9) were plotted against the electron densities calculated by the CNDO/2 and EHT methods and the line of best fit drawn (see page 76). The calculated electron densities for 1H-pyrrolo[2,3-c]pyridine (7) were then used to predict the ^{13}C chemical shifts, the results

Graphs to show lines of best fit for ^{13}C chemical shift and electron density

+ 1H-pyrrolo [2,3-b] pyridine
• 1H-pyrrolo [3,2-b] pyridine
° 1H-pyrrolo [3,2 c] pyridine





are shown below:-

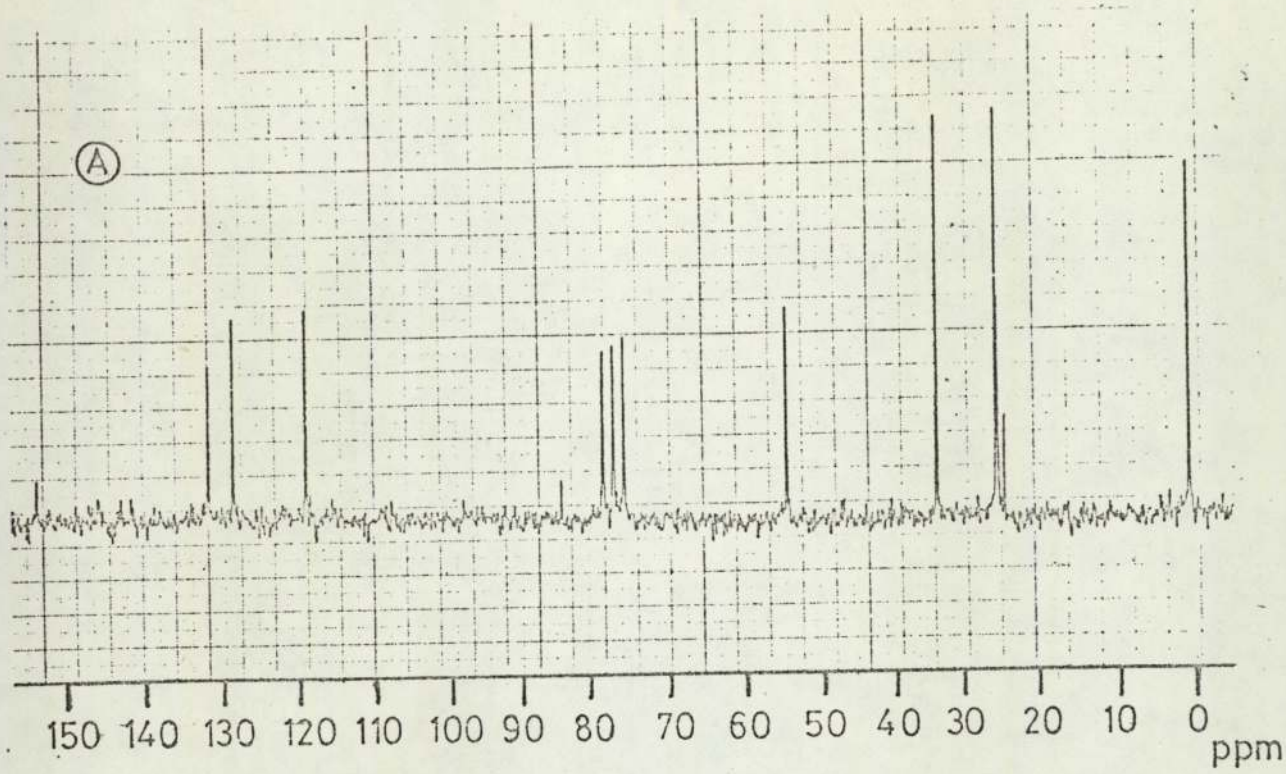
Calculated ^{13}C shifts for 1H-pyrrolo[2,3-c]pyridine

Calcn. by:-	C-2	C-3	C-4	C-5	C-7	C-8	C-9
CNDO/2	136.1	105.9	114.5	133.9	130.1	131.0	126.8
EHT	134.5	106.6	112.3	136.0	137.6	132.2	121.7

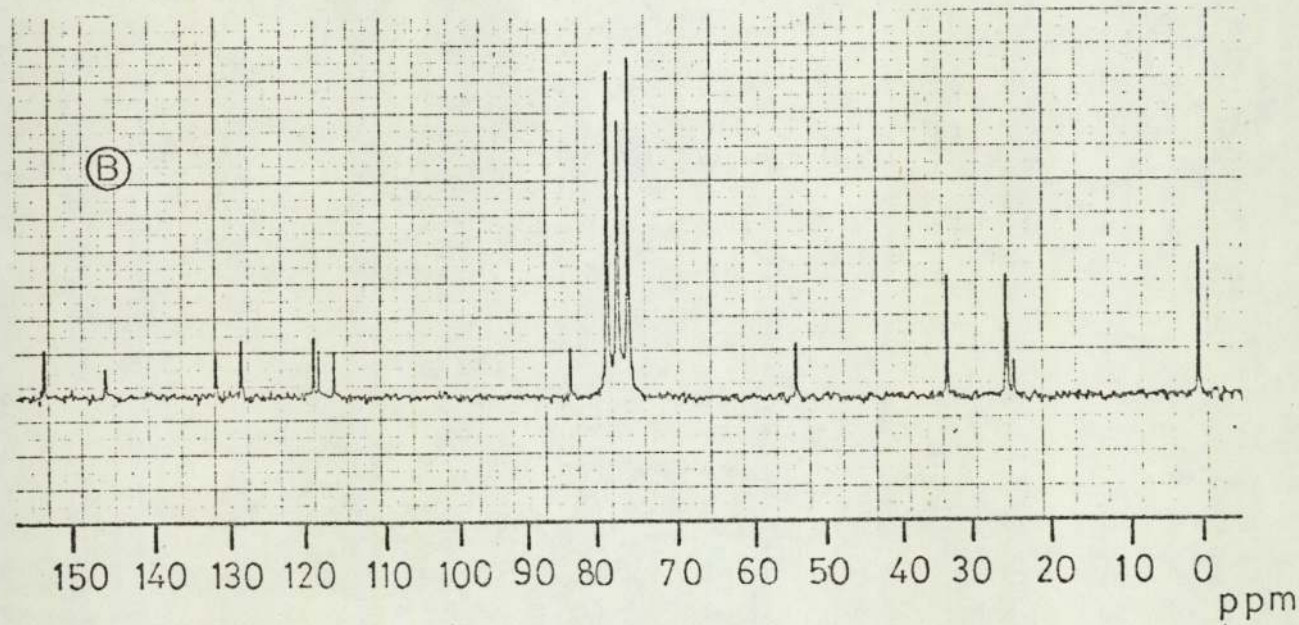
The "insertion" of a nitrogen atom into the benzene ring of indole is predicted to give a downfield shift of 20 ppm at the α-positions, an upfield shift of 4-7 ppm at the β-positions and a downfield shift of 4-7 ppm at the γ-position, a similar effect observed in the three other pyrrolopyridines.

Assignment of the ^{13}C chemical shifts of some pyrrolopyridine derivatives

The pyrrolopyridine derivatives prepared in this work by reaction of aminopyrroles and 1,3-dicarbonyl reagents have been discussed. The orientation of the products from unsymmetrical dicarbonyl reagents was not proven beyond doubt so the ^{13}C n.m.r. spectra of a series of pyrrolopyridines was determined and the introduction of functional groups examined. To complete the series of compounds in which the step-wise addition of a functional group could be observed 3-cyanopyrrolo[2,3-b]pyridine (170) was prepared. The ^{13}C n.m.r. spectra were obtained in deuteriochloroform and the data is listed on pages 88-92. The chemical shifts for 3-cyano-1-cyclohexyl-6-methylpyrrolo[2,3-b]pyridine (154)



C-13 NMR of 3-Cyano-1-cyclohexyl-6-methylpyrrolo[2,3-b]pyridine



C-13 NMR of 3-Cyano-1-cyclohexyl-6-methylpyrrolo[2,3-b]pyridine after the addition of chromic acetylacetonate (50 mg)

were determined with the aid of chromic acetylacetonate an organometallic complex. This has the effect of reducing the peak height of the protonated carbon atoms but allowing the observation of bridgehead carbon atoms which may otherwise be masked. The spectra obtained by this technique are shown on page 81. The assignment of the chemical shifts for 3-cyano-1-cyclohexylpyrrolo[2,3-b]pyridine (157) was aided by single frequency off-resonance decoupling. The data for the series of pyrrolopyridines is shown in Table 6 for comparison.

The reduced ^{13}C-H coupling constants for the four unsubstituted positions in 3-cyano-1-cyclohexylpyrrolo[2,3-b]pyridine (157) were plotted against the chemical shift value of the centre of the decoupling irradiation according to the method of Ernst[164]. The relationship between the reduced coupling and the frequency of irradiation is:-

$$J_r = J_{(C-H)} \times \Delta f$$

J_r = the reduced splitting

$J_{(C-H)}$ = the true splitting

Δf = the offset proton decoupler frequency

Extrapolation of the reduced coupling constants gave a calculated ^1H chemical shift which was compared to the observed chemical shift. These results indicate the ^{13}C chemical shifts to be in the order C-5; C-2; C-4; and C-6; for increasing values downfield. The same order is observed for the ^1H chemical shifts with the 6-H proton being most deshielded and the 5-H proton most shielded.

Pyrrolopyridine (154) was established as the 6-methyl derivative by comparison with the available data for methyl substituted pyridines[165,166] and the data for 3-cyano-1-cyclohexyl-4,6-dimethylpyrrolo[2,3-b]pyridine (136). The two methyl groups in pyrrolopyridine (136) have chemical shifts of 24.4 ppm and 17.7 ppm, the former shift was assigned to the C-6 substituent and the latter to the C-4 methyl group. These shifts were in the range expected for an α-methylpyridine and a γ-methylpyridine, the chemical shift of the methyl group of 2-picoline is 24.2 ppm and that of the methyl group of 4-picoline is at 20.6 ppm. The methyl group in pyrrolopyridine (154) was found to have a chemical shift of 24.6 ppm and was, therefore, established as the 6-methyl isomer. In pyridines the methyl groups cause a downfield shift of about 9 ppm for the carbon atom of attachment and in 4,6-dimethylpyrrolopyridine (136) the downfield shifts are 10-12 ppm. A similar downfield shift of 10 ppm is observed in 6-methylpyrrolopyridine (154) and gives rise to the peak at 154.3 ppm. The pyrrolopyridines prepared from 1-phenylbutan-1,3-dione are clearly seen to be isomers with chemical shifts at 18.1 ppm and 24.5 ppm. The nitrile group causes an upfield shift of 16 ppm for the C-3 atom and is unaltered at 83-84 ppm throughout the series. The chemical shift of the nitrile carbon is 115-117 ppm . Comparison of the data for pyrrolopyridines (157) and (170) indicates that the cyclohexyl-group has no additive effects on the chemical shifts of the ring carbon atoms. The chemical shifts for the cyclohexyl-group are almost identical to those found for cyclohexylamine

which are at 50.4 ppm, 36.7 ppm, 25.7 ppm and 25.1 ppm[167]. The most deshielded carbon atom is nearest to the nitrogen atom and gives rise to the shift at 50.4 ppm, and the most shielded position being furthest away. Only two shifts are observed for the remaining four carbon atoms which are in two identical pairs.

Instrumental

The ^{13}C spectra were determined on a Bruker HX 90E spectrometer operating at 21.14 Kgauss, equivalent to 22.63 MHz for ^{13}C nuclei and 90MHz for ^{1}H nuclei. Samples were deuteriochloroform solutions with a deuterium lock signal equivalent to TMS =0. The pulsewidth was 11 sec and the pre-delay 143 sec. The listing of the computer print-out has the following significance:-

Column 1: channel number in computer memory. Zero is at the left-hand side of the spectrum.

Column 2: frequency in Hz. relative to the internal standard unless otherwise stated.

Column 3: chemical shift in ppm relative to the internal standard.

Column 4: integrated peak intensity relative to the largest peak = 1000.

PCMU NO. F.464/4

TAPE FILE NO 464C/4

SAMPLE NO. 1H-pyrrolo[2,3-b]pyridine (6)
(undecoupled)

PP				
1267	1381.8359	61.0621	PPM	370
1284	1373.5351	60.6953	PPM	93
1401	1316.4062	58.1708	PPM	398
1409	1312.5000	57.9982	PPM	345
1415	1309.5703	57.8687	PPM	268
1424	1305.1757	57.6745	PPM	295
1763	1139.6484	50.3600	PPM	401
1772	1135.2539	50.1658	PPM	338
1778	1132.3242	50.0364	PPM	301
1786	1128.4179	49.8638	PPM	287
2016	1016.1132	44.9011	PPM	657
2030	1009.2773	44.5990	PPM	604
2039	1004.8828	44.4048	PPM	171
2153	949.2187	41.9451	PPM	691
2168	941.8945	41.6214	PPM	554
2175	938.4765	41.4704	PPM	86
2336	859.8632	37.9966	PPM	164
2350	853.0273	37.6945	PPM	774
2362	847.1679	37.4356	PPM	437
2529	765.6250	33.8323	PPM	716
2544	758.3007	33.5086	PPM	1000
2583	739.2578	32.6671	PPM	157
2635	713.8671	31.5451	PPM	198
2640	711.4257	31.4372	PPM	303
2651	706.0546	31.1999	PPM	278
2657	703.1250	31.0704	PPM	295
2665	699.2187	30.8978	PPM	123
2961	554.6875	24.5111	PPM	135
2973	548.8281	24.2522	PPM	364
2978	546.3867	24.1443	PPM	168
2982	544.4335	24.0580	PPM	198
2990	540.5273	23.8854	PPM	306
2998	536.6210	23.7128	PPM	110
3330	374.5117	16.5493	PPM	279
3336	371.5820	16.4198	PPM	281
3343	368.1640	16.2688	PPM	209
3349	365.2343	16.1393	PPM	271
3690	198.7304	8.7817	PPM	349
3695	196.2890	8.6738	PPM	259
3702	192.8710	8.5228	PPM	238
3708	189.9414	8.3933	PPM	237

SAMPLE NO. (decoupled)

PP				
1440	3370.9055	148.9573	PPM	188
1550	3209.1255	141.8084	PPM	1000
1748	2917.9217	128.9404	PPM	626
1800	2841.4439	125.5609	PPM	963
1874	2732.6101	120.7516	PPM	306
1956	2612.0105	115.4224	PPM	629
2189	2269.3312	100.2797	PPM	656
3732	0.0000	0.0000	PPM	127

PCMU NO. F465/4

TAPE FILE NO. 465/4

SAMPLE NO. 1H-pyrrolo[3,2 c]pyridine (8)
(undecoupled)

PP				
295	1856.4453	82.0347	PPM	585
317	1845.7031	81.5600	PPM	633
463	1774.4140	78.4098	PPM	607
481	1765.6250	78.0214	PPM	663
508	1752.4414	77.4388	PPM	45
520	1746.5820	77.1799	PPM	260
537	1738.2812	76.8131	PPM	347
552	1730.9570	76.4894	PPM	174
657	1679.6875	74.2239	PPM	601
680	1668.4570	73.7276	PPM	608
828	1596.1914	70.5343	PPM	573
851	1584.9609	70.0380	PPM	622
953	1535.1562	67.8372	PPM	614
970	1526.8554	67.4704	PPM	579
1246	1392.0898	61.5152	PPM	427
1331	1350.5859	59.6812	PPM	522
1348	1342.2851	59.3144	PPM	681
1883	1081.0546	47.7708	PPM	602
1897	1074.2187	47.4687	PPM	583
2158	946.7773	41.8372	PPM	582
2177	937.5000	41.4273	PPM	511
2222	915.5273	40.4563	PPM	574
2236	908.6914	40.1542	PPM	552
2521	769.5312	34.0049	PPM	546
2537	761.7187	33.6596	PPM	540
3413	333.9843	14.7584	PPM	1000
3478	302.2460	13.3559	PPM	944
3487	297.8515	13.1618	PPM	32
3543	270.5078	11.9535	PPM	868

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PCMU NO. F444/4

TAPE FILE NO. 444/4

SAMPLE NO. (decoupled)

PP				
1545	3221.8914	142.3283	PPM	976
1574	3178.2403	141.4436	PPM	164
1599	3141.4721	138.8189	PPM	1000
1783	2871.8594	126.8637	PPM	788
1836	2837.3317	126.3659	PPM	155
2081	2432.5819	117.4936	PPM	763
2175	2294.3336	121.3845	PPM	863
2549	1744.2819	77.3742	PPM	96
2571	1713.3966	75.7136	PPM	110
3735	1.0000	1.0000	PPM	316

PCMU NO. F.94/5

TAPE FILE NO. 94A/5

SAMPLE NO. 1H-pyrrolo[3,2-b]pyridine (9)
(undecoupled)

.PP				
22	1493.8033	66.0098	PPM	999
79	1472.9084	65.0865	PPM	175
212	1424.1536	62.9321	PPM	211
222	1420.4878	62.7701	PPM	182
230	1417.5552	62.6405	PPM	179
240	1413.8894	62.4785	PPM	237
255	1408.3908	62.2355	PPM	82
264	1405.0916	62.0897	PPM	82
692	1248.1964	55.1567	PPM	64
703	1244.1640	54.9785	PPM	88
711	1241.2314	54.8489	PPM	95
721	1237.5657	54.6869	PPM	96
1025	1126.1261	49.7625	PPM	134
1047	1118.0614	49.4061	PPM	150
1275	1034.4817	45.7128	PPM	26
1526	942.4707	41.6469	PPM	126
1549	934.0395	41.2743	PPM	118
1658	894.0825	39.5087	PPM	171
1678	886.7510	39.1847	PPM	164
1821	834.3304	36.8683	PPM	84
1823	833.5972	36.8359	PPM	63
1846	825.1659	36.4633	PPM	93
1848	824.4328	36.4309	PPM	58
2104	730.5889	32.2840	PPM	167
2121	724.3571	32.0087	PPM	167
2267	670.8368	29.6436	PPM	92
2269	670.1037	29.6112	PPM	37
2292	661.6724	29.2387	PPM	96
2294	660.9392	29.2063	PPM	36
2710	508.4430	22.4676	PPM	166
2729	501.4780	22.1598	PPM	171
3188	333.2189	14.7246	PPM	233
3205	326.9871	14.4492	PPM	184
3607	179.6229	7.9373	PPM	19

PCMU NO. F94/5

TAPE FILE NO. 94/5

SAMPLE NO. (decoupled)

PP				
1484	3310.6057	146.2927	PPM	141
1542	3225.3035	142.5233	PPM	950
1745	2926.7460	129.3303	PPM	218
1752	2916.4509	128.8754	PPM	896
1903	2694.3712	119.0619	PPM	881
1941	2638.4836	116.5922	PPM	999
2162	2313.4530	102.2294	PPM	912
2527	1776.6378	78.5080	PPM	354
2549	1744.2818	77.0782	PPM	394
2571	1711.9258	75.6485	PPM	298
3735	0.0000	0.0000	PPM	225

PCMU NO. F74/5

TAPE FILE NO.

SAMLE NO. 3-cyano-1-cyclohexyl-6-methylpyrrolo [2,3-b] pyridine (154)

.PP				
1362	3491.5051	154.2865	PPM	57
1715	2972.3385	131.3450	PPM	351
1765	2898.8022	128.0955	PPM	336
1915	2678.1932	118.3470	PPM	456
2443	1901.6495	84.0322	PPM	69
2529	1775.1670	78.4430	PPM	550
2550	1744.2818	77.0782	PPM	651
2572	1711.9258	75.6485	PPM	463
2909	1216.2909	53.7468	PPM	443
3219	760.3656	33.5998	PPM	916
3341	580.9370	25.6711	PPM	1000
3344	576.5248	25.4761	PPM	396
3358	555.9346	24.5662	PPM	222
3736	0.0000	0.0000	PPM	736

SAMPLE NO. (after chromic acetylacetonate)

PP				
1361	3490.0343	154.2215	PPM	42
1486	3306.1935	146.0978	PPM	33
1711	2975.2800	131.4750	PPM	52
1764	2897.3315	128.0305	PPM	51
1913	2678.1932	118.3470	PPM	49
1923	2663.4859	117.6971	PPM	32
1955	2616.4227	115.6174	PPM	32
2442	1900.1788	83.9672	PPM	24
2518	1788.4036	79.0279	PPM	912
2539	1757.5183	77.6632	PPM	999
2561	1725.1623	76.2334	PPM	958
2908	1214.8202	53.6818	PPM	43
3218	758.8949	33.5349	PPM	138
3339	580.9370	25.6711	PPM	137
3342	576.5248	25.4761	PPM	58
3355	557.4054	24.6312	PPM	37
3734	0.0000	0.0000	PPM	169

PCMU NO. F91/4

TAPE FILE NO. 91/4

SAMPLE NO. Pyrrolopyridines (168) and (169) prepared from 1-phenylbutan-1,3-dione.

PP				
1362	3488.5636	154.1565	PPM	78
1381	3460.6198	152.9217	PPM	102
1481	3313.5471	146.4227	PPM	78
1522	3253.2473	143.7581	PPM	66
1560	3197.3597	141.2885	PPM	67
1588	3156.1794	139.4688	PPM	43
1631	3092.9381	136.6742	PPM	37
1686	3012.0482	133.0997	PPM	82
1693	3001.7531	132.6448	PPM	218
1746	2923.8046	129.2003	PPM	163
1754	2912.0387	128.6804	PPM	999
1760	2903.2144	128.2905	PPM	205
1779	2875.2706	127.0557	PPM	578
1782	2870.8584	126.8607	PPM	97
1906	2688.4883	118.8019	PPM	95
1915	2675.2517	118.2170	PPM	84
1934	2647.3079	116.9822	PPM	82
1938	2641.4250	116.7222	PPM	198
1947	2628.1885	116.1373	PPM	40
1970	2594.3618	114.6425	PPM	37
2446	1894.2959	83.7072	PPM	61
2453	1884.0008	83.2523	PPM	49
2525	1778.1085	78.5730	PPM	156
2547	1745.7525	77.1432	PPM	232
2569	1713.3965	75.7135	PPM	224
2899	1228.0567	54.2667	PPM	161
2906	1217.7616	53.8118	PPM	116
3219	757.4242	33.4699	PPM	208
3221	754.4827	33.3399	PPM	359
3339	580.9370	25.6711	PPM	596
3343	575.0541	25.4111	PPM	301
3357	554.4639	24.5012	PPM	86
3455	410.3327	18.1322	PPM	138
3734	0.0000	0.0000	PPM	260

PCMU NO. F93/5

TAPE FILE NO. 93A/5

SAMPLE NO. 3-cyanopyrrolo[2,3-b]pyridine (170)
(undecoupled)

PP				
340	2204.8950	97.4323	PPM	75
350	2199.0262	97.1730	PPM	332
359	2193.7443	96.9396	PPM	157
381	2180.8330	96.3691	PPM	25
410	2163.8136	95.6170	PPM	245
417	2159.7055	95.4355	PPM	162
645	2025.8976	89.5226	PPM	94
657	2018.8551	89.2114	PPM	312
665	2014.1601	89.0039	PPM	114
711	1987.1638	87.8110	PPM	462
1039	1794.6683	79.3048	PPM	1000
1052	1787.0389	78.9676	PPM	276
1322	1628.5823	71.9656	PPM	259
1334	1621.5397	71.6544	PPM	163
1401	1582.2190	69.9168	PPM	196
1416	1573.4159	69.5278	PPM	189
1491	1529.4001	67.5828	PPM	53
1503	1522.3576	67.2716	PPM	104
1637	1443.7162	63.7965	PPM	268
1684	1416.1330	62.5776	PPM	273
1700	1406.7429	62.1627	PPM	153
2867	721.8581	31.8982	PPM	291
3352	437.2229	19.3205	PPM	319
3429	392.0335	17.3236	PPM	459
3495	353.2996	15.6120	PPM	591
3511	343.9096	15.1970	PPM	238
3548	322.1952	14.2375	PPM	283

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PCMU NO. F93/5

TAPE FILE NO. -

SAMPLE NO. (decoupled)

PP				
1386	3340.0202	147.5925	PPM	214
1425	3282.6619	145.0579	PPM	950
1574	3063.5236	135.3744	PPM	1000
1698	2881.1535	127.3156	PPM	910
1825	2694.3712	119.0619	PPM	176
1843	2667.8981	117.8920	PPM	996
1879	2614.9520	115.5524	PPM	73
2371	1891.3544	83.5773	PPM	143
3018	939.7943	41.5286	PPM	147
3032	919.2041	40.6188	PPM	374
3046	898.6139	39.7089	PPM	460
3061	876.5530	38.7341	PPM	407
3075	855.9629	37.8242	PPM	254
3657	0.0000	0.0000	PPM	158

PCMU NO. F90/4

TAPE FILE NO. 90/4

SAMPLE NO. 3-cyano-1-cyclohexyl-4,6-dimethylpyrrolo [2,3-b] pyridine (136)

PP				
1363	3488.5636	154.1565	PPM	454
1487	3306.1935	146.0978	PPM	156
1571	3182.6524	140.6386	PPM	430
1713	2973.8093	131.4100	PPM	573
1896	2704.6663	119.5168	PPM	640
1933	2650.2494	117.1122	PPM	194
1937	2644.3665	116.8522	PPM	218
2457	1879.5886	83.0573	PPM	128
2524	1781.0499	78.7030	PPM	169
2546	1748.6940	77.2732	PPM	152
2567	1717.8087	75.9084	PPM	147
2909	1214.8202	53.6818	PPM	385
3220	757.4242	33.4699	PPM	999
3340	580.9370	25.6711	PPM	856
3344	575.0541	25.4111	PPM	628
3360	551.5225	24.3712	PPM	394
3462	401.5083	17.7423	PPM	402
3735	0.0000	0.0000	PPM	298

PCMU NO. F156/5

TAPE FILE NO. 156/5

SAMPLE NO. 3-cyano-1-cyclohexylpyrrolo [2,3-b] pyridine (157)

PP				
1509	3276.7790	144.7980	PPM	342
1700	2995.8702	132.3848	PPM	400
1766	2898.8022	128.0955	PPM	485
1919	2673.7810	118.1520	PPM	467
2901	1229.5274	54.3317	PPM	325
3222	757.4242	33.4699	PPM	891
3342	580.9370	25.6711	PPM	1000
3346	575.0541	25.4111	PPM	546
3737	0.0000	0.0000	PPM	162

.PP

1495	3295.8984	145.6428	PPM	145
1521	3257.6595	143.9531	PPM	118
1687	3013.5189	133.1647	PPM	112
1711	2978.2214	131.6050	PPM	92
1751	2919.3924	129.0054	PPM	19
1754	2914.9802	128.8104	PPM	57
1757	2910.5680	128.6154	PPM	17
1776	2882.6242	127.3806	PPM	122
1912	2682.6054	118.5419	PPM	131
1926	2662.0152	117.6321	PPM	112
2440	1906.0617	84.2272	PPM	7
2528	1776.6378	78.5080	PPM	28
2550	1744.2818	77.0782	PPM	28
2571	1713.3965	75.7135	PPM	24
2901	1228.0567	54.2667	PPM	198
3221	757.4242	33.4699	PPM	569
3341	580.9370	25.6711	PPM	1000
3359	554.4639	24.5012	PPM	16
3729	10.2950	0.4549	PPM	24
3743 -	10.2951 -	0.4549	PPM	27

PCMU NO. F.1567/5

TAPE FILE NO. -

SAMPLE NO. 3-cyano-1-cyclohexylpyrrolo[2,3-b] pyridine (157) irradiating at τ3.7

PP				
1499	3291.0155	145.3829	PPM	319
1517	3263.5424	144.2131	PPM	329
1688	3012.0482	133.0997	PPM	205
1710	2979.6922	131.6700	PPM	329
1753	2916.4509	128.8754	PPM	76
1756	2912.0388	128.6804	PPM	149
1758	2909.0973	128.5504	PPM	79
1774	2885.5657	127.5106	PPM	387
1907	2689.9593	118.8669	PPM	194
1910	2685.5468	118.6719	PPM	96
1929	2657.6033	117.4371	PPM	300
2528	1776.6378	78.5080	PPM	52
2549	1745.7525	77.1432	PPM	84
2571	1713.3965	75.7135	PPM	81
2887	1248.6469	55.1766	PPM	202
2916	1205.9958	53.2919	PPM	183
2920	1200.1129	53.0319	PPM	62
3184	811.8411	35.8745	PPM	108
3222	755.9535	33.4049	PPM	507
3259	701.5366	31.0002	PPM	125
3304	635.3539	28.0757	PPM	185
3344	576.5248	25.4761	PPM	1000
3380	523.5786	23.1364	PPM	246
3387	513.2836	22.6815	PPM	76
3717	27.9438	1.2348	PPM	50

(G) Mass Spectra

Mass spectral details for most of the compounds prepared in this work are recorded in the experimental section, and are presented as $^{m}/_{e}$ readings with the percentage abundance in parentheses. The mass spectra of compounds considered to be typical of a group are shown graphically on pages 100-102.

(I) Aminomethylenesuccinonitriles

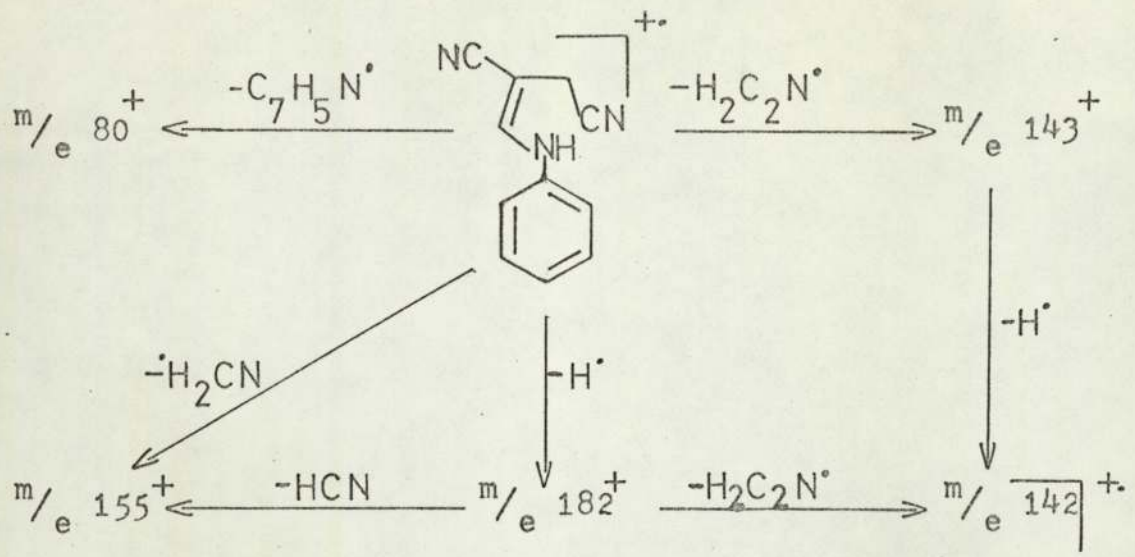
The mass spectra of the aminomethylenesuccinonitriles have a common fragmentation pathway with the exception of the three alkyl derivatives benzyl-, phenethyl-, and cyclohexyl-.

The base peak in the mass spectra is usually the molecular ion. However, in the case of ortho-substituted phenylaminomethylenesuccinonitriles (88) and (89) the base peak corresponds to the molecular ion less 18 or 32 mass units. This is explained by the rearrangement of these molecules to the more stable pyrroloquinazolines (via the aminopyrrole) with the elimination of water or methanol. The fragmentation pathway then follows that of the pyrroloquinazolines prepared experimentally. The remaining aminomethylenesuccinonitriles have a fragmentation which is summarised in Table 8. The common losses are M-H ; M-H_2CN ; M-CH_2CN ; M-R (where R = the phenyl ring substituent group and is at $^{m}/_{e}$ 182); M-R-H_2CN at $^{m}/_{e}$ 155; and M-R-102 at $^{m}/_{e}$ 80.

The mass spectra of anilinomethylenesuccinonitrile is shown on page 100 and the breakdown pathway is postulated to be:-

TABLE 8

Compound No	M^+	M-H	M-HCN	M-CH_2CN	M-R	M-R-HCN	$^m/_e$ 155	$^m/_e$ 80
76	100	19	7	12	18	10	25	8
77	100	22	10	13	7	11	28	10
78	100	26	13	17	59	13	30	13
79	100	8	--	--	83	10	10	10
80	100	9	--	15	11	--	14	23
81	100	3	--	--	3	16	--	--
82	100	8	9	--	77	15	74	10
83	100	19	5	9	23	14	53	31
84	100	5	--	--	47	--	17	42
85	100	7	--	--	44	--	19	16
86	100	3	--	--	42	--	19	17
87	100	--	--	--	5	--	3	5
88	100	--	--	--	22	--	19	3
89	100	3	--	--	15	--	7	3
90	100	7	3	--	15	4	--	3



The benzyl and phenethyl derivatives (74) and (75) have mass spectra characterised by the formation of a tropylium ion and this is the base peak for these derivatives. M-91 peaks are also present. The cyclohexyl derivative (72) is also atypical of the aminomethylenesuccinonitriles, the loss of 1 mass unit and then 81 mass units rather than a direct loss of 82 mass units indicates the main fragmentation is from the cyclohexyl group. The base peak at $^{m}/_{e}$ 55 is due to such a breakdown giving rise to a fragment of molecular formula C_4H_7 .

(II) Aminopyrroles

The aminopyrroles have the molecular ion as the most abundant ion and the common losses give rise to peaks at M-1 $^{+}$; M-28 $^{+}$; M-R $^{+}$. The peak at $^{m}/_{e}$ 80 ($C_4H_4N_2$) is also present indicating the breakdown of the intermediate aminomethylenesuccinonitriles may follow the rearrangement of the molecular ion to the aminopyrrole.

The benzyl-, phenethyl-, and cyclohexylpyrroles exhibit a fragmentation pathway based on the pyrrole N-

substituent. The common peaks for the aryl-substituted pyrroles are shown in Table 9 and the spectrum for the N-benzylpyrrole is shown on page 101

TABLE 9

Compound No.	M^+	M-1	M-28	$^m/_e$ 182	$^m/_e$ 80
92	100	10	14	10	16
95	100	21	11	25	8
97	100	18	10	15	19
98	100	9	--	37	3
99	100	6	--	4	19
100	100	3	6	34	28
101	100	6	6	34	28
102	100	3	6	46	50
103	100	3	6	23	23
104	100	3	--	28	16
105	100	--	--	31	12
106	100	--	5	3	22

(III) Acylaminopyrroles

The molecular ion of the acylaminopyrroles loses ketone $CH_2=C=O$ to give the base peak at M-42 for most of the acylaminopyrroles. The other abundant peaks occur at the molecular ion and $^m/_e$ 43. The M-R peak is less significant in these compounds. The breakdown of the cyclohexyl-, benzyl-, and phenethyl- derivatives show the characteristics of that group in preference. The mass spectrum of 2-acetamido-4-cyano-1-(m-chlorophenyl)pyrrole is shown on page 102. The chlorophenyl derivative is

particularly useful in determining the fragmentation pathway by the presence of paired peaks in the 3:1 ratio expected of chlorine containing compounds. Table 10 shows the common ions and percentage abundance for the aryl pyrroles.

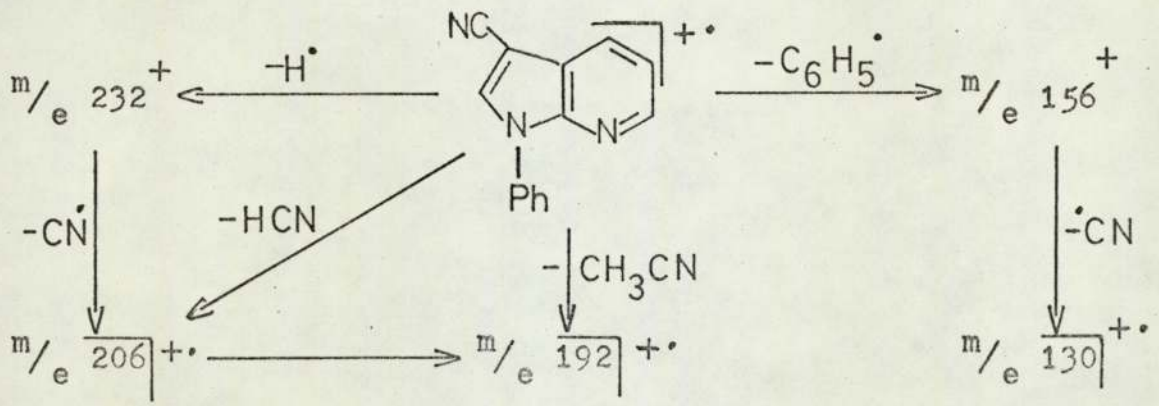
TABLE 10

Compound No.	M^+	M-42	$^m/_e$ 80	$^m/_e$ 42
108	20	100	7	24
112	70	100	16	63
113	24	100	7	25
114	68	100	6	100
115	34	100	20	100
116	43	100	8	60
119	28	100	17	83
120	15	100	8	100
121	55	90	5	100

(IV) Pyrrolopyridines

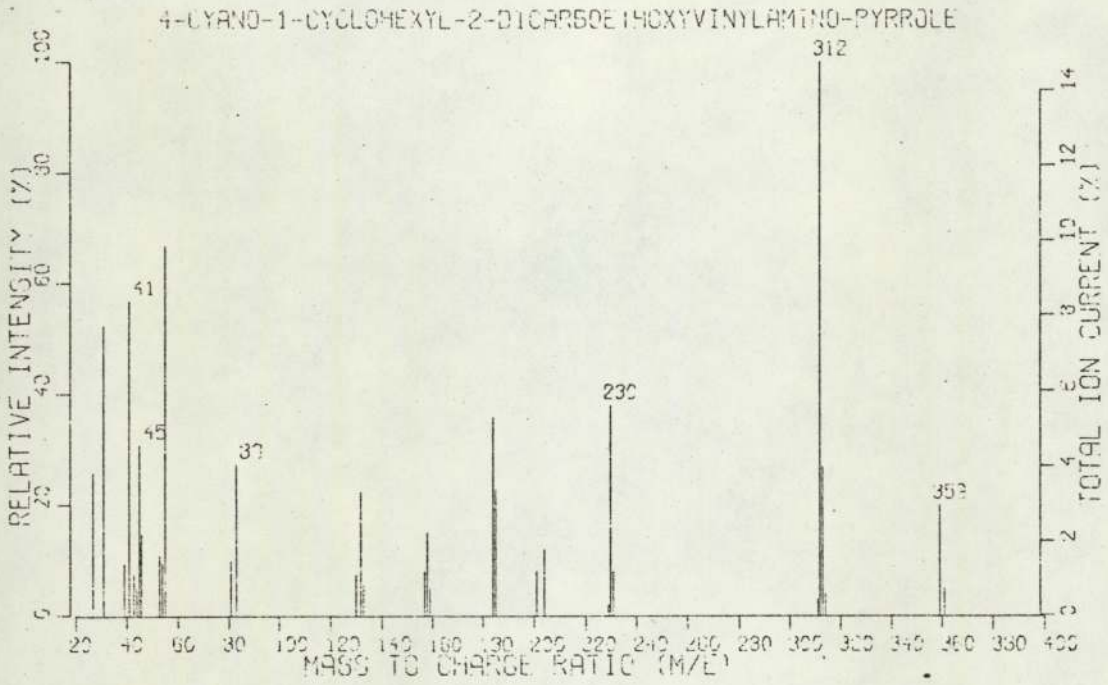
The spectra of simple unsubstituted heterocycles are characterised by very intense peaks of the molecular ions[167]. The mass spectrum of the parent 1H-pyrrolo[2,3-b] pyridine was found to be no exception[168]. The base peak was found to be the molecular ion and the fragmentation pathway was similar to indole in that the first loss was to M-H in 9% abundance. The most abundant peak after the molecular ion was found to be due to the expulsion of one molecule of HCN, and in common with other heterocycles a $C_3H_3^+$ fragment was produced. The pyrrolopyridines prepared in this work showed a strong molecular ion peak of 100% in most cases; N-benzyl-, N-phenethyl- and N-cyclohexyl- derivatives being the only exceptions.

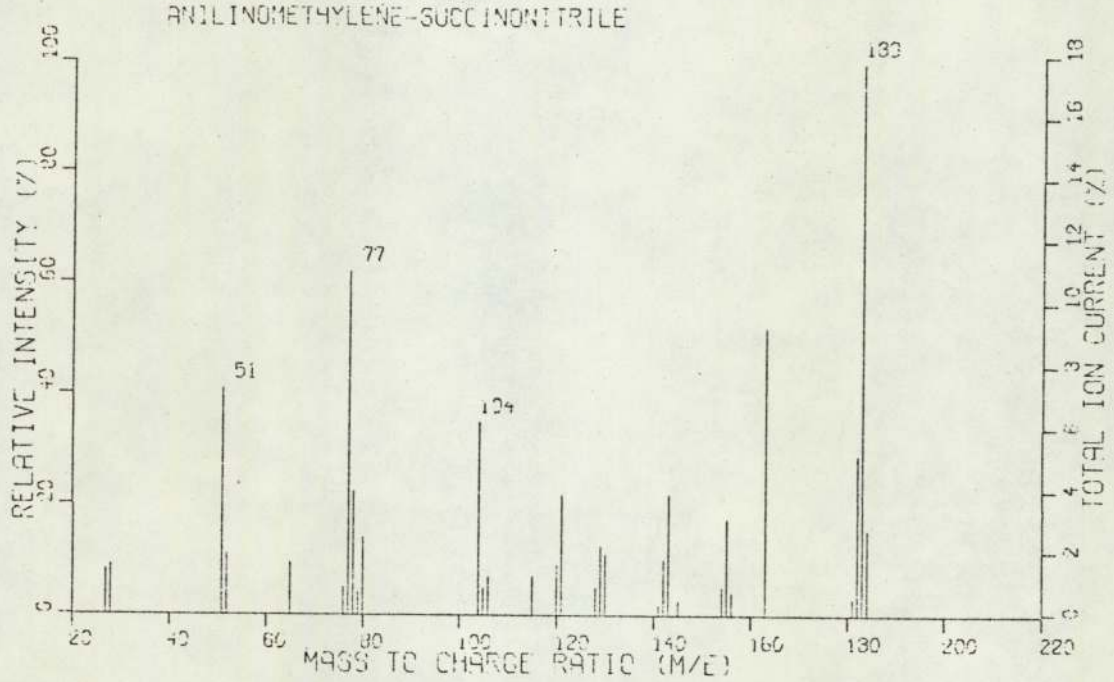
The main degradation routes of the molecular ion peak correspond to those requiring the least amount of energy, therefore the weakest bonds are cleaved and the most stable degradationproducts formed. The high degree of stability of pyrrolopyridines to chemical and catalytic reactions previously noted were found to be mirrored by the lack of any notable electron impact-induced fragmentation. The typical fragmentation of the 4,6-dimethylpyrrolopyridines was an initial loss of 1 mass unit followed by the loss of a neutral HCN molecule. M-15 losses and M-R losses were also common (R=phenyl ring substituent). Peaks were found at the usual $^{m}/_{e}$ 77; $^{m}/_{e}$ 41; $^{m}/_{e}$ 39; $^{m}/_{e}$ 27 positions. The use of mass spectrometry in the structural proof of pyrrolopyridines prepared from 4,4-dimethoxbutan-1-one and 1-phenylbutan-1,3-dione were hampered by the low abundance of the peaks produced by fragmentation of the molecular ion. However detailed examination of the mass spectrum of 3-cyano-6-methyl-1-phenylpyrrolo[2,3-b]pyridine (155) indicated the correct orientation had been postulated. The spectrum showed a loss of acetonitrile (CH_3CN) and was determined by accurate mass measurement and ion source determination, this is consistent with the methyl group being at the C-6 position. The fragmentation pathway is postulated to be:-

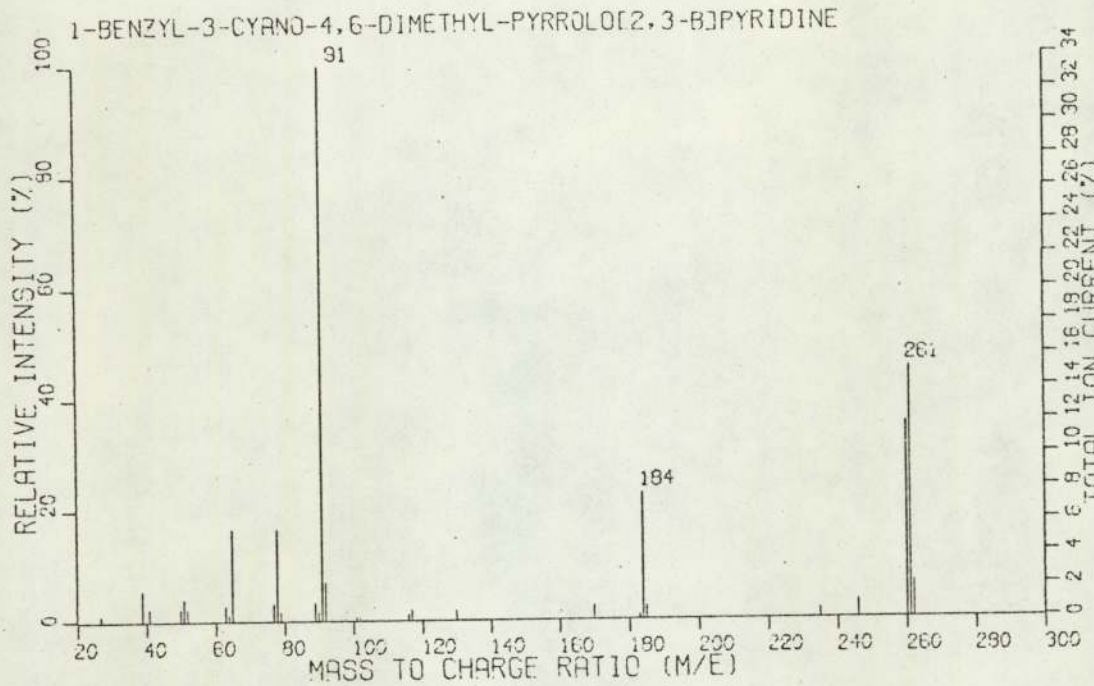


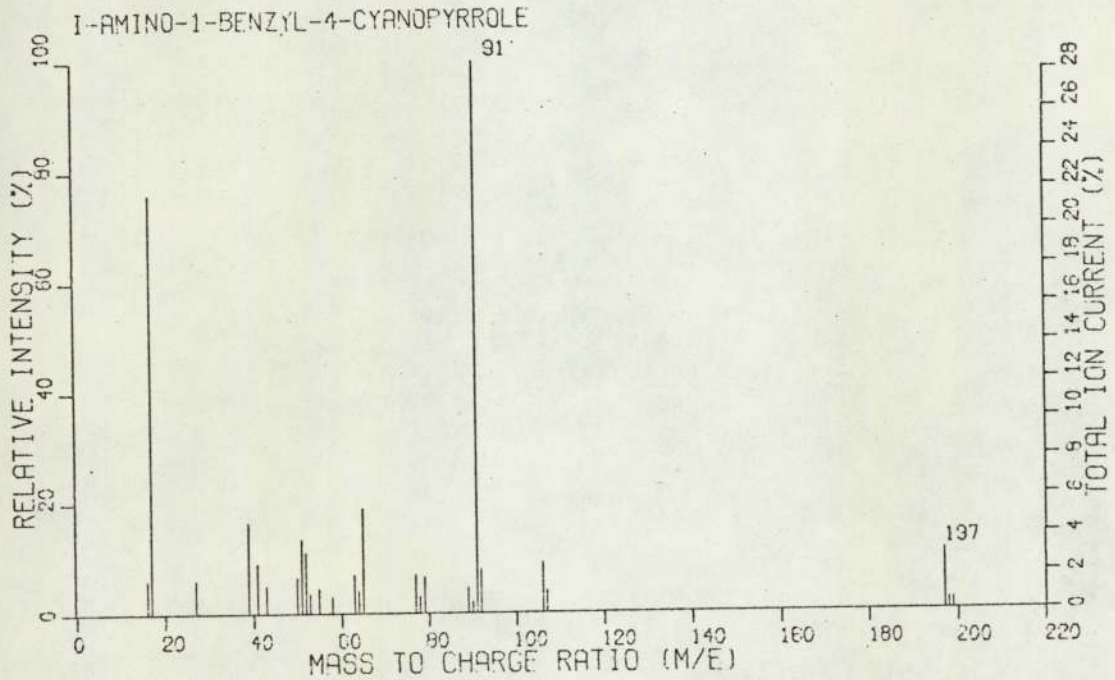
(V) Pyrrolopyridinones

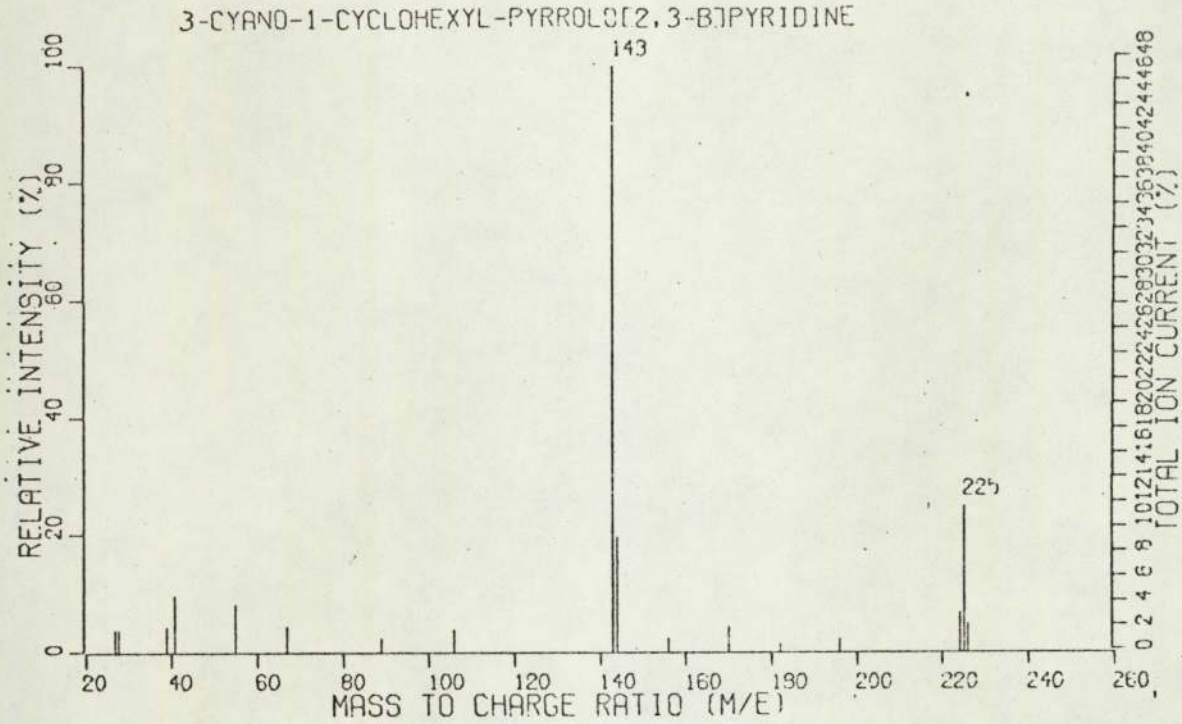
The mass spectra of the pyrrolopyridinones may be expected to show losses of carbon monoxide to give peaks at M-28, analagous to pyridones and quinolones[169]. However, the pyrrolopyridinones prepared in this work have a fragmentation pathway characteristic of the cyclohexyl group. A loss of 28 mass units is observed in low abundance and arises from the M-1 peak. The fragmentation of the pyrrolopyridinones produced ions in low abundance as in the pyrrolopyridines indicating these stuctures are also stable to electron impact. The 2(2',2'-diethoxycarbonyl)vinylaminopyrroles showed a base peak at M-46, this was attributed to the loss of ethanol and the subsequent pyrrolopyridin-4(7H)-one formation. The mass spectrum of 4-cyano-1-cyclohexyl-2(2',2'-diethoxycarbonyl)vinylaminopyrrole (189) is shown on page 100.

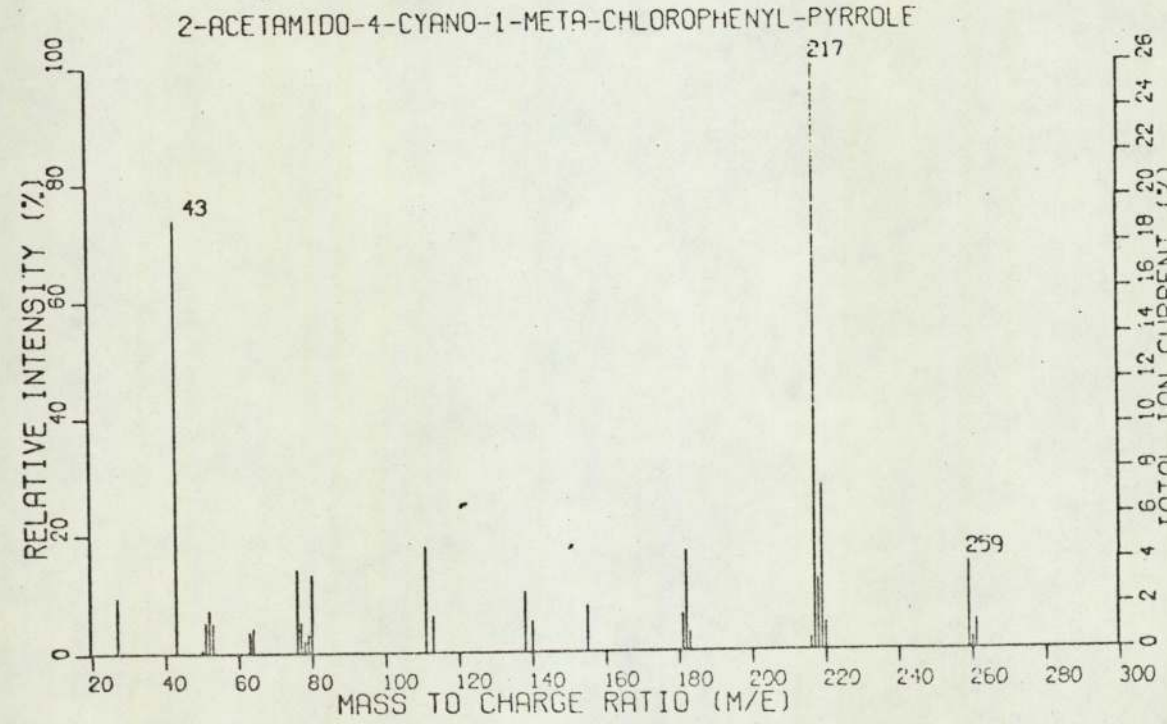

4-CYANO-1-CYCLOHEXYL-2-DICARBOETHOXYVINYLAMINO-PYRROLE
RELATIVE INTENSITY (%)
TOTAL ION CURRENT (%)
MASS TO CHARGE RATIO (M/E)
312
41
45
39
230
359


ANILINOMETHYLENE-SUCCINONITRILE
RELATIVE INTENSITY (%)
TOTAL ION CURRENT (%)
MASS TO CHARGE RATIO (M/E)
130
77
51
104


1-BENZYL-3-CYANO-4,6-DIMETHYL-PYRROLO[2,3-B]PYRIDINE
91
261
184
RELATIVE INTENSITY (%)
TOTAL ION CURRENT (%)
MASS TO CHARGE RATIO (M/E)


1-AMINO-1-BENZYL-4-CYANOPYRROLE
91
197
RELATIVE INTENSITY (%)
TOTAL ION CURRENT (%)
MASS TO CHARGE RATIO (M/E)


3-CYANO-1-CYCLOHEXYL-PYRROLO[2,3-B]PYRIDINE
143
225
RELATIVE INTENSITY (%)
TOTAL ION CURRENT (%)
MASS TO CHARGE RATIO (M/E)


2-ACETAMIDO-4-CYANO-1-META-CHLOROPHENYL-PYRROLE
217
43
259
RELATIVE INTENSITY (%)
TOTAL ION CURRENT (%)
MASS TO CHARGE RATIO (M/E)

EXPERIMENTAL

Infra-red spectra were determined, unless otherwise stated as Nujol mulls, with a Unicam SP 200 spectrophotometer.

^{1}H Nuclear magnetic resonance spectra were measured, unless otherwise stated, with tetramethyl-silane (TMS) as internal standard, on a Varian A60-A or a Varian HA-100 spectrometer. The peaks are assigned in terms of values and the abbreviations used in the interpretation of the n.m.r. spectra are:

s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; J = coupling constant; D = exchanges with addition of Deuterium oxide; br = broad.

Ultra-violet spectra were determined with a Unicam SP 8000 spectrophotometer.

Mass spectra were determined on a A.E.I. MS9 spectrometer, operating at 100 μa and at 70 eV. $\underline{M}^{+}$ signifies the molecular ion peak, m^{*} signifies a metastable peak. Spectra are presented as $^{m}/_{e}$ readings with the percentage abundance in parentheses. Abbreviations used in ion source determinations are:

v = very; s = small; m = medium; l = large to describe the size of the deflection on the collector meter, the value of the scan is presented as a kV reading.

Melting points are uncorrected. Light petroleum refers to the fraction boiling at 60-80°, unless otherwise stated. Microanalyses were performed by Dr.F.B. Strauss of Oxford, The National Physical Laboratory and The Butterworth Microanalytical Consultancy.

Potassioformyl Succinitrile (71)

The potassioformyl derivative of succinonitrile (71) was prepared by the method of Grob and Ankli [103], with the following modifications. Toluene was used in place of benzene and potassium tert-pentoxide in tert-pentyl alcohol was a 30% solution. Succinonitrile (50g), ethyl formate (52g) and the equivalent of 26 grams of potassium in tert-pentyl alcohol after 2 hours stirring under a nitrogen atmosphere gave 78g of the potassioformyl derivative (71) (Lit. 82g m.p.205-210°).

The product from the above method was reacted with an amine to yield an aminomethylenesuccinonitrile by the following general method.

General Method For Aminomethylenesuccinonitriles.

The potassioformyl derivative of succinonitrile (71) (0.025mol) was dissolved in water ($10cm^3$), the solution was then treated with the appropiate amine (0.025mol) and sufficient glacial acetic acid to give a solution (usually $10cm^3$ or less). The solution was heated on a steam bath for 10-20 minutes during which time the solution became dark. A precipitate formed, or was induced to form by trituration, on cooling. The product was collected and recrystallised from a suitable solvent with the use of decolourising charcoal where neccessary.

(A) Aminomethylenesuccinonitriles

Cyclohexylaminomethylenesuccinonitrile (72)

The potassioformyl derivative of succinonitrile (71) and cyclohexylamine yielded 56% of the nitrile (72) as colourless needles, m.p. 110-111°, from ethanol.

Found: C,70.0; H,7.7; N,21.9%; $\underline{M}^+$ 189.136372. $C_{11}H_{15}N_3$ requires C,69.8; H,8.0; N,22.2%; $\underline{M}$, 189.126591.

ν_{max} 3300(NH), 2250 and 2200(CN), 1650, 1300, 1250, 1150, 1090, 905, 895, 720 cm^{-1}.

$\tau(CDCl_3)$ 3.10(1H, d, J=14Hz, =$\underline{CH}$-NH-), 4.15(1H, br, D, -$\underline{NH}$), 6.85(2H, s, $-CH_2CN$), 7.90-8.80(11H, m, C_6H_{11}).

$m/_e$ 190(7), 189(36), 188(9), 146(56), 145(9), 133(6), 119(6), 108(20), 107(27), 106(9), 93(13), 83(96), 82(23), 81(17), 67(29), 56(11), 55(100), 54(22), 53(16), 41(87), 39(31), 29(24), 28(29), 27(3).

m^* 61.7(189→108).

Anilinomethylenesuccinonitrile (73)

The potassioformyl derivative of succinonitrile (71) and aniline yielded 53% of the nitrile (73) as colourless needles, m.p. 148-150°, from methanol. (Lit. 71%, m.p. 148-155°).

Found: $\underline{M}^+$ 183.079421. $C_{11}H_9N_3$ calc. $\underline{M}$, 183.079643.

ν_{max} 3300(NH), 3150(CH Ar), 2300, and 2225(CN), 1650, 1620, 920, 820, 760, 695 cm^{-1}.

$\tau(CDCl_3)$ 2.60(5H, s, Ph), 3.00(1H, d, J=12Hz, =$\underline{CH}$-NH), 4.50(1H, br,D, CH=$\underline{NH}$), 6.90(2H, s, CH_2CN).

$m/_e$ See diagram on page 100.

Benzylaminomethylenesuccinonitrile (74)

The potassioformyl derivative of succinonitrile (71) and benzylamine yielded 53% of the nitrile (74) as colourless needles, m.p. 87-88°, from ethanol (charcoal).

Found: C, 72.8; H, 5.7; N, 21.55%;
M^+, 197.094291. $C_{12}H_{11}N_3$

requires C, 73.1; H, 5.6; N, 21.3%; M, 197.095293.

ν_{max} 3375(NH), 2300, and 2250(CN), 1650, 1600, 1150, 820, 740 cm^{-1}.

$\tau(CDCl_3)$ 2.75(5H, s, Ph), 3.10(1H, d, J=12Hz, =CH-NH), 4.10(1H, br, D, =CH-NH), 5.65(2H, J=5Hz, $NHCH_2$), 6.90(2H, s, CH_2CN).

m/e 198(3), 197(15), 135(13), 134(3), 107(3), 106(6), 92(7), 91(100), 90(3), 89(3), 79(3), 78(3), 77(5), 69(3), 65(8), 64(3), 63(3), 55(3), 53(4), 52(3), 51(5), 50(3), 41(3), 40(3), 39(4), 28(5), 27(6), 17(4).

Phenethylaminomethylenesuccinonitrile (75)

The potassioformyl derivative of succinonitrile (71) and phenethylamine yielded 47% of the nitrile (75), after refrigeration of the solution overnight, as lustrous plates, m.p. 104-105°, from ethanol (charcoal).

Found: C, 73.4; H, 6.25; N, 19.7%;
M^+, 211.110693. $C_{13}H_{13}N_3$

requires C, 73.9; H, 6.3; N, 19.9%; M, 211.110942.

ν_{max} 3300(NH), 2300, and 2250(CN), 1640, 1600, 1580, 1540, 1150, 740, 690 cm^{-1}.

$\tau(CDCl_3)$ 2.80(5H, s, Ph), 3.20(1H, d, J=12Hz, NH-CH=), 4.75(1H, br. D, NH-CH=), 6.5(2H, q, J=6Hz, NH-CH_2-CH_2), 6.95(2H, s, CH_2CN), 7.05(2H, q, J=6Hz, NH-CH_2CH_2)

m/e 212(5), 211(18), 210(3), 182(6), 170(3), 158(4), 155(3), 143(3), 142(3), 135(5), 130(3), 121(6), 120(100), 115(9), 114(9), 113(5), 95(4), 94(85), 93(15), 92(36), 91(3), 79(5), 78(5), 77(13), 66(11), 65(13), 64(5), 63(5), 53(3), 52(6), 51(9), 50(3), 41(4), 39(12), 27(6).

ortho-Toluidinomethylenesuccinonitrile (76)

The potassioformyl derivative of succinonitrile (71) and ortho-toluidine yielded 52% of the nitrile (76) as colourless needles, m.p. 89-90°, from methanol.

Found: C, 73.0; H, 5.6; N, 21.6%;

M^+, 197.095017. $C_{12}H_{11}N_3$

requires C, 73.1; H, 5.6; N, 21.3%; M, 197.095293.

ν_{max} 3300(NH), 2300, and 2225(CN), 1650, 1615, 1540, 1130, 970, 770, 760, 700 cm^{-1}.

m/e 198(14), 197(100), 196(19), 182(18), 181(14), 178(7), 170(7), 169(19), 157(12), 155(25), 154(14), 142(10), 130(6), 128(5), 119(9), 118(84), 117(11), 106(6), 104(6), 92(13), 91(56), 90(7), 89(14), 80(8), 79(8), 77(15), 76(3), 65(43), 64(11), 63(17), 53(8), 52(19), 51(21), 50(6), 43(15), 41(13), 39(31), 28(15), 27(12).

meta-Toluidinomethylenesuccinonitrile (77)

The potassioformyl derivative of succinonitrile (71)

and meta-toluidine yielded 53% of the nitrile (77) as pale yellow needles, m.p. 151-153°, from 95% ethanol (charcoal).

Found: C, 72.8; H, 5.7; N, 21.5%;
M^+, 197.095293. $C_{12}H_{11}N_3$
requires C, 73.1; H, 5.6; N, 21.3%; M, 197.095293.

ν_{max} 3300(NH), 2300, and 2225(CN), 1650, 1600, 1230, 1100, 970, 920, 770,730 cm^{-1}.

$m/_e$ 198(13), 197(100), 196(22), 182(7), 181(6), 170(10), 169(22), 157(13), 155(28), 154(3), 143(5), 142(11), 119(10), 118(45), 117(5), 106(5), 92(10), 91(52), 90(3), 89(3), 80(10), 78(3), 77(10), 65(32), 64(10), 63(15), 55(3), 53(8), 52(10), 51(15), 50(3), 41(12), 39(8), 27(10).

para-Toluidinomethylenesuccinonitrile (78)

The potassioformyl derivative of succinonitrile (71) and para-toluidine yielded 50% of the nitrile (78) as colourless needles, m.p.156-157°, from ethanol.

Found: C, 72.8; H, 5.7; N, 21.4%
M^+, 197.095834. $C_{12}H_{11}N_3$
requires C, 73.1; H, 5.6; N, 21.3%; M, 197.095293.

ν_{max} 3300(NH), 2300, and 2250(CN), 1650, 1620, 1130, 970, 910, 830, 770, 695 cm^{-1}.

$m/_e$ 198(16), 197(100),196(26), 182(59), 170(13), 169(37), 157(17), 156(8), 155(30), 143(10), 142(13), 118(38), 92(17), 91(52), 90(3), 89(13), 80(13), 78(3), 77(17), 65(33), 63(15), 55(10), 52(16), 51(17), 41(16), 39(3), 27(3).

ortho-Anisidinomethylenesuccinonitrile (79)

The potassioformyl derivative of succinonitrile (71) and ortho-anisidine yielded 46% of the nitrile (79) as colourless needles, m.p. 131-132°, from ethanol.

Found: C,67.4; H,5.3; N,19.6%;
M^+,213.089551. $C_{12}H_{11}N_3O$

requires C, 67.6; H, 5.2; N, 19.7%; M, 213.090207.

ν_{max} 3300,and 3200(NH), 2250,and 2225(CN), 1650, 1600, 1580, 1520, 1260, 1080, 970, 920, 770, 730 cm^{-1}.

$\tau(CDCl_3)$ 2.65(1H, d, J=8Hz, -NH=CH-), 3.0(5H, m, NH and C_6H_4) 6.0(3H, s, OCH_3), 6.55(2H, s, CH_2CN).

$m/_e$ 214(10), 213(100), 212(8), 198(14), 197(4), 183(12), 182(84), 172(5), 171(30), 170(8), 158(6), 155(10), 142(10), 134(32), 120(34), 108(10), 93(12), 91(8), 80(10), 79(10), 79(10), 77(26), 65(38), 64(26), 63(27), 53(9), 52(30), 51(32), 41(5), 39(32), 27(8), 15(8).

meta-Anisidinomethylenesuccinonitrile (80)

The potassioformyl derivative of succinonitrile (71) and meta-anisidine yielded 42% of the nitrile(80) as pale yellow needles, m.p. 106-108°, from methanol.

Found: C, 67.5; H, 5.3; N,19.9%;
M^+, 213.089772. $C_{12}H_{11}N_3O$

requires C, 67.6; H, 5.2; N, 19.7%; M, 213.090207.

ν_{max} 3350(NH), 2250, and 2200(CN), 1650, 1600, 1520, 1230, 1180, 1030, 960, 910, 830, 730, 690 cm^{-1}.

$\tau(CDCl_3)$ 2.55-2.80(4H, m, C_6H_4), 3.4(1H, d, J=8Hz, NH-CH=)
6.2(3H, s, OCH_3), 6.85(2H, s, CH_2CN)

$m/_e$ 214(16), 213(100), 212(9), 198(16), 197(43), 196(9), 185(13), 182(11), 181(9), 173(15), 171(9), 170(16), 155(14), 144(9), 134(19), 118(22), 107(11), 92(19), 91(17), 80(23), 79(9), 78(12), 77(25), 65(25), 64(32), 63(24), 53(13), 52(21), 51(13), 50(10), 41(10), 39(24), 31(12), 28(24), 27(20), 15(12).

para-Anisidinomethylenesuccinonitrile (81)

The potassioformyl derivative of succinonitrile (71) and para-anisidine yielded 55% of the nitrile (81) as colourless needles, m.p. 147-148°, from ethanol (charcoal).

Found: C, 67.4; H, 5.4; N, 19.8%;
M^+, 213.089984. $C_{12}H_{11}N_3O$

requires C, 67.6; H, 5.2; N, 19.7%; M, 213.090207.

(CF_3COOH) 2.8(1H, d, J=8Hz, NH-CH=), 3.15(4H, s, C_6H_4)
6.3(3H, s, OCH_3), 6.75(2H, s, CH_2CN).

$m/_e$ 214(3), 213(100), 212(3), 198(44), 185(10), 182(3), 171(47), 158(21), 157(16), 143(15), 142(16), 134(9), 120(10), 116(13), 92(16), 91(3), 78(3), 77(20), 65(17), 64(30), 63(23), 52(3), 51(23), 41(3), 39(9), 29(28), 28(3), 27(3), 15(4).

m^* 184.4(213→198), 152.5(198→171).

Accurate mass measurement on selected ions:

$m/_e$ 171 Found 171.055793, $C_{10}H_7N_2O$ requires 171.055834.

$m/_e$ 158 Found 158.048049, $C_9H_6N_2O$ requires 158.048010.

ortho-Chlorophenylaminomethylenesuccinonitrile (82)

The potassioformyl derivative of succinonitrile (71) and ortho-chloroaniline yielded 48% of the nitrile (82) as colourless needles, m.p. 84-87°, from ethanol.

Found: C, 60.5; H, 3.9; N, 19.3%;
M^+, 217.040539. $C_{11}H_8N_3Cl$

requires C, 60.7; H, 3.7; N, 19.3%; M, 217.040672

ν_{max} 3300(NH), 2250, and 2225(CN), 1650, 1600, 1230, 1100, 1080, 970, 770, 760, 700 cm^{-1}.

m/e 220(4), 219(34), 218(13), 217(100), 216(8), 191(7), 190(9), 189(15), 183(8), 182(77), 156(8), 155(74), 142(15), 140(16), 138(52), 129(8), 127(24), 113(8), 111(24), 102(5), 99(5), 80(10), 77(14), 76(7), 75(25), 65(8), 64(10), 63(10), 52(9), 51(10), 50(11), 41(5), 39(10), 36(7), 27(6).

meta-Chlorophenylaminomethylenesuccinonitrile (83)

The potassioformyl derivative of succinonitrile (71) and meta-chloroaniline yielded 66% of the nitrile (83) as colourless needles, m.p. 160-161°, from ethanol.

Found: C, 60.6; H, 3.5; N, 1945%;
M^+, 217.041148. $C_{11}H_8N_3Cl$

requires C, 60.7; H, 3.7; N, 19.3%; M, 217.040672.

ν_{max} 3300(NH), 2250, and 2225(CN), 1660, 1600, 1230, 1100, 1080, 970, 870, 770, 730 cm^{-1}.

$\tau[(CD_3)_2SO]$ 2.15(1H, d, J=12Hz, NH-CH=), 2.5-2.8(4H, m, C_6H_4) 4.2(1H, s, D, NH-CH=), 6.35(1H, s, CH_2CN) (TMS ext).

m/e 220(3), 219(33), 218(19), 217(100), 216(19), 191(7), 190(5), 189(20), 183(27), 181(5), 177(9), 156(6), 155(53), 142(14), 140(12), 138(33),

128(4), 127(6), 114(5), 113(10), 112(8), 111(38), 106(5), 104(40), 99(4), 91(5), 85(4), 80(31), 79(7), 77(20), 76(11), 75(45), 74(7), 65(6), 64(10), 63(11), 62(4), 54(3), 53(11), 52(20), 51(20), 50(30), 43(3), 41(3), 39(11), 36(5), 27(3).

para-Chorophenylaminomethylenesuccinonitrile (84)

The potassioformyl derivative of succinonitrile (71) and para-chloroaniline yielded 62% of the nitrile (84) as colourless needles, m.p. 168-170°, from ethanol.

Found: C, 60.7; H, 3.9; N, 19.4%;
M*, 217.040933. $C_{11}H_8N_3Cl$

requires C, 60.7; H, 3.7; N, 19.3%; M, 217.040672.

ν_{max} 3300(NH), 2250 and 2225(CN), 1640, 1600, 1300, 1280, 1100, 1005, 830, 760, 710, 695 cm^{-1}.

m/e 220(4), 219(32), 218(15), 217(100), 216(5), 191(3), 189(5), 183(5), 182(47), 181(5), 165(3), 155(17), 140(10), 138(27), 131(3), 128(3), 127(3), 114(3), 113(7), 112(7), 111(23), 106(4), 104(7), 91(5), 80(42), 79(9), 77(11), 76(6), 75(23), 65(3), 64(4), 63(6), 53(17), 52(17), 51(9), 50(10), 43(3), 41(3), 39(3), 27(3).

m^* 152.6(217→182), 132.1(182→155).

meta- Nitrophenylmethylenesuccinonitrile (85)

The potassioformyl deivative of succinonitrile (71) and meta-nitroaniline yielded 64% of the nitrile (85) as pale yellow needles, m.p. 176-178°, from methanol (charcoal).

Found: C, 57.9; H, 3.5; N,24.6%;
M*, 228.064794. $C_{11}H_8N_4O_2$

requires C, 57.9; H, 3.5; N,24.55%; M, 228.064721.

ν_{max} 3250 and 3200(NH), 2225 and 2195(CN), 1640, 1620,

1580, 1525 and 1350(NO_2), 930, 900, 810, 795, 715 cm^{-1}.

τ[$(CD_3)_2SO$] 2.2(1H, d, J=10Hz, NH-CH=), 2.8(4H, m, $-C_6H_4-$), 4.2(1H, br, D, NH-CH=), 6.2(2H, s, CH_2CN).

m/e 229(11), 228(100), 211(7), 198(7), 183(5), 181(23), 180(9), 155(19), 138(25), 128(9), 106(6), 104(8), 92(30), 80(16), 79(7), 77(20), 76(22), 75(11), 57(8), 56(6), 55(9), 53(9), 52(20), 51(14), 50(20), 41(15), 39(22), 28(42), 27(14), 16(30).

para-Nitrophenylaminomethylenesuccinonitrile (86)

The potassioformyl derivative of succinonitrile (71) and para-nitroaniline yielded 66% of the nitrile (86) as pale yellow needles, m.p. 189-190°, from ethanol.

Found: C, 57.9; H, 3.5; N, 24.6%;
M^+, 228.064794. $C_{11}H_8N_4O_2$

requires C, 57.9; H, 3.5; N, 24.55%; M, 228.064721.

ν_{max} 3250(NH), 2225, and 2200(CN), 1640, 1620, 1580, 1530, and 1350(NO_2), 1100, 830, 760, 710, 700 cm^{-1}.

m/e 229(11), 228(100), 211(7), 198(10), 183(5), 180(6), 156(15), 155(19), 138(20), 128(8), 124(28), 119(5), 109(24), 108(7), 106(9), 104(9), 102(7), 96(12), 95(7), 92(14), 91(5), 80(17), 79(9), 78(14), 77(22), 76(16), 75(7), 66(10), 65(25), 64(12), 63(10), 60(6), 53(9), 52(20), 51(16), 50(19), 43(12), 42(13), 41(8), 39(22), 28(60), 27(10), 16(5).

para-Ethoxycarbonylphenylaminomethylenesuccinonitrile (87)

The potassioformyl derivative of succinonitrile (71) and para-amino ethyl benzoate yielded 51% of the nitrile (87) as colourless needles, m.p. 210-211°, from ethanol.

Found: C, 65.95; H, 5.2; N, 16.6%;

M^+, 255.100662. $C_{14}H_{13}N_3O_2$

requires C, 65.9; H, 5.1; N, 16.5%; M, 255.100770.

ν_{max} 3350(NH), 2275 and 2225(CN), 1710(C=O), 1650, 1600, 1520, 1510, 1280, 1190, 1110, 1030, 960, 920, 830, 780, 700 cm^{-1}.

m/e 256(4), 255(18), 227(3), 210(4), 182(5), 165(40), 155(3), 138(8), 121(9), 120(100), 105(3), 93(3), 92(14), 91(3), 80(5), 77(3), 76(3), 65(12), 64(3), 63(3), 60(3), 53(3), 52(3), 51(3), 50(3), 41(3), 39(3), 29(7), 28(6), 27(5).

ortho-Methoxycarbonylphenylaminomethylenesuccinonitrile (88)

The potassioformyl derivative of succinonitrile (71) and methyl anthranilate yielded 48% of the nitrile (88) as colourless needles, m.p. 183-184°, from ethanol.

Found: C, 64.9; H, 4.7; N, 17.6%;

M^+, 241.085870. $C_{13}H_{11}N_3O$

requires C, 64.7; H, 4.6; N, 17.4%; M, 241.085121.

ν_{max} 3250(NH), 2250 and 2225(CN), 1690(C=O), 1650, 1620, 1530, 1280, 1140, 990, 770, 760, 700 cm^{-1}.

$\tau(CF_3COOH)$ 1.8-2.2(4H, m, C_6H_4), 2.7(1H, d, J=10Hz, NH-CH=) 5.9(2H, s, CH_2CN), 6.4(3H, s, OCH_3).

m/e 242(10), 241(66), 211(3), 210(25), 209(100), 208(8), 198(3), 183(7), 182(22), 181(66), 180(10), 171(3), 170(15), 156(3), 155(19), 154(14), 153(3),

143(3), 141(3), 132(3), 130(4), 128(4), 127(6), 119(3), 115(4), 114(3), 106(7), 105(26), 104(35), 103(12), 92(6), 91(4), 90(4), 80(3), 78(5), 77(29), 76(19), 75(5), 65(7), 64(9), 63(7), 52(7), 51(16), 50(13), 41(3), 39(11), 31(3), 29(3), 28(3), 27(4), 15(3).

ortho-Acetophenylaminomethylenesuccinonitrile (89)

The potassioformyl derivative of succinonitrile (71) and ortho-aminoacetophenone yielded 51% of the nitrile (89) as colourless needles, m.p. 195-196°, from ethanol.

Found: C, 69.5; H, 5.1; N, 19.0%;
M^+, 225.090125. $C_{13}H_{11}N_3O$
requires C, 69.3; H, 4.9; N, 18.65%; M, 225.090207.

ν_{max} 3250(NH), 2250 and 2225(CN), 1650(C=O), 1620, 1590, 1530, 1250, 1070, 960, 770,750, 720 cm^{-1}.

$\tau[(CD_3)_2SO]$ 2.0(4H, m, C_6H_4), 2.6(1H, d, J=8Hz, NH-CH=), 3.8(1H, br, NH-CH=), 6.2(2H, s, CH_2CN), 7.15(3H, s, CH_3CO).

m/e 226(3), 225(15), 224(3), 211(3), 210(28), 209(4), 208(23), 207(100), 206(20), 198(3), 197(3), 183(8), 182(15), 179(13), 171(3), 170(14), 155(7), 154(5), 153(4), 152(3), 146(12), 142(4), 136(4), 135(44), 133(6), 130(6), 129(5), 128(6), 121(6), 120(82), 115(5), 106(3), 105(5), 104(4), 103(6), 102(9), 101(6), 92(28), 91(9), 90(8), 80(3), 77(34), 76(9), 75(8), 65(24), 64(8), 63(13), 52(10), 51(26), 50(12), 43(52), 41(4), 39(16), 28(40), 27(13), 17(20), 15(3).

ortho-Hydroxyphenylaminomethylenesuccinonitrile (90)

The potassioformyl derivative of succinonitrile (71) and ortho-aminophenol yielded 52% of the nitrile (90) as colourless needles, m.p. 185-186°, from ethanol.

Found: C, 66.5; H, 4.7; N, 20.9%;
M^+, 199.074643. $C_{11}H_9N_3O$

requires C, 66.3; H, 4.55; N, 21.1%; M, 199.074557.

ν_{max} 3400(OH), 3300 and 3250(NH), 2250(CN), 1640, 1600, 1520, 1310, 1270, 1250, 1090, 950, 910, 830, 780, 750, 730 cm^{-1}.

m/e 200(15), 199(100), 198(7), 182(15), 171(15), 170(22), 120(40), 109(18), 80(26), 79(9), 77(8), 65(22), 64(11), 63(10), 51(11), 50(3), 41(3), 39(9), 39(21), 28(20), 27(7), 17(3).

Accurate mass measurement on selected ion:

m/e 109 Found 109.051934, C_6H_7NO requires 109.052761.

(B) 2-Amino-4-cyanopyrroles

General Method For 2-Amino-4-cyanopyrroles

The appropiate aminomethylenesuccinonitrile (0.01mol) was stirred at room temperature, for 2h, in a solution of potassium ethoxide prepared from potassium (0.025mol) dissolved in ethanol (25cm^3). The ethanol was reduced in volume and the residue triturated with water to yield the aminopyrrole as a solid or a viscous oil. In the case of of non-solid products the aminopyrrole was extracted into ether, the ethereal extract washed with acid, the acid washing was basified and extracted with ether. The combined ether extracts were dried over magnesium sulphate and the ether evapo rated off *in vac uo*, to yield the aminopyrrole as a red-brown oil which solidified on addition of petroleum ether or was distilled. The following aminopyrroles were made with the stated modifications.

2-Amino-4-cyano-1-cyclohexylpyrrole (91)

The nitrile (72) and potassium ethoxide solution gave a 75% yield of the amine (91) on addition of water. The product was recrystallised from CCl_4 as pale pink needles, m.p. 95-96°.

Found: C, 69.7; H, 8.05; N,22.4%;
M^+, 189.126892. $C_{11}H_{15}N_3$

requires C, 69.8; H, 8.0; N, 22.2%; M, 189.126591.

ν_{max} 3450, 3380 and 3150(NH), 2250 (CN), 1650, 1630, 1580, 1540, 1090, 975, 905, 770 cm^{-1}.

$\tau(CDCl_3)$ 3.15(1H, d, J=2Hz, 5-H), 4.35(1H, d, J=2Hz, 3-H), 6.65(2H, br, D, NH_2), 8.0-8.9(11H, m, C_6H_{11}).

$m/_e$ 190(4), 189(29), 134), 133(3), 132(3), 121(3), 120(3), 109(3), 108(9), 107(100), 106(4), 84(3), 83(10), 82(3), 81(6), 80(6), 67(4), 63(3), 56(3), 55(30), 54(3), 53(3), 52(4), 41(22), 39(5), 29(4), 28(49), 27(5), 18(31), 17(25), 15(3).

m^* 60.4(188→107) (1.758 vs).

m^* 85.4(134→107) (1.252 vs).

Accurate mass measurement on selected ion:

$m/_e$ 107 Found 107.047859, $C_5H_5N_3$ requires 107.048345.

2-Amino-4-cyano-1-phenylpyrrole (92)

The nitrile (73) and potassium ethoxide solution gave a 79% yield of the amine (92) as yellow oil after distillation at 185-190°/2.0 mmHg. (Lit. 100%, at 120°/0.3 mmHg) .

Found: $\underline{M}^+$, 183.079421. $C_{11}H_9N_3$ $\underline{M}$, calc. 183.079643.

ν_{max} 3450, 3375 and 3175(NH), 2250(CN), 1620, 1600, 1580, 1530, 1500, 1305, 1170, 1105, 730, 700 cm^{-1}.

$m/_e$ 184(10), 183(100), 182(10), 156(3), 155(14), 130(3), 125(3), 124(20), 123(3), 80(16), 79(3), 78(7), 77(25), 53(5), 52(7), 51(16), 50(4), 41(3), 39(3), 27(3).

Accurate mass measurement on selected ions:

$m/_e$ 155 Found 155.060985, $C_{10}H_7N_2$ requires 155.060920.

$m/_e$ 80 Found 80.037402, $C_4H_4N_2$ requires 80.037446

2-Amino-1-benzyl-4-cyanopyrrole (93)

The nitrile (74) and potassium ethoxide solution gave a pale yellow oil after distillation at 224-228°/1.5 mmHg. The oil later solidified on trituration with petroleum ether to yield an amorphous powder, m.p. 55-58°.

Found: C, 73.2; H, 5.6; N, 21.6%; $\underline{M}^+$, 197.094459.

$C_{12}H_{11}N_3$ requires

C, 73.1; H, 5.6; N, 21.3%; $\underline{M}$, 197.095293.

ν_{max}(KBr) 3425, 3350 and 3150(NH), 2225(CN), 1620, 1570, 1530, 1500, 1450, 1390, 1350, 1300, 1200, 1140, 1080, 1030, 990, 720, 700 cm^{-1}.

$\tau(CDCl_3)$ 2.8(5H, m, C_6H_5), 3.2(1H, d, J=2Hz, 5-H), 4.3(1H, d, J=2Hz, 3-H), 5.1(2H, s, CH_2), 6.8(2H, br, D, NH_2).

m/e 198(3), 197(11), 107(4), 106(9), 92(8), 91(100), 90(3), 89(4), 79(6), 78(3), 77(7), 65(9), 64(4), 63(8), 57(3), 55(4), 53(3), 52(11), 51(13), 50(6), 43(5), 41(9), 39(16), 27(6), 17(76), 15(6).

Accurate mass measurements on selected ions:

m/e 106 Found 106.040328, $C_5H_4N_3$ requires 106.040520.

m/e 79 Found 79.029274, $C_4H_3N_2$ requires 79.029622.

2-Amino-4-cyano-1-phenethylpyrrole (94)

The nitrile (75) and potassium ethoxide solution gave a pale yellow oil, which remained as an oil, after distillation at 210-216°/2.0 mmHg.

Found: C, 73.6; H, 6.2; N, 19.5%; $\underline{M}^+$, 211.110766.

$C_{13}H_{13}N_3$ requires

C, 73.9; H, 6.3; N, 19.9%; $\underline{M}$, 211.110942.

ν_{max} 3400, 3350 and 3150(NH), 2250(CN), 1615, 1570, 1530, 1500, 1190, 1140, 1080, 1030, 990, 750, 700 cm^{-1}.

$m/_e$ 212(13), 211(95), 210(4), 183(3), 182(3), 172(3), 147(3), 121(3), 120(30), 119(3), 118(3), 107(5), 106(9), 105(100), 104(77), 103(12), 93(12), 92(7), 91(27), 81(27), 80(3), 79(15), 78(6), 77(23), 66(6), 65(10), 64(3), 63(5), 54(3), 53(4), 52(8), 51(11), 50(3), 42(4), 41(8), 39(14), 30(11), 27(4), 17(10).

Accurate mass measurements on selected ions:

$m/_e$ 120 Found 120.055917, $C_6H_6N_3$ requires 120.056169.

$m/_e$ 93 Found 93.045334, $C_5H_5N_2$ requires 93.045271.

Ion source determination. Meta-stable scan at 4-8 Kv.

$m/_e$ 120 208 → 120 (0.731 m)

$m/_e$ 93 118 → 93 (0.273 m)
132 → 93 (0.419 s)
157 → 93 (0.688 s)

2-Amino-4-cyano-1-(o-tolyl)pyrrole (95)

The nitrile (76) and potassium ethoxide solution gave a 74% yield of the amine (95) as a tan solid on addition of water. Recrystallisation from CCl_4 gave pale pink plates, m.p. 89-91°(decomp.).

Found: C, 72.6; H, 5.6; N, 21.6%; $\underline{M}^+$, 197.095231.
$C_{12}H_{11}N_3$ requires
C, 73.1; H, 5.6; N, 21.3%; $\underline{M}$, 197.095293.

ν_{max} 3450, 3375 and 3150 (NH), 2250(CN), 1620, 1600, 1550, 1305, 1150, 970, 770, 760, 700 cm^{-1}.

$\tau(CDCl_3)$ 2.25(4H, m, C_6H_4), 2.75(1H, d, J=2Hz, 5-H), 3.95 (1H, d, J=2Hz, 3-H), 6.5(2H, br, D, NH_2), 7.75(3H, s, CH_3).

$^{m}/_{e}$ 198(20), 197(100), 196(21), 183(3), 182(25), 181(20), 180(5), 179(7), 170(3), 169(11), 156(3), 155(16), 154(21), 153(4), 142(4), 140(3), 130(3), 128(5), 118(26), 117(6), 116(13), 115(5), 106(5), 104(5), 92(9), 91(40), 90(5), 89(9), 80(8), 79(6), 78(5), 77(9), 76(3), 66(3), 65(32), 64(7), 63(12), 53(6), 52(10), 50(5), 43(9), 39(22), 27(7), 17(6).

2-Amino-4-cyano-1-(m-tolyl)pyrrole (96)

The nitrile (77) and potassium ethoxide solution yielded 82% of the amine (96) as a tan precipitate on addition of water. The product was recrystallised from $CHCl_3$/petroleum ether 1:1, to give pale pink prisms, m.p. 87-89°.

Found: C, 73.0; H, 5.3; N, 21.0%; $\underline{M}^+$, 197.095616.

$C_{12}H_{11}N_3$ requires

C, 73.1; H, 5.6; N, 21.3%; $\underline{M}$, 197.095293.

ν_{max} 3400, 3300 and 3150(NH), 2250(CN), 1620, 1590, 1570, 1540, 1210, 1150, 1040, 980, 920, 890, 750, 700 cm^{-1}.

2-Amino-4-cyano-1-(p-tolyl)pyrrole (97)

The nitrile (78) and potassium ethoxide solution gave a 90% yield of the amine (97) as pale pink needles, m.p. 110-111°, from CCl_4.

Found: C, 73.0; H, 5.8; N, 21.1%; $\underline{M}^+$, 197.095338.

$C_{12}H_{11}N_3$ requires

C, 73.1; H, 5.6; N, 21.3%; $\underline{M}$, 197.095293.

ν_{max} 3400, 3300 and 3150(NH), 2225(CN), 1605, 1595, 1530, 1305, 1295, 1240, 1200, 1180, 1150, 1050, 1020, 875, 850, 760 cm^{-1}.

$\tau(CDCl_3)$ 2.80(4H, s, C_6H_4), 3.15(1H, d, J=2Hz, 5-H), 4.35(1H, d, J=2Hz, 3-H), 6.5(2H, br, D, NH_2), 7.6(3H, s, CH_3).

$m/_e$ 198(18), 197(100), 196(18), 183(3), 182(15), 181(4), 170(3), 169(10), 168(3), 140(3), 129(3), 119(3), 118(37), 116(3), 115(4), 92(3), 91(25), 90(4), 89(4), 88(6), 8019), 79(5), 78(3), 77(5), 65(16), 64(4), 63(6), 62(3), 54(3), 53(6), 52(7), 51(7), 50(3), 43(3), 41(5), 39(7), 27(17), 17(5).

2-Amino-4-cyano-1-(o-methoxyphenyl)pyrrole (98)

The nitrile (79) and potassium ethoxide solution gave a 82% yield of the amine (98) as a tan precipitate on addition of water. Recrystallisation from $CHCl_3$/petroleum ether gave pale pink needles, m.p. 79-82°(decomp.).

Found: C, 67.6; H, 5.2; N, 19.9%; M^+, 213.090264.

$C_{12}H_{11}N_3O$ requires

C, 67.6; H, 5.2; N, 19.7%; M, 213.090207.

ν_{max} 3300, 3250 and 3200(NH), 2250(CN), 1610, 1570, 1530, 1300, 1160, 980, 790, 770, 700 cm^{-1}.

$\tau(CDCl_3)$ 2.50(4H, m, C_6H_4), 2.95(1H, d, J= 2Hz, 5-H), 4.15 (1H, d, J=2Hz, 3-H), 5.95(3H, s, OCH_3), 6.4(2H, br, D, NH_2).

$m/_e$ 214(12), 213(100), 212(9), 199(3), 198(28), 197(3), 195(3), 194(18), 184(4), 183(7), 182(37), 181(4), 171(7), 170(17), 158(4), 155(6), 143(4), 142(4), 134(6), 121(4), 120(21), 119(3), 116(3), 114(3), 108(7), 107(3), 106(4), 104(4), 93(9), 92(11), 90(5), 89(3), 80(3), 79(9), 78(13), 77(29), 76(4), 64(25), 63(25), 62(18), 53(7), 52(25), 51(25), 50(8), 43(3), 41(30), 39(18), 27(5), 17(4).

2-Amino-4-cyano-1-(m-methoxyphenyl)pyrrole (99)

The nitrile (80) and potassium ethoxide solution gave a 91% yield of the amine (99) as a tan precipitate on addition

on addition of water. Recrystallisation from CCl_4 gave colourless needles, m.p. 65-68°.

Found: C, 67.5; H, 5.3; N, 19.9%; $\underline{M}^+$, 213.090621.

$C_{12}H_{11}N_3O$ requires

C, 67.6; H, 5.2; N, 19.7%; $\underline{M}$, 213.090207.

ν_{max} 3450, 3350 and 3150(NH), 2225(CN), 1605, 1595, 1530, 1305, 1295, 1240, 1200, 1180, 1150, 1050, 1020, 875, 850, 760 cm^{-1}.

$m/_e$ 214(13), 213(100), 212(6), 199(14), 183(3), 182(4), 171(4), 170(14), 155(3), 134(16), 123(7), 94(8), 93(6), 92(9), 80(19), 79(6), 78(8), 77(16), 65(9), 64(14), 63(10), 55(4), 53(6), 52(9), 51(7), 43(82), 41(10), 39(13), 27(14), 17(45).

2-Amino-4-cyano-1-(p-methoxyphenyl)pyrrole (100)

The nitrile (81) and potassium ethoxide solution gave a 90% yield of the amine (100) as a tan precipitate on addition of water. Recrystallisation from CCl_4 gave colourless needles, m.p. 104-106°.

Found: C, 67.5; H, 5.4; N, 19.9%; $\underline{M}^+$, 213.090197.

$C_{12}H_{11}N_3O$ requires

C, 67.6; H, 5.2; N, 19.7%; $\underline{M}$, 213.090207.

ν_{max} 3400, 3300 and 3100(NH), 2225(CN), 1650, 1610, 1590, 1570, 1515, 1505, 1290, 1250, 1205, 1170, 1150, 1105, 1030, 840, 800, 780 cm^{-1}.

$\tau(CDCl_3)$ 2.75(4H, m, C_6H_4), 3.10(1H, d, J=2Hz, 5-H), 4.25(1H, d, J=2Hz, 3-H), 6.15(3H, s, OCH_3), 6.55(2H, br, D, NH_2).

2-Amino-1-(o-chlorophenyl)-4-cyanopyrrole (101)

The nitrile (82) and potassium ethoxide solution gave a 85% yield of the amine (101) as a precipitate on addition of water. Recrystallisation from CCl_4 gave colourless

needles, m.p. 68-70°.

Found: C, 60.3; H, 3.7; N, 19.3%; $\underline{M}^+$, 217.040503.

$C_{11}H_8N_3Cl$ requires

C, 60.7; H, 3.7; N, 19.3%; $\underline{M}$, 217.040672.

ν_{max} 3350, 3300 and 3150(NH), 2225(CN), 1620, 1520, 1300, 1210, 1170, 1070, 1030, 1000, 970, 950, 780, 750, 720, 700 cm^{-1}.

$\tau(CDCl_3)$ 2.20(4H, m, C_6H_4), 2.75(1H, d, J=2Hz, 5-H), 3.95(1H, d, J=2Hz, 3-H), 6.70(2H, br, NH_2).

$m/_e$ 220(3), 219(31), 218(14), 217(100), 216(3), 191(3), 189(3), 182(34), 181(7), 180(3), 165(3), 156(3), 155(18), 153(4), 140(8), 139(3), 138(22), 130(3), 128(3), 127(4), 113(3), 112(6), 111(15), 106(3), 104(6), 103(3), 91(4), 80(28), 79(6), 77(17), 76(4), 75(17), 74(3), 64(5), 63(4), 57(6), 55(3), 53(7), 52(13), 51(8), 50(7), 43(5), 41(4), 39(3), 27(4).

2-Amino-1-(m-chlorophenyl)-4-cyanopyrrole (102)

The nitrile (83) and potassium ethoxide solution gave a 96% yield of the amine (102) as a precipitate on addition of water. Recrystallisation from benzene/petroleum ether gave pale pink needles, m.p. 123-124°.

Found: C, 60.5; H, 3.8; N, 19.2%; $\underline{M}^+$, 217.040933.

$C_{11}H_8N_3Cl$ requires

C, 60.7; H, 3.7; N, 19.3%; $\underline{M}$, 217.040672.

ν_{max} 3450, 3375 and 3175(NH), 2250(CN), 1605, 1600, 1540, 1320, 1205, 1150, 1090, 890, 820, 780, 710, 695 cm^{-1}.

$\tau(CDCl_3)$ 2.6(4H, m, C_6H_4), 3.10(1H, d, J=2Hz, 5-H), 4.25(1H, d, J=2Hz, 3-H), 6.65(2H, br, D, NH_2).

$m/_e$ 220(4), 219(34), 218(13), 217(100), 216(6), 191(3), 189(6), 183(5), 182(46), 181(6), 155(27), 140(10), 139(3), 138(27), 130(3), 128(3), 127(4), 113(9), 111(32), 106(7), 104(9), 103(9), 102(80), 99(3), 91(9), 84(4), 80(50), 79(14), 78(5), 77(21), 76(9), 75(38), 74(4), 65(5), 64(10), 63(7), 53(25), 52(28), 51(14), 50(13), 41(3), 39(4), 27(5), 17(3).

2-Amino-1-(p-chlorophenyl)-4-cyanopyrrole (103)

The nitrile (84) and potassium ethoxide solution gave a 94% yield of the amine (103) as a precipitate on addition of water. Recrystallisation from $CHCl_3$/ CCl_4 gave pale pink microprisms, m.p. 158-159°.

Found: C, 60.9; H, 3.6; N, 19.2%; $\underline{M}^+$, 217.041012.
$C_{11}H_8N_3Cl$ requires
C, 60.7; H, 3.7; N, 19.3%; $\underline{M}$, 217.040672.

ν_{max} 3400 and 3300(NH), 2250(CN), 1620, 1590, 1570, 1530, 1500, 1205, 1105, 1090, 1020, 850, 800, 770, 730 cm^{-1}.

$\tau(CDCl_3)$ 2.6(4H, s, C_6H_4), 3.15(1H, d, J=2Hz, 5-H), 4.45(1H,d, J=2Hz, 3-H), 5.95(2H, br, D, NH_2).

$m/_e$ 220(5), 219(33), 218(14), 217(100), 191(3), 189(6), 183(4), 182(45), 181(3), 165(3), 156(3), 155(14), 140(7), 138(20), 130(3), 128(3), 103(3), 102(4), 101(23), 100(3), 91(3), 80(23), 79(5), 78(4), 77(7), 76(4), 75(16), 74(3), 65(3), 64(3), 63(3), 53(8), 52(8), 51(5), 50(3), 41(3), 39(3), 27(4), 17(5).

Accurate mass measurement on selected ion

$m/_e$ 189 Found 189.028114, $C_{10}H_6N_3Cl$ requires 189.021949.

$m/_e$ 155 Found 155.060671. $C_{10}H_7N_2$ requires 155.060920.

2-Amino-4-cyano-1-(m-nitrophenyl)pyrrole (104)

The nitrile (85) (2.3g) and triethylamine (15g) were refluxed in ethanol ($50cm^3$) for 4h on a steam bath. The solvent was evapourated *in vaccuo* and the residue was triturated with water to yield 99% of the amine (104). Recrystallisation from CCl_4(charcoal) gave orange prisms, m.p.144-145°.

Found: C, 57.65; H, 3.6; N, 24.3%; M^+, 228.065019.
$C_{11}H_8N_4O_2$ requires
C, 57.9; H, 3.5; N, 24.55%; M, 228.064721.

ν_{max} 3450 3350 and 3150(NH), 2225(CN), 1630, 1590, 1530 and 1350(NO_2), 1310, 1290, 1180, 1090, 900, 890, 805, 735, 705, 685 cm^{-1}.

$m/_e$ 229(11), 228(100), 212(3), 211(6), 198(7), 187(4), 183(4), 182(28), 181(16), 180(7), 173(9), 155(15), 149(5), 138(43), 128(8), 116(5), 114(10), 113(6), 99(7), 93(4), 92(37), 91(7), 90(5), 84(10), 80(16), 79(9), 78(6), 77(20), 76(10), 75(3), 65(37), 64(18), 63(14), 60(12), 57(7), 55(9), 53(10), 52(22), 51(15), 50(25), 44(50), 43(18), 41(19), 39(24), 27(38), 17(77).

2-Amino-4-cyano-1-(p-nitrophenyl)pyrrole (105)

The nitrile (86) (2.3g) and triethylamine (15g) were refluxed in ethanol ($50cm^3$) for 4h on a steam bath. The solvent was evapourated *in vaccuo* and the residue was triturated with water to yield 97% of the amine (105). Recrystallisation of the amine from CCl_4 gave yellow needles m.p. 195-196°.

Found: C, 57.7; H, 3.5; N, 24.5%; $\underline{M}^+$, 228.065019.

$C_{11}H_8N_3O$ requires

C, 57.9; H, 3.5; N, 24.55%; $\underline{M}$, 228.064721.

ν_{max} 3450, 3350 and 3300(NH), 2250(CN), 1620, 1590, 1525 an 1350(NO_2), 1180, 1150, 1100, 860, 850, 750, 720, 700 cm^{-1}.

$m/_e$ 229(11), 228(100), 197(12), 183(13), 182(31), 181(10), 155(11), 138(15), 128(6), 108(6), 105(7), 104(6), 92(10), 91(6), 80(12), 79(6), 78(6), 77(18), 76(10), 75(6), 65(21), 64(8), 63(7), 53(6), 52(12), 51(10), 50(12), 43(6), 41(7), 39(12), 27(6), 17(30).

2-Amino-4-cyano-1-(p-ethoxycarbonylphenyl)pyrrole (106)

The nitrile (87) and potassium ethoxide solution gave a 82% yield of the amine (106) as a precipitate on addition of water. Recrystallisation from $CHCl_3$/petroleum ether gave colourless needles, m.p.125-126°.

Found: C, 65.9; H, 5.2; N, 16.6%; $\underline{M}^+$, 255.100175.

$C_{14}H_{13}N_3O_2$ requires

C, 65.9; H, 5.1; N, 16.5%; $\underline{M}$, 255.100770.

ν_{max} 3450 and 3300(NH), 2225(CN), 1695(C=O), 1640, 1600, 1530, 1290, 1270, 1230, 1190, 1150, 1120, 1030, 890, 780, 750, 705, 695 cm^{-1}.

$m/_e$ 256(4), 255(100), 238(3), 227(5), 220(4), 219(20, 218(9), 210(4), 205(3), 204(3), 203(100), 189(3), 182(7), 181(3), 176(4), 175(3), 163(6), 162(3), 161(17), 155(3), 145(3), 143(3), 129(3), 128(3), 115(3), 105(5), 91(5), 80(22), 79(4), 78(3), 77(6), 76(3), 65(5), 57(7), 55(3), 53(3), 51(3), 41(12), 39(6), 36(5), 29(8), 27(4), 17(5).

(C) 2-Acetamido-4-cyanopyrroles

General Method For 2-Acetamido-4-cyanopyrroles

The aminopyrrole (1.0g) and acetic anhydride (6cm^3) were heated together on a steam bath for 10 minutes. The reaction mixture was cooled to 0°, and the solid acetamidopyrrole filtered off. The product was washed with water and recrystallised from methanol or ethanol together with decolourising charcoal where neccessary.

2-Acetamido-4-cyano-1-cyclohexylpyrrole (107)

The amine (91) and acetic anhydride gave a 98% yield of the acetyl derivative (107) as colourless needles, m.p. 143-144°, (ethanol).

Found: C, 67.8; H, 7.2; N, 18.05%; $\underline{M}^+$, 231.13668.

$C_{13}H_{17}N_3O$ requires

C, 67.5; H, 7.4; N, 18.2%; $\underline{M}$, 231.137155.

ν_{max} 3300(NH), 2250(CN), 1670(C=O), 1570, 1520, 1300, 1270, 1190, 1180, 1160, 1140, 1115, 1005, 980, 960, 900, 820, 810, 770, 740, 720 cm^{-1}.

$\tau(CF_3COOH)$ 2.60(1h, s, 5-H), 3.55(1H, s, 3-H), 7.60(3H, s, $COCH_3$), 8.0-8.6(11H, m, C_6H_{11}).

$m/_e$ 232(4), 231(24), 190(4), 189(26), 188(3), 150(3), 149(12), 108(11), 107(100), 106(14), 84(3), 83(18), 82(3), 81(6), 67(8), 64(19), 57(4), 56(5), 55(48), 54(8), 53(6), 52(5), 48(7), 43(43), 41(43), 39(11), 27(3).

2-Acetamido-4-cyano-1-phenylpyrrole (108)

The crude amine (92) and acetic anhydride gave a 75% yield of the acetyl derivative (108) after two stages. The product was recrystallised from ethanol(charcoal), to give colourless needles, m.p. 189-190°.

Found: $\underline{M}^+$, 225.090280. $C_{13}H_{11}N_3O$ calc. $\underline{M}$, 225.090207.

ν_{max} 3300(NH), 2250(CN), 1680(C=O), 1600, 1570, 1520, 1500, 1280, 1180, 1040, 1020, 970, 835, 760, 695 cm^{-1}.

$m/_e$ 226(4), 225(20), 224(3), 184(13), 183(100), 182(9), 156(3), 155(7), 142(3), 111(3), 109(3), 104(14), 97(3), 95(3), 93(3), 81(3), 80(7), 79(3), 78(4), 77(25), 71(3), 69(3), 64(4), 57(3), 55(3), 52(3), 51(10), 43(24), 41(3), 39(3), 27(3).

2-Acetamido-1-benzyl-4-cyanopyrrole (109)

The crude amine (93) and acetic anhydride gave a 75% yield of the acetyl derivative after two stages, as colourless needles, m.p. 173-174°, (ethanol,charcoal).

Found: C, 70.2; H, 5.5; N, 17.5%; $\underline{M}^+$, 239.105637.

$C_{14}H_{13}N_3O$ requires

C, 70.3; H, 5.5; N, 17.6%; $\underline{M}$, 239.105865.

ν_{max} 3250(NH), 2250(CN), 1670(C=O), 1570, 1550, 1520, 1270, 1200, 1180, 1140, 1110, 810, 750, 705, 695 cm^{-1}.

$\tau(CF_3COOH)$ 2.75(5H, m, C_6H_5), 3.05(1H, d, J=2Hz, 5-H), 3.80(1H, d, J=2Hz, 3-H), 5.2(2H, s, $\underline{CH_2}C_6H_5$), 8.0(3H, s, $COCH_3$)

$m/_e$ 240(3), 239(12), 197(8), 196(3), 103(3), 92(9), 91(100), 77(3), 65(12), 51(3), 43(16), 39(6), 27(3).

2-Acetamido-4-cyano-1-phenethylpyrrole (110)

The crude amine (94) and acetic anhydride gave a 70% yield of the acetyl derivative (110) after two stages, as colourless needles, m.p. 151-152°, from ethanol(charcoal).

Found: C, 71.2; H, 6.0; N, 16.3%; $\underline{M}^+$, 253.121359.

$C_{15}H_{15}N_3O$ requires

C, 71.1; H, 6.0; N, 16.6%; M, 253.121505.

ν_{max} 3250(NH), 2250(CN), 1670(C=O), 1570, 1550, 1520, 1270, 1200, 1180, 1140, 1110, 890, 750, 705 cm^{-1}.

$\tau(CDCl_3)$ 2.80(5H, m, C_6H_5), 3.15(1H, d, J=2Hz, 5-H), 3.95(1H, d, J=2Hz, 3-H), 6.1(2h, t, J=6Hz, $\underline{CH_2}.CH_2.C_6H_5$), 7.15(2H, t, J=6Hz, $CH_2.\underline{CH_2}.C_6H_5$), 8.10(3H, s, $COCH_3$).

$m/_e$ 254(7), 253(100), 212(7), 211(46), 210(5), 149(3), 120(12), 119(3), 118(5), 107(13), 106(8), 105(100), 104(83), 103(11), 93(8), 92(7), 91(11), 80(3), 79(14), 78(7), 77(20), 65(10), 51(8), 43(58), 41(8), 39(7), 27(3), 17(3).

2-Acetamido-4-cyano-1-(o-tolyl)pyrrole (111)

The amine (95) and acetic anhydride gave a 82% yield of the acetyl derivative (111) as tan needles, m.p. 119-122°, from ethanol.

Found: C, 70.5; H, 5.6; N, 17.9%; $\underline{M}^+$, 239.105904.

$C_{14}H_{13}N_3O$ requires

C, 70.3; H, 5.5; N, 17.6%; M, 239.105856.

ν_{max} 3250(NH), 2250(CN), 1660(C=O), 1600, 1570, 1520, 1300, 1160, 980, 790, 770, 700 cm^{-1}.

$\tau(CDCl_3)$ 2.2(4H, m, C_6H_4), 2.7(1H, d, J=2Hz, 5-H), 3.2(1H, d, J=2Hz, 3-H), 5.1(1H, br, D, NH_2), 7.7(3H, s, $\underline{CH_3}.C_6H_4$), 8.05(3H, s, $COCH_3$).

2-Acetamido-4-cyano-1-(m-tolyl)pyrrole (112)

The amine (96) and acetic anhydride gave a 94% yield of the acetyl derivative (112) as colourless needles, m.p. 145-146°, from ethanol(charcoal).

Found: C, 70.1; H, 5.4; N, 17.5%; $\underline{M}^+$, 239.106123.

$C_{14}H_{13}N_3O$ requires

C, 70.3; H, 5.4; N, 17.6%; M^+, 239.105856.

ν_{max} 3250(NH), 2250(CN), 1660(C=O), 1605,1595, 1570, 1520, 1270, 1190, 1150, 1020, 970, 910, 815, 790, 695 cm^{-1}.

m/e 240(11), 239(70), 199(3), 198(31), 197(100), 196(22), 182(8), 181(6), 180(3), 170(3), 169(7), 168(3), 155(7), 154(3), 142(3), 140(3), 119(3), 118(25), 107(3), 104(3), 92(6), 91(43), 90(3), 89(6), 80(16), 79(3), 77(5), 65(3), 64(4), 63(5), 53(3), 52(4), 51(5), 50(3), 43(63), 41(4), 39(11), 28(37), 27(3), 17(3).

2-Acetamido-4-cyano-1-(p-tolyl)pyrrole (113)

The amine (97) and acetic anhydride gave a 95% yield of the acetyl derivative (113) as colourless needles, m.p. 202-203°, from ethanol.

Found: C, 70.1; H, 5.4; N, 17.7%; M^+, 239.105512.

$C_{14}H_{13}N_3O$ requires

C, 70.3; H, 5.5; N, 17.6%; M^+, 239.105856.

ν_{max} 3200(NH), 2250(CN), 1670(C=O), 1585, 1570, 1520, 1280, 1180, 1140, 1110, 1030, 1015, 975, 850, 830, 820, 720 cm^{-1}.

m/e 240(3), 239(24), 199(3), 198(4), 197(100), 196(8), 183(3), 182(5), 181(5), 169(4), 155(5), 118(14), 104(3), 92(3), 91(19), 90(3), 89(3), 80(7), 77(3), 65(9), 64(3), 63(3), 53(3), 52(4), 51(4), 50(3), 43(25), 41(3), 39(4), 27(3).

2-Acetamido-4-cyano-1-(o-methoxyphenyl)pyrrole (114)

The amine (98) and acetic anhydride gave a 88% yield

of the acetyl derivative (114) as colourless needles, m.p. 136-138°, from ethanol.

Found: C, 65.95; H, 5.1; N, 16.9%; $\underline{M}^+$, 255.100640.

$C_{14}H_{13}N_3O_2$ requires

C, 65.9; H, 5.1; N, 16.5%; $\underline{M}^+$, 255.100770.

ν_{max} 3350(NH), 2225(CN), 1680(C=O), 1600, 1570, 1510, 1280, 1250, 1160, 1140, 1120, 1050, 1070, 1020, 980, 830, 790, 760 cm^{-1}.

m/e 256(9), 255(68), 239(4), 214(12), 213(100), 212(15), 198(20), 197(16), 194(12), 183(3), 182(24), 170(7), 155(4), 134(7), 121(6), 120(21), 108(6), 104(4), 94(6), 93(10), 92(4), 80(6), 79(4), 78(7), 77(20), 71(4), 69(4), 65(14), 63(8), 60(4), 57(6), 55(5), 52(8), 51(10), 50(4), 43(100), 41(5), 39(8), 31(11), 27(6), 17(15).

2-Acetamido-4-cyano-(m-methoxyphenyl)pyrrole (115)

The amine (99) and acetic anhydride gave a 94% yield of the acetyl derivative (115) as colourless needles, m.p. 138-139°, from ethanol.

Found: C, 66.0; H, 5.0; N, 16.7%, $\underline{M}^+$, 255.100562.

$C_{14}H_{13}N_3O$ requires

C, 65.9; H, 5.1, N, 16.5%; $\underline{M}$, 255.100770.

ν_{max} 3200(NH), 2250(CN), 1660(C=O), 1600, 1570, 1520, 1500, 1320, 1280, 1210, 1190, 1150, 1030, 820, 795, 690 cm^{-1}.

m/e 256(4), 255(34), 214(18), 213(100), 212(8), 198(8), 197(3), 185(3), 183(3), 182(4), 171(4), 170(8), 155(3), 143(3), 142(3), 135(3), 134(18), 108(4), 107(10), 93(3), 92(20), 91(3), 80(20), 79(3), 78(8), 77(25), 76(5), 65(8), 64(21), 63(12), 62(3), 53(5), 52(7), 51(7), 50(4), 43(100), 39(8), 27(3)

2-Acetamido-4-cyano-1-(p-methoxyphenyl)pyrrole (116)

The amine (100) and acetic anhydride gave a 97% yield of the acetyl derivative (116) as colourless needles, m.p. 167-168°, from aqueous acetone (charcoal).

Found: C, 65.7; H, 4.9; N, 16.4%; $\underline{M}^+$, 255.101407.

$C_{14}H_{13}N_3O_2$ requires

C, 65.9; H, 5.1; N, 16.5%; $\underline{M}$, 255.100770.

ν_{max} 3200(NH), 2250(CN), 1670(C=O), 1590, 1570, 1530, 1500, 1280, 1180, 1090, 1010, 960, 810, 730, 695 cm^{-1}.

$m/_e$ 256(6), 255(43), 214(14), 213(100), 212(8), 199(5), 198(32), 171(3), 170(3), 157(8), 155(3), 143(3), 142(3), 135(3), 134(13), 120(3), 108(6), 104(3), 93(8), 80(8), 78(6), 77(14), 68(4), 65(3), 64(12), 63(8), 53(3), 52(5), 51(5), 50(5), 43(60), 39(3), 27(4), 15(3).

Attempted synthesis of 2-acetamido-1-(o-chlorophenyl)-4-cyanopyrrole (117)

The attempted preparation of the acetyl derivative (117) from the amine (101) was not successful using the general method. No further attempt was made to characterise the amine.

2-Acetamido-1-(m-chlorophenyl)-4-cyanopyrrole (118)

The amine (102) and acetic anhydride gave a 75% yield of the acetyl derivative (118) as colourless needles, m.p. 155-156°, from ethanol.

Found: C, 60.0; H, 3.7; N, 16.1%; $\underline{M}^+$, 259.051462.

$C_{13}H_{10}N_3Cl\ O$ requires

C, 60.1; H, 3.9; N, 16.2%; $\underline{M}$, 259.051235.

ν_{max} 3200(NH), 2250(CN), 1670(C=O), 1600, 1570, 1520, 1280, 1250, 1180, 1040, 960, 840, 730 cm^{-1}.

$m/_e$ See diagram on page 102.

m^* 152.3(216→182)vs.

2-Acetamido-1-(p-chlorophenyl)-4-cyanopyrrole (119)

The amine (103) and acetic anhydride gave a 75% yield of the acetyl derivative (119) as colourless needles, m.p. 216-218° from ethanol.

Found: C, 59.95; H, 3.95; N, 16.3%; $\underline{M}^+$, 259.051902.

$C_{13}H_{10}N_3ClO$ requires

C, 60.1; H, 3.9; N, 16.2%; $\underline{M}$, 259.051235.

ν_{max} 3250(NH), 2250(CN), 1670(C=O), 1590, 1575, 1530, 1500, 1270, 1180, 1150, 1090, 1020, 970, 845, 810, 710 cm^{-1}.

$\tau(CF_3COOH)$ 2.90(4H, m, C_6H_4), 3.15(1H, d, J=2Hz, 5-H), 3.70(1H, d, J=2Hz, 3-H), 8.10(3H, s, $COCH_3$).

$m/_e$ 261(8), 260(4), 259(28), 219(4), 218(33), 217(15), 216(100), 215(4), 182(21), 181(4), 155(5), 140(4), 138(10), 113(5), 111(16), 80(17), 65(20), 64(83), 59(3), 57(6), 56(4), 55(5), 52(3), 51(4), 50(5), 43(83), 39(3), 27(3).

2-Acetamido-4-cyano-1-(m-nitrophenyl)pyrrole (120)

The amine (104) and acetic anhydride gave a 88% yield of the acetyl derivative (120) as colourless needles, m.p. 198-190°, from ethano (charcoal).

Found: C, 57.9; H, 3.6; N, 20.8%; $\underline{M}^+$, 270.070361.

$C_{13}H_{10}N_4O_3$ requires

C, 57.8; H, 3.7; N, 20.7%; $\underline{M}$, 270.075284.

ν_{max} 3200(NH), 2250(CN), 1660(C=O), 1590, 1535 and 1350(NO_2), 1270, 1180, 1150, 1090, 1010, 960, 810, 730, 690 cm^{-1}.

$\tau[(CD_3)_2SO]$ 2.1(4H, m, C_6H_4), 2.5(1H, s, 5-H), 3.6(1H, s, 3-H), 8.1(3H, s, $COCH_3$).

m/e 270(15), 229(13), 228(100), 198(15), 197(10), 183(9), 182(18), 181(10), 155(5), 104(5), 80(8), 77(12), 76(10), 65(6), 64(7), 63(6), 52(5), 51(6), 50(6), 43(100), 39(9), 32(50), 27(5), 17(25).

2-Acetamido-4-cyano-1-(p-nitrophenyl)pyrrole (121)

The amine (105) and acetic anhydride gave a 84% yield of the acetyl derivative (121) as colourless needles, m.p. 214-215°, from ethanol (charcoal).

Found: C, 57.7; H, 3.75; N, 20.5%; $\underline{M}^+$, 270.075683.

$C_{13}H_{10}N_4O_3$ requires

C, 57.8; H, 3.7; N, 20.7%; $\underline{M}$, 270.075284.

ν_{max} 3200(NH), 2250(CN), 1670(C=O), 1600, 1580, 1530 and 1350(NO_2), 1270, 1170, 1140, 1090, 1010, 970, 850, 810, 715 cm^{-1}.

m/e 271(3), 270(15), 229(10), 228(90), 198(11), 197(3), 183(3), 182(18), 181(6), 180(4), 155(4), 149(3), 120(4), 104(4), 103(3), 93(3), 92(3), 80(5), 78(6), 77(10), 76(4), 65(4), 64(4), 63(3), 52(5), 51(4), 50(6), 43(100), 41(4), 39(5), 32(10), 28(61), 27(5), 17(3).

2-Acetamido-4-cyano-1-(p-ethoxycarbonylphenyl)pyrrole (122)

The amine (106) and acetic anhydride gave a 72% yield of the acetyl derivative (122) as colourless needles, m.p. 164-165°, from ethanol.

Found: C, 78.6; H, 5.1; N, 14.2%; $\underline{M}^+$, 297.111811.

$C_{16}H_{15}N_3O_3$ requires

C, 78.8; H, 5.1, N, 14.1%; $\underline{M}$, 297.111334.

ν_{max} 3200(NH), 2225(CN), 1710(C=O), 1660(C=O), 1600, 1590, 1570, 1520, 1280, 1190, 1120, 1100, 1020, 870, 810, 770, 760, 695 cm^{-1}.

$m/_e$ 298(5), 297(55), 256(14), 255(100), 252(8), 228(8), 209(4), 182(8), 181(5), 155(4), 120(3), 104(4), 80(4), 77(5), 76(4), 64(3), 52(3), 43(40), 41(3), 39(3), 29(4), 27(3).

m^* 218(297 → 255)vs.

(D) The Synthesis of 4,6-Dimethylpyrrolopyridines from Aminopyrroles and pentane-2,4-dione.

General Method.

The aminopyrrole (0.01mol), pentane-2,4-dione (0.01mol) and ethanol ($50cm^3$) were heated under reflux for 4h after the addition of conc. hydrochloric acid ($0.1cm^3$) to the boiling solution. The bulk of the ethanol was evapourated off and a little water added until the pyrrolopyridine began to separate from solution. The products were recrystallised from a suitable solvent together with decolourising charcoal where necessary.

3-Cyano-1-cyclohexyl-4,6-dimethylpyrrolo[2,3-b]pyridine (136)

The amine (91) and pentane-2,4-dione gave a 60% yield of the pyrrolopyridine (136) as colourless microprisms, m.p. 151-152°, from ethanol.

Found: C, 75.6; H, 7.6; N, 16.3%; $\underline{M}^+$, 253.157684.

$C_{16}H_{19}N_3$ requires

C, 75.85; H, 7.55; N, 16.6%; $\underline{M}$, 253.157890.

ν_{max} 3090(CH, Ar), 2250(CN), 1640, 1590, 1530, 1280, 1200, 1180, 860, 840, 660 cm^{-1}.

$\tau(CDCl_3)$ 2.35(1H, s, 2-H), 3.25(1H, s, 5-H), 7.35(3H, s, 6-Me), 7.45(3H, s, 4-Me), 7.8-8.8(11H, m, C_6H_{11}).

$m/_e$ 254(5), 253(21), 252(8), 224(3), 198(7), 172(20), 171(100), 170(10), 156(8), 130(4), 55(8), 41(14), 39(6), 29(5), 28(3), 27(5).

m^* 115.6(253→171)m.

m^* 142.3(171→156)s.

3-Cyano-4,6-dimethyl-1-phenylpyrrolo[2,3-b]pyridine (137)

The crude amine (92) and pentane-2,4-dione gave a 54% yield of the pyrrolopyridine (137) as colourless needles, m.p. 184°, from ethanol (charcoal).

Found: C, 77.4; H, 5.5; N, 16.95%; M^+, 247.110445.

$C_{16}H_{13}N_3$ requires

C, 77.7; H, 5.3; N, 17.0%; M, 247.110942.

νmax (CCl_4) 3050(CH, Ar), 2950 and 2850(CH, Aliphatic), 2225(CN), 1595, 1540, 1505, 1420, 1300, 1200, 750, 690 cm^{-1}.

τ($CDCl_3$) 2.60(5H, m, C_6H_5), 2.80(1H, s, 2-H), 3.75(1H, s, 5-H), 7.1(3H, s, 6-Me), 7.3(3H, s, 4-Me).

1-Benzyl-3-cyano-4,6-dimethylpyrrolo[2,3-b]pyridine (138)

The crude amine (93) and pentane-2,4-dione gave a 52% yield of the pyrrolopyridine (138) as colourless needles, m.p. 135-136°, from ethanol (charcoal).

Found: C, 78.2; H, 5.8; N, 16.3%; M^+, 261.126273.

$C_{17}H_{15}N_3$ requires

C, 78.1; H, 5.8; N, 16.1%; M, 261.126591.

νmax 2250(CN), 1620, 1600, 1550, 1170, 980, 970, 790, 700 cm^{-1}.

τ($CDCl_3$) 2.50(1H, s, 2-H), 2.75(5H, s, C_6H_5), 3.15(1H, s, 5-H), 4.60(2H, s, $\underline{CH_2}.C_6H_5$), 7.30(3H, s, 6-Me), 7.40(3H, s, 4-Me).

$m/_e$ See diagram on page 98.

3-Cyano-4,6-dimethyl-1-phenethylpyrrolo[2,3 b]pyridine (139)

The crude amine (94) and pentane-2,4-dione gave a 79% yield of the pyrrolopyridine (139) as colourless needles, m.p. 101-103°, from ethanol (charcoal).

Found: C, 78.35; H, 6.2; N, 15.5%; M^+, 275.142102.

$C_{18}H_{17}N_3$ requires

C, 78.5; H, 6.2; N, 15.3%; M, 275.142240.

ν_{max} 2250(CN), 1610, 1580, 1540, 1510, 1200, 790, 750, 710, 695 cm^{-1}.

$\tau(CDCl_3)$ 2.8(5H, m, C_6H_5), 2.95(1H, s, 2-H), 3.2(1H, s, 5-H), 5.5(2H, t, J=7Hz, $\underline{CH_2}.CH_2.C_6H_5$), 6.85(2H, t, J=7Hz, $CH_2.\underline{CH_2}.C_6H_5$), 7.35(3H, s, 6-Me), 7.45(3H, s, 4-Me).

$m/_e$ 276(7), 275(48), 274(18), 248(3), 234(5), 198(18), 107(5), 106(9), 105(100), 104(78), 103(12), 92(8), 91(30), 90(3), 77(13), 76(5), 65(3), 64(3), 52(4), 51(3), 41(3), 39(5), 27(8).

3-Cyano-4,6-dimethyl-1-(m-tolyl)pyrrolo[2,3-b]pyridine (140)

The amine (96) and pentane-2,4-dione gave a 67% yield of the pyrrolopyridine (140) as colourless needles, m.p. 180-182°, from ethanol.

Found: C, 78.1; H, 5.8; N, 16.1%; M^+, 261.126717.

$C_{17}H_{15}N_3$ requires

C, 78.1; H, 5.8; N, 16.0%; M, 261.126591.

ν_{max} 2250(CN), 1600, 1590, 1530, 1300, 1190, 1070, 860, 850, 810, 790, 700, 670 cm^{-1}.

$m/_e$ 262(15), 261(100), 260(20), 246(4), 245(3), 233(3), 219(3), 203(3), 129(5), 116(4), 105(3), 104(3), 91(7), 90(3), 89(5), 77(3), 65(8), 64(3), 63(4), 51(3), 41(3), 39(6), 27(3).

3-Cyano-4,6-dimethyl-1-(p-tolyl)pyrrolo[2,3-b]pyridine (141)

The amine (97) and pentane-2,4-dione gave a 65% yield of the pyrrolopyridine (141) as colourless needles, m.p. 166-168°, from ethanol.

Found: C, 78.0; H, 5.9; N, 16.1%; M^+, 261.136173.

$C_{17}H_{15}N_3$ requires
C, 78.1; H, 5.8; N, 16.0%; M, 261.126591.

ν_{max} 2250(CN), 1600, 1570, 1520, 1300, 1205, 1195, 1070, 1030, 860, 795, 700 cm^{-1}.

$\tau(CDCl_3)$ 2.15(1H, s, 2-H), 2.55(4H, q, J=9Hz, C_6H_4), 3.1(1H, s, 5-H), 7.2(3H, s, $\underline{CH_3}.C_6H_4$), 7.4(3H, s, 6-Me), 7.5(3H, s, 4-Me).

$m/_e$ 262(18), 261(100), 260(24), 246(4), 245(3), 233(3), 198(3), 156(3), 142(3), 116(3), 104(3), 91(6), 90(3), 89(4), 77(3), 65(9), 64(3), 63(3), 51(3), 41(3), 39(6), 27(3).

3-Cyano-4,6-dimethyl-1-(o-methoxyphenyl)pyrrolo[2,3-b]pyridine (142)

The amine (98) and pentane-2,4-dione gave a 69% yield of the pyrrolopyridine (142) as colourless needles, m.p. 188-190°, from ethanol.

Found: C, 73.8; H, 5.5; N, 15.3%; M^+, 277.121830.
$C_{17}H_{15}N_3O$ requires
C, 73.6; H, 5.45; N, 15.15%; M, 277.121505.

ν_{max} 2225(CN), 1600, 1570, 1520, 1300, 1180, 1160, 1060, 860, 850, 810, 790, 700 cm^{-1}.

$m/_e$ 278(18), 277(100), 276(47), 262(7), 249(8), 248(47), 247(32), 246(39), 172(5), 171(10), 92(3), 91(3), 77(8), 76(3), 65(4), 64(6), 63(7), 57(5), 55(5), 51(8), 50(4), 43(7), 41(7), 39(8), 27(9), 15(3).

3-Cyano-4,6-dimethyl-1-(m-methoxyphenyl)pyrrolo[2,3-b]pyridine (143)

The amine (99) and pentane-2,4-dione gave a 72% yield of the pyrrolopyridine (143) as colourless needles, m.p. 183-184°, from ethanol.

Found: C, 73.6; H, 5.4; N, 15.2%; M^+, 277.120458.

$C_{17}H_{15}N_3O$ requires

C, 73.6; H, 5.45; N, 15.15%; M, 277.121505.

ν_{max} 3075(CH Ar), 2250(CN), 1605, 1535, 1505, 1350, 1315, 1270, 1205, 1195, 1045, 880, 850, 815, 795, 700 cm^{-1}.

$m/_e$ 278(18), 277(100), 276(90), 275(5), 262(5), 261(3), 249(3), 248(21), 247(47), 246(11), 234(4), 233(7), 232(6), 219(3), 206(3), 171(5), 156(3), 139(3), 92(7), 91(3), 77(6), 76(3), 65(3), 64(9), 63(7), 52(5), 51(3), 41(3), 39(4), 27(3).

3-Cyano-4,6-dimethyl-1-(p-methoxyphenyl)pyrrolo[2,3-b]pyridine (144)

The amine (100) and pentane-2,4-dione gave a 75% yield of the pyrrolopyridine (144) as colourless needles, m.p. 179-180°, from benzene/petroleum ether.

Found: C, 73.85; H, 5.6; N, 14.9%; M^+, 277.120032.

$C_{17}H_{15}N_3O$ requires

C, 73.6; H, 5.45; N, 15.15%; M, 277.121505.

ν_{max} 3125(CH Ar), 2250(CN), 1605, 1535, 1350, 1310, 1270, 1200, 1190, 1030, 880, 815, 795, 700 cm^{-1}.

$m/_e$ 278(3), 277(100), 262(28), 261(3), 234(19), 233(3), 156(3), 149(14), 123(25), 108(32), 77(32), 76(10), 64(3), 52(3), 51(3), 41(3), 39(3), 27(9).

1-(o-Chlorophenyl)-3-cyano-4,6-dimethylpyrrolo[2,3-b]pyridine (145)

The amine (101) and pentane-2,4-dione gave a 75% yield of the pyrrolopyridine (145) as colourless needles, m.p. 189-190°, from ethanol.

Found: C, 68.2; H, 4.4; N, 14.9%; M^+, 281.071076.

$C_{16}H_{12}N_3Cl$ requires

C, 68.2; H, 4.3; N, 14.9%; M, 281.071970.

ν_{max} 2250(CN), 1610, 1580, 1530, 1270, 1200, 1070, 1040, 830, 780, 760, 720, 695 cm^{-1}.

1-(m-Chlorophenyl)-3-cyano-4,6-dimethylpyrrolo[2,3-b]pyridine (146)

The amine (102) and pentane-2,4-dione gave a 76% yield of the pyrrolopyridine (146) as colourless needles, m.p. 189-190°, from ethanol.

Found: C, 68.15; H, 4.3, N, 15.1%; M^+, 281.072134.

$C_{16}H_{12}N_3Cl$ requires

C, 68.2; H, 4.3; N, 14.9%; M, 281.071970.

ν_{max} 3100(CH Ar), 2225(CN), 1580, 1530, 1360, 1300, 1200, 860, 840, 770, 750, 690 cm^{-1}.

$\tau(CDCl_3)$ 2.2(1H, s, 2-H), 2.55(4H, m, C_6H_4), 3.1(1H, s, 5-H), 7.3(3H, s, 6-Me), 7.5(3H, s, 4-Me).

$m/_e$ 284(5), 283(35), 282(25), 281(100), 280(10), 266(3), 246(3), 245(3), 244(3), 230(3), 219(3), 217(3), 170(4), 143(3), 141(6), 122(10), 113(3), 111(8), 90(4), 77(3), 76(4), 75(12), 52(5), 51(16), 50(5), 41(3), 39(6), 27(3).

1-(p-Chlorophenyl)-3-cyano-4,6-dimethylpyrrolo[2,3-b]pyridine (147)

The amine (103) and pentane-2,4-dione gave a 72% yield of the pyrrolopyridine (147) as colourless needles, m.p. 235-236°, from ethanol.

Found: C, 67.9; H, 4.3; N, 14.8%; M^+, 281.071025.

$C_{16}H_{12}N_3Cl$ requires

C, 68.2; H, 4.3; N, 14.9%; M, 281.071970.

ν_{max} 3125(CH Ar), 2225(CN), 1590, 1540, 1500, 1305, 1295, 1205, 1090, 860, 830, 705, 675 cm^{-1}.

$\tau(CDCl_3)$ 1.7(1H, s, 2-H), 2.4(4H, q, C_6H_4), 3.1(1H, s, 5-H), 7.4(3H, s, 6-Me), 7.6(3H, s, 4-Me).

$m/_e$ 284(5), 283(33), 282(24), 281(100), 280(22), 266(3), 246(3), 244(3), 199(3), 143(3), 141(6), 123(5), 77(3), 75(5), 52(3), 51(3), 39(3), 27(3).

3-Cyano-4,6-dimethyl-1-(m-nitrophenyl)pyrrolo[2,3-b]pyridine (148)

The amine (104) and pentane-2,4-dione gave a 67% yield of the pyrrolopyridine (148) as colourless needles, m.p. 235-236°, from ethanol (charcoal).

Found: C, 65.4; H, 4.05; N, 18.9%; $\underline{M}^+$, 292.096224.

$C_{16}H_{12}N_4O_2$ requires

C, 65.8; H, 4.1; N, 19.2%; $\underline{M}$, 292.096019.

ν_{max} 3100(CH Ar), 2250(CN), 1580, 1535 and 1350(NO_2), 1305, 1205, 890, 845, 800, 735, 695 cm^{-1}.

$m/_e$ 293(18), 292(100), 291(3), 263(3), 262(5), 261(3), 247(11), 246(58), 245(9), 244(6), 234(3), 233(3), 232(4), 231(5), 230(5), 219(3), 205(3), 170(3), 156(3), 143(3), 142(3), 138(3), 130(3), 129(3), 123(4), 116(3), 103(3), 102(3), 91(3), 90(3), 84(4), 77(5), 76(6), 75(5), 65(4), 64(4), 63(5), 51(4), 50(5), 44(10), 43(9), 41(3), 39(3), 32(3), 27(10).

3-Cyano-4,6-dimethyl-1-(p-nitrophenyl)pyrrolo[2,3-b]pyridine (149)

The amine (105) and pentane-2,4-dione gave a 67% yield of the pyrrolopyridine (149) as colourless needles, m.p. 203-205°, from ethanol (charcoal).

Found: C, 65.95; H, 4.1; N, 19.2%; $\underline{M}^+$, 292.095892.

$C_{16}H_{12}N_4O_2$ requires

C, 65.8; H, 4.1; N, 19.2%; $\underline{M}$, 292.096019.

ν_{max} 3100(CH Ar), 2225(CN), 1605, 1595, 1530 (NO_2), 1500, 1350(NO_2), 1300, 1200, 1110, 1070, 1050, 870, 860, 850, 840, 750, 695 cm^{-1}.

$m/_e$ 293(22), 292(100), 291(6), 277(3), 262(11), 247(10), 246(53), 245(9), 244(7), 234(4), 231(6), 230(6), 171(8), 170(14), 143(4), 138(4), 116(3), 103(3), 102(3), 101(3), 90(4), 89(3), 78(5), 77(7), 76(15), 75(11), 65(6), 64(5), 63(4), 52(5), 51(8), 50(12), 44(4), 41(4), 39(11), 32(2), 27(5).

3-Cyano-4,6-dimethyl-1-(p-ethoxycarbonyl)pyrrolo[2,3-b]pyridine (150)

The amine (106) and pentane-2,4-dione gave a 58% yield of the pyrrolopyridine (150) as colourless needles, m.p. 182-183°, from ethanol.

Found: C, 71.2; H, 5.4; N, 13.1%; M^+, 319.132339.

$C_{19}H_{17}N_3O_2$ requires

C, 71.45; H, 5.4; N, 13.2%; M, 319.132069.

ν_{max} 3100(CH Ar), 2225(CN), 1705(C=O), 1600, 1580, 1535, 1520, 1310, 1280, 1200, 1130, 1105, 1020, 860, 850, 770, 695 cm^{-1}.

$m/_e$ 320(17), 319(100), 318(4), 293(12), 292(5), 278(8), 277(5), 276(8), 248(4), 247(8), 246(19), 245(4), 171(3), 138(5), 77(4), 76(5), 75(3), 69(3), 65(3), 63(3), 57(4), 55(4), 52(4), 51(13), 45(5), 44(10), 43(9), 41(6), 39(3), 29(9), 27(10), 15(10).

(E) The Synthesis of Pyrrolopyridines from Aminopyrroles and 1-Phenylbutane-1,3-dione

3-Cyano-6-methyl-1,4-diphenylpyrrolo[2,3-b]pyridine (151)

The aminopyrrole (92) and 1-phenylbutane-1,3-done (0.01 mol) were heated together in ethanol ($50cm^3$) for 4h with conc. hydrochloric acid ($0.1\ cm^3$) as catalyst. The pyrrolopyridine (151) was isolated in 65% yield after distillation of the excess solvent and dilution with water. Recrystallisation from aqueous ethanol (charcoal) gave prisms, m.p. 171-172°.

Found: C, 81.25; H, 5.1; N, 13.6%; M^+, 309.126514.

$C_{21}H_{15}N_3$ requires

C, 81.5; H, 4.9; N, 13.65%; M, 309.126591.

ν_{max} 3100(CH Ar), 2225(CN), 1590, 1530, 1500, 1300, 1230, 1200, 1100, 1080, 1030, 920, 910, 870, 850, 780, 720, 695 cm^{-1}.

(CF_3COOH) 2.25(1H, s, 2-H), 2.70(1H, s, 5-H), 2.8-3.0(10H, m, -Phenyl protons), 7.35(3H, s, 6-Me).

1-(m-Chlorophenyl)-3-cyano-6-methyl-4-phenylpyrrolo[2,3-b]pyridine (152)

The aminopyrrole (102) (0.01mol) and 1-phenylbutane-1,3-dione (0.01mol) were heated together in butan-1-ol ($50cm^3$) for 2h with conc. hydrochloric acid ($0.1cm^3$). The solvent was reduced in volume to give, on cooling, 61% of the pyrrolopyridine (152) as colourless needles, m.p. 214-215°, from aqueous ethanol (charcoal).

Found: C, 73.4; H, 4.3; N, 19.3%; M^+, 343.086780.

$C_{21}H_{14}N_3Cl$ requires

C, 73.4; H, 4.1; N, 19.2%; M, 343.087620.

ν_{max} 3100(CH Ar), 2250, 1595, 1530, 1405, 1290, 1220 1200, 860, 840, 770, 750, 690, 670 cm^{-1}.

$\tau(CF_3COOH)$ 2.15(1H, s, 2-H), 2.65(1H, s, 5-H), 2.75-2.85(9H, br m, Phenyl protons), 7.30(3H, s, 6-Me).

The Reaction between 2-Amino-4-cyano-1-cyclohexylpyrrole and 1-Phenylbutane-1,3-dione.

The aminopyrrole (91) (0.01mol) and 1-phenylbutane-1,3-dione (0.01mol) were heated together in ethanol ($50cm^3$) with conc. hydrochloric acid ($0.1cm^3$) for 4h in the usual manner. The excess of ethanol was removed *in vaccuo* and the residue triturated with water to give a 67% yield of the 3:2 mixture of pyrrolopyridines (168) and (169). The product had a sharp melting point, 151-152°, from aqueous ethanol.

Found: C, 79.9; H, 6.6; N, 13.25%; M^+, 315.173724.

$C_{21}H_{21}N_3$ requires

C, 80.0; H, 6.7; N, 13.3%; M, 315.173539.

The product was shown to be a mixture of two isomers by n.m.r. spectroscopy:-

$\tau(CDCl_3)$ 1.98 and 2.13(1H, 2x s, 2-H's), 2.25 and 2.30(1H, 2x s, 5-H's), 2.55(5H, br s, C_6H_5's), 7.25 and 7.30(3H, 2x s, CH_3's), 8.25-9.25(11H, m, C_6H_{11}'s).

The isomers were not isolated.

(F) The Synthesis of Pyrrolopyridines from Aminopyrroles and 4,4-Dimethoxybutan-2-one

3-Cyano-1-cyclohexyl-6-methylpyrrolo[2,3-b]pyridine (154)

The aminopyrrole (91) (0.01mol) and 4,4-dimethoxybutan-2-one (0.01mol) were heated together in ethanol ($50cm^3$) for 6h with conc. hydrochloric acid ($0.1cm^3$). The excess of ethanol was evapourated off and the solution diluted with water to give the pyrrolopyridine (154) in 89% yield, as yellow prisms, m.p. 137-138°, from petroleum ether.

Found: C, 75.2; H, 7.2; N, 17.6%; M^+, 239.141029.

$C_{15}H_{17}N_3$ requires

C, 75.3; H, 7.2; N, 17.6%; M, 239.142240.

ν_{max} 3100(CH Ar), 2225(CN), 1600, 1570, 1530, 1295, 1275, 1200, 1150, 1030, 1020, 890, 860, 810, 770, 695 cm^{-1}.

$\tau(CDCl_3)$ 2.27(1H, s, 2-H), 2.12(1H, d, J_{4-5}=8Hz, 4-H), 2.92(1H, d, J_{4-5}=8Hz, 5-H), 7.37(3H, s, 6-Me), 7.70-8.60(11H, m, C_6H_{11}).

$m/_e$ 240(5), 239(18), 238(7), 184(4), 170(4), 159(8), 158(21), 157(100), 132(3), 103(4), 67(5), 55(14), 41(23), 28(6), 27(22).

3-Cyano-6-methyl-1-phenylpyrrolo[2,3-b]pyridine (155)

The aminopyrrole (92) (0.01mol) and 4,4-dimethoxybutan-2-one (0.01mol) were heated together in ethanol ($50cm^3$) for 6h wth conc. hydrochloric acid ($0.1cm^3$). The pyrrolopyridine was isolated in 78% yield after working up in the usual manner. Recrystallisation from petroleum ether gave colourless matted needles, m.p. 153-154°.

Found: C, 77.0; H, 4.9; N, 18.2%; M^+, 233.094980.

$C_{15}H_{11}N_3$ requires

C, 77.2; H, 4.75; N, 18.0%; M, 233.095293.

ν_{max} 3100(CH Ar), 2225(CN), 1600, 1570, 1530, 1295, 1275, 1200, 1150, 1030, 1020, 890, 860, 810, 77 cm^{-1}.

$\tau(CF_3COOH)$ 1.60(1H, d, J_{4-5}=8Hz, 4-H), 2.15(1H, s, 2-H , 2.60(1H, d, J_{4-5}=8Hz, 5-H), 2.75(5H, br, s, C_6H_5), 7.35(3H, s, 6-Me).

$m/_e$ 234(17), 233(100), 232(32), 231(5), 218(5), 217(3), 206(5), 205(5), 204(5), 192(3), 156(3), 130(3), 129(4), 116(3), 103(5), 91(3), 77(15), 76(3), 62(3), 52(3), 51(10), 50(3), 41(3), 39(5), 27(4).

Accurate mass measurements on selected ions:

$m/_e$ 206 Found 206.083884, $C_{14}H_{10}N_2$ requires 206.084394.

$m/_e$ 39 Found 39.023631, C_3H_3 requires 39.083474

$m/_e$ 192 and 41 too small to calculate.

Ion source determination; metastable scan at 4-8Kv.

$m/_e$ 206(232→206) 0.126vs

192(206→192) 0.074m

192(217→192) 0.130vs

192(231→192) 0.204s

1-(m-Chlorophenyl)-3-cyano-6-methylpyrrolo 2,3-b pyridine (156)

The aminopyrrole (102) (0.01mol) and 4,4-dimethoxybutan-2-one (0.01mol) were refluxed in butan-1-ol ($50cm^3$) for 2h with conc. hydrochloric acid ($0.1cm^3$). The solvent was evapourated and the residue triturated with petroleum ether to give the pyrrolopyridine (156) in 92% yield, as needles, m.p. 174-175°, from ethanol (charcoal).

Found: C, 67.3; H, 3.8; N, 15.7%; M^+, 267.056314.

$C_{15}H_{10}N_3Cl$ requires

C, 67.8; H, 3.8; N, 15.7%; M, 267.056321.

ν_{max} 3100(CH Ar), 2225(CN), 1580, 1530, 1280, 1260, 1220, 860, 810, 780, 770, 740, 690 cm^{-1}.

$\tau[(CD_3)_2SO]$ 1.50(1H, s, 2-H), 2.20(4H, m, C_6H_4), 2.70(1H, d, J_{4-5}=8Hz, 4-H), 2.95(1H, d, J_{4-5}=8Hz, 5-H), 7.30(3H, s, 6-Me).

m/e 270(4), 269(33), 268(23), 267(100), 266(20), 240(3), 232(3), 231(3), 230(3), 205(3), 156(3), 141(4), 130(3), 129(3), 125(3), 116(5), 111(4), 101(4), 100(5), 92(3), 91(3), 77(3), 76(4), 75(5), 63(3), 51(3), 50(3), 41(3), 39(3), 27(4).

(G) The Synthesis of Pyrrolopyridines from Aminopyrroles and 1,1,3,3-Tetramethoxypropane

3-Cyano-1-cyclohexylpyrrolo[2,3-b]pyridine (157)

The aminopyrrole (91) (0.01mol) and 1,1,3,3-tetramethoxy propane (0.01mol) were refluxed in ethanol ($50cm^3$) for 6h after the addition of conc. hydrochloric acid ($0.1cm^3$). The solution was distilled off to give the pyrrolopyridine (157) as a tan precipitate in 76% yield. Recrystallisation from petroleum ether gave colourless prisms, m.p. 116-117°.

Found: C, 74.4; H, 6.8; N, 18.9%; M^+, 225.126917.

$C_{14}H_{15}N_3$ requires

C, 74.6; H, 6.7; N, 18.65%; M, 225.126591.

ν_{max} 3125(CH Ar), 2225(CN), 1605, 1570, 1525, 1280, 1270, 1220, 1200, 1150, 1130, 1020, 900, 850, 800 cm^{-1}.

$\tau(CDCl_3)$ 1.56(1H, q, J_{5-6}=6Hz, J_{4-6}=1.2Hz, 6-H), 1.92(1H, q, J_{4-5}=8Hz, J_{4-6}=1.2Hz, 4-H), 2.20(1H, s, 2-H), 2.81(1H, q, J_{4-5}=8Hz, J_{5-6}=6Hz, 5-H), 7.6-8.6(11H, m, C_6H_{11}).

$m/_e$ 226(5), 225(25), 224(7), 196(3), 182(5), 170(5), 156(3), 144(20), 143(100), 116(5), 89(3), 67(5), 55(8), 41(10), 39(5), 29(3), 28(4), 27(3).

3-Cyano-1-phenylpyrrolo[2,3-b]pyridine (158)

The aminopyrrole (92) (0.01mol) and 1,1,3,3-tetramethoxy propane (0.01mol) were refluxed in butan-1-ol ($50cm^3$) with conc. hydrochloric acid ($0.1cm^3$) for 2h. The pyrrolopyridine was isolated in 43% yield by concentration of the solution to give, on cooling, prisms m.p. 205-206°, from ethanol (charcoal).

Found: C, 76.8; H, 4.3; N, 19.3%; M^+, 219.079126.

$C_{14}H_9N_3$ requires

C, 76.7; H, 4.1; N, 19.2%; M, 219.079643.

ν_{max} 2250(CN), 1600, 1580, 1540, 1510, 1300, 1290, 1230, 1130, 860, 800, 780, 760, 695 cm^{-1}.

$\tau(CF_3COOH)$ 1.5(1H, d, J_{5-6}=8Hz, 6-H), 1.85(1H, d, J_{4-5}=6Hz, 4-H), 2.15(1H, s, 2-H), 2.50(1H, q, J_{4-5}=6Hz, J_{5-6}=8Hz, 5-H), 2.90(5H, br s, C_6H_5).

$m/_e$ 220(14), 219(100), 218(40), 217(4), 192(5), 165(3), 143(3), 116(4), 110(7), 96(3), 89(3), 77(6), 51(7), 39(3), 27(3).

1-(m-Chlorophenyl)-3-cyanopyrrolo[2,3-b]pyridine (159)

The aminopyrrole (102) (0.02mol) and 1,1,3,3-tetramethoxy propane (0.02mol) were refluxed in butan-1-ol (100cm^3) for 3h with conc. hydrochloric acid (0.2cm^3). The solvent was reduced in volume to 25cm^3 and the pyrrolopyridine (159) precipitated out on trituration with petroleum ether in 81% yield. Recrystallisation from aqueous acetone (charcoal) and then acetone/petroleum ether gave colourless prisms, m.p. 223-224°.

Found: C, 66.0; H, 3.1; N, 16.5%; M^+, 253.040587.

$C_{14}H_8N_3Cl$ requires

C, 66.3; H, 3.2; N, 16.6%; M, 253.040672.

ν_{max} 3100(CH Ar), 2225(CN), 1600, 1540, 1495, 1290, 1270, 1230, 1170, 1130, 1110, 1070, 870, 860, 820, 800, 790, 780, 710, 695 cm^{-1}.

$\tau(CF_3COOH)$ 1.4(1H, d, J_{5-6}=8Hz, 6-H), 1.75(1H, d, J_{4-5}=6Hz, 4-H), 2.05(1H, s, 2-H), 2.35(1H, m, 5-H), 2.75(4H, m, C_6H_4).

$m/_e$ 255(26), 254(21), 253(100), 252(27), 218(8), 217(20), 191(7), 189(3), 183(20), 182(7), 164(4), 155(4), 153(8), 143(3), 140(3), 138(4), 137(4), 129(4),

127(14), 117(3), 115(8), 111(4), 109(12), 91(4), 80(6), 79(4), 78(5), 77(4), 76(4), 75(13), 71(8), 70(4), 65(5), 64(3), 63(3), 41(3), 39(6), 27(4).

1-(p-Chlorophenyl)-3-cyanopyrrolo[2,3-b]pyridine (160)

The aminopyrrole (103) (0.01mol) and 1,1,3,3-tetramethoxy propane (0.01mol) were refluxed in ethanol (50cm^3) with conc. hydrochloric acid (0.1cm^3) for 6h. The ethanol was reduced in volume and a little water added to yield the pyrrolopyridine (160) as colourless needles, m.p. 196-197°, from ethanol (charcoal).

Found: C, 65.8; H, 3.3; N, 16.4%; M$^+$, 253.041050.

$C_{14}H_8N_3Cl$ requires

C, 65.3; H, 3.2; N, 16.6%; M, 253.040672.

ν_{max} 3100(CH Ar), 2225(CN), 1600, 1570, 1530, 1270, 1210, 1190, 1140, 1090, 1050, 870, 850, 810, 750, 710, 695 cm^{-1}.

m/e 256(4), 255(36), 254(22), 253(100), 252(17), 219(3), 218(5), 217(10), 191(10), 182(3), 164(3), 155(3), 151(3), 143(3), 141(3), 138(3), 129(3), 127(10), 116(8), 113(3), 109(5), 89(4), 77(3), 76(3), 75(13), 64(3), 63(3), 62(3), 51(4), 50(5), 39(3), 36(8), 27(5).

3-Cyano-1-cyclohexyl-4,6-diphenylpyrrolo [2,3-b] pyridine (153)

The aminopyrrole (91) (0.01mol) and dibenzoylmethane (0.01mol) were heated under reflux in ethanol ($50cm^3$) with conc. hydrochloric acid ($0.1cm^3$) for 4h. The excess of ethanol was removed by evapouration to yield the pyrrolo 2,3-b pyridine (42%) as colourless needles, m.p. 224-225°, from ethanol.

Found: C, 82.6; H, 6.1; N, 11.2%; M^+, 377.187974.

$C_{26}H_{23}N_3$ requires

C, 82.7; H, 6.1; N, 11.1%; M, 377.189188.

νmax 3100(CH Ar), 2225(CN), 1590, 1570, 1520, 1500, 1290, 1270, 1200, 1180, 1140, 1120, 1030, 870, 780, 760, 740, 700 cm^{-1}.

3-Cyano-1-cyclohexyl-5-nitropyrrolo[2,3-b]pyridine (161)

The aminopyrrole (91) (0.01mol) and nitromalondialdehyde (0.01mol) liberated from its sodio-derivative by glacial acetic acid were refluxed in ethanol ($50cm^3$). After 4h the solution was cooled in ice/water to yield 72% of the pyrrolo 2,3-b pyridine (161) as matted needles, 224-225°, from ethanol (charcoal).

Found: C, 62.0; H, 5.4; N, 20.9%; M^+, 270.110544.

$C_{14}H_{14}N_4O_2$ requires

C, 62.2; H, 5.2; N, 20.7%; M, 270.111669.

νmax 3100(CH Ar), 2225(CN), 1600, 1575, 1525 and 1505 (NO_2), 1350 and 1330(NO_2), 1280, 1210, 1190, 1140, 1120, 1075, 940, 920, 890, 860, 820, 790, 780, 750 cm^{-1}.

$\tau(CDCl_3)$ 0.75(1H, d, J_{4-6}=1.2Hz, 6-H), 1.15(1H, d, J_{4-6}=1.2 Hz, 4-H), 2.00(1H, s, 2-H), 7.70-8.80(11H, m, C_6H_{11}).

(H) The Synthesis of Pyrrolopyridines from -Keto esters.

3-Cyano-1-cyclohexyl-4-methylpyrrolo[2,3-b]pyridin-6(7H)-one (176)

The aminopyrrole (91) (0.01mol) and ethyl acetoacetate (0.01mol) were refluxed in butan-1-ol ($50cm^3$) for 3h with conc. hydrochloric acid ($0.1cm^3$). The pyrrolopyridinone (176) was isolated in 85% yield after concentration of the solvent. Recrystallisation from chloroform gave colourless needles, m.p. 283-284°.

Found: C, 70.6; H, 6.7; N, 16.6%; M^+, 255.150648.

$C_{15}H_{17}N_3O$ requires

C, 70.6; H, 6.7; N, 16.5%; M, 255.149730.

ν_{max} 3150(NH), 2250(CN), 1640(C=O), 1580, 1530, 1510, 1290, 1265, 1250, 1210, 1180, 1150, 1080, 1050, 1030, 1000, 965, 940, 910, 900, 850, 810, 780, 755 cm^{-1}.

$\tau(CF_3COOH)$ 2.0(1H, s, 2-H), 3.05(1H, s, 5-H), 7.1(3H, s, 4-Me), 7.8-8.3(11H, m, C_6H_{11}).

$m/_e$ 256(4), 255(32), 254(3), 238(3), 226(3), 211(3), 201(3), 200(3), 186(3), 174(14), 173(100), 172(3), 156(3), 144(4), 143(9), 117(3), 90(3), 89(4), 81(4), 67(3), 55(9), 54(3), 53(3), 41(9), 39(4), 27(4), 17(4).

3-Cyano-1-cyclohexyl-4,5-dimethylpyrrolo[2,3-b]pyridin-6(7H)-one (178)

The aminopyrrole (91) (0.01mol) and ethyl 2-methylacetoacetate (0.01mol) were refluxed in butan-1-ol ($50cm^3$) for 3h with conc. hydrochloric acid ($0.1cm^3$). The pyrrolopyridinone (178) was isolated in 79% yield by concentration of the solvent, as before, to give colourless needles, m.p. 290°(decomp.).

Found: C, 70.85; H, 6.9; N, 15.55%; $\underline{M}^+$, 269.152799.

$C_{16}H_{19}N_3O$ requires

C, 71.3; H, 7.1; N, 15.6%; $\underline{M}$, 269.152804.

ν_{max} 3150(NH), 2250(CN), 1640(C=O), 1580, 1550, 1290, 1280, 1210, 1180, 1150, 1130, 920, 890, 840, 820, 760, 730, 695 cm^{-1}.

$m/_e$ 270(8), 269(42), 268(5), 256(3), 255(13), 254(3), 188(13), 187(100), 186(7), 174(5), 173(43), 172(5), 158(6), 144(5), 83(4), 81(4), 64(5), 55(11), 45(8), 44(40), 43(14), 42(5), 41(11), 29(3), 27(3).

Accurate mass measurements on selected ions:

$m/_e$ 255 Found 255.136910, $C_{15}H_{17}N_3O$ requires 255.137155.

$m/_e$ 187 Found 187.074569, $C_{10}H_9N_3O$ requires 187.074557.

$m/_e$ 173 Found 173.058915, $C_9H_7N_3O$ requires 173.058909.

$m/_e$ 158 Found 158.072426, $C_9H_8N_3$ requires 158.071819.

$m/_e$ 144 Found 144.055441, $C_8H_6N_3$ requires 144.056169.

Metastable scan 4-8Kv determination

$m/_e$ 187(188→187) 0.148s

187(254→187) 0.358vs

187(267→187) 0.430m

173(188→173) 0.086s

173(254→173) 0.462vs

3-Cyano-1-cyclohexyl-4-phenylpyrrolo[2,3-b]pyridin-6(7)-one (179)

The aminopyrrole (91) (0.01mol) and ethyl benzoylacetate (0.01mol) were refluxed in butan-1-ol ($50cm^3$) for 2h with conc. hydrochloric acid ($0.1cm^3$). The pyrrolopyridinone (179) was isolated in 76% yield, after concentration of the solvent, as colourless microprisms, m.p. 313-314° (ethanol).

Found: C, 75.5; H, 6.0; N, 13.4%; M^+, 317.152097.

$C_{20}H_{19}N_3O$ requires

C, 75.7; H, 6.0; N, 13.2%; M, 317.152804.

ν_{max} 3125(NH), 2250(CN), 1640(C=O), 1595, 1570, 1530, 1500, 1270, 1205, 1190, 1150, 1130, 1075, 1025, 1000, 970, 925, 900, 890, 880, 855, 830, 810, 770 760, 750, 700 cm^{-1}.

$\tau[(CD_3)_2SO]$ 1.7(1H, s, 2-H), 2.4(5H, s, C_6H_5), 3.4(1H, s, 5-H), 5.5(1H, br, NH), 7.8-8.7(11H, m, C_6H_{11}).

(I) The Synthesis of a Pyrrolopyridine from a 1,3-Diester

3-Cyano-1-cyclohexyl-4-hydroxypyrrolo[2,3-b]pyridin-6(7H)-one (185)

The aminopyrrole (91) (1.8g) and diethyl malonate (1.7g) were heated together in diphenyl ether (10g) to 145° for 15 minutes, the temperature was slowly raised until the mixture began to reflux. The mixture was held at reflux for a further 105 minutes, during which time there was an obvious evolution of ethanol. The mixture was cooled and diluted with petroleum ether to yield 83% of the pyrrolopyridinone (185) as colourless prisms, m.p. 238-240 (decomp.) from pyridine/water and then from dimethylformamide/water.

Found: C, 65.3; H, 6.0; N, 16.0%; $\underline{M}^+$, 257.116184.

$C_{14}H_{15}N_3O_2$ requires

C, 65.4; H, 5.9; N, 16.3%; $\underline{M}$, 257.116685.

ν_{max} 3200(NH), 2600(OH), 2250(CN), 1640(C=O), 1560, 1520, 1320, 1310, 1290, 1210, 1170, 1100, 1000, 950, 900, 890, 830, 810, 770, 750, 710, 700, 660 cm^{-1}.

$\tau[(CD_3)_2SO]$ 2.15(1H, s, 2-H), 4.15(1H, s, 5-H), 5.4(1H, br, NH), 7.9-8.8(11H, m, C_6H_{11}).

$m/_e$ 258(7), 257(48), 256(7), 203(4), 176(12), 175(100), 174(3), 158(3), 134(5), 133(13), 107(10), 105(3), 83(3), 81(3), 67(3), 55(8), 41(9), 32(4), 28(24), 27(13), 17(3).

Accurate mass measurements on selected ions:

$m/_e$ 175 Found 175.039405, $C_8H_5N_3O_2$ requires 175.038173.

m^* 119(257→175)m.

m^* 101(175→133)m.

(J) The Synthesis of Pyrrolopyridines from Diethyl ethoxymethylenemalonate

General Method for the preparation of 2(2',2'-diethoxycarbonyl)vinylaminopyrroles

The aminopyrrole (0,01mol) and diethyl ethoxymethylenemalonate (0.011mol) were heated together in ethanol or butan-1-ol for the stated time and the products isolated by an appropiate method of concentration or dilution. The abbreviation EMME is used for diethyl ethoxymethylenemalonate.

4-Cyano-1-cyclohexyl-2(2',2'-diethoxycarbonyl)vinylaminopyrrole (189)

The aminopyrrole (91) and EMME were refluxed in butan-1-ol for 3h and gave an 80% yield of the vinylaminopyrrole (189) as colourless needles, m.p. 131-132°, from aqueous ethanol (charcoal).

Found: C, 63.6; H, 7.1; N, 11.5%; $C_{19}H_{25}N_3O_4$ requires C, 63.5; H, 7.0; N, 11.7%.

ν_{max} 3175(NH), 2225(CN), 1700(C=O), 1650, 1605, 1240, 1080, 820, 800 cm^{-1}.

$\tau(CDCl_3)$ 2.0(1H, d, J=12 Hz, NH-CH=), 3.0(1H, d, 5-H), 3.9 (1H, d, J=2 Hz, 3-H), 5.85(4H, q, J=7 Hz, 2x CH_2CH_3) 7.9-8.6(11H, m, C_6H_{11}), 8.75(6H, t, J=7 Hz, 2x CH_2CH_3).

4-Cyano-2(2',2'-diethoxycarbonyl)vinylamino-1-phenylpyrrole (190)

The aminopyrrole (92) and EMME were refluxed in ethanol for 14h and a 72% yield of the vinylaminopyrrole was obtained on concentration. Recrystallisation from ethanol(charcoal) gave colourless needles, m.p.159-160°.

Found: C, 64.4; H, 5.2; N, 11.85%; $\underline{M}^+$, 353.137265.
$C_{19}H_{19}N_3O_4$ requires
C, 64.6; H, 5.4; N, 11.9%; $\underline{M}$, 353.137546.

ν_{max} 3150(NH), 2250(CN), 1690(C=O), 1640, 1600, 1530, 1500, 1270, 1180, 1150, 1100, 1030, 980, 880, 810, 800, 760, 740, 695 cm^{-1}.

$\tau(CDCl_3)$ 2.0(1H, d, J=12 Hz, NH-$\underline{CH}$=), 2.6(5H, m, C_6H_5), 2.85(1H, d, J=2 Hz, 5-H), 3.7(1H, d, J=2 Hz, 3-H), 5.8(4H, q, J=7 Hz, 2x $\underline{CH_2}CH_3$), 8.8(6H, t, J=7 Hz, 2x $CH_2\underline{CH_3}$).

1-Benzyl-4-cyano-2(2',2'-diethoxycarbonyl)vinylaminopyrrole (191)

The aminopyrrole (93) and EMME were refluxed in butan-1-ol for 3h and a 75% yield of the vinylaminopyrrole (191) was obtained on concentration. Recrystallisation from ethanol (charcoal) gave colourless needles, m.p. 111-112°.

Found: C, 65.4; H, 5.8; N, 11.4%; $C_{20}H_{21}N_3O_4$ requires
C, 65.4; H, 5.8; N, 11.4%.

ν_{max} 3150(NH), 2225(CN), 1710(C=O), 1660, 1600, 1520, 1500, 1220, 1140, 1060, 1020, 980, 805, 795, 740, 700 cm^{-1}.

$\tau(CDCl_3)$ 2.1(1H, d, J=12 Hz, NH-$\underline{CH}$=), 2.7(5H, br, s, C_6H_5), 3.05(1H, d, J=2 Hz, 5-H), 3.85(1H, d, J=2 Hz, 3-H), 5.0(2H, s, $\underline{CH_2}C_6H_5$), 5.9(4H, q, J=7 Hz, 2x $\underline{CH_2}CH_3$), 8.8(6H, t, J=7 Hz, 2x $CH_2\underline{CH_3}$).

4-Cyano-2(2',2'-diethoxycarbonyl)vinylamino-1-(p-tolyl)-pyrrole (192)

The aminopyrrole (97) and EMME were refluxed in butan-1-ol for 2h and a 90% yield of the vinylaminopyrrole (192) was obtained on concentration. Recrystallisation from CCl_4

gave colourless needles, m.p. 153-154°.

Found: C, 65.2; H, 5.8; N, 11.7%; $C_{20}H_{21}N_3O_4$ requires C, 65.4; H, 5.8; N, 11.4%.

ν_{max} 3200(NH), 2250(CN), 1730(C=O), 1660, 1600, 1540, 1300, 1250, 1150, 1080, 1040, 970, 830, 800, 740, 710 cm^{-1}.

$\tau(CDCl_3)$ 1.95(1H, d, J=13 Hz, and s, after D, NH-CH=), 2.70 (4H, q, C_6H_4), 2.90(1H, d, J=2Hz, 5-H), 3.75(1H, d, J=2 Hz, 3-H), 5.5(4H, q, J=7 Hz, 2x CH_2CH_3), 7.55(3H, s, $CH_3C_6H_4$), 8.7(6H, t, J=7Hz, 2x CH_2CH_3).

4-Cyano-2(2',2'-diethoxycarbonyl)vinylamino-1-(p-methoxyphenyl)pyrrole (193)

The aminopyrrole (100) and EMME were refluxed in butan-1-ol for 2h and a 91% yield of the vinylaminopyrrole (193) was obtained on concentration. Recrystallisation from ethanol gave colourless needles, m.p.177-179°.

Found: C, 62.9; H, 5.4; N, 10.9%; $C_{20}H_{21}N_3O_5$ requires C, 62.65; H, 5.5; N, 11.0%.

ν_{max} 3200(NH), 2250(CN), 1720(C=O), 1650, 1610, 1530, 1290, 1270, 1250, 1180, 1080, 990, 850, 800, 740 cm^{-1}.

$\tau(CDCl_3)$ -0.65(1H, br, D, NH-CH=), 1.95(1H, d, J=13 Hz, and s, after D, NH-CH=), 2.90(5H, m, C_6H_4 and 5-H), 3.7(1H, d, J=2 Hz, 3-H), 5.8(4H, q, J=7 Hz, 2x CH_2CH_3), 6.15(3H, s, $CH_3O.C_6H_4$), 8.8(6H, t, J=7 Hz, 2x CH_2CH_3).

1-(m-Chlorophenyl)-4-cyano-2(2',2'-diethoxycarbonyl)vinylaminopyrrole (194)

The aminopyrrole (102) and EMME were refluxed in ethanol for 6h and a 91% yield of the vinylaminopyrrole (194) was was obtained on dilution with water. Recrystallisation

from acetone/petroleum ether gave colourless prisms, m.p. 155-157°.

Found: C, 59.1; H, 4.8; N, 10.6; Cl, 9.4%;
$\underline{M}^+$, 387.098972. $C_{19}H_{18}N_3O_4Cl$ requires
C, 58.8; H, 4.7; N, 10.8; Cl, 9.1%;
M, 387.098575.

νmax 3125(NH), 2250(CN), 1690(C=O), 1640, 1600, 1590, 1530, 1270, 1250, 1090, 800, 740, 695 cm^{-1}.

$\tau(CDCl_3)$ -0.75(1H, br, D, NH-CH=), 1.95(1H, d, J=13 Hz, and s, after D, NH-CH=), 2.65(4H, m, C_6H_4), 2.8(1H, d, J=2 Hz, 5-H), 3.65(1H, d, J=2 Hz, 3-H), 5.8(4H, t, J=7 Hz, 2x $\underline{CH_2}CH_3$), 8.7(6H, t, J=7 Hz, 2x $CH_2\underline{CH_3}$).

1-(p-Chlorophenyl)-4-cyano-2(2',2'-diethoxycarbonyl)vinylaminopyrrole (195)

The aminopyrrole (103) and EMME were refluxed in ethanol for 6h and an 89% yield of the vinylaminopyrrole (195) was obtained on dilution with water. Recrystallisation from ethanol(charcoal) gave colourless needles, m.p. 144-145°.

Found: C, 59.0; H, 4.8; N, 10.8; Cl, 9.3%;
$\underline{M}^+$, 387.099695. $C_{19}H_{18}N_3O_4Cl$ requires
C, 58.8; H, 4.7; N, 10.8; Cl, 9.1%;
M, 387.098575.

νmax 3150(NH), 2250(CN), 1710(C=O), 1650, 1620, 1540, 1520, 1300, 1250, 1160, 1100, 1030, 850, 810, 790, 740, 710 cm^{-1}.

$\tau(CDCl_3)$ -0.65(1H, br, D, NH-CH=), 1.95(1H, d, J=12 Hz, and s, after D, NH-CH=), 2.65(4H, q, C_6H_4), 2.8(1H, d, J=2 Hz, 5-H), 3.7(1H, d, J=2 Hz, 3-H), 5.75(4H, q, J=7 Hz, 2x $\underline{CH_2}CH_3$), 8.7(6H, t, J=7 Hz, 2x $CH_2\underline{CH_3}$).

General Method for Cyclisation of 2(2',2'-diethoxycarbonyl) vinylaminopyrroles

The vinylaminopyrrole (1g) was heated in diphenyl ether (25g) for 20 minutes at 250°. The solution was cooled and diluted with petroleum ether to yield the pyrrolopyridin-4(7H)-one.

Ethyl 3-cyano-1-cyclohexylpyrrolo[2,3-b]pyridin-4(7H)-one-5-carboxylate (196)

The vinylaminopyrrole (189) was cyclised in diphenyl ether to give the pyrrolopyridinone (196) in 63% yield. Recrystallisation from chloroform and ethanol gave colourless needles, m.p. 220-221°.

Found: C, 65.1; H, 6.2; N, 13.6%; $C_{17}H_{19}N_3O_3$ requires C, 65.2; H, 6.1; N, 13.4%.

ν_{max} 3150(NH), 2250(CN), 1660(C=O), 1620(C=O), 1540, 1210, 1010, 930, 810, 800, 790 cm^{-1}.

Ethyl 1-benzyl-3-cyanopyrrolo[2,3-b]pyridin-4(7H)-one-5-carboxylate (197)

The vinylaminopyrrole (191) was cyclised in diphenyl ether to give the pyrrolopyridinone (197) in 58% yield. Recrystallisation from aqueous ethanol gave matted needles, m.p. 307-308°.

Found: C, 67.75; H, 4.8; N, 13.1%; $C_{18}H_{15}N_3O_3$ requires C, 67.3; H, 4.7; N, 13.1%.

ν_{max} 3125(NH), 2250(CN), 1680(C=O), 1630(C=O), 1570, 1530, 1500, 1280, 1190, 1030, 970, 820, 780, 760, 695 cm^{-1}.

$\tau(CF_3COOH)$ 0.95(1H, s, 6-H), 2.1(1H, s, 6-H), 2.65(5H, m, C_6H_5), 4.35(2H, s, $\underline{CH_2}C_6H_5$), 5.25(2H, q, J=8 Hz, $\underline{CH_2}CH_3$), 8.45(3H, t, J=8 Hz, $CH_2\underline{CH_3}$).

Ethyl 3-cyano-1-(p-tolyl)pyrrolo[2,3-b]pyridin-4(7H)-one-5-carboxylate (198)

The vinylaminopyrrole (192) was cyclised in diphenyl ether to give the pyrrolopyridinone (198) in 74% yield. Recrystallisation from aqueous acetone (charcoal) gave colourless prisms, m.p. 234-235°.

Found: C, 67.1; H, 4.8; N, 12.95%; $C_{18}H_{15}N_3O_3$ requires C, 67.3; H, 4.7; N, 13.1%;

ν_{max} 3150(NH), 2250(CN), 1680(C=O), 1640(C=O), 1590, 1580, 1540, 1500, 1320, 1230, 1090, 1070, 1010, 900, 830, 750, 720, 690 cm^{-1}.

$\tau[(CD_3)_2SO]$ 1.42(1H, s, 6-H), 1.7(1H, s, 2-H), 2.68(4H, q, C_6H_4), 5.65(2H, q, J=6.5 Hz, $\underline{CH_2}CH_3$), 7.5(3H, s, $\underline{CH_3}.C_6H_5$), 8.75(3H, t, J=6.5 Hz, $CH_2\underline{CH_3}$).

(K) Synthesis of Pyrrolo[1.2-a]quinazolines

2-Cyanopyrrolo[1.2-a]quinazol-5(4H)-one (127)

The nitrile (88) (0.01mol) and potassium ethoxide solution were reacted in the manner described for aminopyrroles. After stirring at room temperature for 10 minutes a product began to seperate from solution. After two hours the mixture was diluted out to yield the sparingly soluble pyrroloquinazolone (127) in 95% yield. The product was soluble in NaOH and was recrystallised from dimethylformamide as a colourless solid, M.P. 300°.

Found: C, 68.8; H, 3.5; N, 20.25%; $\underline{M}^+$, 209.05900.

$C_{12}H_7N_3O$ requires

C, 68.9; H, 3.4; N, 20.1%; $\underline{M}$, 209.058908.

λ_{max} ($MeOH/H^+$) 263, 232, and 226 nm.

($EtOH/OH^-$) 294, 285, 268, and 259 nm.

ν_{max} 3100(NH), 2250(CN), 1690(C=O), 1600, 1589, 1540, 1220, 1200, 1160, 1130, 790, 750 cm^{-1}.

$\tau[(CD_3)_2SO]$ (100°) 1.3(1H, d, J=1.5 Hz, 1-H), 1.4-2.2(4H, m, 6, 7, 8, 9-H's), 3.7(1H, d, J=1.5 Hz, 3-H).

2-Cyano-5-methylpyrrolo[1,2-a]quinazoline (128)

The nitrile (89) and potassium ethoxide solution in a similar manner gave the pyrroloquinazoline (128) as a 84% yield. Precipitation started after 10 minutes and the mixture was diluted with water after two hours. Recrystallisation from aqueous acetone gave colourless needles, M.P. 267-268°.

Found: C, 75.2; H, 4.35; N, 20.3%; $\underline{M}^+$, 207.079829.

$C_{13}H_9N_3$ rquires

C, 75.3; H, 4.4; N, 20.3%; $\underline{M}$, 207.079643.

ν_{max} 3100(CH, Ar), 2225(CN), 1610, 1590, 1540, 1500, 1300, 1200, 1150, 1120, 1080, 950, 860, 830, 780, 750 cm^{-1}.

$\tau(CF_3COOH)$ 2.1(1H, s, 1-H), 3.0(4H, s, 6, 7, 8, 9-H's), 3.3(1h, s, 3-H), 6.5(3H, s, 5-Me).

(L) Hydrolysis of Pyrrolopyridines

4,6-Dimethyl-1-phenylpyrrolo[2,3-b]pyridine-3-carboxamide (200)

The pyrrolopyridine (137) (1g), concentrated sulphuric acid ($5cm^3$) and water ($0.5cm^3$) were heated together at 100° for 4h. The solution was poured onto crushed ice (50g) and basified with 10% sodium hydroxide to give the carboxamide (200) in 52% yield, m.p. 234-235°, from chloroform/carbon tetrachloride.

Found: C, 72.3; H, 5.7; N, 15.7%; $C_{16}H_{15}N_3O$ requires C, 72.4; H, 5.7; N, 15.8%;

ν_{max} 3405 and 3215(NH), 1640(C=O), 1620, 1600, 1555, 1520, 1290, 1220, 1130, 1040, 930, 850, 820, 770, 750, 700 cm^{-1}.

1-(p-Chlorophenyl)-4,6-dimethylpyrrolo[2,3-b]pyridine-3-carboxamide (201)

The pyrrolopyridine (147) (1g), concentrated sulphuric acid ($5cm^3$) and water ($0.5cm^3$) were heated together at 100° for 4h. The solution was poured onto crushed ice (50g) and basified with 10% sodium hydroxide to give the carboxamide (201) in 51% yield, m.p. 211-212°, from ethanol.

Found: C, 63.9; H, 4.9; N, 14.2%; $C_{16}H_{14}N_3OCl$ requires C, 64.1; H, 4.7; N, 14.0%;

ν_{max} 3400 and 3300(NH), 1650(C=O), 1620, 1600, 1580, 1520, 1290, 1270, 1120, 1100, 860, 840, 810, 710, 670 cm^{-1}.

$\tau(CDCl_3)$ 1.3(1H, s, 2-H), 1.95(4H, m, C_6H_4), 2.9(1H, s, 5-H), 7.15(3H, s, 6-Me), 7.5(3H, s, 4-Me).

1-Cyclohexylpyrrolo[2,3-b]pyridine-3-carboxamide (202)

The pyrrolopyridine (157) (1g), concentrated sulphuric acid ($5cm^3$) and water ($0.5cm^3$) were heated together at 100° for 4h. The solution was poured onto crushed ice (50g) and basified with 10% sodium hydroxide to give the carboxamide (202) in 54% yield, m.p. 249-250°, from ethanol.

Found: C, 68.8; H, 7.1; N, 17.1%; M^+, 243.137567.

$C_{14}H_{17}N_3O$ requires

C, 69.1; H, 7.0; N, 17.3%; M, 243.137155.

ν_{max} 3350 and 3150(NH), 1660, 1600, 1570, 1520, 1270, 1210, 1180, 1010, 900, 860, 770, 700 cm^{-1}.

$m/_e$ 244(5), 243(24), 242(7), 226(3), 225(15), 224(4), 214(3), 199(5), 188(5), 171(4), 170(3), 161(7), 160(64), 156(3), 146(5), 145(71), 144(18), 143(100), 132(4), 118(4), 117(7), 116(6), 90(4), 89(3), 85(22), 83(43), 81(3), 67(4), 65(4), 55(14 , 53(5), 51(3), 49(3), 48(4), 47(8), 45(5), 43(4), 41(20), 39(11), 29(7).

4,6-Dimethyl-1-phenylpyrrolo[2,3-b]pyridine-3-carboxylic acid (203)

The pyrrolopyridine (137) (1g) was dissolved in ethanol ($25cm^3$), a solution of sodium hydroxide (2.5g) in water ($25cm^3$) was added and the mixture refluxed for 15h. The solution was concentrated and acidified to give the carboxylic acid (203) in 44% yield, as microprisms, m.p. 233-234°(decomp.) from ethanol.

Found: C, 72.0; H, 5.3; N, 10.0%; M^+, 266.105237.

$C_{16}H_{14}N_2O_2$ requires

C, 72.2; H, 5.3; N, 10.5%; M, 266.105521.

ν_{max} 2800-2600(OH), 1690(C=O), 1600, 1280, 1180, 1050, 960, 920, 820, 800, 750, 710, 695 cm^{-1}.

$m/_e$ 267(22), 266(100), 265(36), 250(3), 249(18), 248(7), 243(5), 222(25), 221(18), 220(6), 219(8), 205(5), 133(10), 118(3), 117(4), 104(4), 103(5), 91(5), 78(4), 77(27), 76(3), 65(5), 63(5), 51(15), 44(4), 41(3), 39(9), 27(4), 17(4).

Accurate mass measurement on selected ion:

$m/_e$ 222, Found: 222.115693. $C_{15}H_{14}N_2$ requires 222.116596.

3-Cyano-1-cyclohexylpyrrolo[2,3-b]pyridin-4(7H)-one-5-carboxylic acid (204)

The crude ester (196) and 10% sodium hydroxide ($50cm^3$) were refluxed together for 4h. The solution was cooled and extracted with ether to remove any diphenyl ether, the aqueous solution was acidified with 10% hydrochloric acid and the precipitate was collected. The carboxylic acid (204) was recystallised from ethanol to give prisms, m.p. 266-267° (decomp.).

Found: C, 63.1; H, 5.3; N, 14.7%; $C_{15}H_{15}N_3O_3$ requires C, 63.2; H, 5.25; N, 14.9%.

ν_{max} 3300(NH), 2775-2550(OH), 1700(C=O), 1640(C=O), 1520, 1280, 1170, 980, 970, 900, 820, 810, 730 cm^{-1}.

(M) Miscellaneous Syntheses

3-Cyanopyrrolo[2,3-b]pyridine (170)

A solution of 1H-pyrrolo[2,3-b]pyridine (6) (2.4g) and hexamethylenetetramine (4.2g) in 33% acetic acid (25cm^3) was refluxed for 6h. The resulting solution was diluted with water (50cm^3) and left to crystallise overnight in a refrigerator. The product was 3-formylpyrrolo[2,3-b]pyridine (1.5g) and was used immediately in the next stage. Sodium bicarbonate (1.5g), hydroxylamine hydrochloride (1.0g) and the 3-formylpyrrolo 2,3-b pyridine were heated on a steam bath for 1h with water (50cm^3), the solution gave, on cooling, 1H-pyrrolo[2,3-b]pyridine-3-carboxaldehyde oxime (1.5g) which was dehydrated in acetic anhydride (10cm^3) at 100°, the product formed on cooling. Recystallisation of this product from water gave matted needles, m.p. 262-263°, of the desired 3-cyanopyrrolo[2,3-b]pyridine (170) (Lit.[130] m.p. 262-265°).

2-Amino-3-cyano-4-phenylpyrrole (58)

This was prepared by the method of Gewald[90], pale yellow prisms, m.p. 172-173° (Lit. 172-174°).

ν_{max} 3400(NH), 3250(NH), 2225(CN), 1600, 1500, 740 cm^{-1}.

2-Acetamido-3-cyano-4-phenylpyrrole (59)

This was prepared by the method of Duffy[86], colourless needles, m.p. 289-290°, from methanol (charcoal). (Lit. 290°)

ν_{max} 3300(NH), 3250(NH pyrrole), 2225(CN), 1665(C=O),

2-Phenylacetamido-3-cyano-4-phenylpyrrole (60)

The aminopyrrole (58) (0.6g) and dry pyridine (10cm^3) were stirred together at room temperature as phenylacetyl chloride (1.0g) was added slowly over 1h. The reaction

mixture was cooled to yield the phenylacetamidopyrrole (60) as colourless needles, m.p. 252-254°, from methanol.

Found: C, 75.6; H, 5.0; N, 13.7%; $\underline{M}^+$, 301.122361

$C_{19}H_{15}N_3O$ requires

C, 75.7; H, 5.0; N, 13.95%; $\underline{M}$, 301.121505

ν_{max} 3350(NH), 2225(CN), 1660(C=O), 1610, 1510, 750, 720, 695 cm^{-1}.

2-Chloroacetamido-3-cyano-4-phenylpyrrole (61)

The aminopyrrole (58) (0.6g) and dry pyridine ($10cm^3$) were stirred together at room temperature as chloroacetyl chloride was added dropwise. After 1h the mixture was cooled to yield the chloroacetyl derivative (61) as colourless needles, m.p. 276-277°, from methanol (charcoal).

Found: C, 60.5; H, 4.1; N, 16.0%; $\underline{M}^+$, 259.051902.

$C_{13}H_{18}N_3OCl$ requires

C, 60.35; H, 3.9; N, 16.25%; $\underline{M}$, 259.051235.

ν_{max} 3350(NH), 3150(NH pyrrole) 2225(CN), 1680(C=O), 1620, 1520, 760, 720, 695 cm^{-1}.

2-Propionamido-3-cyano-4-phenylpyrrole (62)

The aminopyrrole (58) (1.0g) and propionic anhydride ($5cm^3$) were heated together on a steam bath for 0.5h and the propionamidopyrrole was precipitated on cooling. Recrystallisation from methanol gave needles, m.p. 259-260°.

Found: C, 70.0; H, 5.6; N, 17.8%; $\underline{M}^+$, 239.105457.

$C_{14}H_{13}N_3O$ requires

C, 70.0; H, 5.5; N, 17.6%; $\underline{M}$, 239.105856.

ν_{max} 3350(NH), 3150(NH pyrrole), 2225(CN), 1670(C=O), 1600, 1500, 750, 695 cm^{-1}.

2-amino-5-nitroso-4-phenylpyrrole-3-carboxylic acid (68)

(A) From 2-acetamido-3-cyano-4-phenylpyrrole (59)

The acetamidopyrrole (59) (1.0g) and conc. sulphuric acid ($7cm^3$) were stirred together at room temperature for 2h. The solution was poured onto crushed ice (50g) to liberate the 3-amidopyrrole. A solution of sodium nitrite (0.75g in $10cm^3$) was slowly added to the ice-cooled mixture over 1h after which time the solution was allowed to rise to room temperature. The solution was gently heated for 0.5h on a steam bath and the precipitate collected on cooling. Recrystallisation from ethanol gave prisms, m.p. 273-274°.

Found; C, 56.8; H, 4.4; N, 18.2%; M^+, 231.064155.

$C_{11}H_9N_3O_3$ requires

C, 57.1; H, 3.9; N, 18.2%; M, 231.064386

ν_{max} 3400(NH), 3300(NH), 3150(NH pyrrole), 2700-2600(OH) 1710(C=O), 1650, 1600 cm^{-1}.

(B) From 2-propionamido-3-cyano-4-phenylpyrrole (62)

The above reaction was repeated with 2-prpionamido-3-cyano-4-phenylpyrrole (62) and the precipitate was found to be almost identical , m.p. 270-272°, from methanol.

Found; C, 57.3; H, 4.2; N, 17.9%; M^+, 231.065002

$C_{11}H_9N_3O_3$ requires

C, 57.1; H, 3.9; N, 18.2%; M, 231.064386.

ν_{max} 3400(NH), 3250(NH) 3200(NH pyrrole), 2700-2600(OH), 1700(C=O), 1650, 1610, 1510, 740 cm^{-1}.

2-Amino-3,4-diethoxycarbonylpyrrole (69)

This was made by the method of Gewald [92], prisms, m.p. 203-204° (Lit. 203-206°).

ν_{max} 3500, 3350, 3300(NH), 1700(C=O), 1620, 1600, 790, 760, 690 cm^{-1}.

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