1977

AN INVESTIGATION INTO THE SYNTHESIS OF THE DIPYRROLO PYRROLO AND IMIDAZOPYRROLOPYRIDINE SYSTEMS

FREDERICK ARTHUR CHARLES COOKE

PHD

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AN INVESTIGATION INTO THE SYNTHESIS OF THE DIPYRROLO PYRROLO AND IMIDAZOPYRROLOPYRIDINE SYSTEMS

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by

FREDERICK ARTHUR CHARLES COOKE, M.R.I.C., C.Chem.

CONTENTS

PREFACE

The practical work described in this thesis was carried out by the author, in the laboratories of the Chemistry Department, School of Environmental Sciences, Plymouth Polytechnic, between November 1972 and December 1975.

The author wishes to thank Dr. K.C.C. Bancroft, of Plymouth Polytechnic, and Dr. K. Brown, of Fisons Pharmaceuticals Limited, for their guidance, criticism, encouragement and friendship throughout this work.

The author would also like to thank Fisons Pharmaceuticals Limited, for their help with the elemental analyses, N.M.R. and Mass Spectra.

Finally, the author would like to thank all those on whom he has inflicted himself whilst in the act of producing this work.

SUMMARY

Previous work on the production of dipyrrolo and imidazopyrrolo-pyridine systems has been reviewed.

Methods for the preparation of 2,4-diaminopyridines have been reviewed and attempted. The resulting diamines have been subjected to the Bischler reaction to produce a new dipyrrolopyridine system and new derivatives of known systems.

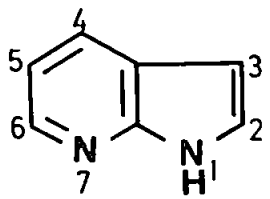
The application of the Bischler reaction to all the possible diaminopyridines has been attempted. This produced a number of new derivatives and ring systems. Some information of the factors influencing the effectiveness of the Bischler reaction on the pyridine system have been obtained.

In an attempt to extend the number of systems known and to provide the unsubstituted dipyrrolopyridines the Gassman reaction using alkylthioketones with aminopyridines was employed. A new derivative of a known system has been produced, however attempts to modify this reaction to produce dipyrrolopyridines were not successful. A number of new pyridine derivatives have been produced and information regarding the mechanism of the breakdown of N-chloraminopyridines has been obtained.

The mechanism of a Mannich reaction on an imidazopyrrolopyridine has been elucidated. The structure of 2,4-dihydroxypyridine has been elucidated from NMR and infrared data and a number of interesting NMR spectra have been obtained and interpreted. The mass spectra of the synthesised ring systems have been obtained and are of interest especially as some have been shown to fragment contrary to expectations.

Over the last five years considerable interest has been shown in pyrrolopyridines. The interest in these systems has been mainly synthetic and chemical as shown by two comprehensive reviews on the subject[1,2]. With the realisation that these systems may have some biological activity, because of their close relationship with indole, interest has been heightened even further.

Fusion of a pyrrole ring to a pyridine ring can give rise to five structures as shown below:



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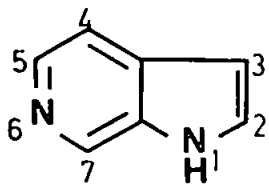

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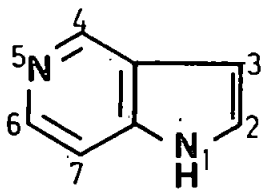

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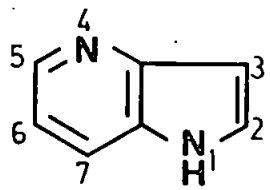

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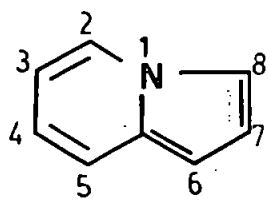
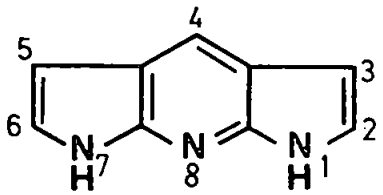


(5)

These systems are named as follows: 1H-pyrrolo[2,3-b]pyridine (1), 1H-pyrrolo[2,3-c]pyridine (2), 1H-pyrrolo[3,2-c]pyridine (3), 1H-pyrrolo[3,2-b]pyridine (4), and pyrrolo[1,2-a]pyridine (5). The positions are numbered as shown. Pyrrolo[1,2-a]pyridine differs considerably chemically and structurally from the other systems and is usually considered separately. The systems (1)-(4) may also be named

as aza or diaza analogues of indole or indene respectively. Consequently the azaindole nomenclature gives: 7-azaindole (1), 6-azaindole (2), 5-azaindole (3), and 4-azaindole (4). The diazaindene nomenclature gives 1,7-diazaindene (1), 1,6-diazaindene (2), 1,5-diazaindene (3), and 1,4-diazaindene (4).

The fusion of two pyrrole rings to the pyridine ring can give rise to seven isomers, these are as follows:



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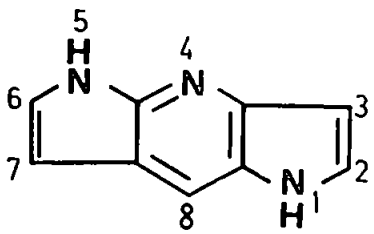

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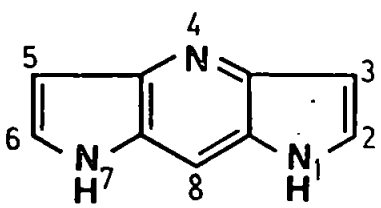

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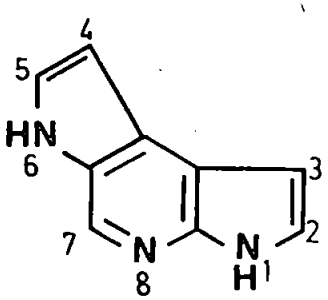

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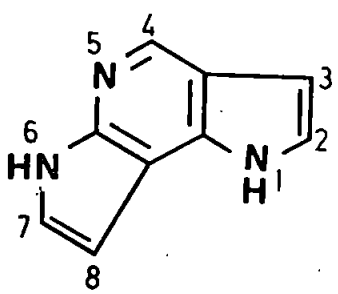

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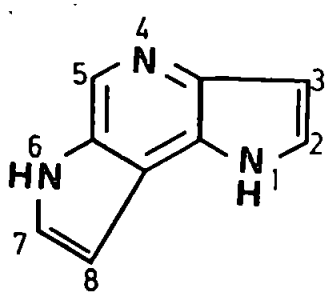

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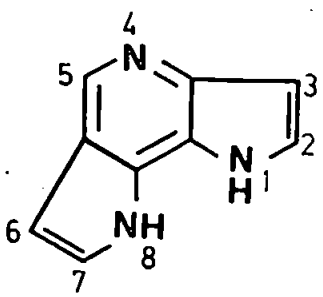
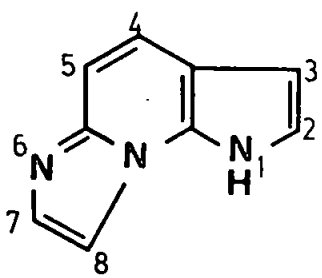


(12)

These systems are named as: 1H,7H-dipyrrol[2,3-b:3',2'-e]pyridine (6), 1H,5H-dipyrrolo[2,3-b:2',3'-e]pyridine (7), 1H,7H-dipyrrolo[3,2-b:2'3'-e] pyridine (8), 1H,6H-dipyrrolo[2,3-b:3'2'-d]pyridine (9), 1H,6H-dipyrrolo[2,3-b:2',3'-d]pyridine (10), 1H,6H-dipyrrolo[3,2-b:3',2-d] pyridine (11) and 1H,8H-dipyrrolo[3,2-b:2',3'-d]pyridine (12). They are numbered as shown above. Only the 1H,7H-dipyrrolo[2,3-b:3',2'-e]pyridine system is known[3,4]. The synthesis of other systems in the series was one of the objectives of this work.

Consideration of the introduction of an imidazole ring instead of one of the pyrrole rings fused to the pyridine ring in the above systems gives six isomers viz:



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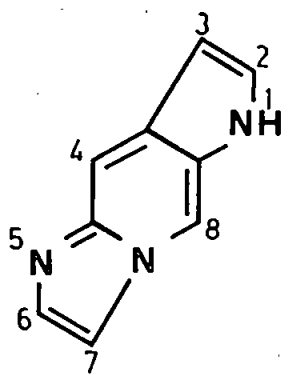

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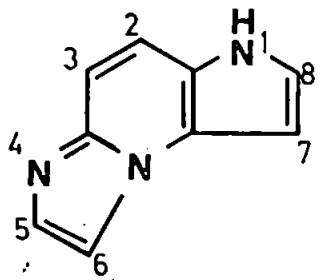

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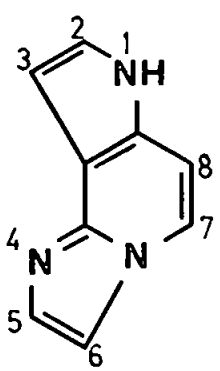

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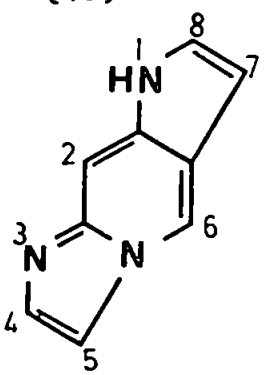

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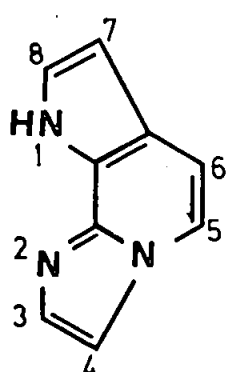


(18)

These systems are named as: 1H-imidazo[1,2-a]pyrrolo[3,2-e]pyridine (13), 1H-imidazo[1,2-a]pyrrolo[3,2-d]pyridine (14), 1H-imidazo[1,2-a] pyrrolo[2,3-e]pyridine (15), 1H-imidazo[1,2-a]pyrrolo[3,2-c]pyridine (16), 1H-imidazo[1,2-a]pyrrolo[2,3-d]pyridine (17), and 1H-imidazo[1,2-a] pyrrolo[2,3-c]pyridine (18). They are numbered as above. One of these systems, 1H-imidazo[1,2-a]pyrrolo[3,2-e]pyridine is known[3]. The synthesis of some of these systems formed another objective of the present work.

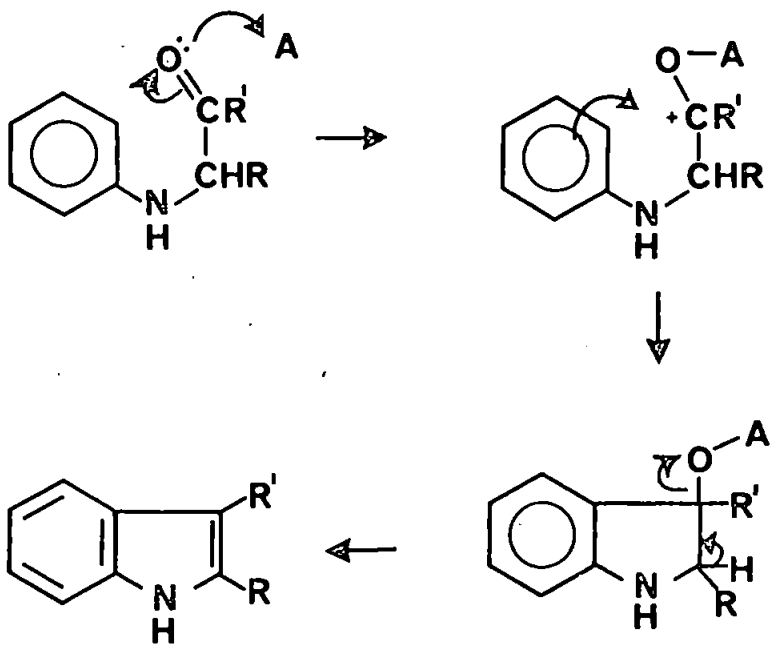
It is hoped that these systems will have some biological activity, especially as the two systems already known have shown a slight activity in tests for anti-immflamatory action.[5]

The synthesis of derivatives of known systems and the production of new systems has been attempted by two main routes, the Bischler reaction, and a reaction discovered by P.G. Gassman et.al.[6] both of which will be reviewed later.

THE BISCHLER REACTION

The Bischler reaction for the synthesis of indoles has been known for many years[7]. The reaction involves the cyclization of an α-anilinoketone, the cyclization being enhanced by the presence of a proton or other Lewis acid.

The reaction may be represented as:



where R = Alkyl

R' = Alkyl

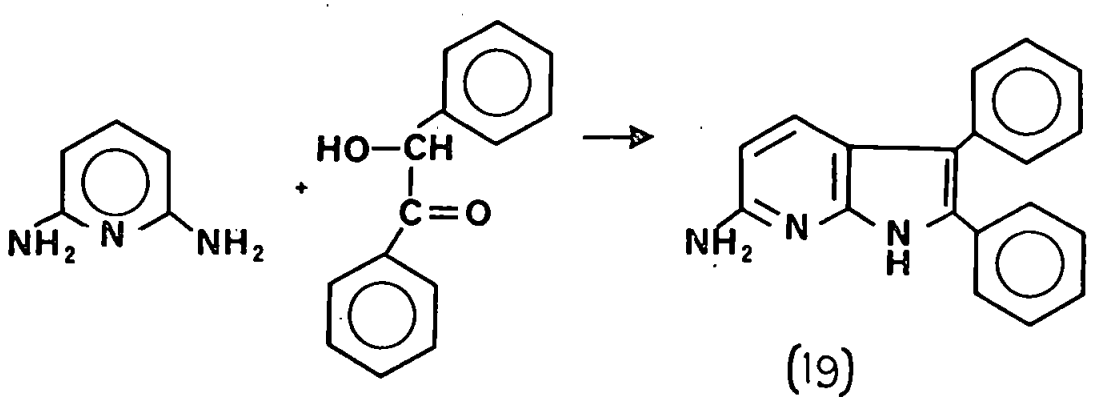
A = Proton or Lewis acid

However, in the majority of cases this reaction does not take place by a direct ring closure. The mechanism of this reaction has been the subject of much debate and a number of reviews have been published including a comprehensive review by Julian et al[8]. They point out the difficulty of establishing a uniformly applicable mechanism for indole formation from aryl-amino ketones. Much of the controversy has centred around the formation of 2-phenylindole, rather than 3-phenylindole, from the reaction between phenacyl bromide and aniline. The problem was finally solved by the tracer work of Weygand and Richter[9]. They carried out a cyclization of phenacylaniline to 2-phenylindole in the presence of aniline labelled with radioactive carbon and catalytic

amounts of aniline hydrobromide. An almost equal distribution of radioactivity was found in the resulting 2-phenylindole and the remaining aniline. A similar distribution of radioactivity was discovered for the cyclization of phenacyl-3-bromoaniline in the presence of 3-^{82}bromoaniline and catalytic amounts of 3-bromoaniline hydrobromide.

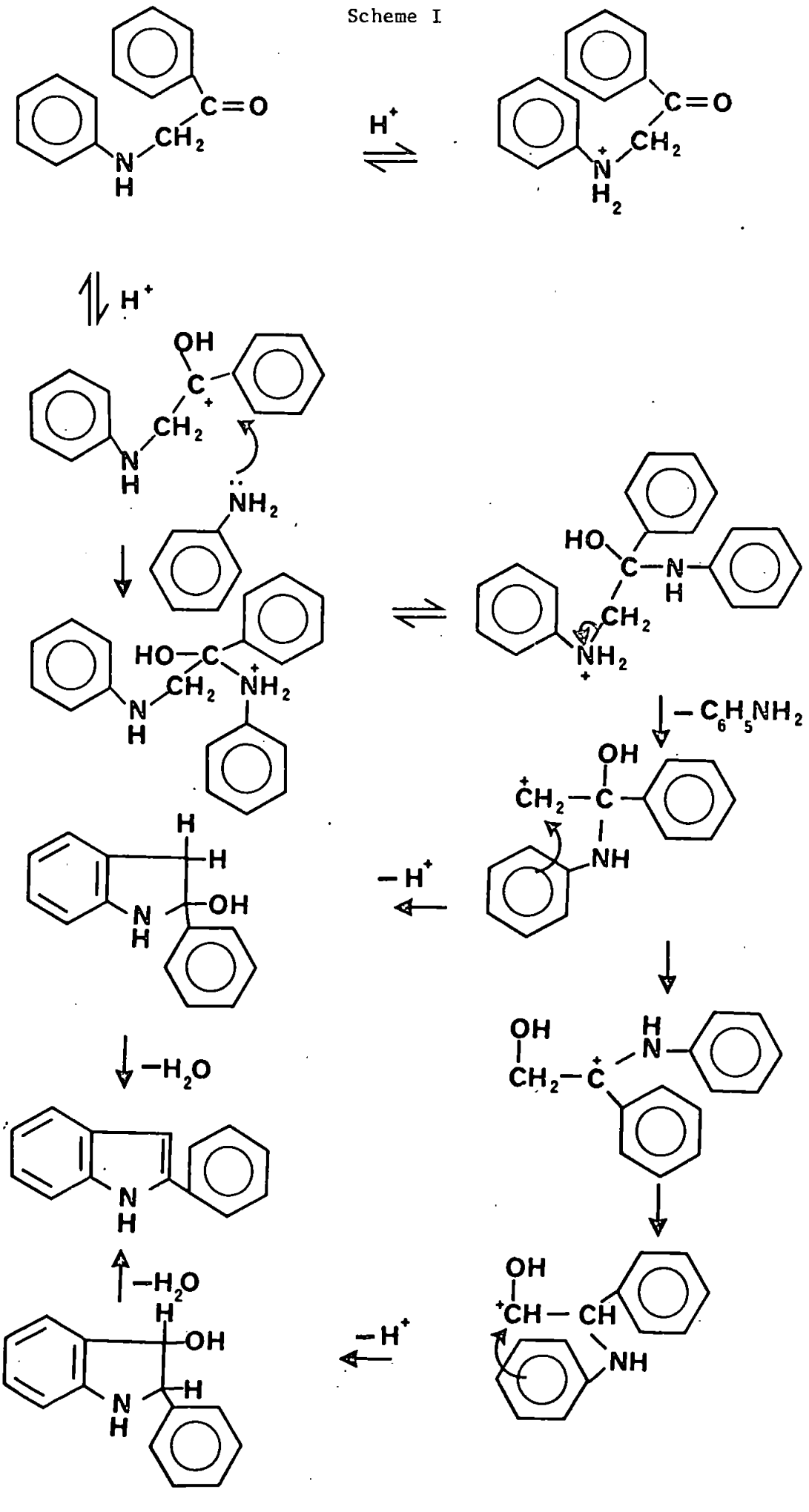
This provided unequivocal evidence that exchange occurs between the "original" and "contributed" amines in the Bischler synthesis and ruled out the possibility of a simple direct cyclization. The Bischler mechanism supported by Julian et al[8], involving combination of the phenacylaniline with the "contributed" amine to give a diamine from which the "original" amine is split out on indole formation was also eliminated. This mechanism would require the 2-phenylindole to have the same molar radioactivity as the "contributed" amine, which was not the case. The exchange experiments clearly demonstrate the important role of the aniline added to the cyclization of phenacylaniline. The role of the added amine, together with the equal distribution of radioactivity in the products and the "rearrangement" of the phenyl group support a modified Bischler mechanism as shown in scheme I.

The first application of this reaction to the synthesis of pyrrolo[2,3-b]pyridines was by Bernstein et al[10] in 1947 when they produced 6-amino-2,3-diphenyl-1H-pyrrolo[2,3-b]pyridine(19) in 81% yield from 2,6-diaminopyridine and benzoin at 185°C under melt conditions, viz:



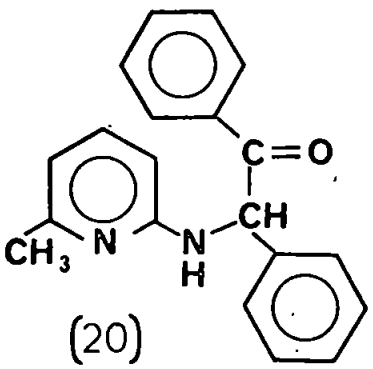
(19)

Scheme I



Herbert and Wibberly[11] tried to extend this reaction and managed to prepare 6-amino-2,3-di(4-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridine in 79% yield from 4,4'-dimethoxybenzoin and 2,6-diaminopyridine. Their efforts to increase the range of this reaction were unsuccessful. They attempted reactions with 4-hydroxyhexan-3-one and 1-hydroxyacetophenone but only starting material was recovered in both cases.

2-(α-Benzoyl-benzyl)amino-6-methylpyridine (20) was prepared but could not be cyclised



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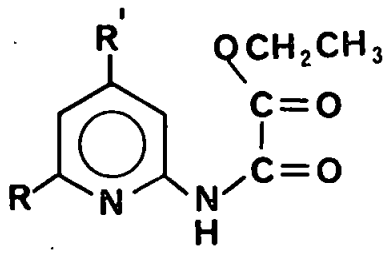
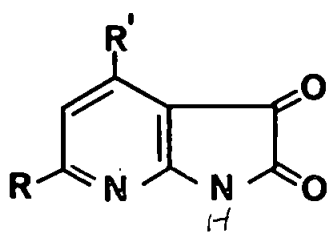


(21)

a ; R = R' = CH_3

b ; R' = H R = $NHCOCH_3$

2-Ethoxyalkylaminopyridines (21a) and 21(b) were also prepared, but could not be cyclised to (22a) and (22b) respectively.



a: R' = R = CH_3

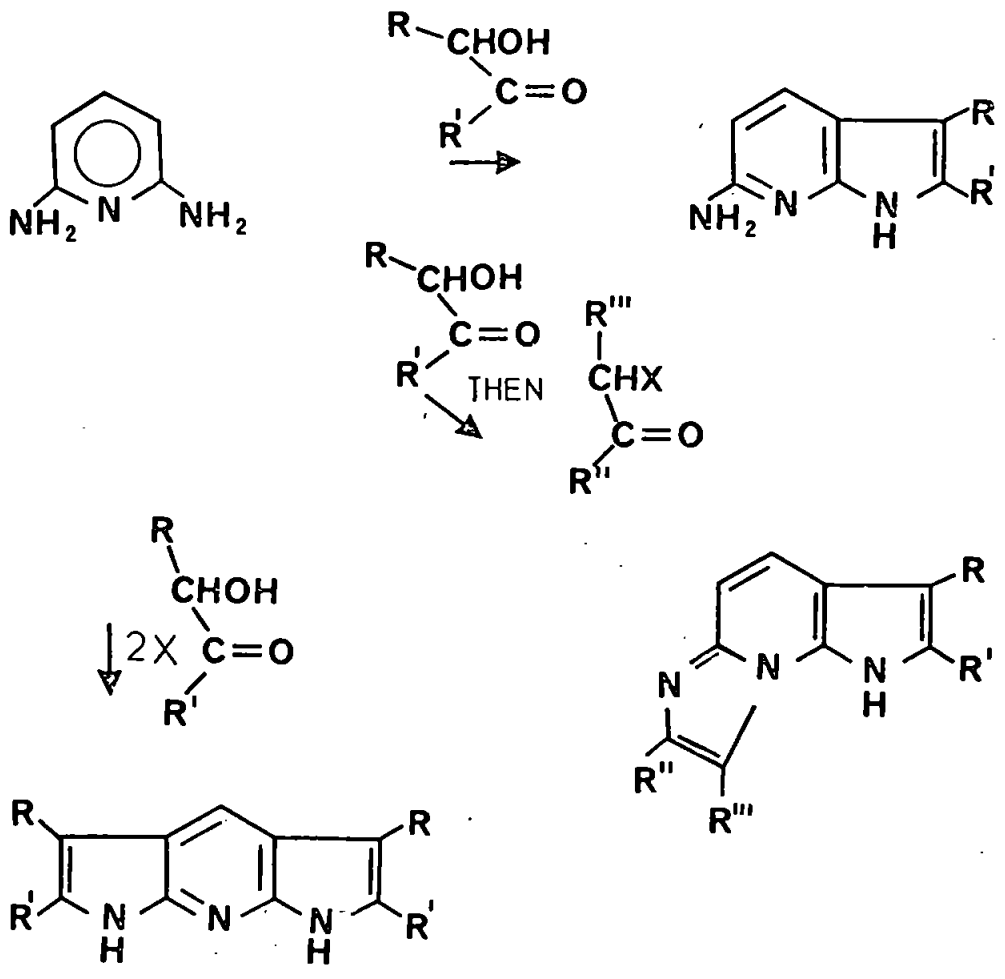
b: R' = H R = $NHCOCH_3$

(22)

There was no further work done on the application of the reaction until Ward[3] published his thesis in 1972. Employing the melt conditions of Bernstein et al[10] or by using solvent boiling at over 100°C in a Dean and Stark apparatus he achieved the preparation of a large number of pyrrolo [2,3-b]pyridines from 2,6-diaminopyridine and α-hydroxyketones or aldehydes.

He also managed to achieve the preparation of the then unknown 1H,7H-dipyrrolo [2,3-b:3',2'-α]pyridine and 1H-imidazo[1,2-α]pyrrolo[3,2-b]systems from 2,6-diaminopyridine and α-hydroxy or α-halogeno carbonyl compounds, as shown in Scheme 2.

Scheme 2



The aim of this present work was to determine whether or not this type of reaction could be used for the synthesis of other members of these ring systems.

2,4-Diaminopyridine

This compound is an important starting material for two reasons:

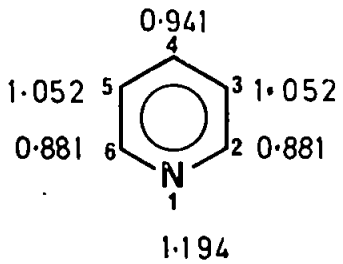
a) The amine groups should have similar activity to 2,6-diaminopyridine as they are in similar positions in the ring with respect to the electronic influence of the pyridine nitrogen atom.

b) The most favourable positions for ring closure in the Bischler reaction, are the most electron-rich positions of the pyridine ring. These positions are available for ring closure when the 2 and 4 amino groups are utilised in the reaction.

Unfortunately 2,4-diaminopyridine is not commercially available so the methods by which it could be made were reviewed. The proposed routes were those of Schneiderwirth[12] involving direct amination; Knoevenagel and Fries[13] together with an extension of the scheme involving the formation of 2,4-dibromopyridine; Meyer and Tropsch[15] involving the substitution of 2,4-dihydroxypyridine via the Curtius reaction; and that of Rowsowsky and Papathanasopoulos[17] involving substitution of hydroxyl groups by use of phenylphosphorodiamidate.

The route of Schneiderwirth[12] was attempted first as this was one of the most recent and therefore hopefully an improvement on older methods. It also used a readily available substrate and was a one step process. The method is based on the well known Tschitschibabin reaction using sodamide at high temperatures on 2-amino-6-methylpyridine. The methyl group is used to block the 6-position from attack by NH_2^- forcing attack to occur at the 4-position. Several attempts were made using Schneiderwirth's reaction as reported on 1-methylpyridine including and starting with 2-amino-6-methylpyridine. T.L.C. indicated that no product was present; only substrate was recovered

in each case. Schneiderwirth claims that 2,5-diamino-6-methylpyridine is formed at the same time. If we consider the relative electron densities of pyridine as stated by Miller et al[16], shown in (23):



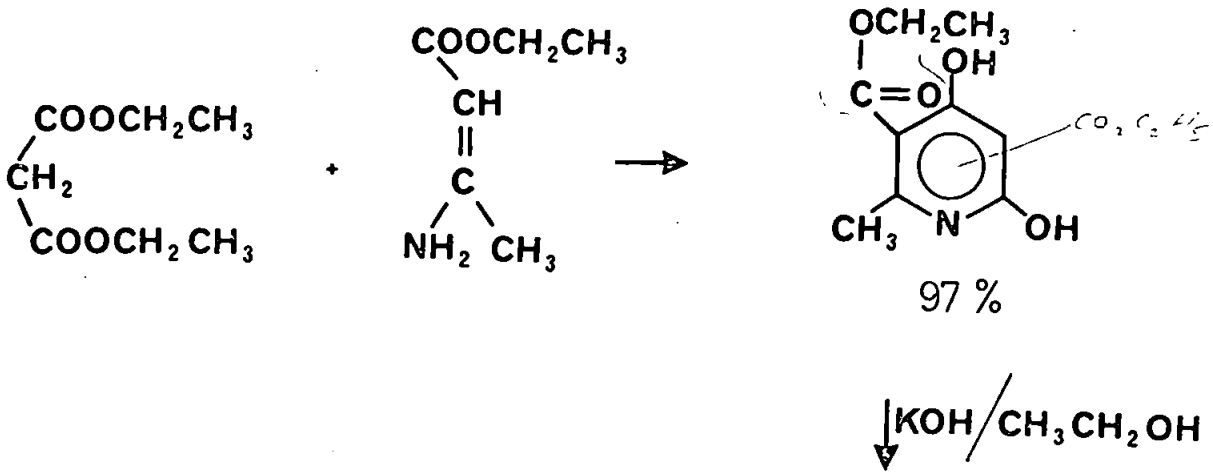
(23)

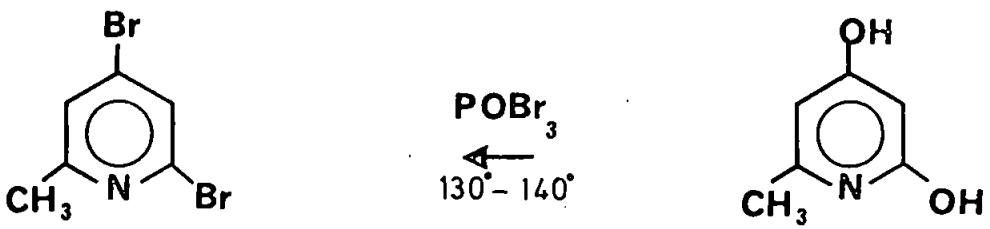
The 3 and 5 positions are the most electron rich positions other than at the pyridinium nitrogen. When we further add the inductive effect of the methyl group in the 6-position the attack of NH_2^- at the 5-position is highly unlikely.

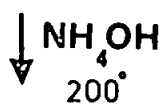
The melting point of the supposed 2,4-diamino-6-methylpyridine formed in this patent was 52°C - 53°C, which is considerably lower than 117°C - 118°C quoted by Bernstein et al[10] for the material made by another route. All these facts must throw considerable doubt on the veracity of this patent.

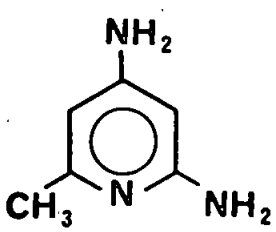
A method of preparing 2,4-diamino-6-methylpyridine was next attempted as shown in Scheme 3. The first two steps are well documented[13,14], and the yields are high. The yield in the conversion of the 2,4-dihydroxy to dibromocompound in the third step was improved to 78% by the use of phosphorus oxybromide compared with the literature yield[10] of 30% using phosphorus tribromide. The final step to give the 2,4-diamino-6-methylpyridine is that of Bernstein et al[10].

Scheme 3





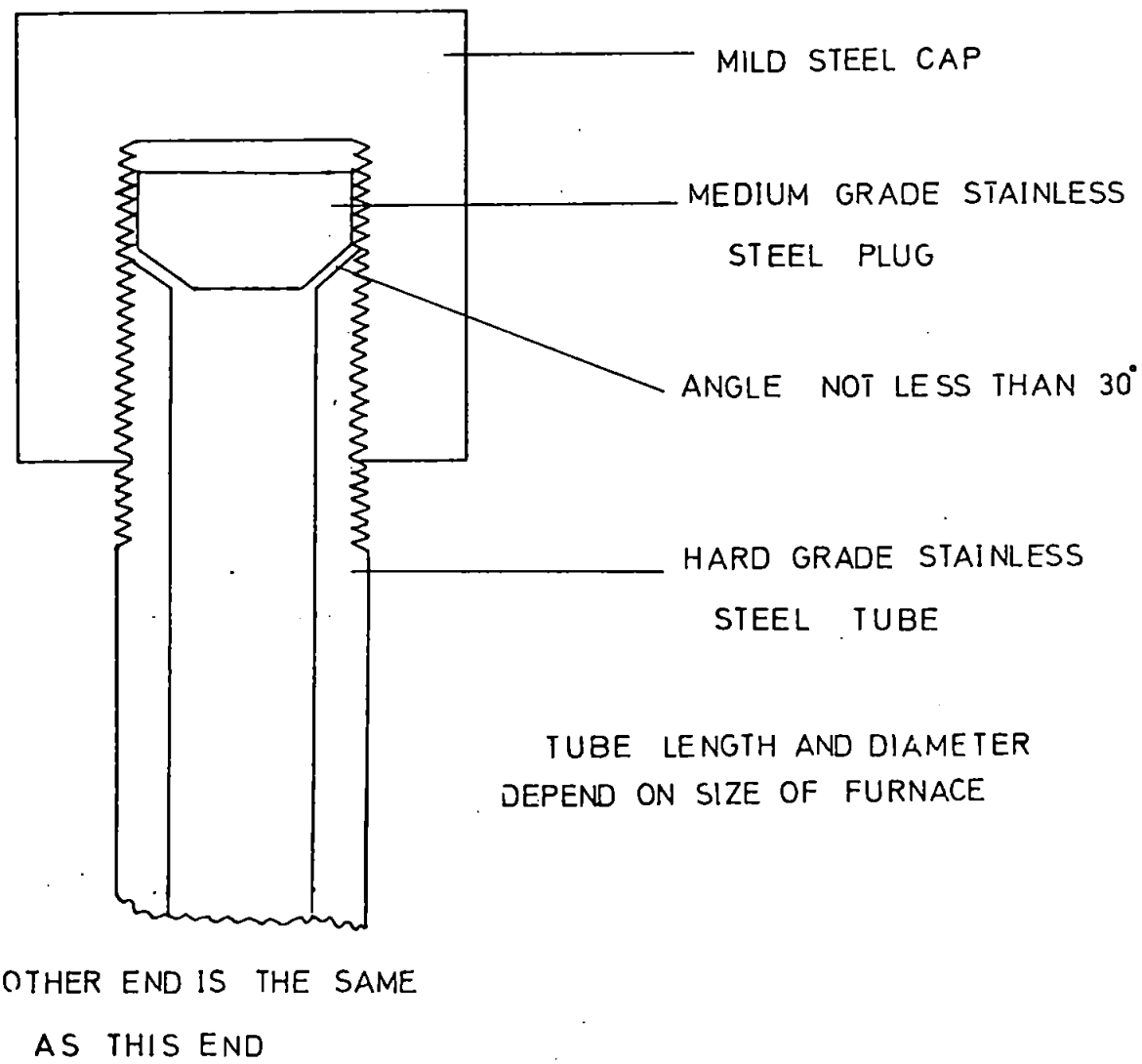




66·7%

YIELD BASED ON ONE TUBE FROM FOUR

A special vessel had to be designed for the last two stages as funds did not permit the purchase of an autoclave. The vessel was designed to fit into a Carius furnace and consisted of a tube of hard grade stainless steel with slightly softer grade end plugs with mild steel screw on caps, viz:-



This vessel has the following advantages:-

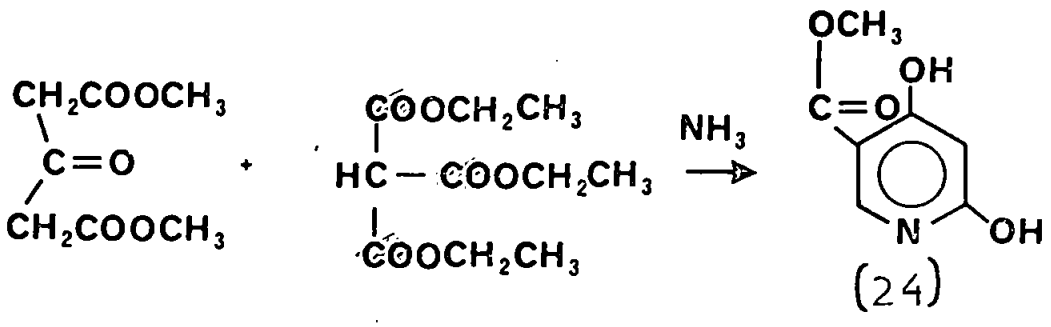
1) Low cost
2) Low thermal mass
3) Fairly easy to produce
4) Fits into existing equipment.

Whilst the yields for individual steps are excellent to moderate, the overall yield of 2,4-diamino-6-methylpyridine produced by this method however is unacceptably low due to vessel failure in the final stage.

A total of 4 grammes of 2,4-diamino-6-methylpyridine was produced by this route.

An attempt was made to produce 2,4-diaminopyridine by this method.

2,4-Dihydroxypyridine-5-carboxylic acid methyl ester (24) was produced by Den Hertog's[18] modification of Errera's[19] method viz:-



(24)

Attempts to decarboxylate (24) by the method used for the 6-methyl derivative met with no success. Only the carboxylic acid was formed. Errera's method involves heating 2 grammes of the ester in hydrochloric acid in small bore glass tubes. For this synthesis to be viable this step had to be carried out in reasonably large quantities. Tests were carried out with the object of finding a material from which a large vessel could be constructed that would withstand the pressure, temperature (180°C - 200°C) and acidity (50% hydrochloric acid) involved.

The following were tested but found unsuitable:

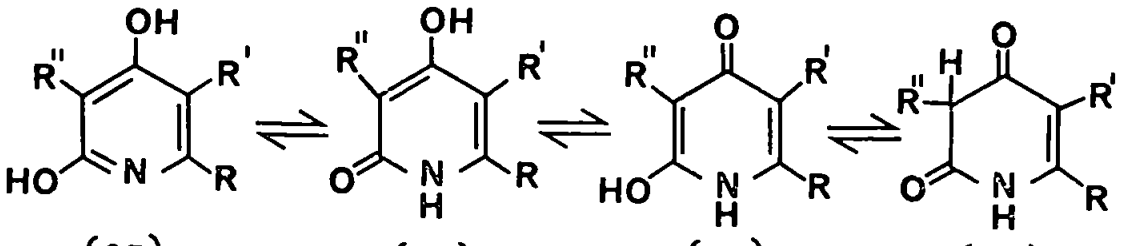
a) Hard grade stainless steel;

b) Hastalloy 'B';

c) Nickel 200.

Glass could not be used as it would not withstand the pressure and ceramic liners for a pressure vessel were unable to withstand expansion. Large volume platinum or gold vessel liners would have been very expensive so consequently another route to 2,4-diaminopyridine was sought.

An interesting point arises however from this work, namely the structure of the 2,4-dihydroxypyridines. The possible structure of 2,4-dihydroxypyridines has been discussed previously by Woodburn and Hellman[20]. Their conclusions were not clear and they were only able to say that 2,4-dihydroxypyridines possess one active hydroxyl group. The possible structures for 2,4-dihydroxypyridines are as follows:-



(25) (26) (27) (28)

$R = R' = H$

$R'' = H$ OR COOH OR $COOCH_2CH_3$

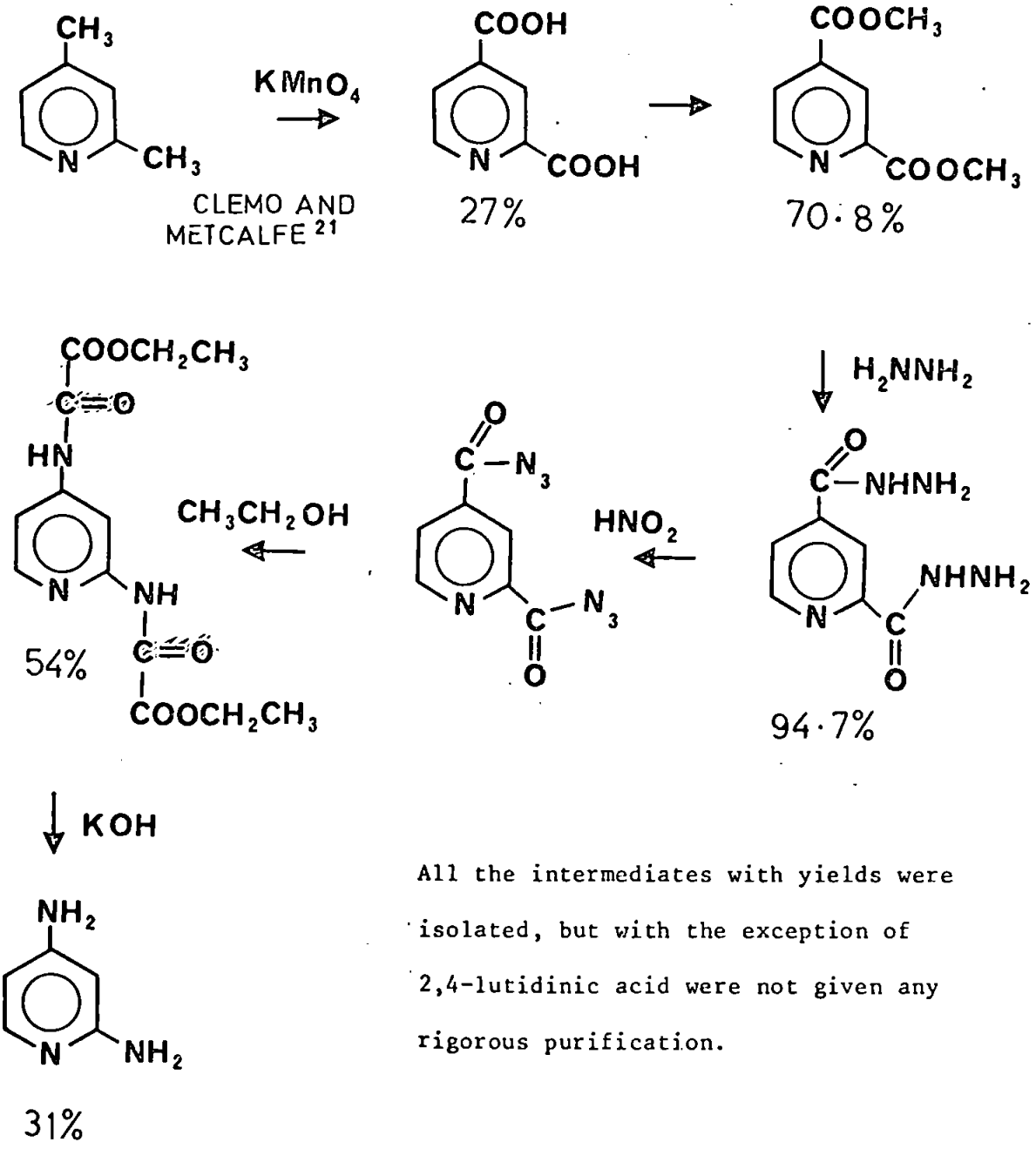
Of these structures only (28) is ruled out by Woodburn and Hellman's work using classical qualitative analysis and examination of the U.V. spectra.

The NMR spectra of the 2,4-dihydroxypyridines available by the previous synthetic scheme all contain a resonance due to an amino nitrogen proton. Integration shows this resonance as being nearly equal to one proton, indicating a predominance of structures (26) and/or (27).

The infrared spectra show an absorption due to a carbonyl group and a secondary amino group at approximately 1650 cm^{-1} and 3000 1600 cm^{-1} respectively. Absorptions in this region are associated with amides, making (26) the most likely structure although the occurence of some (27) cannot be ruled out.

A third approach not involving pressure vessels was then tried. This was based on work done by Meyer and Tropsch[15] as outlined in Scheme 4.

Scheme 4



All the intermediates with yields were isolated, but with the exception of 2,4-lutidinic acid were not given any rigorous purification.

2,4-diaminopyridine was eventually made by this route but it was not considered a viable route because:-

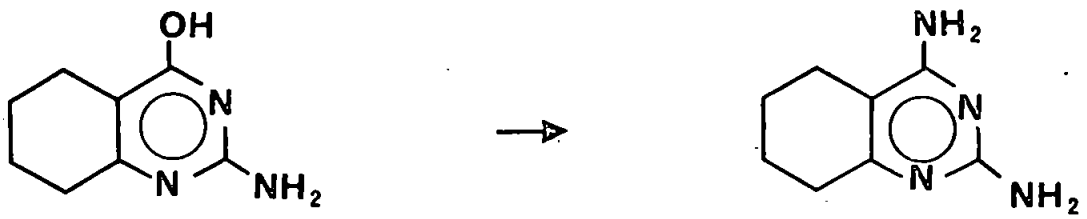
1) The overall yield from 2,4-lutidine was only 3.6%;

2) The volumes involved, 20 litres, for the amount of product produced (≃ 1 gram) makes the method very labour intensive and time consuming.

The reactions undertaken with the 2,4-diaminopyridine available will be dealt with later.

A fourth and final approach was that using phenyl phosphorodiamidate. This reagent has been successfully used in the direct conversion of hydroxyl groups to amino groups in pyrimidine chemistry[17].

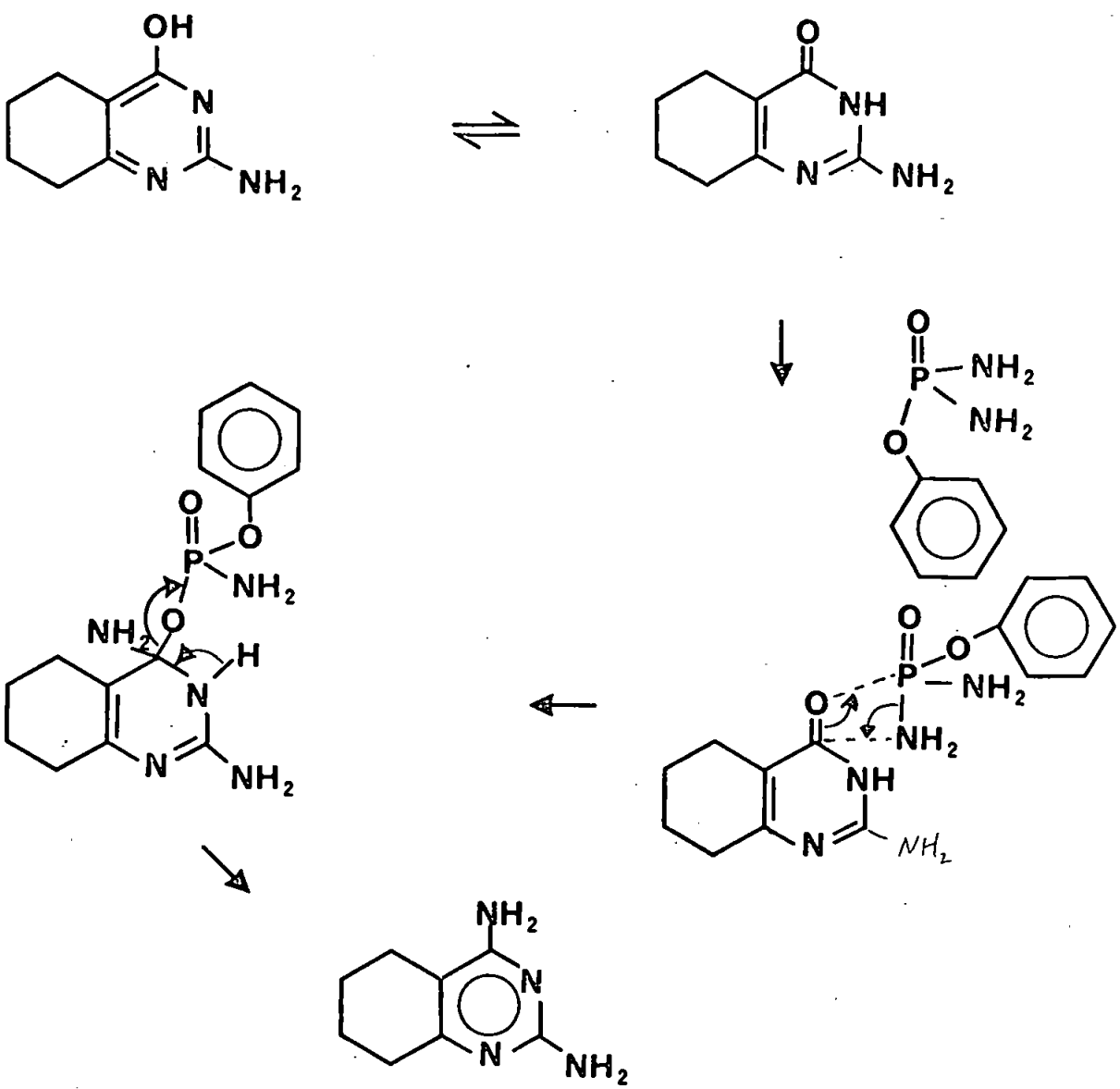
e.g.



(29)

The proposed mechanism of this conversion is as in Scheme 5.

Scheme 5



The requirements for the reagent to work are that the hydroxyl group should be tautomerically convertible to a carbonyl group. For 2,4-dihydroxypyridines this has already been proved. Phenyl phosphorodiamidate was made by the method of Audrieth and Toy[22] using conditions which gave the optimum yield.

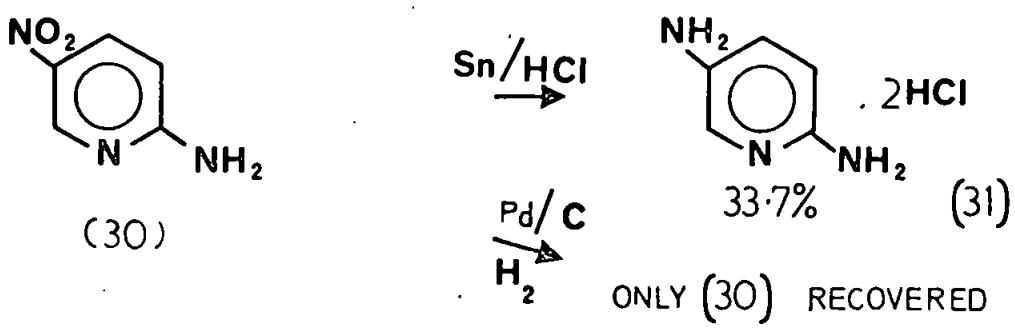
Several attempts, under differing conditions, were made on 2,4-dihydroxy-6-methylpyridine but with no success. It was thought that the reason for this failure was the severe conditions used. It is reported that the reagent is only effective at temperatures in excess of 200°C. From previous experience we know that the hoped for product, 2,4-diamino-6-methylpyridine, is heat, light and air sensitive, and it was thought that any product formed was broken down under these reaction conditions. The pyrimidine derivatives (29) are highly stable, with melting points above 250°C and are unchanged by the conditions of reaction.

Before continuing on to the reactions of the 2,4-diaminopyridines, under Bischler conditions, we need to consider the other isomers of diaminopyridines so as to obtain the complete picture of the applicability of the Bischler reaction in the series.

The 2,3, 3,4 and 2,6-diaminopyridines are all commercially available.

2,5-Diaminopyridine

2,5-Diaminopyridine dihydrochloride was prepared by the method of Gomez-Revilla[23] from 2-amino-5-nitropyridine (30).



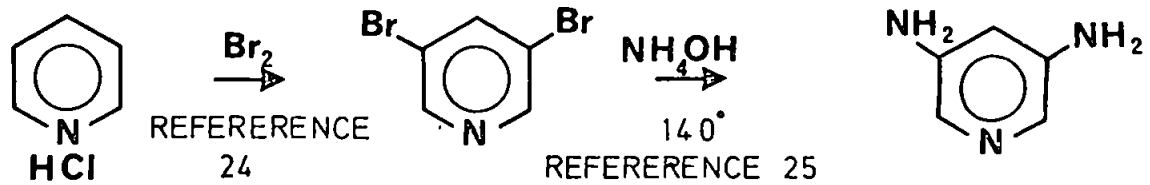
An attempt at improving this synthesis by catalytic reduction using hydrogen under pressure in the presence of palladised carbon was not successful. The reactions of (31) will be dealt with later.

3,5-Diaminopyridine

For the synthesis of 3,5-diaminopyridine two possible routes were considered.

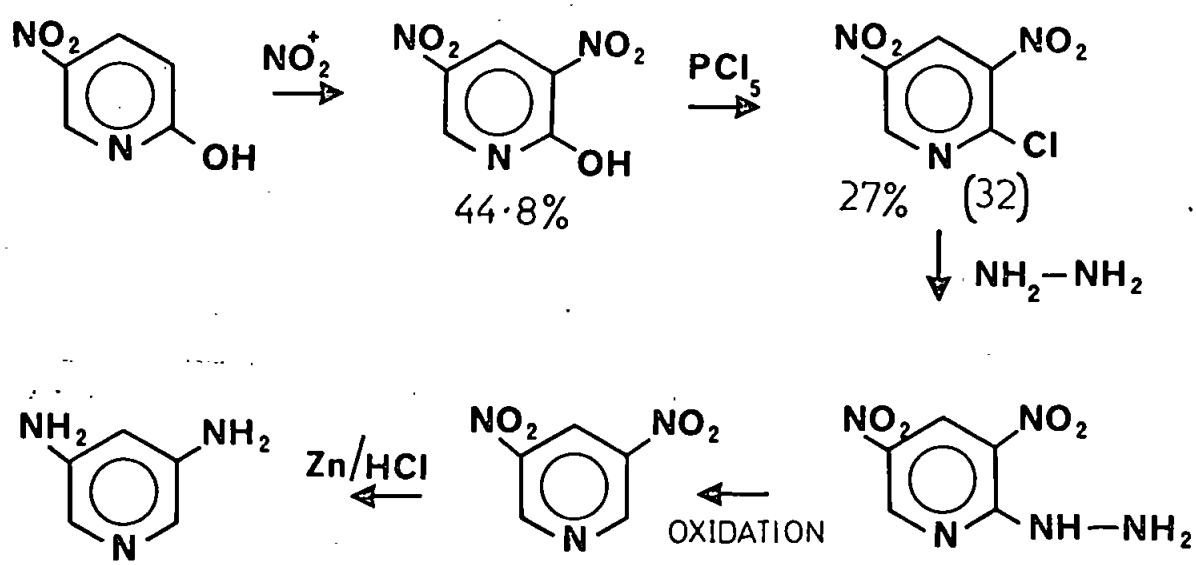
1) From pyridine hydrochloride via 3,5-dibromopyridine as in Scheme 6:-

Scheme 6



2) From 2-hydroxy-5-nitropyridine by the method of Plazek[26] as shown in Scheme 7:-

Scheme 7



The scheme is lengthy and so it was decided to shorten it by the direct reduction of (32) to 2-chloro-3,5-diaminopyridine. The fact that the 2-position is substituted should not impair the diamine's reactivity in the Bischler reaction, but is advantageous in as much that it reduces the number of possible positions for ring closure to take place.

The steps arriving at 2-chloro-3,5-dinitropyridine went according to plan but unfortunately the direct reduction of the 2-chloro-3,5-dinitropyridine using the conditions for 3,5-dinitropyridine was not clean. As time was pressing and of the diaminopyridines 3,5-diaminopyridine is theoretically one of the least likely to react this approach had to be abandoned. Unfortunately there was not enough time to follow Scheme 7 to give 3,5-diaminopyridine.

REACTIONS OF DIAMINES IN THE BISCHLER REACTION

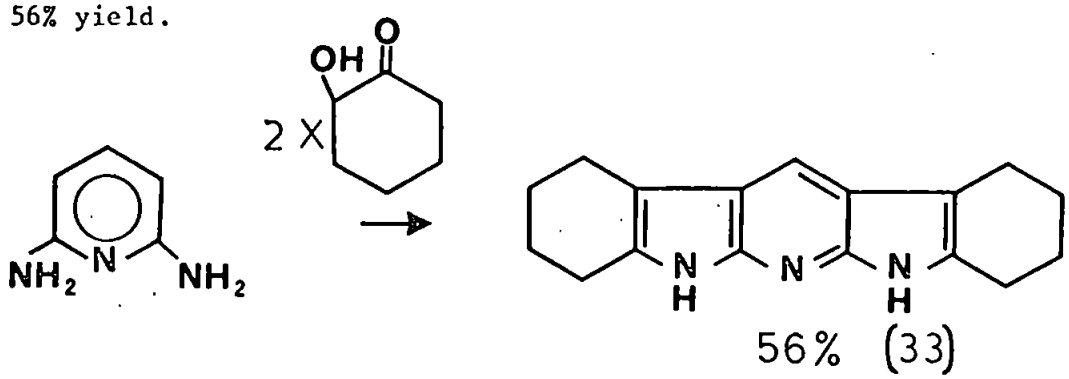
2,6-Diaminopyridine

This work is an extension of that by Ward[3] on 2,6-diaminopyridine. The two conditions which were used throughout this work were

a) Melt. This consisted of two stages of heating at 110°C - 120°C and at 180°C - 190°C. This two stage heating was used to minimise decomposition of products and to drive off water formed in the first part of the reaction.

b) Solvent. This consisted of heating the reaction mixture in toluene for about 20 hours using a Dean and Stark apparatus to remove water.

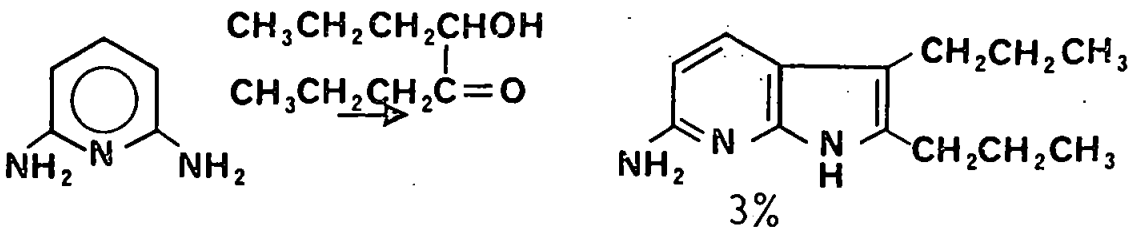
The first reaction to be attempted was a continuation of Ward's[3] work and involved the synthesis of the novel 1,2,3,4,5,7,8,9,10,11-decahydropyrido-[2,3-b:6,5-b']diindole (33) from 2,6-diaminopyridine and 2-hydroxycyclohexanone in 56% yield.



56% (33)

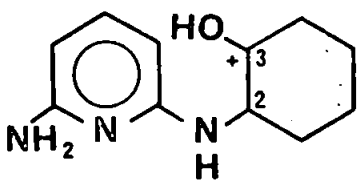
The comparatively high yield of this compound obtained under melt conditions is in some way indicative of the importance of steric considerations in the reaction. In this reaction the carbonyl group and the hydroxyl group are 'locked' in position relative to each other.

Following on from this the novel 2,3-di-n-propyl-6-amino-1H-pyrrolo [2,3-b]pyridine (34) was prepared from 2,6-diaminopyridine and 4-hydroxyoctan-5-one in 3% yield. The 4-hydroxyoctan-5-one was prepared by the acyloin synthesis[27].

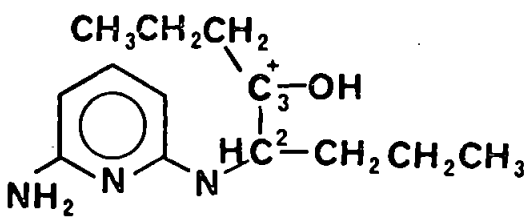


(34)

It is of interest to compare the yields of 1,2,3,4,5-pentahydro-7-aminopyrido[2,3-b]indole (49.5%) as in Ward's work[3] with the yield of 6-amino-2,3-di-n-propyl-1H-pyrrolo[2,3-b]pyridine. The difference in the yields may be explained if we consider the two transition states involved i.e. (35) and (36) respectively.



(35)



(36)

It seems reasonable to assume that the inductive contribution from adjacent carbons to the stabilisation of the carbonium ion centre should be very similar in both cases. The entropy change in reaching the transition state for ring closure in the case of the cyclohexyl group will be much less than that for the di-n-propyl compound where free rotation about the C_2-C_3 bond is possible.

6-amino-2,3-diphenyl-1H-pyrrolo[2,3-b]pyridine was formed in high yield (89%) by Bernstein et al[10]. Whilst here there is free rotation about the C_2-C_3 bond, the reason for the high yield can be attributed to the stabilisation of the carbonium ion formed in the transition state by involvement of the phenyl groups.

Another point of interest arises if we examine the yields of the 6-amino-2,3-dimethyl, 2,3-diethyl and 2,3-di-n-propyl-1H-pyrrolo[2,3-b]-pyridines. They are in the order

CH_3	CH_3CH_2	$CH_3CH_2CH_2$
75%	37.5%	11.6%

Based on crude material before final purification.

This again may be explained by an increase in the degrees of freedom in forming the transition states on going from the dimethyl to the di-n-propyl derivative, the change in entropy becoming less favourable as we ascend the series. The inductive effect increases as we ascend the series, this may be shown by consideration of the pK_A's of the monocarboxylic acids[28], and hence an increase in the stability of the transition state should result. However this is outweighed by the adverse steric effects in forming the transition state. This serves to reinforce the importance of steric considerations especially when one realises that the total inductive effect of the cyclohexyl and the di-n-propyl groups is nearly the same.

2,4-Diaminopyridines

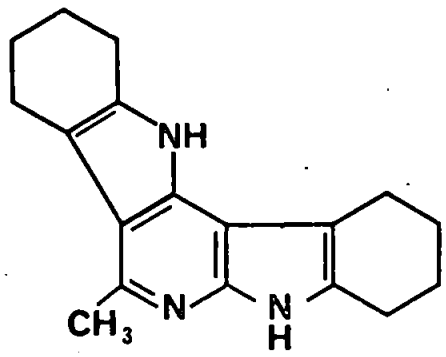
2,4-Diamino-6-methylpyridine was reacted firstly with 2-hydroxycyclohexanone under solvent conditions. This reagent was chosen because:-

a) it reacts in fairly high yield with 2,6-diaminopyridine;

b) the structure of the expected product should be readily interpretable by N.M.R.

2,4-Diamino-6-methylpyridine was recovered in 72% yield; some product was indicated by T.L.C.

A melt reaction using the same reagents was attempted. The novel 1,2,3,4,5,8,9,10,11,12-decahydro-7-methylpyrido[2,3-b:4,5-b]diindole (37) was synthesised in 35% yield.



(37)

The fact that the novel 1H,6H-dipyrrolo[2,3-b:2',3'-d]pyridine system was produced validates the original premise that the activity of 2,4-diaminopyridine is similar to the activity of 2,6-diaminopyridine in the Bischler reaction. Also it is interesting that the dipyrrolo compound was formed despite the reagents being reacted in a 1:1 molar ratio. This seems to indicate that the bi-condensation of the amino groups of 2,4-diamino-6-methylpyridine with the carbonyl group of the 2-hydroxycyclohexanone is a necessary condition before attack on the ring can take place. A melt reaction was then tried with 2-hydroxybutan-3-one. 2-Hydroxybutan-3-one was used as the expected product should be easily characterised and it gave high yields with 2,6-diaminopyridine in Ward's[3] work. No product could be isolated and a complicated mixture was shown to be present by high pressure liquid chromatography. The failure of this reaction is a reflection of the instability of the 2,4-diaminopyridine and 2-hydroxybutan-3-one to high temperatures probably breaking down before they are able to react. Also it is a reflection of the relative stability of the transition state compared to that derived from 2-hydroxycyclohexanone, by a similar argument that was applied earlier.

No further experiments were carried out on this system as there was no more 2,4-diamino-6-methylpyridine available.

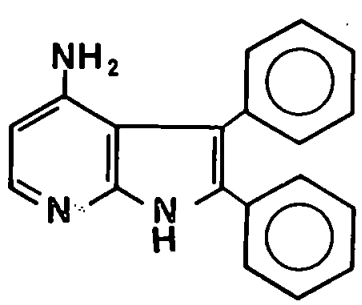
2,4-Diaminopyridine was reacted as follows:-

1) Under solvent conditions with 2-hydroxycyclohexanone. This led to complete recovery of both starting materials with no product formation indicated.

2) Under melt conditions with 2-hydroxycyclohexanone. This was not a 'clean' reaction, a lengthy work up failed to produce any product. Again this reflects the instability of 2,4-diaminopyridines to heat. The fact that no product was obtained whereas a product was obtained with 2,4-diamino-6-methylpyridine suggests that the reduced electron density within the pyridine ring deactivated the ring closure step and allowed polymerization to take place in a similar manner to that suggested by Ward[3].

3) Under solvent conditions with benzoin. Benzoin was chosen as it gave very high yields of product with 2,6-diaminopyridine, probably due to the stabilisation of the transition state by the phenyl groups. This reaction yielded complete recovery of both starting materials.

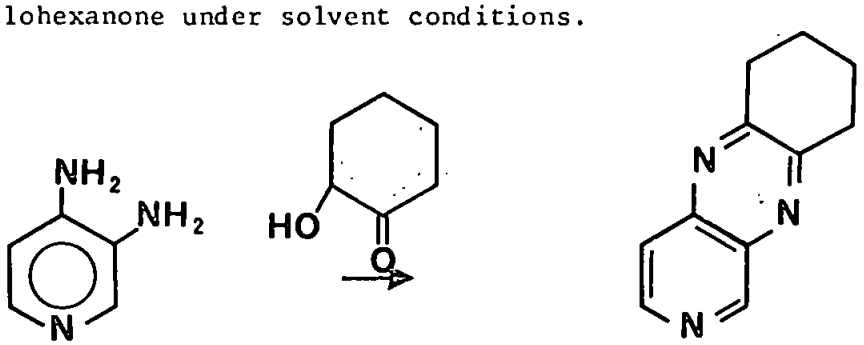
4) Under melt conditions with benzoin. This led to the formation of the novel 4-amino-2,3-diphenyl-1H-pyrrolo[2,3-b]pyridine (38) in low yield (2.45%). The formation of this mono-ring closed derivative reflects the greater stability of the transition state compared to that of the cyclohexyl derivative which has to undergo dicondensation of the amino groups before ring closure.



(38)

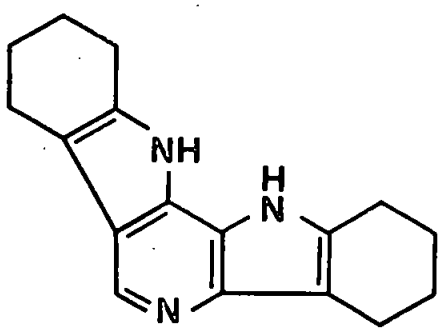
3,4-Diaminopyridine

The commercially available diaminopyridine was reacted with 2-hydroxycyclohexanone under solvent conditions.



39·4 %

(39)



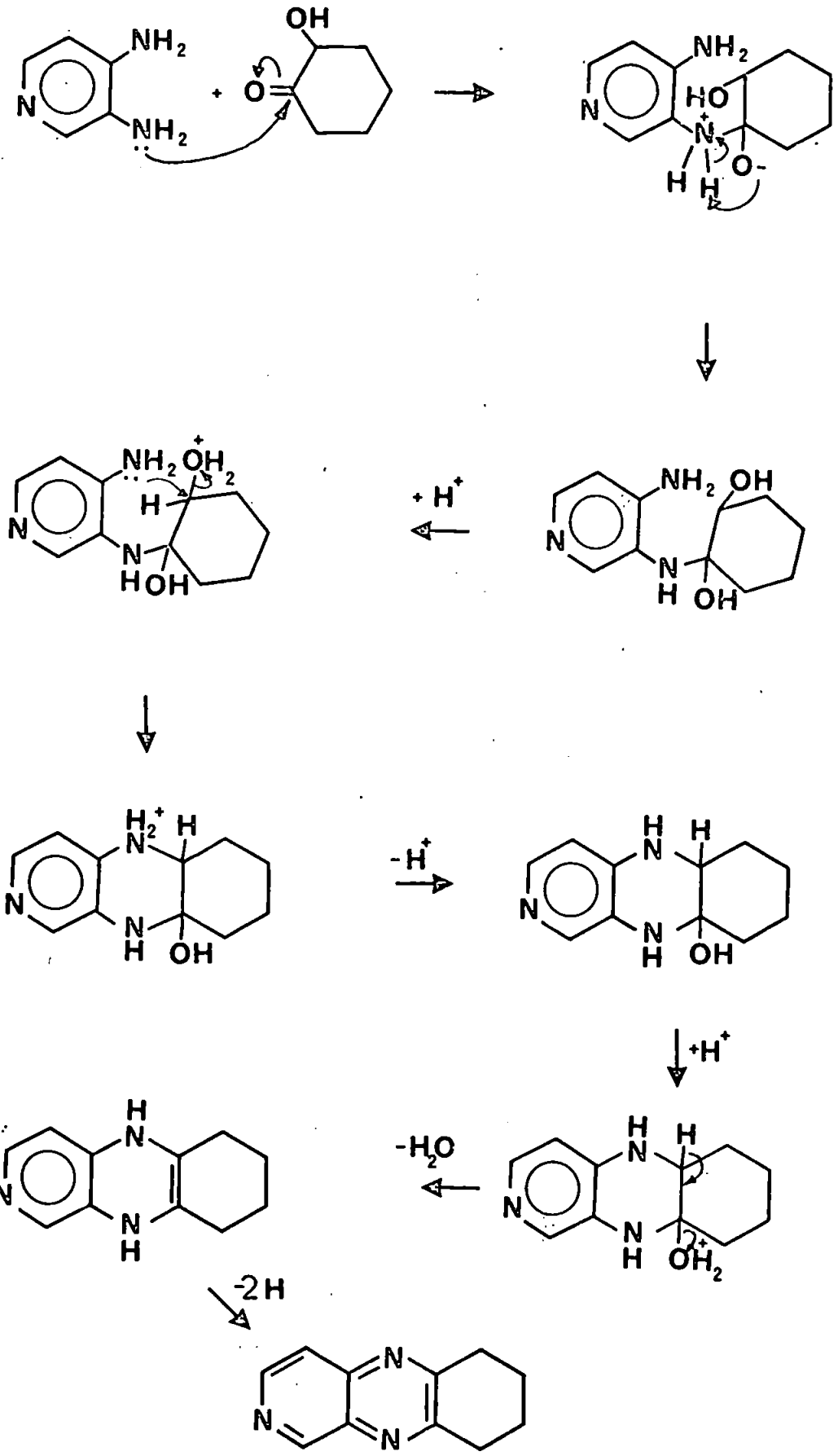
(40)

The novel 6,7,8,9-tetrahydropyrido[3,4-b]quinoxaline (39) was formed, in 39.4% yield. None of the expected product (40) was detected. This illustrates the importance of the electron density at the position of ring closure in the Bischler reaction. Ward[3] tried to ring close 2-amino-6-methylpyridine with no success even though the electron availability is only slightly reduced, compared to 2,6-diaminopyridine.

Here the possibility of electrophilic attack at the 2-position of the pyridine ring by the carbonium ion formed in the Bischler reaction is small. The electron density is low at the 2-position as it is adjacent to the pyridinium nitrogen. Ring closure to the 5-position is also difficult because the electron supplying amino group in the 3-position cannot effectively supply electrons to the 5-position. The formation of (39) is thought to follow the mechanism shown in Scheme 8.

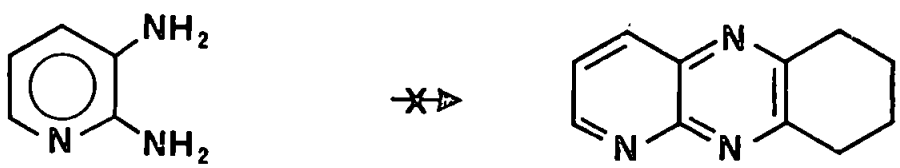
The mechanism of the last step is not clear but the driving force for this reaction must be the achievement of the stable delocalised aromatic system.

Scheme 8

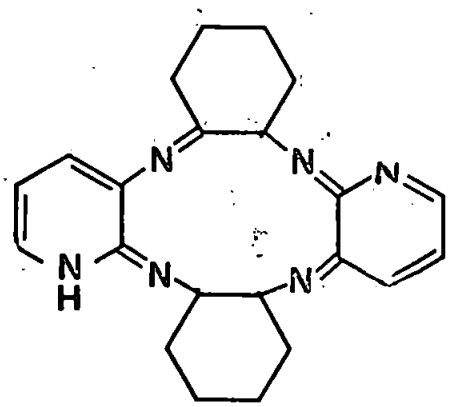


2,3-Diaminopyridine

This diaminopyridine was reacted with 2-hydroxycyclohexanone under solvent conditions.



(41)



(42)

The expected product (41) was not formed instead 5,6,7,8,9,15,16,17,18,19,20-undecanydrodibenzo[b,h]-N-hydropyrido[2,3-e]pyrido[2,3-k][1,4,7,10]-tetra-azacyclododecine (42) was formed in 21.5% yield.

The mechanism of the formation of (42) is not clear but obviously a bi condensation has taken place because this seems to be more energetically favourable than the expected condensation leading to (41). Also there must

have been a hydride shift as one of the cyclohexyl rings is fully hydrogen substituted.

The evidence to support the structure of (42) is given in the chapter on review of spectra.

2,5-Diaminopyridine

This diaminopyridine was reacted with 2-hydroxycyclohexanone under solvent conditions. No product was detected in the resulting black tar from which 80% of the diamine was recovered.

An attempted melt reaction failed to yield any product. A possible product was indicated by T.L.C. but only in very small amounts, by far the major component seemed to be dark material at very low R_f's. 2,5-Diaminopyridine in the free state is heat, light and air sensitive and probably breaks down under melt condition before it has time to react.

The observation that no product was formed under solvent condition further emphasises the importance of relatively high electron density at the point of ring-closure.

The 5-amino group is not able to greatly increase the electron density at the 3-position and this may be a reason for the failure of the ring closure reaction.

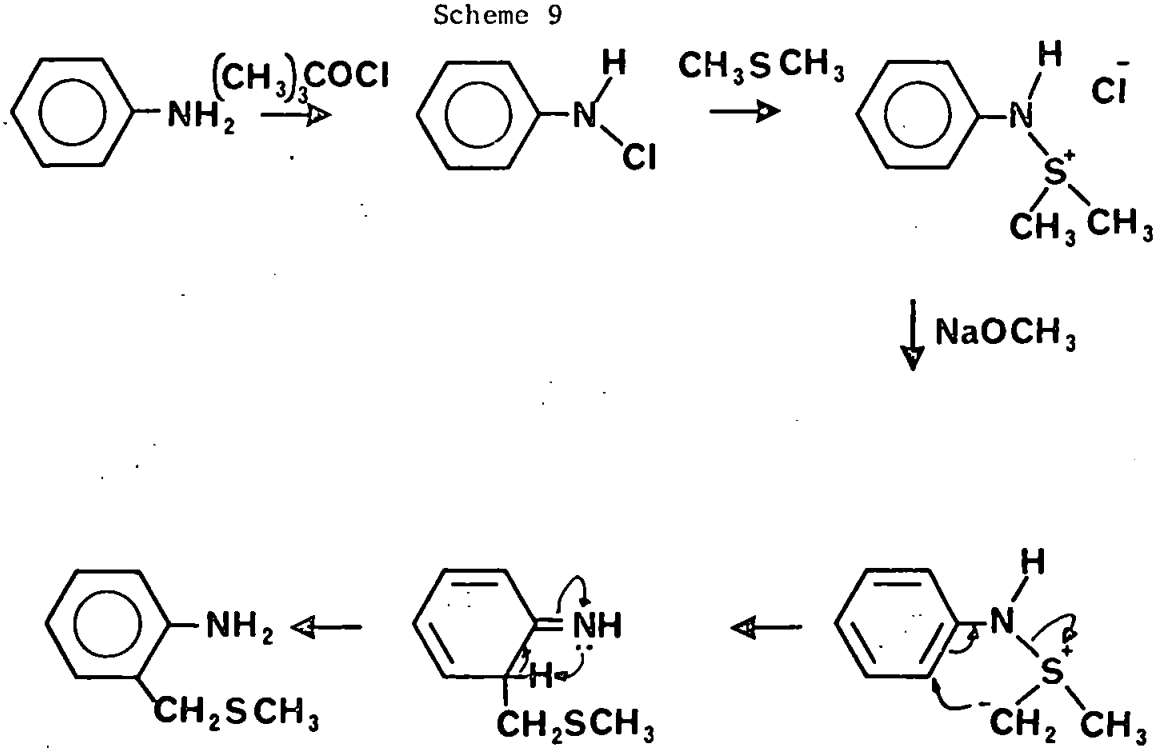
THE GASSMAN REACTION

The applicability of the Bischler reaction has been shown to extend only to 2,4-diamino and 2,6-diaminopyridine. These gave rise to the 1H,6H-dipyrrolo[2,3-b:2',3'-d]pyridine, 1H,7H-dipyrolo[2,3-b:3',2'-e]pyridine and 1H-imidazo[1,2-a]pyrrolo[2,3-b]pyridine systems, the last two being synthesised in Ward's[3] work.

To obtain other systems a new synthetic scheme was needed. To suit the pyridine system the ring closure step needs to be nucleophilic in nature, this would also enable the scheme to work in conjunction with the Bischler reaction.

In 1973 Gassman et al[29] published a synthesis for the specific ortho-alkylation of aromatic amines. The synthesis is as in Scheme 9.

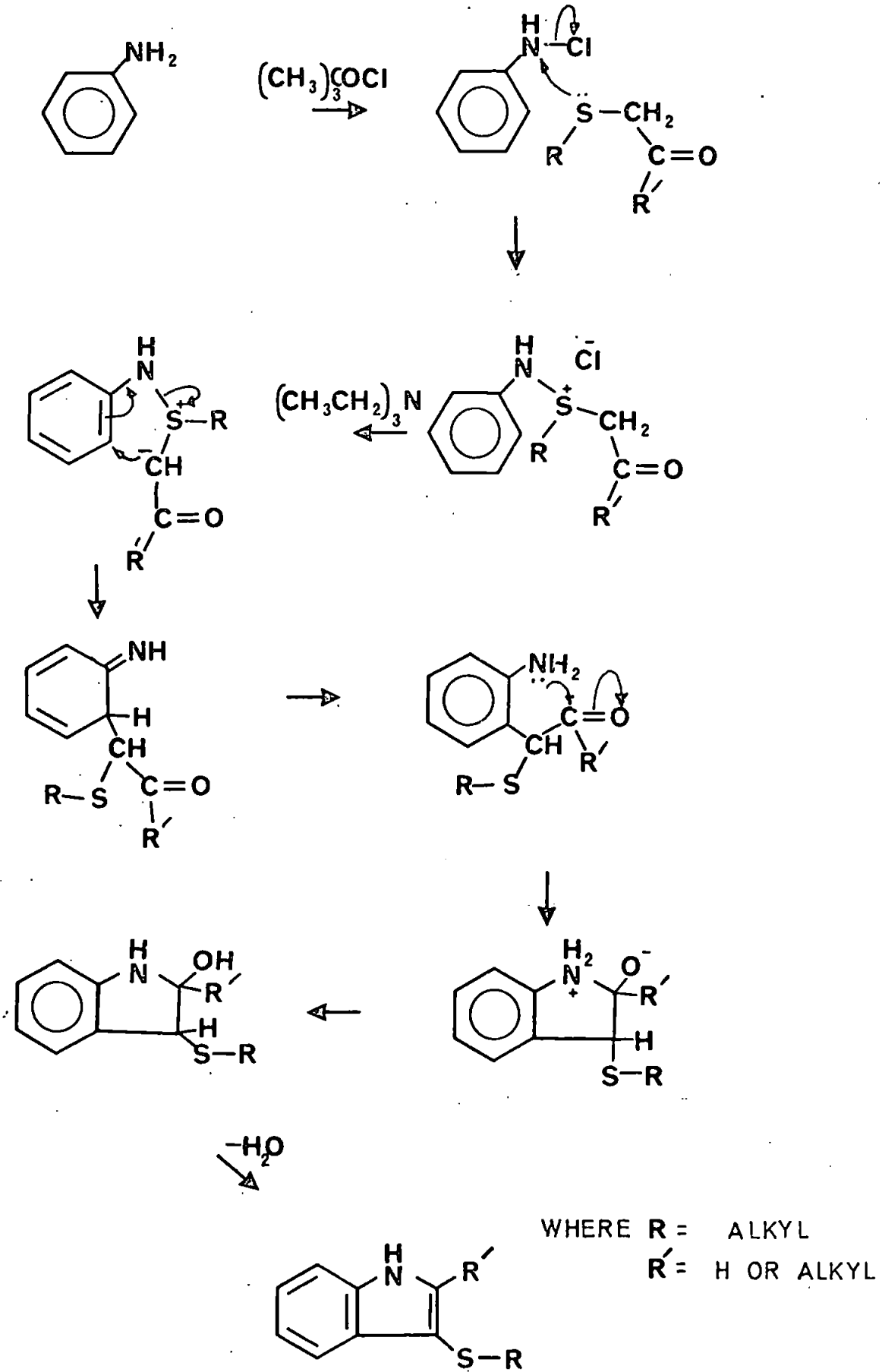
Scheme 9



This scheme was of interest because it involves nucleophilic attack on the ring, and with modification could be of use in producing pyrrolopyridines. Gassman and Van Bergen[6] adapted the reaction for the production of indoles. They used an alkylthioketone in place of the sulphide and used triethylamine as a base instead of sodium methoxide.

The proposed mechanism for the reaction is as in Scheme 10.

Scheme 10



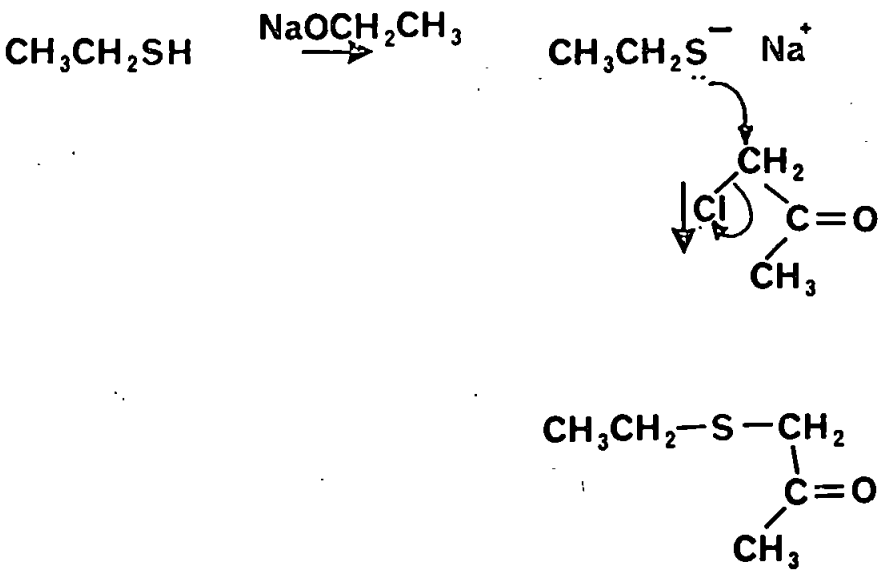
The conditions of the reaction consist of stirring the reagents at -65° C in dichloromethane. The reagents are not added simultaneously but at intervals.

The advantages of this reaction over the Bischler reaction applied to the pyridine system are:-

1) The ring closure step is nucleophilic.
2) The reaction conditions are very mild permitting the use of heat sensitive amines.
3) The electron density of the aromatic nucleus seems to play little part in the reaction. The reaction works in the benzene series with electron donating as well as electron withdrawing substituents[29].

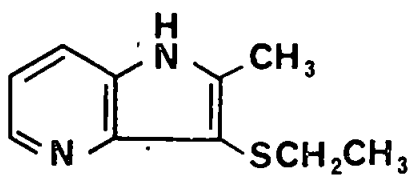
Application to Pyridines

Accordingly, the following reagents were prepared. Tertiary-butyl hypochlorite was synthesised using the method of Teeter and Bell[30] i.e. the chlorination of tertiary-butanol. Ethylthiopropan-2-one (43) was prepared by the method of Bradsher et al[31] as follows:-



(43)

The ethyl derivative was chosen because the ethanthiol was less obnoxious and more easily handled than the gaseous methanthiol. Gassman et al[29] stated that the nature of the alkyl group attached to the sulphur atom should have little effect on the reactivity. 3-Aminopyridine was chosen initially as the starting material because the amino group is in one of the most electron rich positions in the pyridine ring and therefore it should be similar to the amino group of aniline in reactivity. On performing the synthesis the novel 2-methyl-3-ethylthio-1H-pyrrolo[3,2-b]pyridine (44) was produced in 2.6% yield together with large amounts of ethylthiopropanone.



(44)

This yield was surprisingly low and it was decided to investigate the early stages of the reaction to ensure that Scheme 10 was indeed operative.

Chlorination Stage

This step was suspect because of the large amount of ethylthiopropan-2-one recovered. This seemed to indicate that only a small amount of chloramine was being formed.

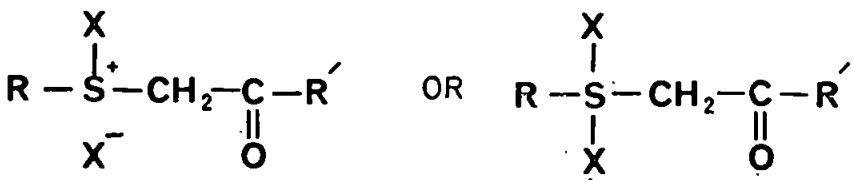
Since 1883 when Hoffman[32] discovered the N-halogenation of amines using Hypohalite ion, there has been a steady interest in this reaction. The first attempt at producing an aromatic N-chloramine was that of Goldschmidt[33] who produced NN'-dichloroaniline using hypochlorous acid in ether at -20° C. The instability of the aromatic chloramines is illustrated by the fact that NN'-dichloroaniline is explosive above 0° C. There have been no detailed investigations into the mechanism of amine chlorination by hypochlorite. The reactive species could be either hypochlorous acid or hypochlorous ion.

There have been suggestions[34] however, that there is hydrogen bonding between the amine and the hypochlorite ion.

The mono-N-chloro derivates were unknown until 1964 when Neale et al[35] proved their existence as intermediates in the chlorination of aromatic amines. Further proof was found in 1965[36] by the use of infra-red spectroscopy and titration of the active chlorine.

The rather transitory nature of aromatic N-chloroamines suggests that in our procedure the low overall yield might be due to a low concentration of N-chloramine when the alkylthioketone is added.

With this in mind it was thought that if the alkylthioketone could be introduced at the site of reaction as soon as the chloramine was formed the yields might improve. Gassmán et al[37] used a halogen/alkylthioketone complex (45) of the type



(I) (45) (II)

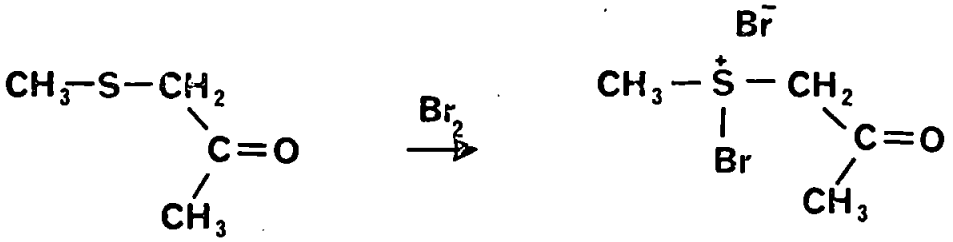
where R = Alkyl X = Chlorine or Bromine

R' = H or Alkyl

Similar complexes of this type have been known for some time[38] and they have been discussed in terms of both[39,40] the halosulfonium halide salt structure (I) and the sulphurane structure (II). The exact structure of these complexes has not been rigorously determined in all cases, but it appears that the halosulfonium halide (I) might be a better structure than the sulphurane for halide displacement by a nucleophile[40].

It was stated that there was no significant difference between the activity of the chlorine and bromine complexes[37]. We formed a complex at -65°C

in dichloromethane between methylthiopropan-2-one (46) synthesised in 64.2% yield by the method of Bradsher et al[31] and bromine.

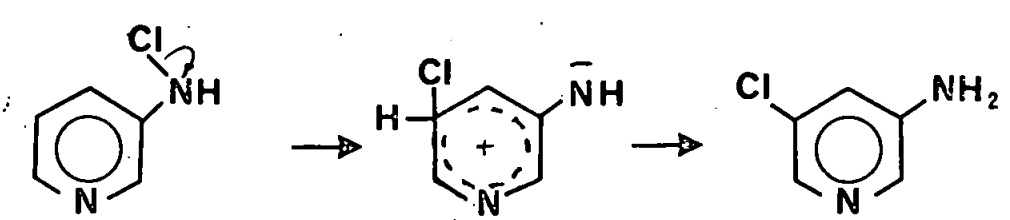


(46) (47)

This complex was not isolated but reacted immediately with 3-aminopyridine in dichloromethane.

This gave 55% recovery of 3-aminopyridine together with an intractable black tar in which no product could be identified by T.L.C. Gassman et al[37] state that the yields decrease as the electron availability of the ring decreases, for indoles. The original plan of simultaneous addition of alkylthioketone to the N-chloramine is still valid. It may be that the limited electron availability of the pyridine ring prevents the final ring closure step.

It is possible that the failure of the overall reaction at the chlorination stage could have been due to the breakdown of the N-chloramine to give 5-chloro-3-aminopyridine (48).

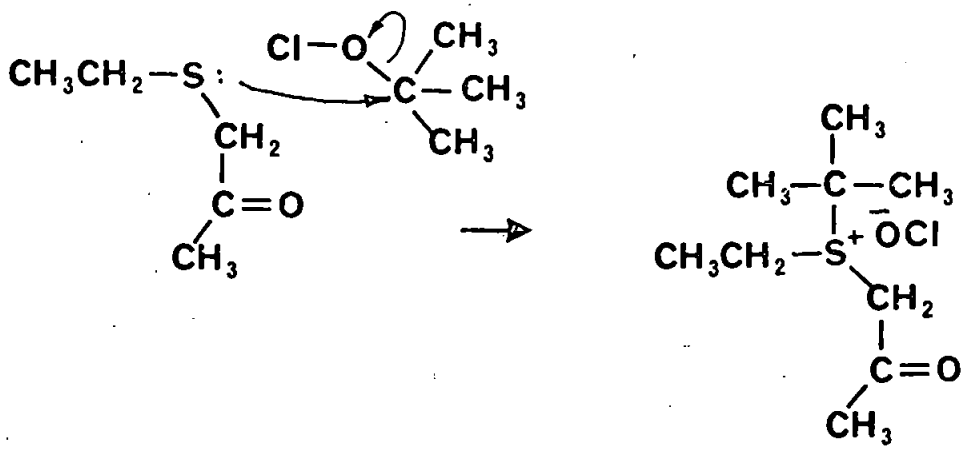


(48)

If twice the normal amount of tertiary-butyl hypochlorite was used in the first step of the reaction then even if (48) was formed the extra chlorinating agent should form the chloramine. A reaction was attempted using twice the amount of chlorinating agent with 3-aminopyridine and ethylthiopropan-2-one. The yield of 2-methyl-3-ethylthio-1H-pyrrolo[2,3-b]pyridine (44) was considerably reduced (0.25%) and no 2-methyl-3-ethylthio-5-chloro-1H-pyrrolo[2,3-b]pyridine or 3-amino-5-chloropyridine were found.

We conclude that whilst the N-chloramine must be formed to some extent (if the mechanism is correct) in the route to 2.6% of ring closed product, major loss of N-chloramine to 5-chloro-3-aminopyridine is not a significant factor in the low overall yield.

The drop in yield from 2.6% to 0.25% was thought to be due to the formation of an alkylthioketone tertiary-butyl hypochlorite complex (49) formed from ethylthiopropan-2-one and the excess hypochlorite viz:



(49)

When these two reagents are mixed together there is a strong heat of reaction and a red/orange colouration is produced.

This is analogous to the formation of the halogen/alkylthioketone complexes like (45), where an exotherm occurs[37].

Semi-quantitative evaluation of the N-chlorination of 3-aminopyridine was undertaken. Tertiary-butyl hypochlorite and N-chlorosuccinimide were dissolved both in tetrahydrofuran and methylene chloride at 0°C under nitrogen.

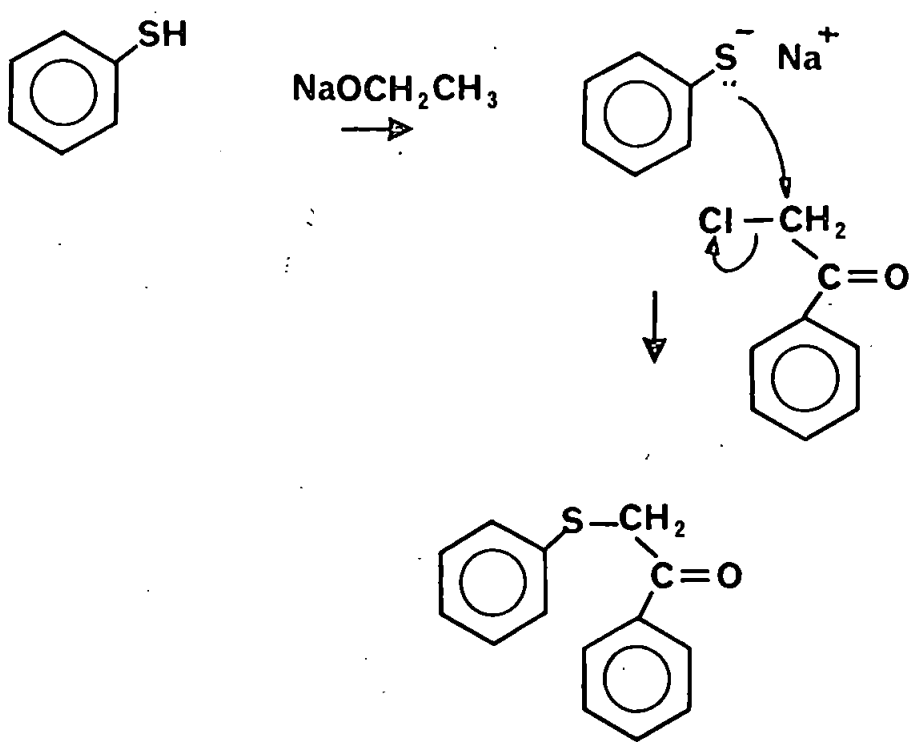
This temperature was chosen as N-chlorosuccinimide in methylene chloride had successfully been used at 0°C to N-chlorinate aminosteroids[41]. A solution of 3-aminopyridine was added to each system. The concentrations used were the same as used in Gassman's synthesis. Aliquots were taken and examined by T.L.C. at various time intervals. N-chlorosuccinimide seemed the more effective reagent especially in tetrahydrofuran for N-chlorination, but even after a long time (24 hours) large amounts of 3-aminopyridine were left unchanged.

Two experiments were then carried out using N-chlorosuccinimide and 3-aminopyridine at 0°C in tetrahydrofuran:

1) Using phenylthioacetophenone (50).

This was synthesised in 85.2% yield from α-chloroacetophenone and the sodium salt of thiophenol as in Scheme 11.

Scheme 11



(50)

Phenylthioacetophenone was chosen in the hope that the phenyl groups may help the stabilisation of the cation formed as part of the azasulphonium salt in Gassman's[6] synthesis. Phenylthioacetophenone (57%) was recovered from an intractable black tar. A product whose Rf and colour reaction on T.L.C. were similar to (44), was detected by T.L.C., but even using preparative T.L.C. not enough could be recovered for identification.

2) Using ethylthiopropan-2-one.

This gave 47% recovery of ethylthiopropan-2-one 8.5% of 3-aminopyridine and 0.5% of product, 2-methyl-3-ethylthio-1H-pyrrolo[3,2-b]pyridine.

No improvement seems to have been made using N-chlorosuccinimide, this is somewhat surprising in the light of the T.L.C. results earlier. Again large amounts of recovered alkyl and phenylthioketones suggest the failure of the chlorination stage.

The conditions under which tertiary-butyl hypochlorite has to react were then reviewed. Under basic conditions (pyridine) tertiary butyl hypochlorite will act as an oxidising agent.[42] The pyridine neutralises the hydrochloric acid formed in the reaction. As 3-aminopyridine is a strong base relative to aniline it was thought perhaps oxidation of the amine was taking place in competition with N-chlorination. If the reaction could be carried out under acidic conditions this oxidation reaction may be inhibited.

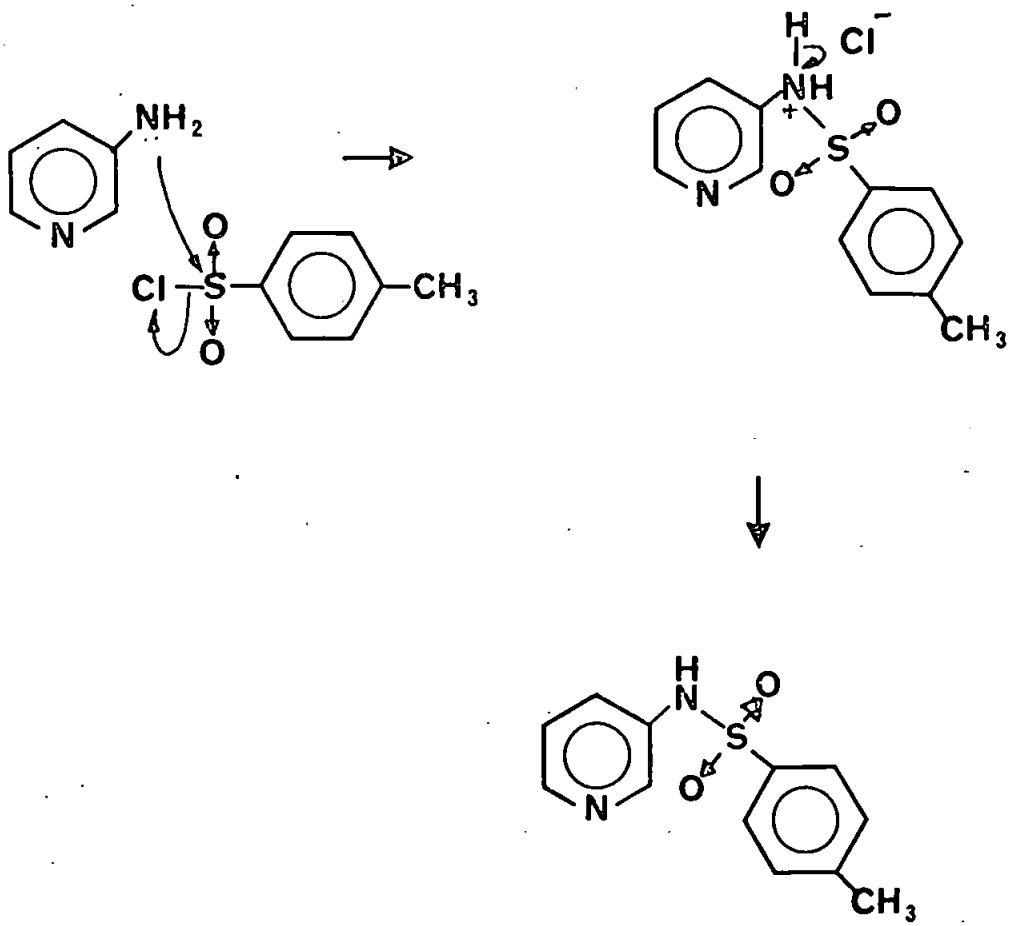
3-Aminopyridine hydrochloride was synthesised in 94.5% yield by passing hydrogen chloride into a solution of 3-aminopyridine in benzene. This product was then reacted with ethylthiopropan-2-one and tertiary-butyl hypochlorite under Gassman's[6] conditions. Ethylthiopropan-2-one was recovered in 65.3% yield together with some product in trace amounts, and 3-aminopyridine in 50.0% yield.

As N-chlorination of 3-aminopyridine seems so difficult it was thought that another leaving group might serve the purpose equally as well as chlorine. There are two main criteria for the selection of the group:

1) It must readily form a derivative with 3-aminopyridine.

2) It must be electron withdrawing so as to facilitate nucleophilic attack on the amino nitrogen by the sulphur atom of the alkylthioketone.

The novel 3-N-tosylaminopyridine (51) was produced from 3-aminopyridine and p-toluenesulphonyl chloride in refluxing pyridine in 82.9% yield.



(51)

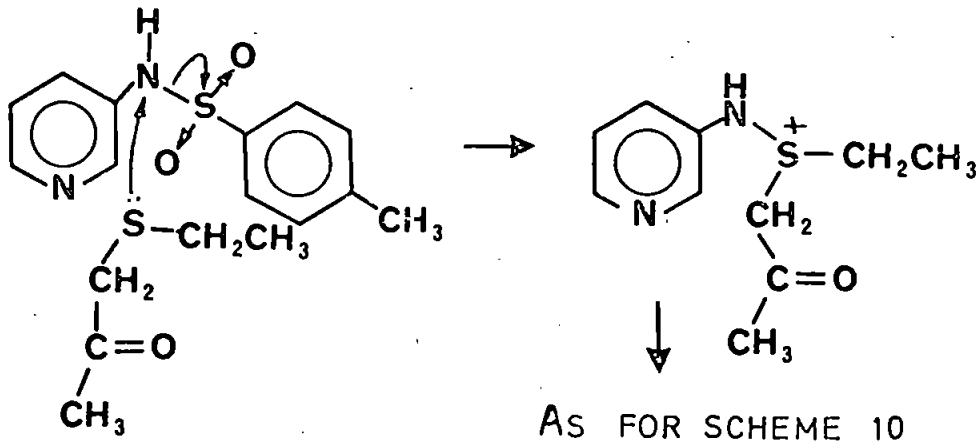
Compound (51) was then reacted with ~~tertiary-butyl-hypochlorite and~~ ethylthiopropan-2-one

1) at room temperature - 85.5% recovery of (51)

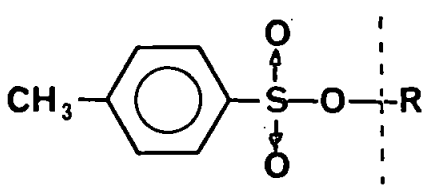
2) in refluxing dichloromethane - 84.1% recovery of (51)

3) in refluxing ethyl alcohol - 98.5% recovery of (51)

The mechanism that was hoped to be favoured was:



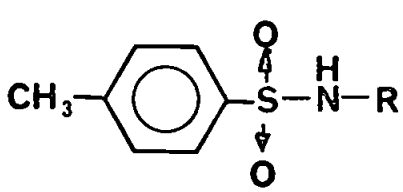
However, whilst tosylate esters (52) readily cleave at the carbon-oxygen bond,



(52)

where R = alkyl or other alkyl like system

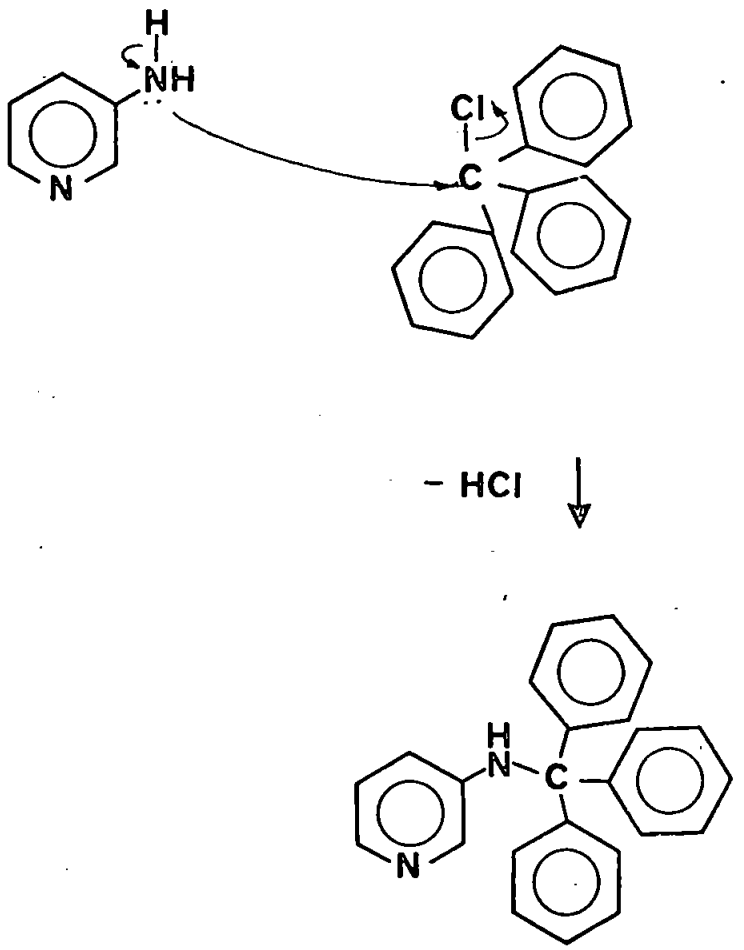
the sulphonamides (53) are not readily cleaved by even strong base[43] and therefore are not likely to yield to a nucleophile of the strength of the alkylthioketones.



(53)

where R = alkyl
carboxy-alkyl
phenyl

In a further attempt to overcome the leaving group problem the novel 3-N-triphenylmethylaminopyridine (54) was produced from triphenylchloro-methane and 3-aminopyridine in pyridine (50.4% yield).



(54)

When the reaction was performed in pyridine, the normal solvent, a complex was produced. The exact nature of the complex was not determined. It was thought to consist of 3 moles of pyridine, 1 mole of 3-triphenylmethyl-aminopyridine and 2 moles of hydrogen chloride.

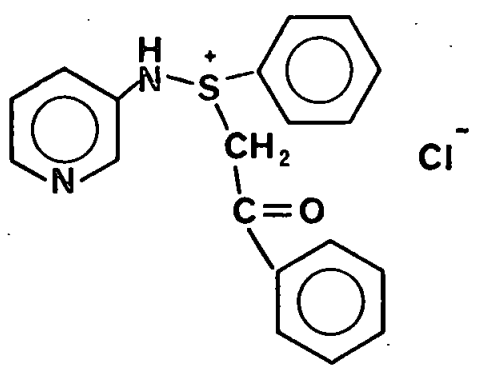
This is based on evidence from the mass spectrograph and the elemental analysis. To obtain the pure derivative the complex must be treated at room temperature with a base such as triethylamine in dichloromethane.

The intention was to chlorinate (54) with tertiary butyl hypochlorite under Gassman's[6] conditions and react it accordingly with ethylthiopropan-2-one, in the hope that some stability might be imparted to the chloroamine by the

involvement of the phenyl groups. This reaction was not performed however because of correspondence with Dr. P.G. Gassman. This will be dealt with later.

The donation of electrons from the sulphur atom

In order to see if this step is working efficiently we need to vary the electron density at the sulphur atom. To this end phenylthioacetophenone was produced. This was reacted with 3-aminopyridine under Gassman's[6] conditions. This led to 85% recovery of the phenylthioacetophenone together with an intractable black tar that contained some 3-aminopyridine and no 2-phenyl-3-thiophenyl-1H-pyrrolo[3,2-b]pyridine by T.L.C. This indicated that the stability of the azasulphonium ion (55), which should be enhanced



(55)

by the presence of the phenyl groups is not a limiting factor.

The next point to consider was the strength of base in abstracting the proton from the methylene group of the alkylthioketone, Sodium methoxide was going to be tried as this had been used in the original method for alkylating aromatic amines.

At this point in time we learnt by personal communication[44] that Gassman had managed to ring-close amino pyridines.

The new method consisted of using stronger base (sodium methoxide and potassium tertiary butoxide) and protecting the carbonyl group of the alkylthioketone by forming the ethylene ketal or diethyl acetal. The latter

measure was made to prevent the possible early condensation with an amino group and also possible polymerisation.

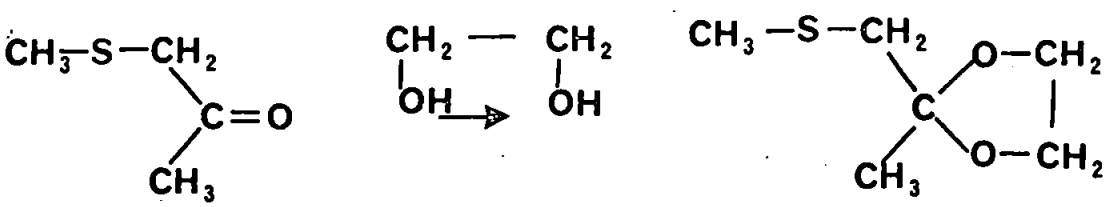
For the N-chlorination of 3-aminopyridine they used N-chlorosuccinimide, in preference to tertiary-butyl hypochlorite; this bears out the T.L.C. work done before on these two reagents.

The reaction involves the formation of the N-chloramine which forms an azasulphonium salt with an alkylthioketone ethylene ketal, and is then converted to the sulphilimine (56) with sodium methoxide. The sulphilimine is equilibrated with potassium tertiary butoxide whereupon the pyridine ring is substituted. Finally ring closure is performed by stirring with acid to remove the ketal and condense the carbonyl group formed with the free amine group. The mechanism is thought to follow scheme 12.

If we compare the two mechanisms shown in schemes 10 and 12 the only real difference is in the formation of sulphilimine prior to ylide formation. This appears to be the result of base strength, and there seems no reason why this step could not be excluded and 2 moles of the stronger base used straightaway.

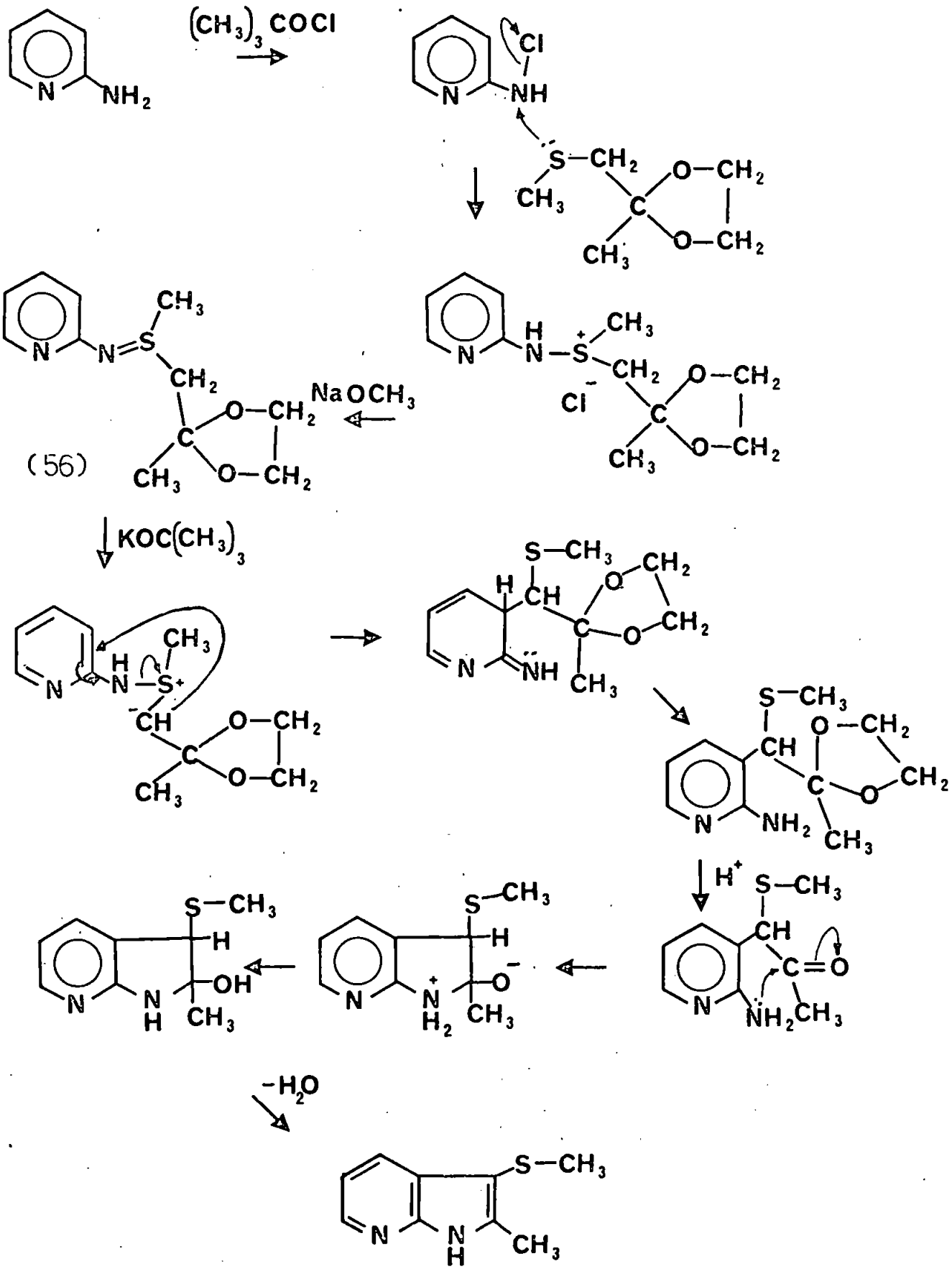
A reaction with 2-aminopyridine and methylthiopropan-2-one ethylene ketal (57) using Gassman's new conditions[44] was attempted. Methylthiopropan-2-one ethylene ketal was prepared in 51.4% yield from methylthiopropan-2-one and 1,2-ethandiol by modification of Renoll and Newman's method for the preparation of DL-isopropylideneglycerol[45],

viz:

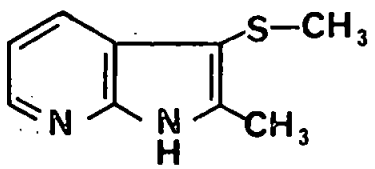


(57)

Scheme 12

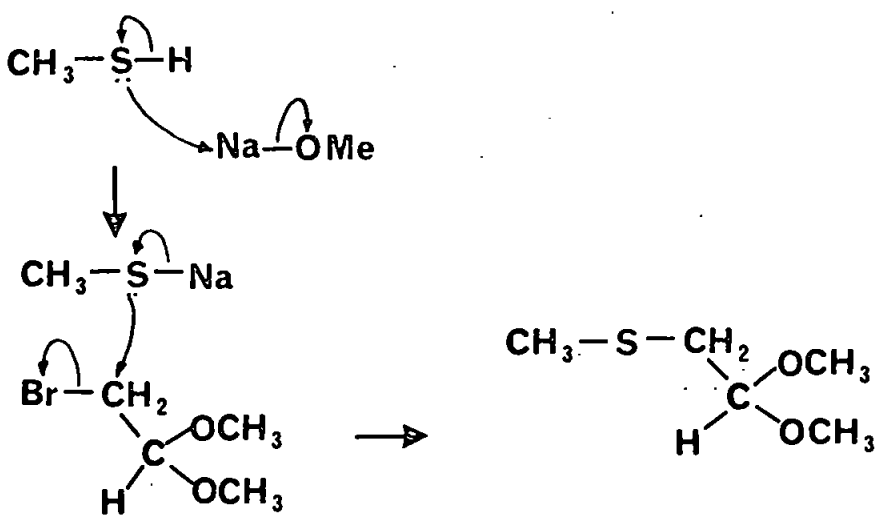


The reaction gave 2-methyl-3-methylthio-1H-pyrrolo[2,3-b]pyridine (58) in 17% yield 35.5% based on unrecovered 2-aminopyridine.



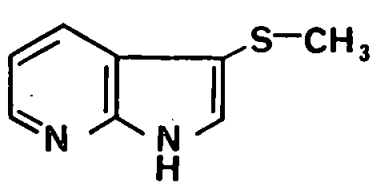
(58)

A reaction was also tried under Gassman's new conditions[44] with methylthioethan-2-one dimethyl acetal (59) and 2-aminopyridine. Methylthioethan-2-one dimethyl acetal was prepared from bromoethan-2-one dimethyl acetal and sodium methanthioxide by the method of Wick et al[46] in 50.0% yield.



(59)

The reaction gave 3-methylthio-1H-pyrrolo[2,3-b]pyridine (60) in 17.1% yield, 19.1% based on recovered substrate.

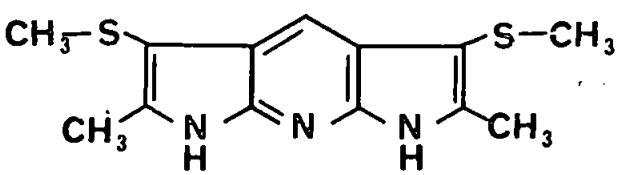


(60)

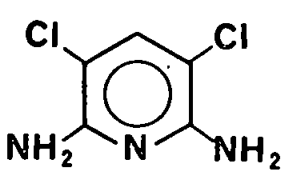
Having established that the method for synthesising monopyrrolopyridines was satisfactory the synthesis of a dipyrrolopyridine using this method was undertaken.

2,6-Diaminopyridine and methylthiopropan-2-one ethylene ketal were used. 2,6-Diaminopyridine was chosen because the amino groups should have similar activity as the amino group in 2-aminopyridine. Methylthiopropan-2-one ethylene ketal was chosen because based on previous experience the substituted 1H,7H,-dipyrrolo[2,3-b:3',2'-c]pyridines are more stable towards light, heat and air than the unsubstituted derivatives.

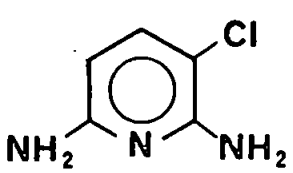
No expected product (61) could be detected but instead the novel 2,6-diamino-3,5-dichlorodiaminopyridine (62) and the novel 2,6-diamino-3-chloropyridine (63) were formed in 71.4% and 4.5% yield respectively.



(61)



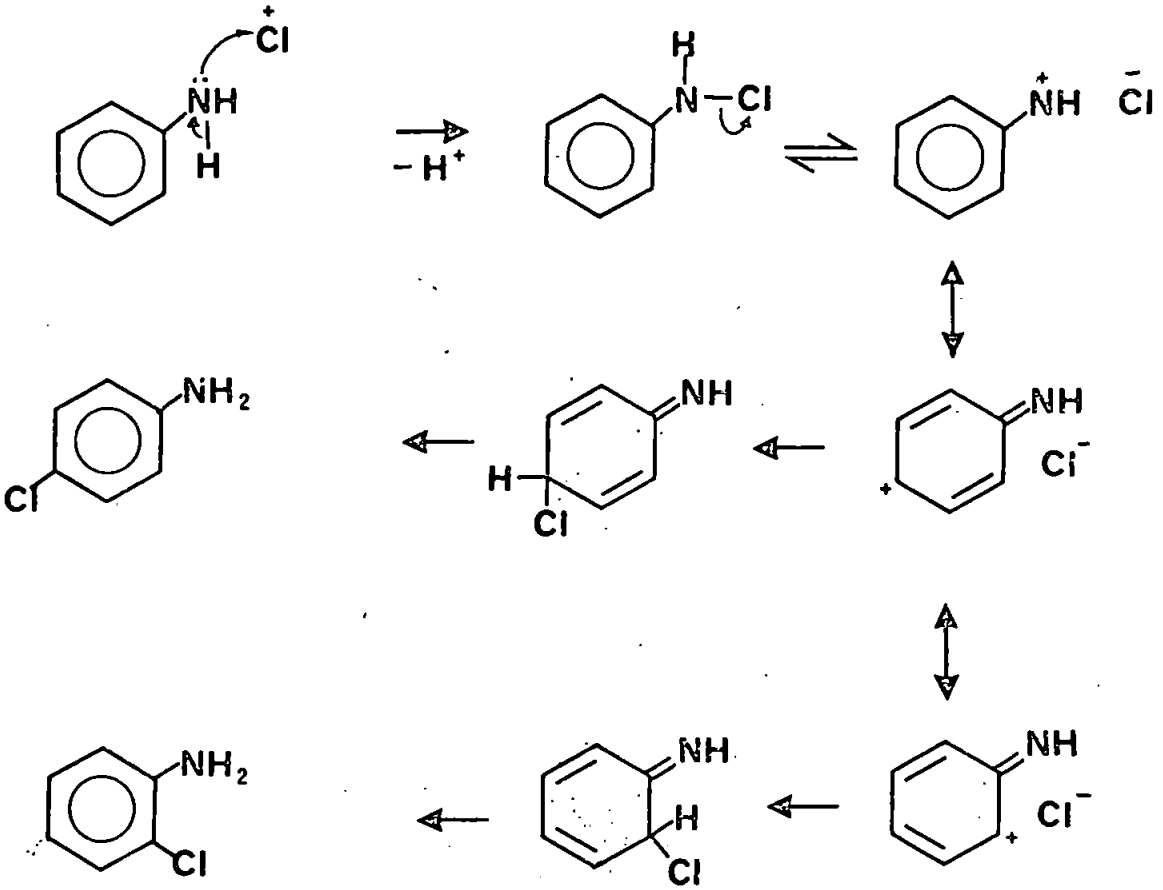
(62)



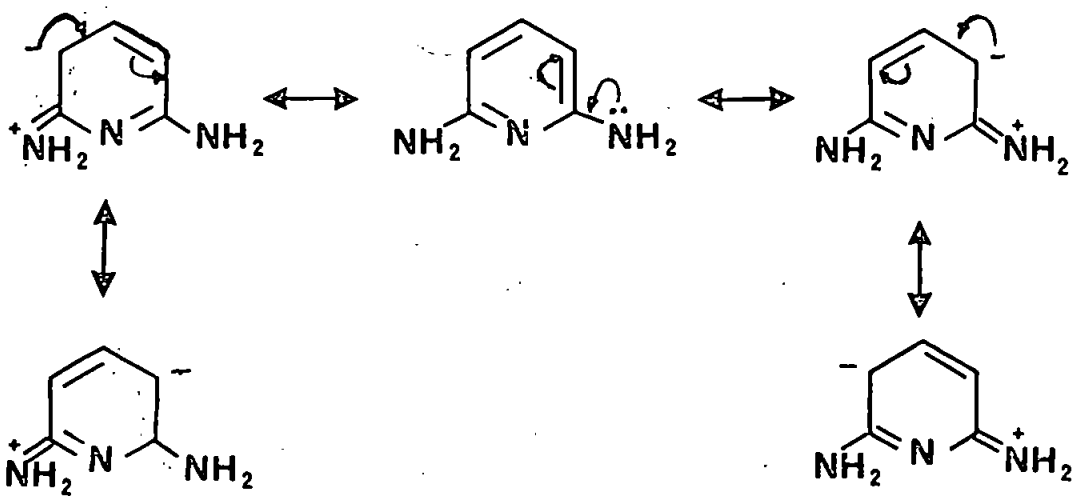
(63)

It appears that the N-chloramine is unstable and breaks down to the ring chlorinated product before it can react. The product of this breakdown however are interesting. It has been shown for anilines[47] that the mechanism for the rearrangement involves a nitrenium ion and a chloride ion as in Scheme 13.

Scheme 13

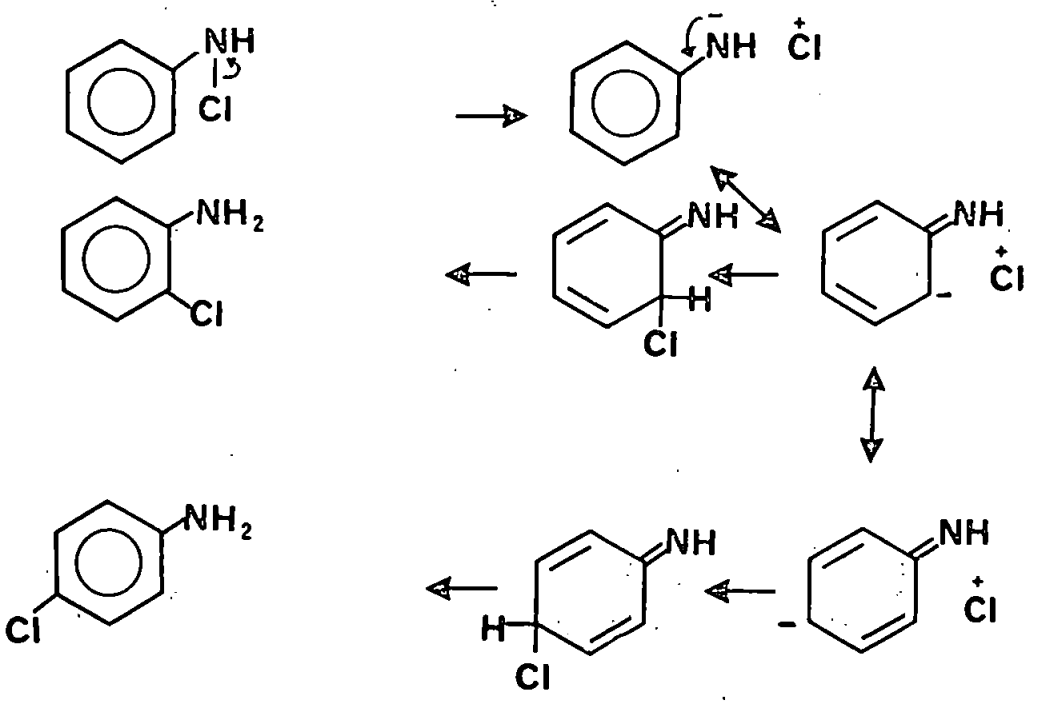


If we consider the electron densities of 2,6-diaminopyridine then even by classical consideration the 3 and 5 position are electron rich in comparison to the 4-position viz:



This is also true for pyridine itself[16] and the presence of amino groups in the 2 and 6 positions should enhance this effect. If the rearrangement of the N-chloramine of 2,6-diaminopyridine obeys the mechanism shown in Scheme 13 then the delocalisation of the positive charge would be expected to occur mainly at the 1,3 and 5 positions of the ring thus reducing the electron density at these positions. Subsequent attack by Cl^- on these positions would lead to the products obtained i.e. (63) and (64) the chlorination and rearrangement taking place on one amino group and then another chlorination and rearrangement taking place. However with the already low electron density at the 4-position it is somewhat surprising that no 4-chloro-2,6-diaminopyridine was isolated. The reaction may have occurred by heterolytic cleavage of the N-Cl bond to give an amino nitrogen anion and a chlorine cation by the mechanism shown in Scheme 14.

Scheme 14



This leads to the same products as Scheme 13 but in the case of aniline the mechanism of Scheme 13 has been shown[47] to be correct. If the mechanism in Scheme 14 is operating for the N-chloramine of 2,6-diaminopyridine 3,5-dichloro- and 3-chloro-2,6-diaminopyridine would have been produced but no 4-chloro-2,6-diaminopyridine would have been found. In view of the evidence so far the mechanism of Scheme 14 seems favoured.

An attempt was made using N-chlorosuccinimide as a chlorinating agent on 2,6-diaminopyridine. An intractable, insoluble solid was formed which melted above 360°C.

As N-chloramine stability appears to play such an important part in the reaction a means of increasing the stability was needed. A reaction using 2-amino-5-nitropyridine and methylthioethan-2-one dimethyl acetal under Gassman's new conditions[44] was attempted. The reasons for using 2-amino-5-nitropyridine were as follows:

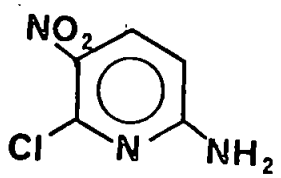
1) The nitro group is readily convertible under a mild process to an amino group which could be reacted further.
2) The nitro group blocks one position of possible ring chlorination.
3) The result should throw some light on the mechanism of chlorination.

The reaction gave at -15°C 82.5% recovery of 2-amino-5-nitropyridine and at 20°C using methylthiopropan-2-one ethylene ketal 71.4% recovery.

The fact that no ring chlorinated product was obtained means that either the N-chloramine did not form or that on breakdown before reaction with the thioketone the formation of the ring chlorinated product was not favoured.

The presence of a nitro group in the 5-position in the ring increases the positive character of the 2-amino group and would make the initial attack by Cl^+ to form the N-chloramine less favourable but in view of the very high yields obtained with anilines[36,48] of N-chloramines it is unlikely it does not form. The mechanism of the breakdown of the N-chloramine to give starting amine has been explained for anilines[47] to be due to the

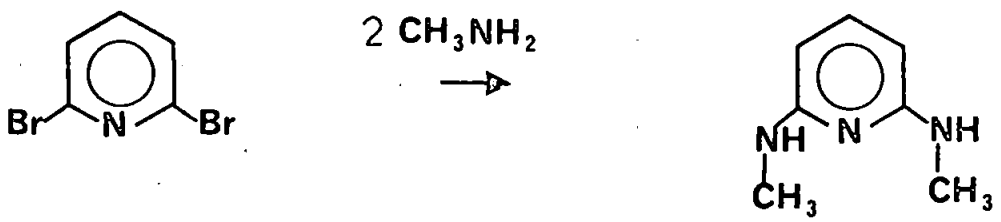
inability of the ring to delocalise the positive charge on the amino nitrogen. The yield of recovered aniline was from 1% for p-methyaniline to 29% for p-cyanoaniline increasing with increasing strength of electron withdrawing substituents. It was suggested[47] that the lack of an effective positive charge on the ring made attack by Cl^- difficult and that the starting amine arises *via* a hydride abstraction mechanism or *via* spin inversion of the singlet nitrenium ion to the hydrogen abstracting triplet nitrenium ion. In the case of 2-amino-5-nitropyridine the attack by Cl^- however would have been more favoured. The pyridine ring is an electron deficient ring, with respect to benzene, the low electron densities occurring especially in the 2,4 and 6 positions[16], with the presence of the nitro group in the 5 position and with an amino group blocking the 2 position one would expect the 6-position to be relatively electron deficient and attack by Cl^- to give (64) as a distinct possibility.



(64)

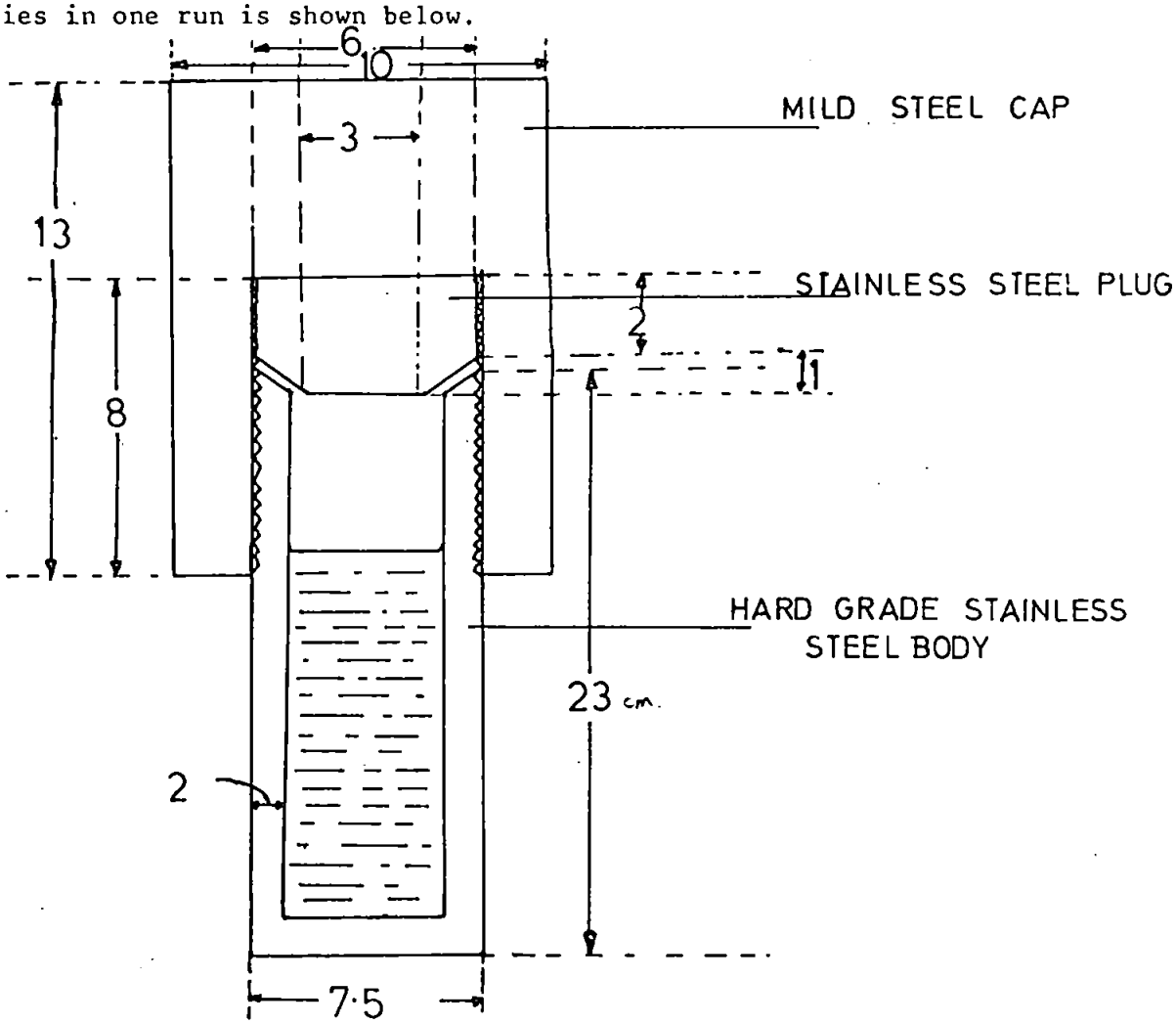
If the mechanism was as in Scheme 14 then the attack of Cl^+ on the ring would be highly unfavourable at positions 4 and 6 and at position 3 the general reduction of the electron density of the ring makes this unlikely. This is borne out by the fact that ring chlorination will take place for 2,6-diaminopyridine but for 2-aminopyridine the breakdown of the chloramine is unfavoured and no ring chlorinated products were detected on its reaction with thioketones under Gassman's new conditions[44]. The fact that no ring chlorinated products were found for the chlorination of 2-amino-5-nitropyridine suggest the mechanism of Scheme 14 is operating.

It has been shown[48] that N-alkylanilines give high yields (85% - 97%) of N-chloramines and that some of them are stable enough to be isolated in crystalline form. 2,6-Di-N-methylaminopyridine (65) was produced by the method of Bernstein et al[10], with slight modifications, in 41% yield. The reaction involved heating 2,6-dibromopyridine with methylamine under pressure at 190° viz



(65)

The apparatus to withstand these pressures, and yet produce large quantities in one run is shown below.



This vessel has the advantage of

a) Low cost of materials;

b) no complicated machining necessary;

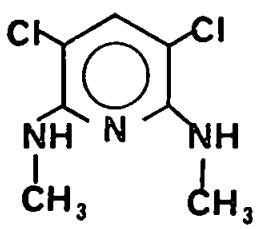
c) it easily fits into a muffle furnace;

d) its relatively large volume (206 cm^3 nominal capacity; 160 cm^3 usable capacity).

The disadvantage of this apparatus however is its relatively large thermal mass, consequently reactions have to be lengthened to allow for the inside of the bomb to come up to temperature.

A reaction using Gassman's modified new conditions[44] was then attempted on 2,6-Di-N-methylaminopyridine using methylthiopropan-2-one ethylene ketal. The modifications involve reacting the azasulphonium salt with 2 moles of potassium tertiary butoxide in refluxing tertiary butanol. This is because with the substitution of one of amino protons with a methyl group the formation of a sulphilimine is not possible.

The novel 3,5-dichloro-2,6-di-(methylamino)-pyridine (66) was produced in 19.1% yield.

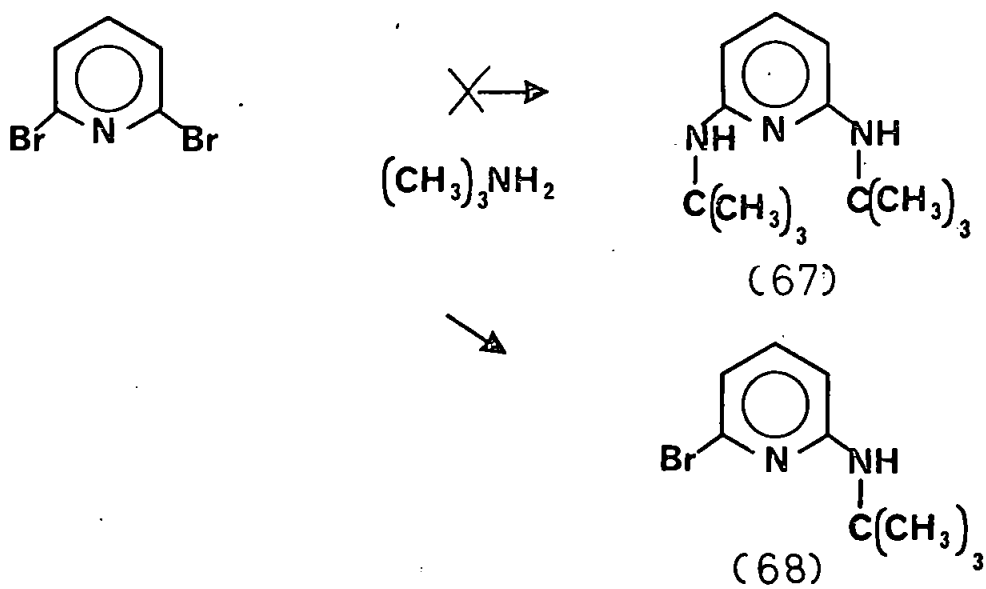


(66)

Despite N-alkylation the N-chloramine seems to be still unstable. If the breakdown of the N-chloramine occurs by generation of Cl^- then the attack on the ring to give (66) would be expected to be slightly less favourable than for 2,6-diaminopyridine due to the slightly increased electron density on the ring caused by the two N-methyl groups, however because of this one would expect the possibility of forming the 4-chloro derivative to be increased. No 4-chloroderivative was found. If the breakdown of the N-chloramine occurs by generation of Cl^+ then this generation of Cl^+ would be considerably less favoured due to the increased

electron density on the amino nitrogen. The rate of reaction would be slower and the yield of (66) considerably lower as is the case, and no 4-chloroderivative would be expected to be formed.

In Gassman et al's paper[48] it was shown that the N-chloramines of N-tertiary butylanilines were stable enough to be crystallised, by analogy the di-N-tertiary butyl derivative of 2,6-diaminopyridine should also produce relatively stable N-chloramine. An attempt was consequently made to produce 2,6-Di-N-tertiary butylaminopyridine (67) by reacting tertiary butylamine with 2,6-dibromopyridine at 190°C under pressure.



Under the conditions used however the novel 2-N-tertiary butylamino-6-bromopyridine (68) was formed in 41.8% yield. The fact that the mono N-substituted compound was formed may be due to steric hindrance of the attacking tertiary butylamino group by the already N-substituted tertiary butylamino group.

A reaction was attempted using (68) with methylthioethan-2-one under the same modified conditions used for dimethyl acetal (66).

2-N-Tertiarybutylamino-6-bromopyridine (68) was recovered in 91.2% yield. No ring chlorinated product could be detected. This may indicate that the chloramine does not form, which is unlikely as it had formed, albeit for a short time, for 2,6-Di-N-methylaminopyridine.

The recovery of starting amine may be due to the lowering of the electron density of the ring by the bromine atom in the 2-position. The reasons and mechanisms for the production of the amine are as for 2-amino-5-nitropyridine. The non-reaction of the N-chloramine of 2-N-tertiary butylamino-6-bromopyridine with methylthioethan-2-one dimethyl acetal could be due to the steric hindrance of the tertiary butyl group to attack of the thiocarbonyl compound on the amino nitrogen.

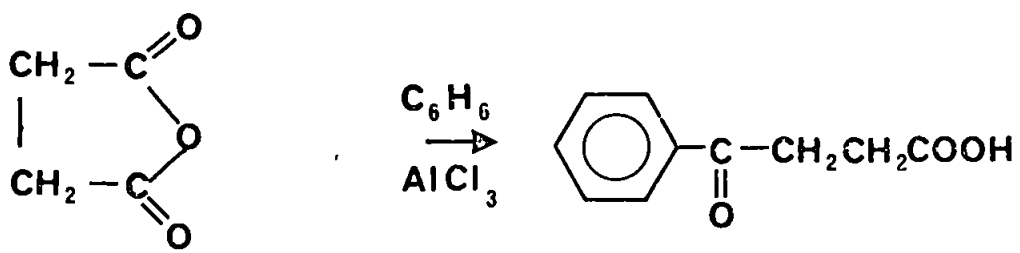
Unfortunately time necessitated that the work stopped at this point, although the possibilities for the production of dipyrrolopyridines had not yet been exhausted. These are further discussed in the conclusions chapter.

D E R I V A T I V E S O F K N O W N S Y S T E M S

The work dealt with here is concerned with the synthesis of derivatives of known systems together with the mechanistic problems that have arisen from Ward's work[3].

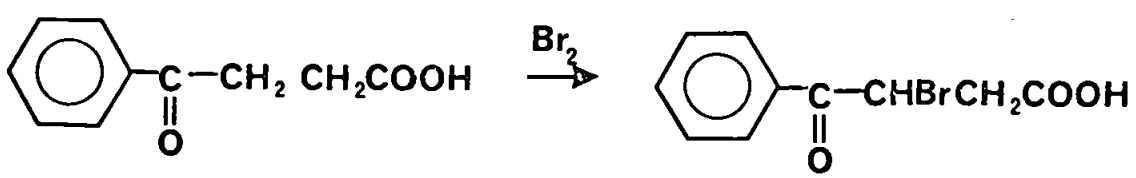
1H-Pyrrolo[2,3-b]pyridine-3-acetic acid like indole-3-acetic acid has been found to be a powerful auxin in pea and oat growth[49]. Therefore if an acetic acid derivative of the 1H-imidazo[1,2-a]pyrrolo[2,3-b]pyridine system could be produced then hopefully this may show similar activity.

β-Benzoyl propanoic acid (69) was produced in 86.5% yield from succinic anhydride and benzene by the method of Somerville and Allen[50].



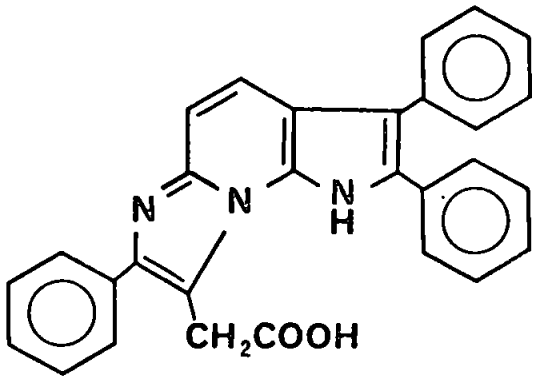
(69)

This compound was then brominated by a modification of the method of Knott[51] to give β-benzoyl-β-bromopropanoic acid (70) in 58.4% yield.



(70)

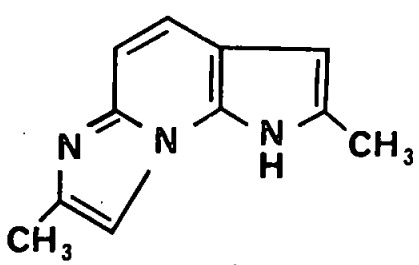
β-Benzoyl-β-bromopropanoic acid was then reacted with 2,3-diphenyl-6-amino-1H-pyrrolo[2,3-b]pyridine under solvent Bischler conditions. There was 84% recovery of 2,3-diphenyl-6-amino-1H-pyrrolo[2,3-b]pyridine; none of the expected product (71) was found.



(71)

It was hoped that the phenyl groups might impart stability to the carbonium ion formed in the reaction. However as 84% of the 2,3-diphenyl-6-amino-1H-pyrrolo[2,3-b]pyridine was recovered but none of the β-benzoyl-β-bromopropanoic acid it was thought that the acid decomposed before it could react.

1-Bromopropan-2-one was prepared by the method of Levene[52] in 40.2% yield. This was then reacted with 2-methyl-6-amino-1H-pyrrolo[2,3-b]pyridine in an attempt to form 2,7-dimethyl-1H-imidazo[1,2-a]pyrrolo[3,2-c]pyridine (72).



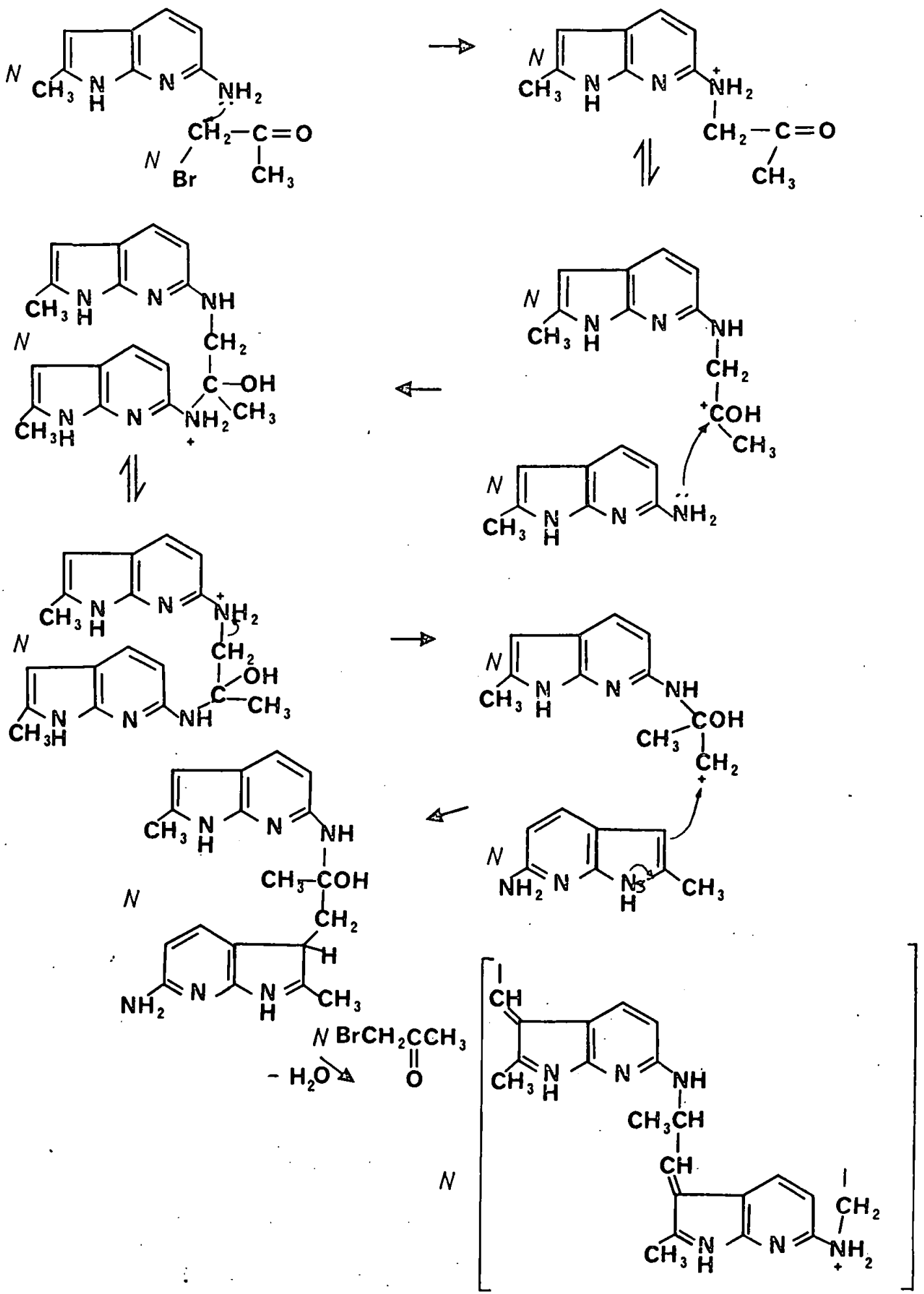
(72)

The reason for trying to make this compound was so that the relative activities of the 3 and 8 positions towards electrophilic reagents might be found, and hence gain an insight into the chemistry of the 1H-imidazo[1,2-a]

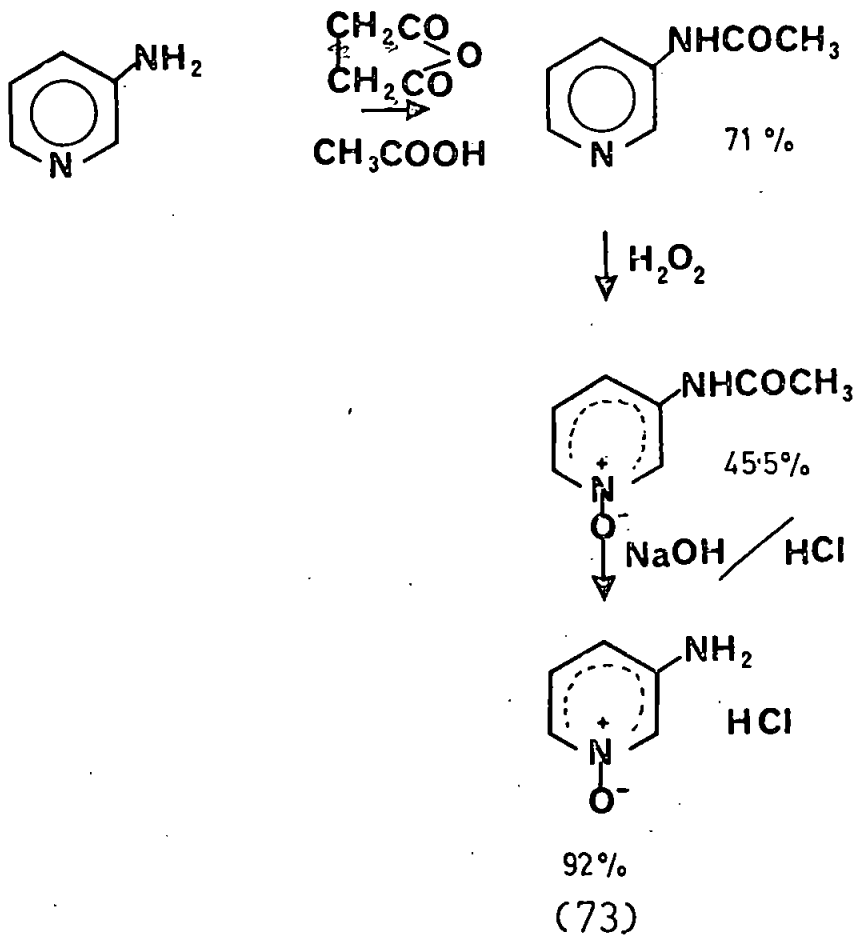
pyrrolo[2,3-b]pyridine system.

Several attempts were made under solvent and melt conditions to produce (73) but all attempts using 1-bromopropan-2-one ended with a black intractable solid. The reaction was also tried using the more heat stable 1-chloropropan-2-one but again the main bulk of the material consisted of a black intractable solid. A possible product was identified by T.L.C. but it was estimated as being present in only 3.4% yield. The failure of the reaction may reflect the activity of the unsubstituted 3-position towards electrophilic attack leading to possible polymer formation as shown in Scheme 15.

Scheme 15



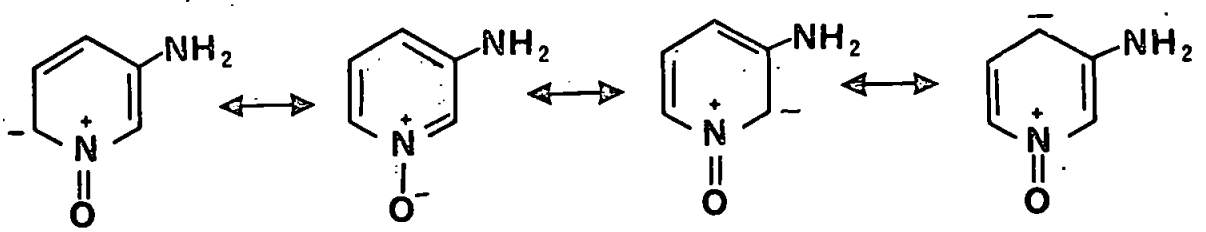
Another attempt at producing a new derivative of a known system and at the same time trying to extend the scope of the Bischler reaction was made using 3-aminopyridine-N-oxide hydrochloride (73). This was produced from 3-aminopyridine as shown in Scheme 16.



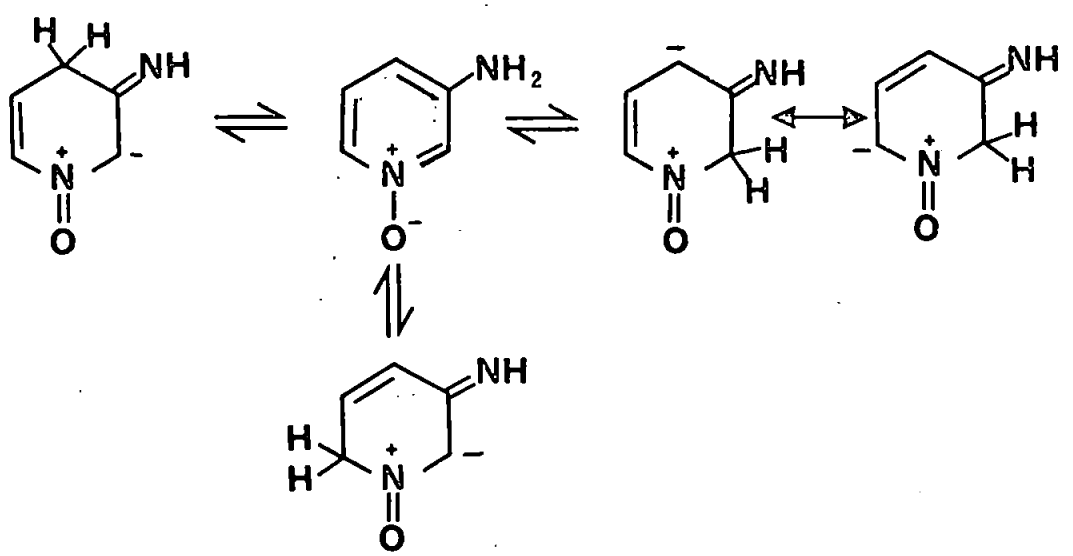
(73)

The conversion to the acetyl derivative was done by the method of Vogel[53] for aniline and the subsequent conversion to the N-oxide was by the method of Jaffe et al[54].

If we consider the resonance forms of 3-aminopyridine-N-oxide as shown overleaf it can be seen that the electron density is probably comparatively high in the 2, 4, and 6 positions and one would expect it to be greatest in the 4 position as this is adjacent to the amino group and furthest away from the pyridinium nitrogen. With this in mind 3-aminopyridine-N-oxide hydrochloride was reacted with 2-hydroxycyclohexanone under solvent conditions.

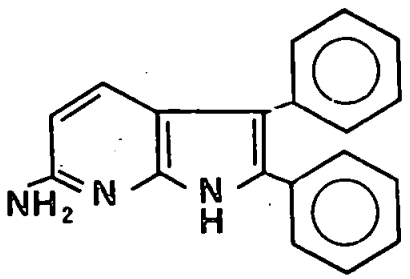


No product was formed only 3-aminopyridine-N-oxide hydrochloride was recovered in 72.8% yield, a melt reaction was not attempted as 3-aminopyridine-N-oxide hydrochloride is extremely heat and air sensitive. The reason for the failure of this reaction could be due to the contribution from the tautomers shown below



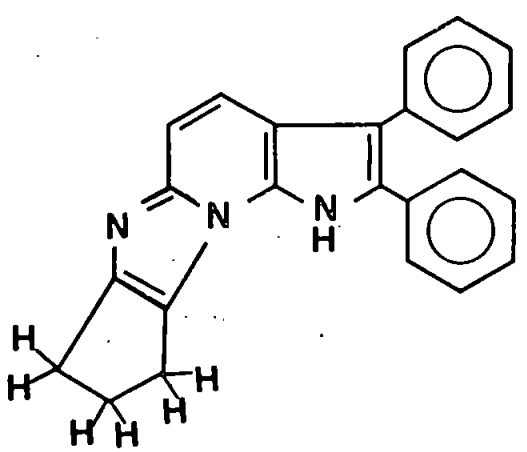
This would deactivate initial condensation with the carbonyl group and lead to a large recovery of unchanged substrate.

In an attempt to find the extent of the applicability of the Bischler reaction to the production of imidazopyridines, 2-chlorocyclopentanone was reacted under solvent conditions with 2,3-diphenyl-6-amino-1H-pyrrolo[2,3-b] pyridine (74) produced in 82.8% yield from benzoin and 2,6-diaminopyridine by the method of Bernstein et al[10].



(74)

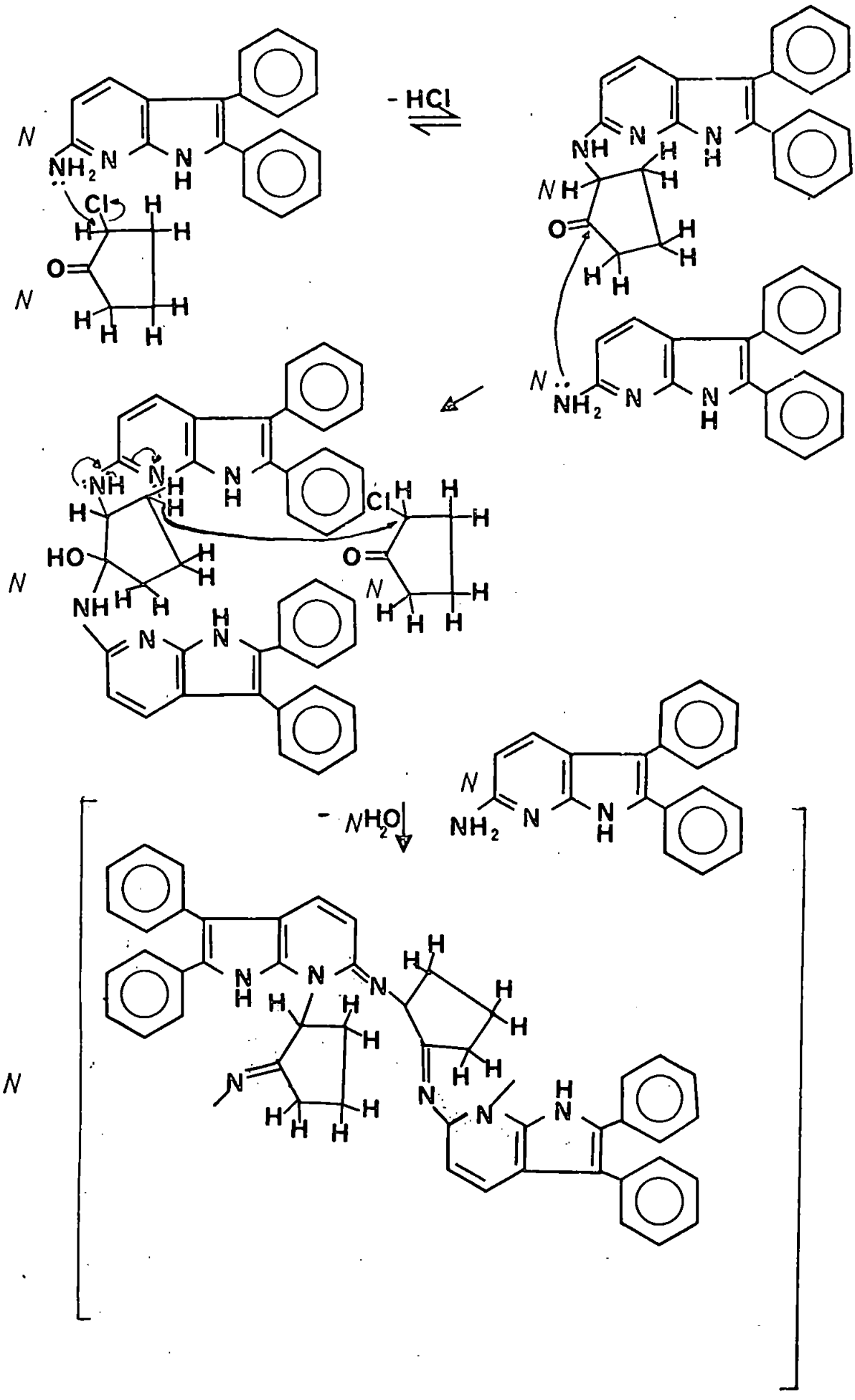
28.6% of (74) was recovered together with a complicated mixture (7 components) containing some (74). These results seem to reflect the importance of steric effect when considering reactions of this type. The intended reaction product (75) would involve the formation of a



(75)

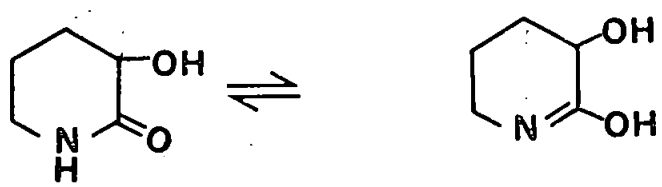
cyclopentene ring. To achieve this involves considerable deformation of the cyclopentane ring, and hence a large activation energy for the reaction to occur, this would explain the recovery of some unchanged (74) together with a large amount of complex reaction product. This product could result from partial condensation of 2-chlorocyclopentanone followed by polymerisation of the type shown in Scheme 17.

Scheme 17



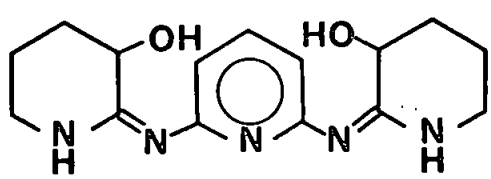
The infra red spectrum of the complex product was similar to (74).

Further to this work a condensation was also attempted under solvent and melt conditions between 2,6-diaminopyridine and 3-hydroxy-2-piperidone. From the solvent reaction 3-hydroxy-2-piperidone was recovered in 57.1% yield. The melt reaction did not yield product but probably unring-closed product which polymerised to give an intractable black solid during attempted work up, using acetic acid. The fact that no probable product could be detected by T.L.C. may well be a reflection of the electron withdrawing characteristics of the piperidine nitrogen, especially when structures such as (75) are considered, destabilising the carbonium ion formed in the transition state.



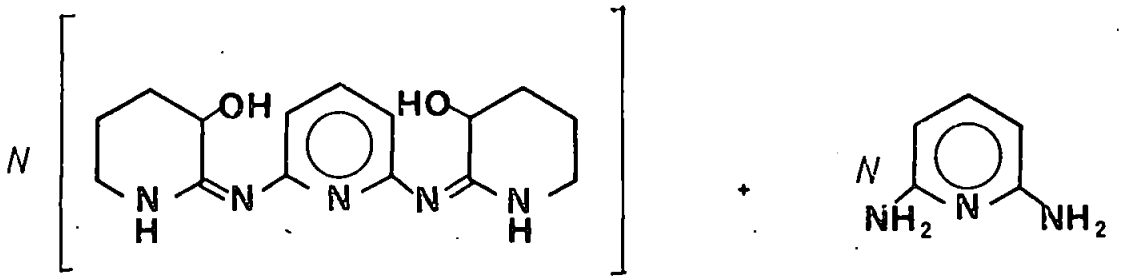
(75)

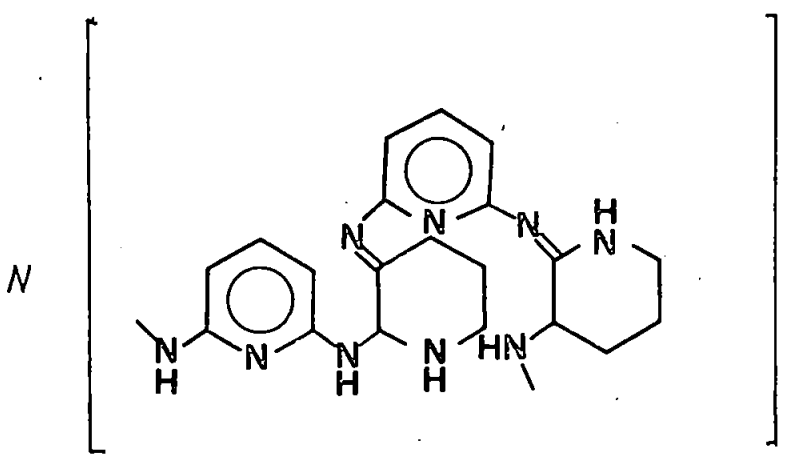
As no 2,6-diaminopyridine could be detected in the product nor any colour reaction for NH groups it is implied that initially a compound of the type (76) is formed.



(76)

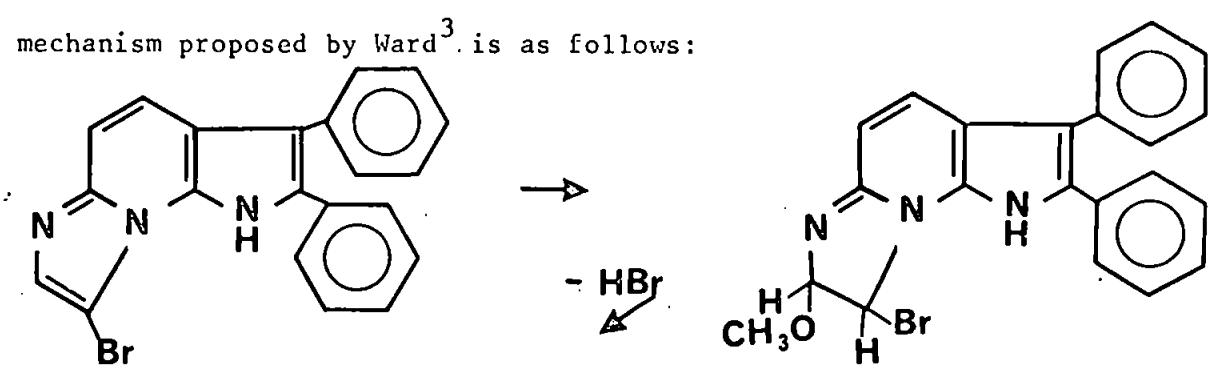
This in an acidic environment could react with excess 2,6-diamino-pyridine to give a polymer as shown overleaf:

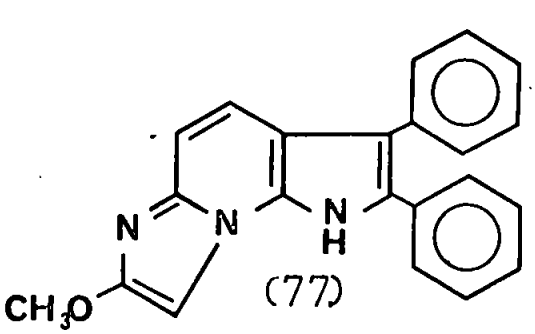




A number of mechanistic points have arisen from Wards[3] thesis and attempts were made to clarify them.

The first of these is the anomalous reaction of 2,3-diphenyl-8-bromo-1H-imidazo[1,2-a]pyrrolo[3,2-e]pyridine with methoxide ion in methanol. The mechanism proposed by Ward[3] is as follows:





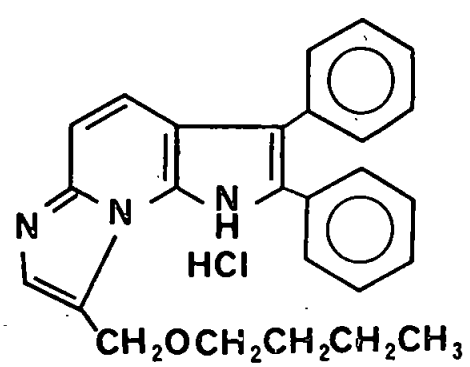
(77)

If the 7-methoxy derivative could be brominated at the 8-position then if the above mechanism operates there will be no reaction with methoxide ion as hydrogen bromide can no longer be eliminated.

A number of attempts were made at brominating the 7-methoxy derivative using chloroform and bromine at $0^{o}C$ but only a complicated mixture consisting of 8 compounds was found. Attempts to separate this mixture by use of preparative T.L.C., sublimation and column chromatography were unsuccessful. 2,3-Diphenyl-7-methoxy-1H-imidazo[1,2-a]pyrrolo[3,2-e] pyridine (77) is extremely susceptible to atmospheric oxidation and is very difficult to obtain in the pure state; it is thought that despite the mild conditions employed (77) is sufficiently sensitive to be partially oxidised by the bromine.

Time did not allow a further investigation into the use of other brominating agents.

In an attempt to produce a Mannich base Ward[3] treated 2,3-diphenyl-1H-imidazo[1,2-a]pyrrolo[3,2-e]pyridine with formaldehyde and dimethylamine hydrochloride under reflux in n-butanol and obtained 8-butoxymethyl-2,3-diphenyl-1H-imidazo[1,2-a]pyrrolo[3,2-e]pyridine hydrochloride (78).



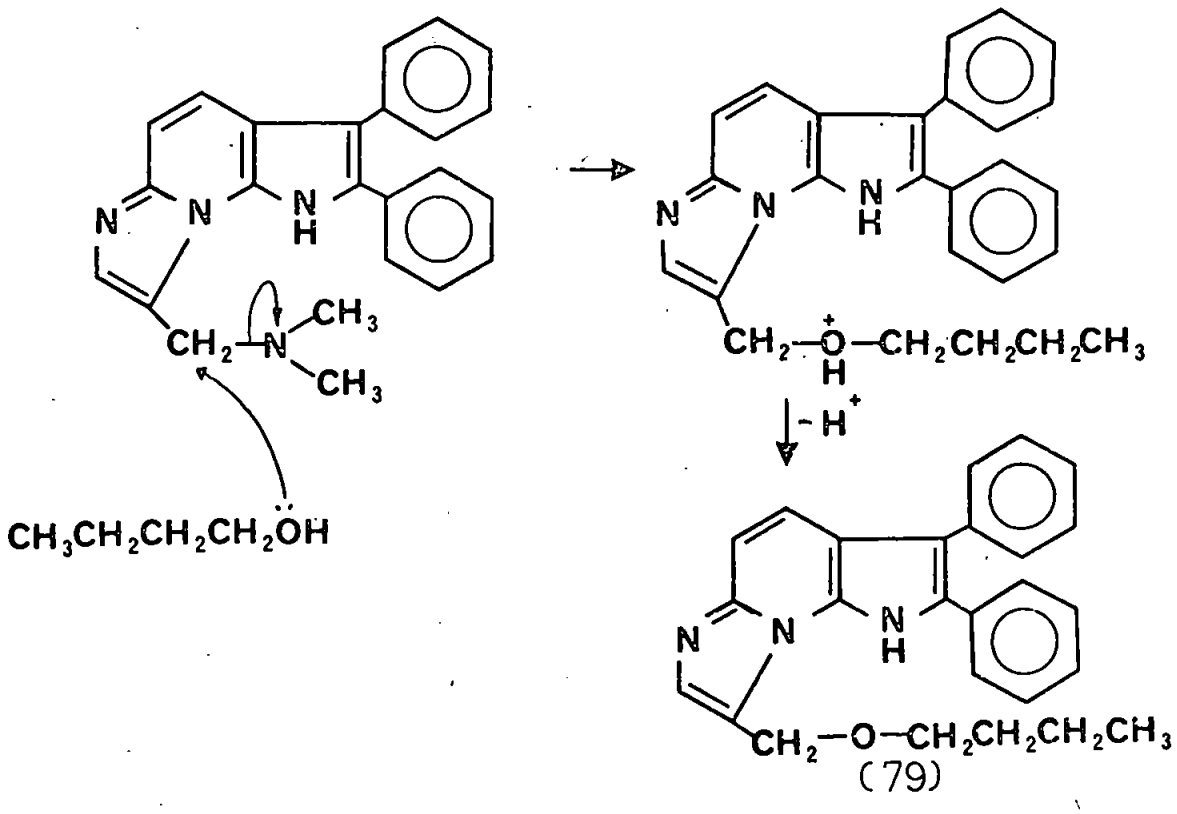
(78)

Ward[3] postulated that (78) was formed by the attack of $nCH_3CH_2CH_2CH_2$-O-CH_2^+ on the starting material

$$nC_4H_9OH + CH_2O \overset{H^+}{\rightleftharpoons} n\text{-}C_4H_9OCH_2OH_2^+ \overset{-H_2O}{\rightleftharpoons} n\text{-}C_4H_9OCH_2^+$$

However an equal possibility could be that the Mannich base is formed

and is substituted by n-butanol as shown in Scheme 18.



(79)

Two experiments should prove one of these mechanisms

1) If by treating 2,3-diphenyl-1H-imidazo[1,2-a]pyrrolo[3,2-e]pyridine with formaldehyde and hydrochloric acid in n-butanol, (79) is/is not produced we should know whether the reaction is proceeding by direct substitution or by substitution of the preformed Mannich base.
2) If the necessity of the preformed Mannich base is indicated then this can be confirmed by treating 2,3-diphenyl-8-dimethylaminomethyl-1H-imidazo[1,2-a]pyrrolo[3,2-e]pyridine with hydrochloric acid and n-butanol.

Experiment 1) gave only 2,3-diphenyl-1H-imidazo[1,2-a]pyrrolo[3,2-e] pyridine in 93.8% yield, showing that the preformed Mannich base is necessary for the reaction to occur.

Experiment 2) gave the novel 2,3-diphenyl-8-n-butoxymethyl-1H-imidazo-[1,2-a]pyrrolo[3,2-e]pyridine in 10.0% yield. This confirms the results of experiment 1) and shows that the mechanism shown in Scheme 18 is the one that is operating.

EXPERIMENTAL PROCEDURES

Melting points were measured on an electrothermal melting point apparatus and are uncorrected.

Attempted preparation of 2,4-diamino-6-methylpyridine using sodamide.

Liquid ammonia (100 cm^3) was condensed into a round-bottomed flask (250 cm^3). A catalytic amount of ferric nitrate hydrate (0.2 g) was added. Sodium (5.75 g 0.25 M) was then added over 0.5 hour. When the reaction was complete NN'-dimethylaniline (30 cm^3) was added and the flask was fitted for reflux. 2-Amino-6-methylpyridine (25 g 0.23 M) was added and the mixture heated for 15 hours at 160° - 170° under an atmosphere of dry ammonia. After cooling, the mixture was dissolved in water (500 cm^3) and the aqueous solution extracted with ether (5 x 200 cm^3). The extracts were combined and dried over anhydrous sodium sulphate. The extracts were then filtered and rotary evaporated to yield a brown oil. This oil was vacuum distilled to yield dimethylaniline (36°C - 42°C, 1 mm Hg 24 cm^3), and 2-amino-6-methylpyridine (90°C - 98°C, 1 mm Hg, 20.5 g, 82%), both being identified by their infra-red spectra. No diamine product could be identified in the residue or as an impurity in the above fractions by T.L.C. (silica gel, 2:1, toluene:acetone, using NN'-p-dimethylaminobenzaldehyde (1% w/v) in hydrochloric acid (50% v/v) as a locating agent).

A modification of the above procedures was attempted using a higher temperature and longer reaction time.

Ammonia (100 cm^3) was condensed into a round-bottomed flask (500 cm^3) and ferric nitrate hydrate (0.2 g) was then added. The addition of sodium (8.0g 0.38 M) over 0.5 hour was followed by the addition of NN'-dimethylaniline (100 cm^3) and the flask fitted for reflux. 2-Amino-6-methylpyridine (25 g 0.23 M) was then added and the mixture refluxed for 21 hours. After cooling a solution of sodium hydroxide (5% w/v, 500 cm^3) was added and the solution extracted with ether (7 x 200 cm^3). The extracts were combined, dried over anhydrous sodium sulphate, filtered and evaporated

to small bulk. The resultant oil was vacuum distilled to yield NN'-dimethyl-animiline (65°C - 73°C, 8 mm Hg, 91 cm^3) 2-amino-6-methylpyridine (98°C - 101°C, 8 mm Hg, 13 g, 52%) and an orange oil (145°C - 150°C, 8 mm Hg, 8.1 g). The first two were identified by their infra-red spectra.

T.L.C. using conditions above showed the orange oil to consist of a complex mixture of materials as follows:-

Series of spots Rf 0.01 - 0.1

spot Rf 0.31 Bright yellow

spot Rf 0.42 Faint yellow

However, attempts to purify this material by use of column chromatography (acidic alumina) met with no success. A large proportion of the oil was retained as a complex mixture of low Rf.

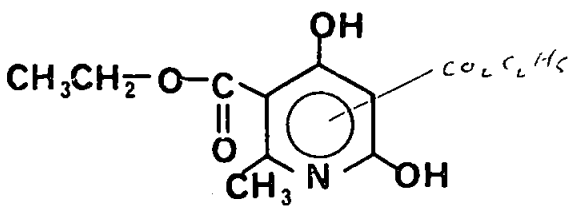
Another attempt involving sodamide was made by using the conditions stated in an American Patent[12].

Ammonia (250 cm^3) was condensed in a round-bottomed flask fitted with a potassium hydroxide guard tube. Ferric nitrate hydrate (0.2 g) was added followed by clean sodium (0.5 g). Dry air was bubbled through the mixture until the blue colour disappeared. Sodium (13.5 g) was then slowly added with stirring and the solution was stirred for 0.3 hour after the addition. The ammonia was allowed to evaporate off and 2-amino-6-methylpyridine (50 g 0.45 M) was added. The mixture was heated, with stirring at 260°C for 16 hours and then at 280° - 300° for 2 hours. After this time water (100 cm^3) was added at such a rate so as to keep the water boiling. The boiling was continued for 1 hour. The mixture was cooled on ice and the solid extracted with benzene. This yielded a brown oil (2 g) which was shown by T.L.C. to consist almost entirely of 2-amino-6-pyridine. The majority of the material had appeared to carbonise.

This experiment was repeated with 2-methylpyridine (41.9 g 0.45 M) with similar results. The brown oil obtained was shown by G.L.C. to contain mainly substrate (96%) with a small amount of what was though to be product.

Attempts by column chromatography (acidic alumina) to isolate this material met with no success.

Preparation of 2,4-dihydroxy-6-methylpyridine-5-carboxylic acid ethyl ester



The method is that of Knoevenagel and Fries[13]. A solution of sodium ethoxide was prepared by dissolving sodium (17.5 g) in absolute ethanol (257.4 cm^3) contained in a round bottomed flask (500 cm^3) fitted with a reflux condenser guarded by a calcium chloride guard tube. The flask was in an ice bath.

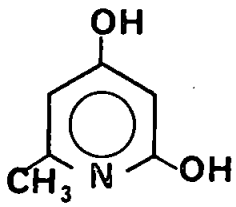
A Carius furnace was prepared at 150°C. Four glass Carius tubes were each loaded with a solution of ethyl-3-aminocrotonate (20 g) in diethylmalonate (25 g, 23 cm^3) together with the sodium ethoxide solution (45 cm^3) prepared above. The tubes were sealed and heated at 140°C - 150°C for 9 hours. A yellow crystalline solid was formed. The tubes were carefully broken open and the solid filtered at the pump and washed with ether. The sodium salt was then dissolved in the minimum quanitity of water to give an orange-brown solution. Dilute hydrochloric acid was then added and the free ester came down as a flocculent cream coloured precipitate. This was filtered off, dried at the pump and dried in a vacuum dessicator. This yielded 105 g (97%) of product (lit yield[13] 75.0%). The melting point after recrystallisation from aqueous ethanol was 212°C - 214°C (lit[13] 206°C - 207°C).

Infra-red (KBr) 2900, 1650, 1500, 1400, 1280, 1110, 890, 832, 660 and 530 cm^{-1}

NMR τ $(CD_3)_2SO$ - 1.3(1H, NH), 4.22(1H, s 3-H), 5.72(2H's, q, CH_2), 63 - 7.0 (diffuse OH), 7.82(3H's, s, 6-CH_3), 8.70(3 H's, t, CH_3 ester).

Mass Spec m/e 197(44.4%), 153(33.3), 152(50.0), 151(49.4), 125(100), 84(22.2), 83(41.7), 42(25.0).

Preparation of 2,4-dihydroxy-6-methylpyridine



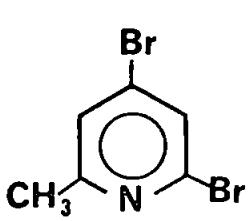
The method is according to Knoevenagel and Fries [13].

2,4-Dihydroxy-6-methylpyridine carboxylic acid ethyl ester (114 g) was refluxed with a solution of potassium hydroxide (171 g) in ethanol (1.5 dm^3) for 2 hours. The solution was filtered and the filtrate rotary evaporated to yield the potassium salt of the acid. The residue and filtrate were combined and dissolved in the minimum quantity of water. Concentrated hydrochloric acid (approximately 250 cm^3) was added and carbon dioxide was evolved. The product precipitated out. When excess acid had been added the solution was neutralised by using sodium carbonate solution (saturated) and then diluted with water to 3 DM^3. The product was filtered off and dried.

This yielded 65.9 g (39.7%) 2,4-dihydroxy-6-methylpyridine (lit[13] 70-80%). After recrystallisation with charcoal treatment from water the melting point was 345°C - 347°C.

Infra-red (KBr)	3100, 2900, 1650, 1600, 1450, 1350, 1268, 1232, 1178, 900, 830, 598 and 410 cm^{-1}.
NMR τ($(CD_3)_2SO$)	-0.5(1H, NH), 4.33(1H, m, 3-H), 4.55(1H, m, 5-H, 7.78(3H's, s, CH_3).
Mass Spec. m/e	125(100), 97(16.9), 96(15.0), 84(90.5), 42(27.9%).

Preparation of 2,4-dibromo-6-methylpyridine

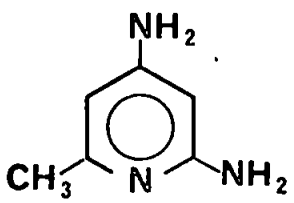


2,4-Dihydroxy-6-methylpyridine (29 g 0.23 M) was placed in 3 Carius tubes together with phosphorous oxybromide (82 g 0.28 M). The tubes were sealed and heated 130° - 140°C for 4 hours. The tubes were emptied with hot water

water and the product was steam distilled over. The liquid product solidified. This was separated off and the aqueous phase extracted with chloroform. The solid product was also dissolved in chloroform. The combined extracts were dried over anhydrous sodium sulphate and then rotary evaporated to dryness. The resulting oil was vacuum distilled and the fraction rolling at 78°C - 81°C at 5 mm Hg collected. This yielded 58.5 g of product (77.8% lit[10] 30.0%) of melting point 26°C - 27°C (lit[10] 27°C).

Infra-red(KBr)	3100, 2960, 2923, 1569, 1533, 1362, 1159, 845, 754 cm^{-1}.
NMR $\tau((CD_3)_2SO)$	2.20(1H s 3-H), 2.35(1H s 5-H), 7.53(3H s CH_3)
Mass Spec. m/e	251(86.0), 249(46.9), 172(97.7), 170(100), 145(11.7) 143(15.6), 91(50.8), 90(70.3), 64(46.9%).

Preparation of 2,4-diamino-6-methylpyridine



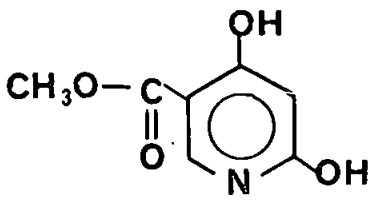
The method is based on that of Bernstein et al[10].

A stainless steel bomb, of the type described earlier, was loaded with 2,4-dibromo-6-methylpyridine (12.5 g 0.049 M) and 0.880 ammonia solution (33 cm^3) and heated for 40 hours at 205°C ± 10°C. After cooling the bomb was carefully opened and the contents filtered. The filtrate was made strongly alkaline with solid sodium hydroxide and extracted with chloroform (3 x 100 cm^3). The extracts were dried over anhydrous sodium sulphate and rotary evaporated to yield a light yellow solid which darkened on exposure to air. The product was recrystallised from chloroform after charcoal treatment to yield a light yellow solid, melting point 112°C - 114°C (lit[10] 117°C - 118°C) in 66.7% (4.1 g) yield (lit[10] 54.0%).

Infra-red (KBr)	3360, 1625, 1572, 1471, 1245, 1195, 994, 860 cm^{-1}.
NMR $\tau((CD_3)_2SO)$	4.30(1H d 5-H J_{35} 2Hz), 4.54(1H d 3-H J_{53} 2Hz) 4.67(2H's m 2-NH_2), 4.83(2H's m 4-NH_2), 7.93 (3H's s CH_3)

Mass Spec. m/e 123(100), 85(82.0), 72(48.0), 58(40.0) 57(56.0), 44(42.0), 43-5-(34.0%).

2,4-Dihydroxypyridine-5-carboxylic acid methyl ester



This compound was produced by Den Hertog's[18] modification of Erreras[19] method for the ethyl ester.

In a round bottomed flask (1 litre) was placed acetone dicarboxylic acid dimethyl ester (174 g 1 M) triethyl orthoformate (148 g 1M) and acetic anhydride 204 g 2 M). The mixture was vigorously stirred for 1 hour. The bright orange contents of the flask were then vacuum distilled until the temperature of the distillation was 46°C at 2 mm of mercury. The residue was cooled in ice and then mixed with 0.880 ammonia solution (280 cm^3). A violent reaction ensues and after a minute the contents changed to a solid yellow crystalline mass. The mass was filtered off and made into a slurry with a little water, hydrochloric acid (25%) was added until the solution was just acid. The solid was then recrystallised from benzene (500 cm^3) to yield 2,4-dihydroxypyridine-5-carboxylic acid methyl ester 99.8 g (59.1%). Melting point 243°C - 245°C).

Infra-red (KBr) 3080, 2800, 1695, 1662, 1440, 1329, 1280, 1233, 1209, 960, 789, 658, 539 cm^{-1}

NMRγ ($(CD_3)_2SO$) -1.2(1H diffuse NH), 1.93(1H s 6-H), 4.35(1H s 3-H), 6.17(3H's s CH_3)

Mass Spec. m/e 169(83.2), 128(43.5), 127(100), 109(55.3), 81(16.5), 70(45.9%).

Attempted decarboxylation of 2,4-dihydroxypyridine-5-carboxylic acid methyl ester

The method is that of Kneovenagel and Freis[13] for the preparation of 2,4-dihydroxy-6-methylpyridine.

2,4-Dihydroxypyridine-5-carboxylic acid methyl ester (55.7 g 0.33 M) was placed in a round bottomed flask (1 litre) and dissolved in a solution of

potassium hydroxide (75 g 1.34 M) in ethanol (500 cm^3). The mixture was refluxed for 2 hours. The solution was cooled in an ice-bath and then filtered. The filtrate was rotary evaporated to yield the potassium salt of the acid. The filter cake and the filtrate residue were combined and dissolved in a small quantity of water, concentrated hydrochloric acid was then added to PH7 and the product filtered off and dried. This gave 2,4-dihydroxypyridine-5-carboxylic acid in 99.9% yield. Melting point 314°C - 316°C.

Infra-red (KBr)	3020, 2480, 1690, 1612, 1474, 1291, 1272, 846, 795, 643 cm^{-1}.
NMR $\tau((CD_3)_2SO)$	1.97(1H s 6-H), 2.25(1H diffuse COOH), 4.34 (1H s 3-H).
Mass Spec. m/e	155(92.8), 138(21.0), 137(100), 123(18.0), 109(99.8), 98(13.8), 97(18.0), 81(29.9), 71(16.8), 70(28.1), 69(68.3%).

An attempt was made using Erreras[19] method of decarboxylation for the ester but on a large scale.

2,4-Dihydroxypyridine carboxylic acid methyl ester (7.5 g 0.044 M), and hydrochloric acid (26 cm^3 0.3 M) were placed in a glass carius tube and heated at 160°C for 2 hours and at 190°C - 200°C for 1 hour. The glass tube exploded.

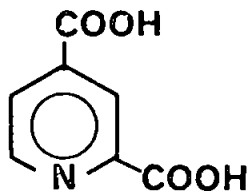
The experiment was repeated using stainless steel bombs but the acid dissolved the seal and iron was taken into solution. Product obtained by neutralising the acid solution with sodium hydroxide solution (10%) was severely contaminated with iron. Attempts to separate the iron met with no success.

Trials were carried out to find a suitable material to make a pressure vessel with. A sample of the material was heated at 190°C - 200°C for 50 hours in a small thick walled glass tube. The loss in weight per cm^2 was calculated. The results were as follows:-

Hastalloy 'B'	0.123 g cm^{-2}
Nickel 200	0.082 g cm^{-2}

Both of these results were considered too high.

Preparation of pyridine-2,4-dicarboxylic acid



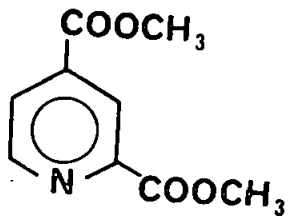
The method is that of Clemo and Metcalfe[21] with slight modifications. A solution of potassium permanganate (300 g) in water (10 litres) was placed in a round bottomed flask (20 litre) fitted with 2 reflux condensers. 2,4-Dimethylpyridine (100 g) was then added and the solution heated at 80°C for 20 hours. A further addition of potassium permanganate (300 g) in water (5 litres) was made and the solution was heated at 80°C for a further 100 hours. The solution was filtered and evaporated to 10 litres and acidified, with dilute sulphuric acid, to litmus paper. The solution was evaporated to 1 litre and ethanol (1 litre) was added. The solution was filtered to removed potassium sulphate and diluted with water to 5 litres. Dilute silver nitrate solution was then added and the precipitate of the silver salt was filtered off and washed with water. The salt was suspended in hot water (2½ litres) and hydrogen sulphide bubbled through the stirred suspension. The precipitated silver sulphide was filtered off and the filtrate allowed to cool. Crystals of the acid came down. These were filtered off and dried. The mother liquor was evaporated to small bulk to obtain a further crop of white crystals. The yield of acid was 42 g (27%) (lit[21] 50.8%) of melting point 248°C - 250°C (lit[14] 248°C - 250°C).

Infra-red (KBr) 3080, 2900, 1703, 1612, 1290, 1248, 1180, 768, 699 cm^{-1}.

NMRγ ($(CD_3)_2SO$) 1.05(1H d 6-H J_{56} 5Hz), 1.56(1H d 3-H J_{53} 2Hz), 1.93 (1H dd 5-H J_{65} 5Hz J_{35} 2Hz).

Mass Spec. m/e 167(3.6), 123(100), 122(18.2), 78(21.3), 77(13.2%)

Preparation of pyridine-2,4-dimethylcarboxylate



The method is based on that of Meyer and Tropsch[14].

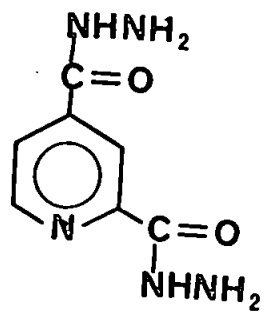
Pyridine-2,4-dicarboxylic acid (20 g 0.11 M) was placed in a round bottomed flask (250 cm^3) fitted with a reflux condenser with a calcium chloride guard tube. To this was added methanol (100 cm^3 3.1 M) and concentrated sulphuric acid (20 g). The mixture was refluxed for 3 hours. The excess methanol was evaporated off and the solution made alkaline with saturated sodium carbonate solution. The resulting solution was extracted with ether and evaporated to dryness. The resulting light amber oil was allowed to crystallise. This yielded 16.5 g of product (70.8% yield lit[14] not given) of melting point 56°C - 58°C (lit[14] 58°C).

Infra-red (KBr) 2960, 2925, 1740, 1723, 1440, 1303, 1258, 1096, 983, 760, 700 cm^{-1}.

NMR $\gamma((CD_3)_2SO)$ 1.05(1H d 6-H J_{56} 5H_z), 1.62(1H d 3-H J_{56} 2H_z), 1.93 (1H dd 5-H J_{65} 5H_z J_{35} 2H_z), 6.07(6H's s CH_3).

Mass Spec. m/e 195(6.5), 165(27.3), 164(22.1), 138(20.8), 132(100), 136(39.0), 108(14.3), 77(13.0%).

Preparation of pyridine-2,4-dicarboxylic acid dihydrazide



The method is based on that of Meyer and Tropsch[14].

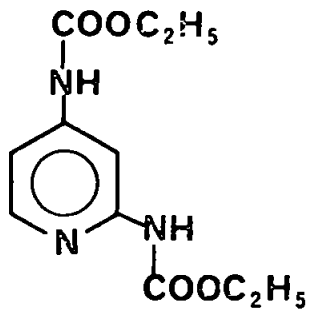
Pyridine-2,4-dimethylcarboxylate (15 g 0.077 M) was dissolved in ethanol (100 cm^3). Hydrazine hydrate (10 g 0.2 M) was added and the solution stirred for 60 hours in a stoppered flask at room temperature.

A green yellow precipitate came down, this was filtered off and dried

at 100°C. The product weighed 14.2 g (94.7% yield, lit[14] not given) and melted at 254°C - 256°C (lit[14] 256°C).

The dihydrazide was used without further purification.

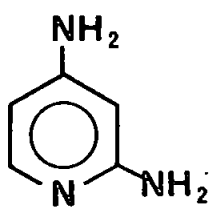
Preparation of 2,4-diurethylpyridine



The method is based on that of Meyer and Tropsch[14].

Pyridine-2,4-dicarboxylic acid dihydrazide (14 g 0.072 M) was dissolved in hydrochloric acid (75 cm^3 2 molar) and water (200 cm^3) in a round bottomed flask (500 cm^3). The mixture was cooled in an ice-salt bath and ether (200 cm^3) was added. Sodium nitrite solution (16 g in 50 cm^3 of water) was slowly added keeping the temperature below 10°C. The intermediate azide separated as a white froth. The ether layer was separated after filtering the mixture. The filtered azide was dissolved in ether and the aqueous layer was extracted with ether. All the ether extracts were combined and washed with saturated sodium bicarbonate solution (200 cm^3) and then dried over anhydrous sodium sulphate. After filtration the ether was carefully rotary evaporated to dryness. Absolute ethanol (150 cm^3) was then added and the mixture refluxed for 3 - 4 hours. The solution was filtered to remove impurities and left to cool. White crystals came down. The mother liquor was evaporated to small bulk to obtain a further crop of crystals. The total weight of product was 9.8 g (54.1% lit[14] not given) of melting point 166°C - 168°C (lit[14] 170°C). The product was used without further purification.

Preparation of 2,4-diaminopyridine



The method is based on that of Meyer and Tropsch[14] with some modification.

A solution of 2,4-diurethylpyridine (9.8 g 0.039 M)

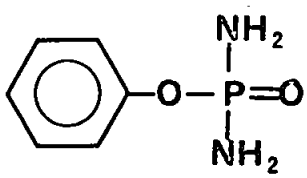
in ethanol (140 cm^3) was refluxed in a round bottomed flask (500 cm^3). To this solution was added a solution of potassium hydroxide (11.2 g 0.2 M) in water (14 cm^3) and ethanol (56 cm^3). The flask contents turned green yellow and after refluxing for 2 hours a salt was precipitated. The solution was made acid with concentrated hydrochloric acid to break down the potassium salt and then made strongly alkaline with solid potassium hydroxide. The solution was evaporated to small bulk. Anhydrous calcium sulphate was added and the resulting solid extracted with sodium dried benzene in a soxhlet apparatus for 50 hours. The benzene solution was rotary evaporated to dryness. The resulting diamine was crystallised from benzene. This yielded white crystals (1.3 g 31% yield) of melting point 105°C - 107°C (lit[14] 107°C).

Infra-red (KBr) 3410, 3350, 3240, 1632, 1605, 1552, 1463, 1270, 1235, 990, 970, 831, 818 cm^{-1}.

NMR $\gamma((CD_3)_2SO)$ 2.58(1H d 6-H J_{56} 6Hz), 4.22(1H dd 5-H J_{65} 6Hz J_{35} 2Hz), 4.44(1H d 3-H J_{53} 2Hz) 4.58(2H's s 2-NH_2), 4.83(2H's s 4-NH_2).

Mass Spec. m/e 109(100), 82(81), 69(54.5), 55(22.0), 54(26.5), 41(23.6), 40(14.9%).

Preparation of phenyl diamidophosphate



This method is a modification of the work by Audrieth and Toy[22].

The conditions below are those which should give the maximum yield of phenyl diamidophosphate. Phosphorous oxychloride (76.7 g 0.5 M) was dissolved in chloroform (375 cm^3) in a round-bottomed flask (1 litre). The solution was cooled in an ice-salt bath. A solution of phenol (47 g 0.5 M) in pyridine (125 cm^3) was added dropwise so that the temperature remained at -2°C ± 2°C. The mixture was stirred for 0.25 hour and then dropped into liquid ammonia (250 cm^3). The solution was filtered and the filtrate was

rotary evaporated to dryness. The retained solid was washed with water and recrystallised from ethanol. The filtrate residue was combined with the evaporated mother liquor from the first recrystallisation and the combined solids were extracted with hot chloroform. This left the remainder of the phenyl diamidophosphate behind. The hot chloroform solution was filtered free from phenyl diamidophosphate and allowed to cool. White crystals of diphenyl amidophosphate came down. The residue phenyl diamidophosphate was recrystallised from ethanol. This gave 30 g (yield 34.9%) of phenyl diamidophosphate of melting point 199°C - 200°C (lit[22] 183°C - 185°C) and diphenyl amidophosphate (10 g 16.1%) of melting point 138°C - 140°C (lit[22] 145°C - 146°C).

The overall yield of the reaction based on available phenol was 50.8%. It was thought that a larger volume of liquid ammonia would result in a higher yield of product. The product was used without further purification.

Attempted reaction of 2,4-dihydroxy pyridine with phenyl diamidophosphate

A mixture of 2,4-dihydroxy-6-methylpyridine (1.25 g 0.01 M) and phenyl diamidophosphate (1.9 g 0.011 M) was heated in an open flask until a clear melt was obtained. The melt was then heated at 235°C - 240°C for 0.3 hours and then cooled, pulverised and digested with sodium hydroxide solution (50 cm^3 of 10%) at 90°C. The solution was filtered free from tar globules and the filtrate extracted with ether. This yielded a yellow oil.

The experiment was repeated but under a nitrogen atmosphere and by digesting with 0.880 ammonia solution (20 cm^3) and evaporating to dryness before ether extraction. This yielded a yellow oil.

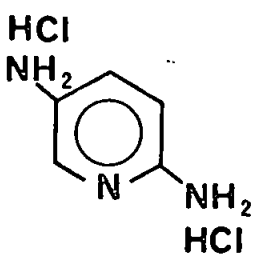
T.L.C. (2:1 toluene:acetone) on the two products showed them both to consist of mainly dark material at a very low Rf together with 2,4-dihydroxy-6-methylpyridine and phenyl diamidophoshate.

A solvent reaction was attempted as follows, 2,4-dihydroxy-6-methyl-

pyridine (1.25 g 0.01 M), phenyl diamidophosphate (4.0 g 0.048 M) and diphenyl ether (200 cm^3) were heated for 20 hours at 245°C. After cooling to room temperature the mixture was filtered and the filtrate diluted with dichloromethane (250 cm^3) and dry hydrogen chloride passed through the solution no appreciable precipitate of hydrochloride was obtained, however a large amount of dark coloured material was filtered off. A shorter reflux time was indicated. The experiment was repeated using a 1 hour reflux time but with the same results. T.L.C. failed to indicate any amine present in the solid or the filtrate.

PREPARATION OF OTHER DIAMINOPYRIDINES

Preparation of 2,5-diaminopyridine dihydrochloride



This method is an attempt at producing the diamine by catalytic reduction. A suspension of 2-amino-5-nitropyridine (25 g 0.18 M) in absolute ethanol (450 cm^3) was stirred with 5% palladised charcoal (5.5 g) for 20 hours under an atmosphere of hydrogen. Treatment with decolourising charcoal and filtration at boiling point gave a blood red solution which on cooling gave fawn crystals. The crystals were filtered off and the mother liquor evaporated to small bulk to give a second crystal crop. The product was recrystallised from absolute ethanol, and was found to be 2-amino-5-nitropyridine (20.2 g 80.8% recovery).

The next method is based on that of Gomez-Revilla[23].

In a 3 necked round bottomed flask (2 litre) fitted with a vibromix stirrer, thermometer and reflux condenser was placed a solution of 2-amino-5-nitropyridine (25 g 0.18 M) in concentrated hydrochloric acid (225 cm^3) and water (225 cm^3). Upon the addition of granulated tin (78 g), added in one portion, the solution warmed up to 90°C and with stirring was allowed to cool to 50°C. The solution was then refluxed for 3 hours and then allowed to stand overnight. Crystals of the tin complex came down. These were

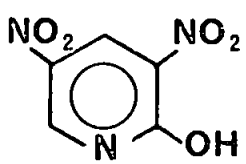
filtered off and dried.

The complex (54 g) was suspended in hot water (1350 cm^3) and decomposed with hydrogen sulphide. The precipitated tin sulphide was filtered off through celite and the resultant solution evaporated to dryness in a rotary evaporator. The crude dihydrochloride was recrystallised from water (38.8 cm^3) and ethanol (194 cm^3) and dried at 110°C.

This yielded 11 g of 2,5-diaminopyridine dihydrochloride (33.7% lit^{23} 62.0%) of melting point 247°C - 248°C (lit^{23} 244°C - 245°C).

The product was used without any further purification.

Preparation of 2-hydroxy-3,5-dinitropyridine



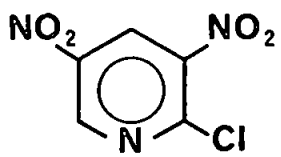
The method is that of Plazek[26]. 2-Hydroxy-5-nitropyridine (20 g 0.25 M) was gradually added with stirring over a period of about 0.5 hour to a mixture of fuming sulphuric acid (40 cm^3 of 40% oleum) and fuming nitric acid (40 cm^3 specific gravity 1.52) held at 80°C. Addition resulted in a vigorous reaction and with a considerable rise in temperature but the addition was such that the temperature was between 80°C - 90°C. After addition the mixture was kept at 100°C on a steam bath for 0.5 hour and then the mixture was poured into ice-water (300 cm^3). On standing for 12 hours a brilliant yellow crystalline precipitate came down, this was filtered off and washed with water. After drying at 110°C the product was pure enough for further work. Yield 14 g (44.8% lit^{26} 44.8%) of light yellow product of melting point 175°C - 176°C (lit^{26} 176°C).

Infra-red (KBr) 3230, 3055, 3020, 1690, 1658, 1570, 1528, 1360, 1340, 1308, 1230, 1137, 818, 753, 720, 707, 590, 531 cm^{-1}

NMR τ($(CD_3)_2SO$) -1.54 (1H diffuse NH) 0.97(1H s 2-H), 1.0(1H, s 4-H).

Mass Spec. m/e 185(100), 139(24.8), 93(11.9), 92(9.5), 65(16.7), 54(21.4%).

Preparation of 2-chloro-3,5-dinitropyridine

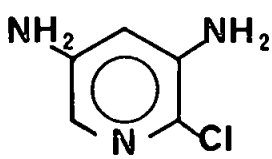


The method is that of Plazek[26]. 2-Hydroxy-3,5-dinitropyridine (20 g 0.16 M) mixed with phosphorus pentachloride (30 g 0.14 M) and moistened with phosphorus oxychloride (1 cm^3) was heated over a bunsen flame to start the reaction and heated on a steam bath for 0.3 hour. The mixture melted and hydrogen chloride was liberated. The mixture was poured onto crushed ice (10.0 g) and was stirred until the ice melted. A powdery yellow precipitate separated out. This was filtered off and washed with water. After drying the product was boiled with benzene (40 cm^3) and the hot solution filtered to remove a small amount of insoluble impurity. Addition of 60^o - 80^o petroleum ether precipitated out the bulk of the product, which was then filtered off and washed with benzene/petroleum ether. The remainder was removed by evaporation of the solvents.

This yielded 8.4 g of product (26.2% lit[26] 27%) of melting point 66^oC - 68^oC (lit[26] 68^oC).

This product was used without further purification.

Attempted preparation of 2-chloro-3,5-diaminopyridine



The method used is based on that of Plazek [26] for 3,5-diaminopyridine. 2-Chloro-3,5-dinitropyridine (8 g (0.039 M) was dissolved in concentrated hydrochloric acid (64 cm^3) and water (16 cm^3). Powdered zinc (32 g) was

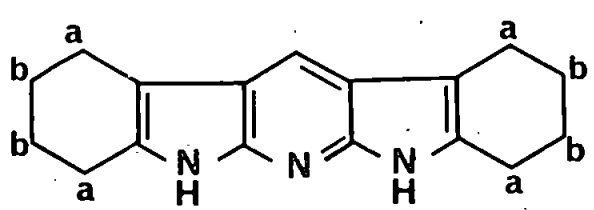
added. The mixture heated spontaneously and boiled, after the reaction subsided the mixture was refluxed for 1 hour and water (160 cm^3) was added. The remaining zinc was filtered off and aqueous potassium hydroxide solution (50%) was added to the filtrate until the solution was basic enough to redissolve any zinc hydroxide initially precipitate. At this stage the solution was a dark brown colour. An attempt was made to extract the solution with ether but the ether solubility of the product was low.

The solution was rotary evaporated to dryness and extracted with glacial acid (3-chloro-2,6-diaminopyridine is very soluble in acetic acid). The acetic acid solution was filtered free of inorganic material and evaporated to dryness. T.L.C. showed that a product was present but there were also present 3 other amines together with inorganic material. Attempts at purifying the product by column chromatography (acidic alumina petrol packed) were partially successful. As time was limited and the reaction was not a 'clean' one it was decided to abandon this approach.

Tin and hydrochloric acid or palladised charcoal and hydrogen would probably give a cleaner reaction

DIAMINOPYRIDINES IN THE BISCHLER REACTION

Preparation 1,2,3,4,5,7,8,9,10,11,-decahydropyrido[2,3-b:6,5-b']diindole



2,6-Diaminopyridine (3.0 g 0.025 M) and concentrated hydrochloric acid (2 cm^3 0.02 M) were heated together and distilled to remove excess water. 2-Hydroxycyclohexanone (5.6 g 0.05 M) was then added and the temperature raised to 130° - 140°C whilst the mixture was stirred. The mixture was kept at this temperature for 0.5 hour and then at 180°C -190°C

for a further 0.5 hour with constant stirring.

The melt was cooled, pulverised and stirred with excess hydrochloric acid (1 molar) for 1 hour. The solution was filtered and stirred with excess ammonia solution and recrystallised from glacial acetic acid. This yielded 3.8 g (56.7%) of product of melting point 282°C - 284°C.

Infra-red (KBr) 3450, 3170, 2910, 2330, 1600, 1403, 1255, 1208, 811, 633 cm^{-1}.

NMR τ (T.F.A.) 0.45(2H's diffuse 1,7-NH's), 1.80(1H s 6-H), 7.24(8H's m a-CH_2's), 8.02(8H's m b-CH_2's)

Mass Spec. m/e 265(100), 264(53.7), 238(21.8), 237(98.8), 209(47.5), 105(43.8%)

Elemental Analysis Theory: C:78.0 H:7.2 N:15.8%

Found: C:78.2 H:7.0 N:15.8%

Preparation of 4-hydroxyoctan-5-one

$CH_3CH_2CH_2CHOH$
$CH_3CH_2CH_2C{=}O$

This method is that of Snell and McEwain[27].

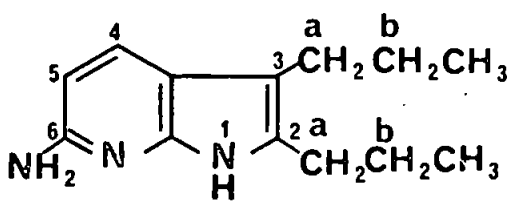
Ethyl-n-butanoate was first purified by washing with 10% aqueous sodium carbonate solution and then washing twice with saturated sodium chloride solution. The ester was then dried overnight with anhydrous potassium carbonate and after filtration was dried for 24 hours over phosphorus pnetoxide. The ester was then distilled directly from the phosphorus pentoxide and the fraction boiling between 121°C and 123°C taken.

Into a dry reaction vessel (1 litre) fitted with a fast mechanical stirrer and reflux condenser fitted with a drying tube was placed pure xylene (50 cm^3) and sodium (30.6 g 13 M). The sodium was finely powdered by heating the vessel until the metal melts and then stirring the mixture until it cools. The xylene was then decanted off and the sodium washed with sodium dried diethyl ether (5 x 50 cm^3). Ether (400 cm^3) was then

added and the vessel fitted with a dropping funnel. The mixture was stirred and ethyl-n-butanoate (62.0 g 0.54 M) was slowly added so that the mixture gently refluxed and the stirring continued until the sodium had changed to a white yellow solid. The mixture was refluxed for a further hour and then cooled in an ice bath. A cooled solution of concentrated sulphuric acid (70 g) in water (117 cm^3) was added and the mixture stood in the ice bath until the lower layer of hydrated sodium sulphate solidified. The ether solution was filtered off and the sodium sulphate crystals were washed with ether (50 cm^3). The combined washing and solution were washed with aqueous sodium carbonate solution (35 cm^3 20% w/v) and dried with anhydrous potassium carbonate overnight. The ether was distilled off and the residue vacuum distilled the fraction boiling at 80°C - 86°C at 12 mm of mercury was collected. This yielded 25 g of product (65.5% lit[27] 65% - 70%).

Infra-red 3470, 2960, 2875, 1709, 1438, 1091, 997 cm^{-1}.

Preparation of 6-amino-2,3-di-n-propyl -1H-pyrrolo[2,3-b]pyridine



2,6-Diaminopyridine (10.9 g 0.1 M), 4-hydroxyoctan-5-one (15 g 0.11 M) and concentrated hydrochloric acid (0.5 cm^3) in toluene (50 cm^3) were refluxed for 24 hours in a Dean and Stark apparatus. On cooling a brown crystalline solid separated out. This was filtered off and the solution evaporated to dryness to yield a brown oil. T.L.C. indicated a mixture of amines and other products. The products were purified by column chromatography (acidic alumina petrol packed). This gave the almost pure product by T.L.C. (product spot R_f 0.08 silica gel 2:1 toluene:acetone pink to 4-NN-dimethylaminobenzaldehyde) as a brown oil 2.5 g (11.6%). The oil was taken up in benzene (50 cm^3) and hydrogen chloride bubbled through. The

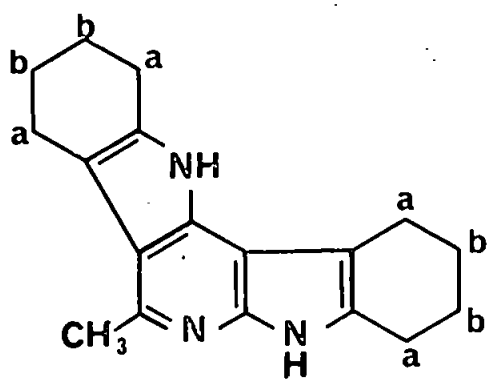
hydrochloride taken up in water (50 cm^3) and ammonia bubbled through and the solution extracted with fresh benzene (50 cm^3) which was then dried over anhydrous sodium sulphate, filtered, and evaporated to dryness. This yielded a fawn crystalline solid of melting point 66°C - 68°C after drying in a vacuum desicator. The yield was 0.65 g (3.0%).

Infra-red (KBr) 3470, 3380, 3180, 2970, 2880, 1620, 1455, 1409, 1353, 1295, 1120, 685 cm^{-1}.

NMR ($(CD_3)_2SO$) -0.29(1H s NH), 2.58(1H d 4-H J_{54} 9H_z), 3.79(1H d 5-H J_{45} 9H_z), 4.60(2H's s NH_2), 4.47(4H's m a-CH_2's) 8.38(4H's m b-CH_2 s), 9.07(6H's t CH_3's).

Mass Spec. m/e 217(36.9), 189(4.2), 188(100), 173(2.6), 160(4.2), 159(6.3), 146(3.2).

Preparation of 1,2,3,4,5,8,9,10,11,12-decahydro-7-methylpyrido[2,3-b:4,5-b] diindole



2,4-Diamino-6-methylpyridine (1.23 g 0.01 M), 2-hydroxycyclohexanone (1.25 g 0.011 M), concentrated hydrochloric acid (0.2 cm^3) and toluene (50 cm^3) were refluxed in a Dean and Stark apparatus for 18 hours. The hot toluene was decanted free of the tarry residue and cooled in ice. The tarry residue was extracted once more with hot toluene (50 cm^3), the combined extracts were then rotary evaporated to dryness to yield a brown solid. The tarry residue was dissolved in ethanol, treated with decolourising charcoal and evaporated to dryness. T.L.C. (silica gel 2:1 toluene:acetone) revealed the following:

Tarry residue:- Mainly 2,4-diamino-6-methylpyridine 0.89 g (72% recovery overall).

Toluene soluble material:- Some 2,4-diaminopyridine together with a spot at R_f 0.04 pink to 4-NN-dimethylaminobenzaldehyde (Ehrlichs reagent) probably product together with 3 unidentified components.

As the reaction appears to have gone only in very small yield a melt reaction was attempted as follows:

A mixture of 2,4-diamino-6-methylpyridine (1.23 g 0.01 M) and concentrated hydrochloric acid (1 cm^3 0.011 M) was heated to dryness. To the residue obtained was added 2-hydroxycyclohexanone (1.25 g 0.11 M) and the mixture was stirred at 130°C - 140°C for 0.5 hour then at 180°C - 190°C for 0.5 hour. The melt was cooled and pulverised and dissolved in dilute hydrochloric acid (10% v/v). The solution was filtered and made basic with ammonia solution (0.880 specific gravity). A khaki oily solid was precipitated. T.L.C. under conditions used previously on this material showed it to consist of 3 product at R_f 0.02, 0.2, 0.3 faint pink to Ehrlich's reagent and one other product at R_f 0.85 strong pink to Ehrlich's reagent.

The solid was heated with methanol (25 cm^3) whereupon the impurities went in solution and a white solid was left behind. The product was filtered off and dried at 110°C. The product weighed 0.54 g (35.0%) and melted at 350°C - 352°C.

Infra-red (KBr) 3140, 3060, 2930, 2850, 1645, 1555, 1440, 1371, 1327, 1240, 1203, 820 cm^{-1}.

NMRτ(CF_3CO_2H) ÷0.68(2H's diffuse NH's), 7.04(3H's s CH_3), 7.15 (8H's m a-CH_2's), 7.98(8H's m b-CH_2's).

Mass Spec. m/e 279(100), 278(40.0), 252(10.0), 251(35.0), 250(12.0) 223(8.0), 222(18.0), 201(5.0), 139(12.0), 125(10.0%).

Elemental Analysis theory C=77.5 H=7.5 N=15.0%

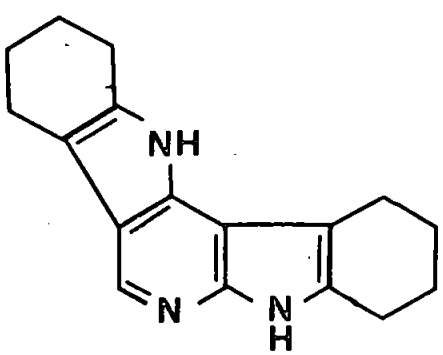
found C=77.7 H=7.1 N=15.2%

Reaction between 2,4-diamino-6-methylpyridine and 2-hydroxybutan-3-one

2,4-Diamino-6-methylpyridine (0.88 g 6.7 M Mol) was heated to dryness with concentrated hydrochloric acid (1 cm^3). 2-Hydroxybutan-3-one (0.60 g 6.7 M Mol) was added and the melt heated and stirred at 130°C - 140°C for 0.5 hours then at 180°C - 190°C for 0.5 hours. The melt was cooled, pulverised and dissolved in water and neutralised with saturated potassium carbonate solution. The resulting tar was boiled with water (3 x 50 cm^3) and the solution allowed to cool and extracted with chloroform (3 x 50 cm^3). After drying over anhydrous sodium sulphate and filtering the combined extracts were evaporated to dryness to yield a brown tar. Attempts at separation by column chromatography and crystallisation were not successful. High pressure liquid chromatography showed the tar to consist of a complicated mixture consisting of 8 components. (We acknowlede the help of Water Associates who carried out this separation).

Reaction of 2,4-diaminopyridine with 2-hydroxycyclohexanone

THEORETICAL PRODUCT



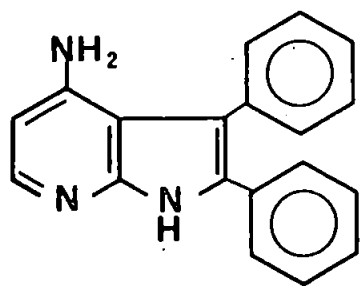
An attempted reaction under solvent conditions was as follows:

2,4-Diaminopyridine (0.94 g 0.01 M), 2-hydroxcyclohexanone (1.25 g 0.011 M), concentrated hydrochloric acid (0.2 cm^3) and toluene (50 cm^3) were refluxed in a Dean and Stark apparatus for 24 hours. The hot toluene was decanted free of the tarry residue and cooled in ice. The residue was dissolved in methanol. T.L.C. under previous conditions on these fractions showed them to consist of starting materials only. A melt reaction was then attempted as follows:

2,4-Diaminopyridine (0.94 g 0.01 M), 2-hydroxycycohexanone (1.25 g 0.011 M), concentrated hydrochloric acid (0.2 cm^3) were heated for 1 hour at 180°C - 190°C. The melt was cooled pulverised and stirred with hydrochloric acid (25 cm^3 1 molar) for 1 hour. The insoluble residue was filtered off and stirred with ammonia solution (25 cm^3 4 molar) for 1 hour.

The solid was filtered off. T.L.C. under previous conditions showed it to consist of three components, two colourless to Ehrlich's reagent and one at R_f 0.01 faint pink. This was thought to be product. The solid was heated with methanol (25 cm^3) and the insoluble residue filtered off. T.L.C. on the residue produced a colourless spot at low R_f, the methanol solution contained material at R_f 0.01 that was faint pink to Ehrlich's reagent. The solution was evaporated to dryness and the resulting solid was subjected to column chromatography (acidic alumina, petrol packed) but with no success as the amount of material was only 12 mgs and that was shown to be still impure by T.L.C. The experiment was abandoned.

Preparation of 2,3-diphenyl-4-amino-1H-pyrrolo[2,3-b]pyridine



An attempted reaction under solvent conditions was as follows:-

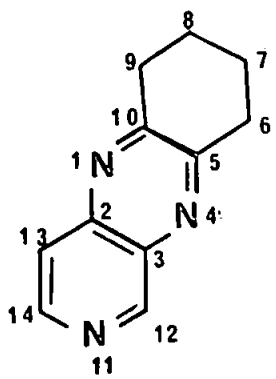
2,4-Diaminopyridine (0.2 g 1.8 m mol), benzoin (0.37 g 1.8 m mol), hydrochloric acid (5% v/v 1 cm^3) and toluene (50 cm^3) were refluxed in a Dean and Stark apparatus for 24 hours. The toluene solution was cooled in ice whereupon crystals came down. These were filtered off and the toluene mother liquor was evaporated to dryness. T.L.C. on the crystals and residue showed them to consist of starting materials only. A melt reaction was consequently attempted as follows:

2,4-Diaminopyridine (0.2 g 1.3 m mol), benzoin (0.37 g 1.8 m mol),

hydrochloric acid (5% v/v 1 cm^3) were heated at 130°C - 140°C for 0.5 hour and 180°C - 190°C for 0.5 hour. After cooling rhe melt was pulverised and stirred with hydrochloric acid (25 cm^3 1 molar) for 1 hour. After filtration the insoluble residue of the hydrochloric acid solution was stirred with ammonia solution (25 cm^3 4 molar) for 1 hour. The solid was filtered off and recrystallised from aqueous methanol. This gave (o.012 g 2.45%) product.

Infra-red (KBr)	3390, 3060, 1650, 1597, 1494, 1448, 1257, 768, 699 cm^{-1}.
NMR $\tau((CD_3)_2SO)$	-1.60(1H, m, N-H), 2.60(14H's, m, Ph, H's, 5 and 6 H's)
Mass Spec. m/e	285(11.0), 284(7.4), 267(2.4), 167(100), 152(25.5), 105(23.6), 77(15.7%).

Preparation of 6,7,8,9-tetrahydropyrido[3,4-b]quinoxaline



3,4-Diaminopyridine (3.6 g 0.033 M) was dissolved in toluene (75 cm^3) and the solution was refluxed via a Soxhlet extractor containing molecular sieve (5A) to remove any water present. Concentrated hydrochloric acid (0.17 cm^3) was added, followed by a slurry of 2-hydroxycyclohexanone (4.25 g 0.037 M) in toluene (100 cm^3). The reflux was continued for 20 hours. The hot toluene was decanted free of the tarry residue and evaporated to dryness. This yielded an oil which solidified on titration with diethyl ether. The solid rapidly darkened on exposure to air. T.L.C. under the conditions use previously on this solid showed it to consist of dark material at R_f 0.0 and product R_f 0.3 brown spot to Ehrlich's reagent. The ether extract consisted solely of the brown spot material. The solid was extracted with ether (20 x 50 cm^3) and the ether extracts passed down a short acid alumina column, using ether as eluent. A light yellow solid came off. Yield of product was 2.4 g (39.4%) of melting point 100° - 102°.

Infra-red (KBr) 3030, 2938, 2865, 1595, 1422, 1388, 1300, 1214, 981, 902, 850, 680, 632, 575, 419 cm^{-1}.

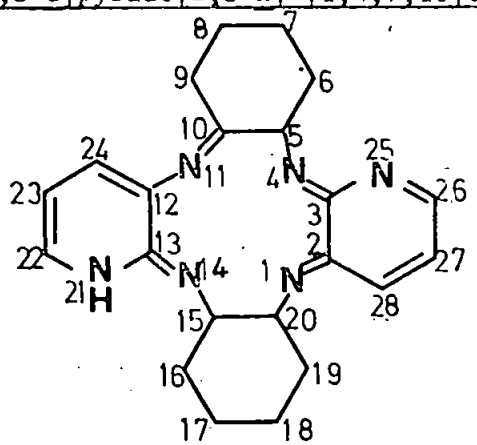
NMR ($(CD_3)_2SO$) 0.69(1H s 12-H), 1.28(1H d 14-H $J_{9,10}$ 6H_z), 2.15(1H d 13-H $J_{10,9}$ 6H_z), 6.91(4H's m 6,9-CH_2's), 8.03(4H's m 7,8-CH_2's.).

Mass Spec. m/e 185(100), 184(38.7), 170(22.8), 156(9.1), 155(6.8), 131(4.5), 103(9.1%).

Elemental Analysis Theory: C=71.3 H=6.0 N=22.7%

Found: C=71.1 H=5.8 N=22.7%.

Preparation of 5,6,7,8,9,15,16,17,18,19,20-undecahydrodibenzo[b,h]-N-hydropyrido-[2,3-e]pyrido[2,3-k] [1,4,7,10]tetra-azacyclododecine.



2,3-Diaminopyridine (7.2 g 0.066 M), 2-hydroxyclcohexanone (6.2 g 0.060 M), concentrated hydrochloric acid (0.4 cm^3) and toluene (150 cm^3) were refluxed in a Dean and Stark apparatus for 20 hours. The hot toluene solution was filtered and evaporated to dryness to yield an oily solid which was titrated with ether to give a buff coloured solid (9.2 g). This was boiled with ethyl acetate and filtered. T.L.C. on this filtrate showed it to contain some product and 2,3-diaminopyridine and 2-hydroxycyclohexanone. The filtrate was evaporated to dryness and recrystallised from ethyl acetate and 60°C - 80°C petroleum ether. This gave crystals of 2,3-diaminopyridine. The residue from the ethyl acetate boiling was washed with methanol and dried. T.L.C. showed this to be pure product. Further work of the mother liquor of the ethyl acetate 60°C - 80°C petroleum ether crystallisation gave further product. Total weight of product obtained was 3.7 g (21.5% yield) and the melting point was 258°C - 260°C.

Infra-red (KBr) 3230, 2940, 2860, 1560, 1460, 1440, 1418, 1346, 1322, 1200, 1189, 1048, 1011 cm^{-1}.

NMR τ (C_5 D_5 N) 1.38(1H d N-H), 4.02(1H, m 26-H), 6.13(1H d d, 27-H), 6.62(1H, d, 28-H), 7.18(10H's, m 5,6,9,16,19,22-H's) 7.87(2H's, s, 15,20-H's), 8.27(9H's, m, 4,7,8,17,18,24-H's 8.60(1H, m 23-H).

Mass Spec. m/e Accurate mass C_{22} H_{26} N_6 requires 374.22212

found 374.22188

374(33.2), 373(11.9), 190(46.7), 188(45.7), 187(100), 186(46.4), 185(19.9), 184(10.3), 170(10.9), 159(10.3), 121(25.6).

Elemental Analysis Theory C=70.6 H=7.0 N=22.4%

Found C=70.6 H=7.1 N=22.3%

Attempted reaction of 2,5-diaminopyridine with 2-hydroxycyclohexanone

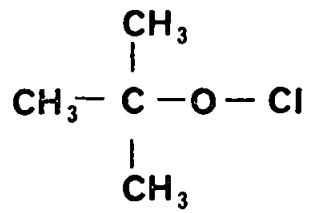
In a round bottomed flask (250 cm^3) fitted with a Soxhlet extractor containing anhydrous calcium chloride, was place 2,5-diaminopyridine dihydrochloride (1.82 g 0.01 M), sodium acetate (0.5 g 0.06 M), 2-hydroxycyclohexanone (1.14g 0.01 M) together with toluene (100 cm^3). The mixture was refluxed for 20 hours. The hot toluene was decanted free from the tarry residue and evaporated to dryness. This yielded a brown oil. T.L.C. under the conditions used previously showed that the oil consisted of 2,5-diaminopyridine (0.8 g 80%) together with product in small amount and 2-hydroxycyclohexanone. Consequently a melt reaction was attempted.

A mixture of 2,5-diaminopyridine dihydrochloride (1.82 g 0.01 M), sodium acetate (0.82 g 0.01 M) and water (5 cm^3) was evaporated to dryness. To the stirred residue obtained was added 2-hydroxycyclohexanone (1.2 g 0.012 M) and the mixture was stirred at 130°C - 140°C for 0.5 hours and then at 180°C - 190°C for 0.5 hours. The melt was cooled, pulverised and dissolved in hot water (50 cm^3). The solution was basified by the addition of solid

sodium carbonate and then refluxed for 0.15 hour. The aqueous extract was filtered through glasswool and rotary evaporated to dryness. This yielded a dark red solid which was shown by T.L.C. to consist mainly of material at very low R_f with some product. Attempts to separate the product by column chromatography and crystallisation met with no success.

THE GASSMAN REACTION

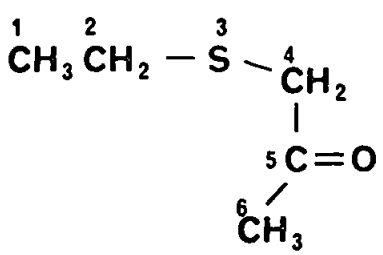
Preparation of tertiary butyl hydrochloride



This is the method of Teeter and Bell[30]. A solution of sodium hydroxide (80 grams 2 M) in water (500 cm^3) was prepared in a reaction vessel (2 litre) fitted with a gas inlet tube reaching nearly to the bottom of the vessel, a gas outlet tube and a mechanical stirrer. The vessel was placed in a water bath at 15°C - 20°C. Tertiary butyl alcohol (74 grams 1 M) was added together with enough water (~500 cm^3) to form an homogeneous solution. Whilst the solution was stirred, chlorine was passed into the solution for 0.5 hour at a rate of approximately 1 litre min^{-1} and then for an additional 0.5 hour at a rate of 0.5 litre min^{-1}.

The upper oily yellow layer was separated and washed with sodium carbonate solution (10% w/v 4 x 50 cm^3) and then washed four times with an equal volume of water and dried over calcium chloride. This yielded 85.9 grams of product (79% lit[30] 72% - 99%) of density 0.91 (Lit[30] 0.910). The product was used without further purification. The product was stored in ampoules in the fridge in the dark to prevent decomposition.

Preparation of ethylthiopropan-2-one



The method is that of Bradsher et al[31]. A solution of sodium (7.7 grams 0.31 M) in absolute ethanol (200 cm^3) was prepared in a reaction vessel (500 cm^3) fitted with a stirrer, dropping funnel and a reflux condenser with an anhydrous calcium chloride guard tube. Ethanthiol (24.8 cm^3, 20.7 grams 0.33 M) was added with stirring and the solution was chilled in an ice bath. Chloropropan-

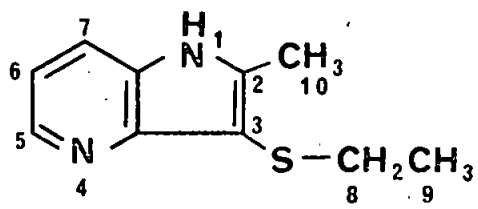
-2-one (33.3 grams, 29.1 cm^3 0.35 M) was added dropwise over 0.3 hour with stirring. The mixture was then returned for 2 hours. The precipitated sodium chloride was filtered off and the solution was fractionally distilled. The fraction boiling at 166°C - 172°C was collected. The yield of pale yellow product was 28.2 grams (71.8% lit[31] 54.0%).

Infra-red (NaCl liquid cell) 2970, 2930, 1709, 1358, 1238, 1150 cm^{-1}

NMR γ ($(CD_3)_2SO$) 6.67(2H's s 4-cm_2), 7.55(2H q 2-$ch_2J_{12}6H_2$), 7.82 (3H's s 6-CH_3), 8.84(3H's - 1-CH_3 J_{21} $7H_2$)

Mass Spec m/e 118(68.2), 75(100), 59(22.7), 47(68.2%)

Preparation of 2-methyl-3-ethylthio-1H-pyrrolo[3,2-b]pyridine



The method is based on Gassman and Van Bergens method[6] for indoles. 3-Aminopyridine(9.4 gram 0.1 M) was dissolved in dichloromethane (100 cm^3) in a reaction vessel fitted with a stirrer, an outlet and a dropping funnel. The solution was cooled to -65°C in a chloroform bath. Tertiary butyl hypochlorite (10.8 grams 0.1 M) at -65°C was added to the vigorously stirred solution and the mixture stirred for 0.15 hour. Ethylthiopropan-2-one (11.8 grams 0.1 M) at -65°C was added and the mixture stirred for 1 hour. Triethylamine (10.1 grams 0.1 M) was added with stirring and the solution allowed to reach room temperature. The solution was washed with sodium carbonate solution (50% w/v 3 X 100 cm^3) and with water (3 x 100 cm^3). After drying over anhydrous sodium sulphate and filtering the solution was evaporated to dryness to yield a black oil.

T.L.C. under conditions used previously on the oil showed it to consist of a large amount of ethylthiopropan-2-one together with 3-aminopyridine and 3 other components. The oil was put down a petrol packed acidic alumina column. A crystalline solid came off which was recrystallised from ethyl acetate, 60°C - 80°C petroleum ether. The product weighed 0.5 grams (2.6%) and melted at 223°C - 225°C. T.L.C. under conditions used previously

showed as a spot yellow to Ehrlichs reagent at Rf 0.49.

Infra-red (KBr) 2920, 1623, 1552, 1488, 1412, 1338, 1221, 1078, 868, 793, 778, 682, 550 cm^{-1}.

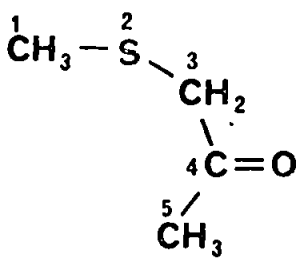
NMR τ ($(CD_3)_2SO$) - 1.42(1H diffuse NH), 1.70(1Hdd 5-H J_{65} $5H_z$ J_{75} $2H_z$), 2.43 (1Hdd 7-H J_{67} $8H_z$ J_{57} $2H_z$), 2.98(1Hdd 5-H J_{56} $5H_z$ J_{76} $6H_z$) 7.30(2H's q CH_2 J_{98} $7H_z$), 7.52(3H's s 2-CH_3)$_1$ 8.92(3H's t 9-CH_3 J_{89} $7H_z$)

Mass Spec m/e 192(100), 164(63.7), 163(70.8), 159(85.0), 132(41.5) 131(37.8), 119(18.9), 104(4.7%)

Elemental Analysis Theory C=62.5 H=6.2 N=14.6 S=16.7%

Found C=62.1 H=6.4 N=14.7 S=16.8%

Preparation of methylthiopropan-2-one



The method is based on that of Bradsher et al[31]. Sodium (103.5 grams 4.5 M) was dissolved in absolute ethanol (2.7 litres) in a reaction vessel (3 litres) fitted with a gas bubbler, stirrer and gas outlet tube. Methanthiol (216 grams 4.5 M) was added with stirring. The solution was divided in half, one half was kept in the fridge in a sealed container for further use. The other half was chilled in an ice bath and chloropropan-2-one (207 grams 2.25 M) was added dropwise with stirring. The mixture was refluxed for 2 hours with vigorous stirring and after cooling the precipitated sodium chloride was removed by filtration The resulting solution was fractionally distilled and the fraction boiling at 152°C - 158°C collected. This yielded 147 grams (64.2% lit[31] 54.0%) of pale yellow product.

Infra-red (NaCl liquid cell) 2970, 2910, 1721, 1350, 1221, 1131 cm^{-1}

N.M.R.τ ($(CD_3)_2SO$) 6.98(2H s 3-CH_2), 7.24(3H's s 4-CH_3) 7.30(3H's 1-CH_3)

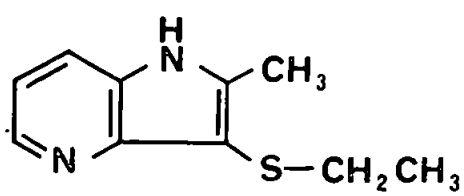
Mass spec m/e 104(56.3), 71(100), 56(61.8), 55(29.2%)

Attempted use of the Bromine complex of methylthiopropan-2-one in the Gassman reaction

The method is based on that of Gassman et al[37].

Methylthiopropan-2-one (10.4 grams 0.1 M) in dichloromethane (20 cm^3) at -65°C was added to a solution of bromine (16 grams 0.1 M) in dichloromethane (250 cm^3) contained in a reaction vessel (500 cm^3), fitted with a stirrer, dropping funnel and outlet, in a chloroform bath at -65°C. The solution was stirred for 0.1 hour and then a solution of 3-aminopyridine (9.4 grams 0.1 M) and triethylamine (10.1 grams 0.1 M) in dichloromethane (50 cm^3) at -65°C was added. The solution was stirred for 2 hours and a solution of sodium methoxide (6.1 grams 0.15 M) in methanol (40 cm^3) at -65°C was added. The mixture was stirred overnight being allowed to reach room temperature. The solution was shaken with water (2 x 250 cm^3) and then dried over sodium sulphate. After filtration, the solution was evaporated to dryness to yield a black tar. Column chromatography using a petrol packed acidic alumina column gave only 3-aminopyridine (5.0 grams 55%). T.L.C. on the eluted fractions showed that no product was formed.

Preparation of 2-methyl-3-ethylthio-1H-pyrrolo[3,2-b]pyridine using twice as much tertiary butyl hypochlorite



To a vigorously stirred solution of 3-aminopyridine (4.2 grams 0.044 M) in dichloromethane (150 cm^3) in a round bottomed flask (250 cm^3) in a chloroform bath at -65°C was added dropwise a solution of tertiary butyl hypochlorite (9.5 grams 0.088 M) in dichloromethane (40 cm^3) at -65°C. After stirring for 0.15 hour ethylthiopropan-2-one (5.2 grams 0.044 M) in dichloromethane (20 cm^3) at -65°C was added and the stirring continued for 1 hour. Subsequently, triethylamine (7.9 grams 0.088 M) in dichloromethane (40 cm^3) at -65°C was added. After this addition the solution was stirred until it had reached room temperature.

The solution was washed with water (200 cm^3), dried over anhydrous sodium sulphate, filtered, and evaporated to yield black tar. Column chromatography of the tar using a petrol packed acidic alumina column gave 0.02 grams (0.25%) or 2-methyl-3-ethylthio-1H-pyrrolo[3,2-b]pyridine of melting point 223°C - 225°C. No other products could be isolated.

Evaluation of the chlorination Stage

3-Aminopyridine (4 x 0.94 grams 0.01 M) was placed in four tubes (30 cm^3). Two of the tubes had dichloromethane (2 x 20 cm^3) placed in them and other two tetrahydrofuran (2 x 20 cm^3). The tubes were shaken until the 3-aminopyridine dissolved. The tubes were placed in an ice bath and kept under a nitrogen atmosphere. Tertiary butyl hypochlorite (2 x 1.1 grams 0.01 M) was added to two of the tubes one of each solvent, and N-chlorosuccinimide (2 x 1.34 grams 0.01 M) in the other two tubes. Aliquots were taken for examination by T.L.C. (2:1 toluene: acetone silica gel) at various time intervals. The results are summarised as follows:-

Tertiary butyl hypochlorite/dichloromethane

Large amount of 3-aminopyridine present even after 4 hours some product at R_f 0.41.

Tertiary butyl hypochlorite/tetrahydrofuran

Large amount of 3-aminopyridine present even after 4 hours some product at R 0.41.

N-chlorosuccinimide/dichloromethane

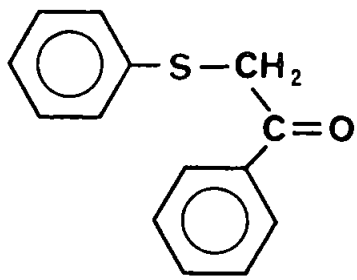
Some 3-aminopyridine present with a product at R_f 0.1 pink to Ehrlichs reagent and another product at R_f 0.41 after 4 hours.

N-chlorosuccinimide/tetrahydrofuran

Some 3-aminopyridine present with a fair amount of product at R_f 0.1, pink to Ehrlichs reagent and another product at R_f 0.41 after 4 hours.

Even after 24 hours there were still considerable amounts of 3-aminopyridine present.

Preparation of phenylthioacetophenone



Into a 3-necked round bottomed flask (500 cm^3) fitted with a stirrer, dropping funnel and reflux condenser fitted with an anhydrous calcium chloride guard tube was placed absolute ethanol (200 cm^3). Sodium (7.7 grams 0.3 M) was added with stirring, after the sodium had dissolved, thiophenol (36.7 grams 0.3 M) was added and the solution stirred overnight. The mixture was chilled in an ice-bath and α-chloroacetophenone (51.5 grams 0.3 M) was added in ethanol (200 cm^3). The mixture was refluxed for 2 hours. After cooling the precipitated sodium chloride was filtered off and washed with hot ethanol (100 cm^3). The combined ethanol solutions were evaporated to dryness to yield a light yellow solid. The solid was recrystallised from aqueous ethanol. This yielded the product as beautiful white needles (59.0 grams 85.2% lit[55] 92%) of melting point 53.5°C - 54.5°C (lit[55] 51°C - 53°C).

Infra-red (KBr) 3080, 2980, 1673, 1600, 1579, 1447, 1440, 1281, 1137, 1014, 743, 690, 558 cm^{-1}.

NMR γ ($(CD_3)_2SO$) 2.53(10H's m phenyl H's), 5.39(2H's s CH_2)

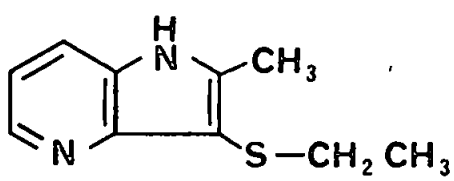
Mass Spec m/e 228(54.5), 123(13.5), 106(12.7), 105(100), 77(45.5), 51(13.5%)

Attempted Gassman reaction using phenylthioacetophenone and N-chlorosuccinimide

3-Aminopyridine (9.4 grams 0.1 M) was dissolved in tetrahydrofuran (150 cm^3). The solution was saturated with nitrogen and cooled to 0°C and left under an atmosphere of nitrogen. A solution of N-chlorosuccinimide (15 grams 0.115 M) in tetrahydrofuran (250 cm^3) was added and the mixture was magnetically stirred for 0.25 hour. Phenylthioacetophenone (22.8 grams 0.1 M) in tetrahydrofuran (100 cm^3) was added and the stirring continued under nitrogen for 1 hour. Triethylamine (10.1 grams 0.1 M) was then added and the mixture stirred under nitrogen whilst it warmed to room temperature.

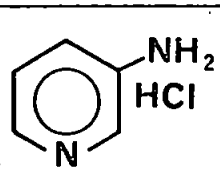
The solvent was evaporated off and the mixture taken up in dichloromethane (250 cm^3) and washed with water (1 litre). The solution was dried over anhydrous sodium sulphate and after filtering was evaporated to dryness to yield a black oil. The oil was titrated with 60°C - 80°C petroleum ether. On evaporation of the petroleum ether 13.0 grams (57%) of phenylthioacetophenone was recovered. T.L.C. (2:1 toloene: acetone) on the oil showed the presence of a probable product (yellow spot to Ehrlichs reagent at R_e 0.40). But attempts to separate this by preparative T.L.C. were not successful due to the very small quantity present.

Preparation of 2-methyl-3-ethylthio-1H-pyrrolo[3,2-b]pyridine using N-chlorosuccinimide



3-Aminopyridine (9.4 grams 0.1 M) was dissolved in nitrogen saturated tetrahydrofuran (150 cm^3) and cooled to 0°C under a nitrogen atmosphere. N-chlorosuccinimide (15.0 grams 0.115 M) in tetrahydrofuran (nitrogen saturated 250 cm^3) was added and the mixture was magnetically stirred under nitrogen for 0.25 hour. Ethylthiopropan-2-one (11.8 grams 0.1 m) was then added slowly with stirring under nitrogen and the solution stirred for 1 hour. Triethylamine (10.1 grams 0.1 M) was added and the solution stirred and allowed to reach room temperature. The solvent was evaporated off and the resulting oil taken up in dichloromethane (250 cm^3) and washed with water (1 litre). After drying over anhydrous sodium sulphate, and filtering the solution was evaporated to dryness to yield a black oil. Column chromatography (acidic alumina petrol packed) of the oil gave ethylythiopropan-2-one (5.5 grams 47.5%), 2-methyl-3-ethylthio-1H-pyrrolo[3,2-b]pyridine (0.11 gram 0.5%) and 3-aminopyridine (0.8 gram 8.5%).

Preparation of 3-aminopyridine hydrochloride



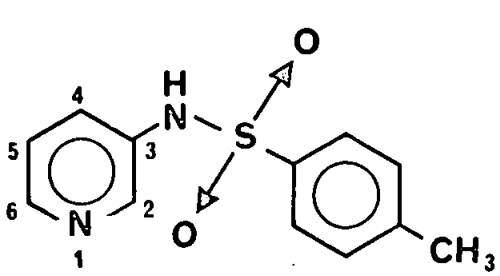
3-Aminopyridine (22.0 grams 0.24 M) was dissolved in benzene (350 cm^3) in a

round bottomed flask fitted with a gas bubbler inlet, a stirrer and an anhydrous calcium chloride guard tube. Dry hydrogen chloride was passed into the solution whilst it was vigorously stirred until the gas issued freely from the outlet. After allowing the mixture to cool, it was filtered and the white product dried in a vacuum dessicator. The hydrochloride weighed 29.5 grams (94.5%) and was used without further purification.

Attempted use of 3-aminopyridine hydrochloride in the Gassman reaction

3-Aminopyridine hydrochloride (13.05 grams 0.1 M) was suspended in dichloromethane (350 cm^3). Nitrogen was passed into the mixture until it was saturated and the mixture cooled to $-70^{\circ}C$ under nitrogen. Tertiary butyl hypochlorite (10.85 grams 0.1 M) in dichloromethane (40 cm^3) was added and the solution magnetically stirred for 0.15 hour under nitrogen. Ethylthiopropan-2-one (11.8 grams 0.1 M) in dichloromethane (40 cm^3) was then added and the mixture stirred for 1 hour under nitrogen. Triethylamine (20.2 grams 0.2 M) was added with stirring and the mixture allowed to reach room temperature. The mixture was washed with water (1 litre) and the solution dried over anhydrous sodium sulphate, filtered and evaporated to dryness to yield a dark brown oil. The material was column chromatographed (acidic alumina petrol packed) to yield ethylthiopropan-2-one (7.7 grams 65.3%), and 3-aminopyridine (4.7 grams 50.0%). Some product was detected by T.L.C. (2:1 toluene: acetone silica gel) in one of the eluted fractions but it was present in very small amounts.

Preparation of 3-p-toluenesulphonylaminopyridine



3-Aminopyridine (9.4 grams 0.1 M) was placed in a round bottomed flask fitted with a reflux condenser. Pyridine (57 cm^3) was added followed by p-toluenesulphonyl chloride (28.6 grams 0.15 M), the solution went dark red. The solution was refluxed

for 0.5 hour and then poured into cold water (95 cm^3) and the mixture was vigorously stirred. The white product was precipitated, filtered off and washed with water (500 cm^3) and dried at 100°C. The product was recrystallised from aqueous ethanol to yield white crystals (20.5 grams 82.9%) of melting point 177°C - 179°C.

Infra red (KBr)	3070, 2650, 1588, 1424, 1359, 1320, 1310, 1265, 1165, 1092, 930, 821, 662, 575, 548 cm^{-1}.
NMRτ($(CD_3)_2SO$)	-0.42(1H diffuse NH), 1.68(1H m 2-H), 1.79(1H m 6-H), 2.50(6H's m 4,5 and phenyl H's) 7.69(3H's s CH_3).
Mass Spec m/e	248(60.0), 155(57.1), 91(100), 66(7.1), 65(7.1%)
Elemental Analysis	Theory C=58.1 H=4.8 N=11.3%
	Found C=58.2 H=4.7 N=11.5%

Attempted use of 3-p-toluenesulphonylaminopyridine in the Gassman reaction

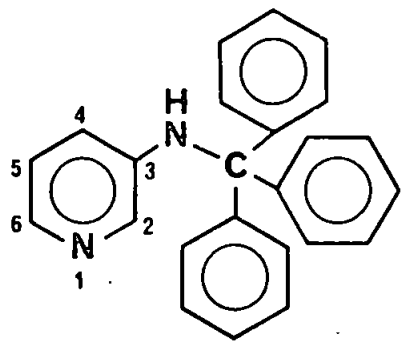
3-p-Toluenesulphonylaminopyridine (8.3 grams 0.03 M) was dissolved in dichloromethane (150 cm^3) in a round bottomed flask (250 cm^3) fitted with a reflux condenser and a dropping funnel. Ethylthiopropan-2-one (3.9 grams 0.03 M) was added.

This was done for a total of three flasks, two with dichloromethane as solvent and one with absolute ethanol (150 cm^3) in place of the dichloromethane. The ethanol and one of the dichloromethane flasks were then refluxed for 1 hour and then triethylamine (3.0 grams 0.03 M) was added and the reflux continued for a further hour. The other flask was stirred for 1 hour at room temperature and the triethylamine (1.77 grams 0.03 M) was added and the mixture stirred for a further hour. All the flasks were filtered and evaporated to dryness. This gave the following

1) Room temperature/dichloromethane 7.1 grams (85.5%) of 3-p-toluenesulphonylaminopyridine were recovered T.L.C. (2:1 tolueneacetone silica gel on recrystallisation. Liquor indicated no product formation.
2) Reflux/dichloromethane 7.0 grams (84.1%) of 3-p-toluenesulphonylaminopyridine were recovered. T.L.C. on recrystallisation. Liquor indicated no product formation.

3) Reflux/ethanol 8.2 grams (98.5%) of 3-p-toluenesulphonylaminopyridine were recovered. T.L.C. on recrystallisation. Liquor indicated no product formation.

The preparation of 3-N-triphenylmethylaminopyridine



3-Aminopyridine (38 grams 0.405 M) was placed in a round bottomed flask (500 cm^3) fitted with a reflux condenser Pyridine (280 cm^3) was added followed by triphenylchloromethane (100 grams 0.405 M). The solution turned red and a violent reaction ensued, after the reaction had subsided the mixture was refluxed for 0.25 hour. The solution was then poured into water (390 cm^3) and the mixture vigorously stirred.

A precipitate formed and this was filtered off to give a light brown solid, the solid was boiled with ethyl acetate (200 cm^3) to remove pyridine, filtered and dried. This was found to be a complex giving the following results:-

Infra-red (KBr)	3200, 3040, 2350, 2075, 1610, 1550, 1493, 1450, 1384, 798, 758, 710 cm^{-1}.
NMR $\tau((CD_3)_2SO)$	2.08(15H's m pyridine H's), 2.71(19H's m tritylamino-pyridine H's).
Mass Spec m/e	276(4.7), 275(18.8), 244(23.6), 198(45.9), 106(23.6), 96(37.7), 95(100), 94(65.9), 78(18.8%).
Elemental Analysis	$C_{37}H_{39}N_5Cl_2$ requires C, 71.3; H, 6.1; N, 11.2; Cl, 11.4;
	found C, 71.4; H, 6.2; N, 11.1; Cl, 11.3%.

These results indicate a complex consisting of 3 moles of pyridine, 1 mole of 3-N-triphenylmethylaminopyridine and 2 moles of hydrogen chloride.

The complex (96 grams) was suspended in dichloromethane (2 litres) and triethylamine (101 grams 1 M) was added and the mixture was stirred at

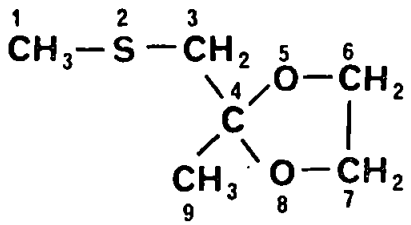
room temperature for 1 hour. The resulting solution was washed with water (2 litres), dried over anhydrous sodium sulphate, filtered and evaporated to dryness. The resulting solid was washed with diethyl ether (500 cm^3) and recrystallised from aqueous methanol after charcoal treatment. The product was obtained as white platelets (69.2 grams 50.4%) of melting point 179°C - 180°C.

Infra-red (KBr)	3280, 3040, 2930, 1580, 1480, 1448, 1318, 1025, 795, 751, 705, 633 cm^{-1}.
NMRτ ($(CD_3)_2SO$)	2.08(1Hm 6-H), 2.36(1Hm 4-H), 2.72(15H's s phenyl H's), 3.00(1H s 2-H), 3.28(1H m 5-H).
Mass Spec m/e	336(6.0), 244(65.4), 243(100), 167(20.0) 166(76.0%)
Elemental Analysis	Theory C=85.7 H=5.9 N=8.4
	Found C=85.3 H=6.1 N=8.6%

Attempted preparation of 2-phenyl-3-phenylthio-1H-pyrrolo[3,2-b]pyridine

3-Aminopyridine (4.2 grams 0.044 M) was dissolved in dichloromethane (150 cm^3) in a round bottomed flask (500 cm^3) fitted with a dropping funnel, stirrer and an anhydrous calcium chloride guard tube. The solution was cooled to -65°C by means of a chloroform bath and tertiary butyl hypochlorite (4.75 grams 0.044 M) in dichloromethane (20 cm^3) at -65°C was added dropwise, with stirring. After 0.2 hour phenylthioacetophenone (10.1 grams 0.044 M) in dichloromethane (40 cm^3) at -65°C was added and the stirring continued for 1 hour. Subsequently triethylamine (3.95 grams 0.044 M) in dichloromethane (20 cm^3) at -75°C was added and the solution stirred until it reached room temperature. Water (50 cm^3) was added and the organic layer separated, dried over anhydrous sodium sulphate, filtered and evaporated to dryness to yield a dark oil which crystallised on standing. The oily solid was subjected to column chromatography but only phenylthioacetophenone (8.6 grams 85.0%) was recovered. Some product was indicated by T.L.C. but it was present only in minute amounts.

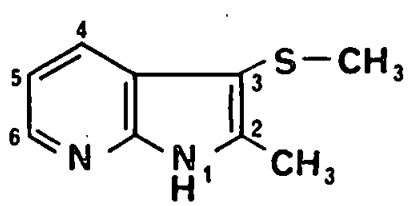
Preparation of methylthiopropan-2-one ethylene ketal



This method is based on that of Renoll and Newmans[45] for the preparation of DL-isopropylideneglycol. In a round bottomed flask (250 cm^3) fitted with a Dean and Stark apparatus was placed methylthiopropan-2-one (52.0 grams 0.5 M), ethandiol (31.0 grams 0.5 M), 60°C - 80°C petroleum ether (100 cm^3) and p-toluenesulphonic acid monohydrate (1.0 gram). The mixture was refluxed for 54 hours and then allowed to cool to room temperature. Powdered freshly fused sodium acetate (1.0 gram) was added and the mixture magnetically stirred for 0.5 hour. The mixture was filtered and excess petrol rotary evaporated off. The residue was vacuum distilled in a modified claisen flask and the fraction boiling at 77°C - 79°C at 7 mm of mercury collected. This gave the product (38.0 grams 51.4%) as a clear yellow pungent liquid.

Infra-red (NaCl liquid cell)	2990, 2920, 2880, 1378, 1220, 1118, 1048 cm^{-1}.
NMR τ($(CD_3)_2SO$)	6.13(3H's s 9-CH_3), 7.39(2H's s 3-CH_2), 7.91(4H's t 6,7-CH_2 J_{67} 6Hz), 8.67(3H's s 1-CH_3).
Mass Spec m/e	148(45.7), 133(50.0), 88(41.4), 87(100), 73(61.4), 61(84.3%).

Preparation of 2-methyl-3-methylthio-1H-pyrrolo[2,3-b]pyridine



The method is that of Gassman[44]. To a stirred solution of 2-aminopyridine (4.7 grams 0.05 M) in dichloromethane (150 cm^3) at -65°C was added dropwise with stirring a solution of tertiary butyl hypochlorite (5.5 grams 0.05 M) in dichloromethane

(12.5 cm^3) at -65°C. The solution was stirred for 0.83 hour. Methylthiopropan-2-one ethylene ketal (7.4 grams 0.05 M) at -65°C was added and the stirring continued for 1 hour. The solution changed to an orange colour. A solution of sodium methoxide (3.0 grams 0.05 M) in methanol (20 cm^3) at -65°C was added. The mixture went wine red and the stirring was continued for 3 hours and then the mixture was allowed to reach room temperature.

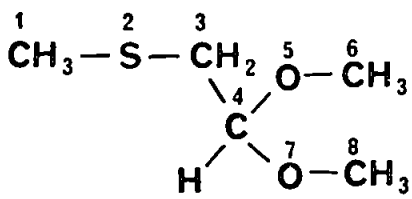
Distilled water (87.5 cm^3) was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (4 x 80 cm^3) and the combined organic solutions were dried over anhydrous sodium sulphate, filtered and evaporated to dryness to yield a dark red oil. The crude sulphinilimine was refluxed with a solution of potassium tertiary butoxide (5.6 grams 0.05 M) in tertiary butanol (275 cm^3) for 7.5 hours. The solution went dark brown. The solvent was removed on a rotary evaporator and distilled water (93.5 cm^3) was added, and the mixture was extracted with diethyl ether (4 x 80 cm^3). The combined extracts were rotary evaporated to dryness to yield a brown oil. The oil was stirred with hydrochloric acid (150 cm^3) for 1 hour and diethyl ether (125 cm^3) for 24 hours at room temperature. The red aqueous layer was separated off and basified to pH 9 - 10 with aqueous sodium hydroxide solution (10% w/v). The resulting cloudy mixture was extracted with diethyl ether (4 x 187.5 cm^3) and the combined extracts were washed with saturated sodium chloride solution (93.5 cm^3), dried over anhydrous sodium sulphate, filtered and evaporated to dryness. This afforded a brown oil which crystallised on standing. This was put onto a silica gel column and eluted with 1:1 60°C - 80°C petroleum ether: ethyl acetate. This gave the product which on recrystallisation from aqueous ethanol melted at 172°C - 173°C (lit[44] 173°C). Some 2-aminopyridine was recovered (2.1 grams) and the yield of product was 1.6 grams (17%, 35.5% based on recovered starting material [lit[44] 37.4%]).

Infra-red (KBr) 2925, 2860, 1590, 1412, 1281, 1260, 1073, 795, 771 cm^{-1}.

NMR $\tau((CD_3)_2SO)$ -2.52(1H diffuse NH), 1.78(1Hdd 6-H J_{56} 6Hz J_{46} 2Hz), 2.04(1Hdd 4-H J_{54} 7Hz J_{64} 2Hz), 2.95(1H dd 5-H J_{45} 6Hz J_{65} 6Hz), 7.43(3H's s S-CH_3), 7.80(3H's s 2-CH_3).

Mass Spec m/e 178(94.5), 163(100), 119(25%).

Preparation of methylthioethan-2-one dimethyl acetal



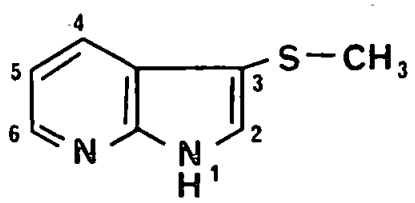
The method is that of Wick et al[46]. Bromoethan-2-one dimethyl acetal (107.5 grams 0.65 M) was added to a chilled solution of sodium methylmercaptide (42 grams 0.6 M) in ethanol (360 cm^3). The reaction mixture was allowed to come to room temperature and was warmed to 50°C - 60°C for 1 hour and then allowed to stand overnight. The precipitated sodium bromide was filtered off and the ethanolic solution diluted with an equal volume of water. The aqueous solution was extracted with twice its volume of diethyl either and the combined extracts were dried over anhydrous sodium sulphate, filtered and evaporated to dryness. The resulting amber coloured liquid was vacuum distilled and the fraction boiling at 55°C at 10 mm of mercury collected. The amber coloured liquid weighed 44.2 grams (50.0% lit[46] 60.8%).

Infra-red (NaCl liquid cell) 2920, 2835, 1445, 1370, 1122, 1062 cm^{-1}

NMR $\tau((CD_3)_2SO)$ 5.57(1H t 4-H J_{34} 6Hz), 6.73(6H's s O-CH_3's), 7.43(2H's d CH_2 J_{43} 6Hz), 7.92(3H's s CH_3-S).

Mass Spec m/e 136(8.1), 105(401.4), 104(100), 91(33.4), 90(800[3]), 75(39.1), 61(98.9).

Preparation of 3-methylthio-1H-pyrrolo[2,3-b]pyridine



The method is that of Gassman[44].

To a stirred solution of 2-aminopyridine (4.7 grams 0.05 M) in dichloromethane (100 cm^3) at -65°C was added dropwise a solution of tertiary butyl hypochlorite (5.43 grams 0.05 M) in dichloromethane (20 cm^3) at -65°C. The reaction mixture was stirred for 1 hour and went yellow. Methylthioethan-2-one dimethyl acetal (6.8 grams 0.05 M) in dichloromethane (10 cm^3) at -65°C was added and the mixture changed to an orange colour and was stirred for 1.5 hours. Sodium methoxide (3.0 grams 0.055 M) in methanol (50 cm^3) at -65°C was added. The solution turned red and was stirred for 2.5 hours and then allowed to reach room temperature. Distilled water (70 cm^3) was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (4 x 60 cm^3). The combined extracts were dried over anhydrous sodium sulphate, filtered and rotary evaporated to dryness to yield an oil. The crude sulphinilimine was refluxed in a solution of potassium tertiary butoxide (5.6 grams 0.05 M) in tertiary butanol (300 cm^3) for 5.5 hours. After being cooled the solvent was rotary evaporated off and distilled water (70 cm^3) was added. The aqueous solution was extracted with diethyl ether (4 x 80 cm^3). The combined extracts were rotary evaporated to dryness to yield an oil. The oil was stirred with hydrochloric acid (100 cm^3 1 hour) and diethyl ether (100 cm^3) for 4.5 hours. at room temperature. The aqueous layer was separated and made basic with saturated aqueous sodium bicarbonate solution and extracted with diethyl ether (4 x 100 cm^3). The combined extracts were dried over anhydrous sodium sulphate, filtered and rotary evaporated to yield a brown crystalline solid.

Chromatography on a silica gel column eluted with 60°C - 80°C petroleum ether/ethyl acetate gave a yellow crystalline solid of melting point 113°C - 115°C (lit[44] 115°C) after recrystallisation from aqueous ethanol. Some 2-aminopyridine (0.5 grams was recovered. Yield 1.4 grams (17.1%,

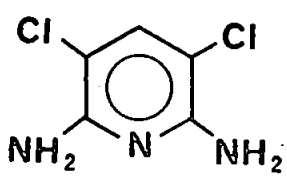
19.1% on recovered substrate (lit[44] 45.0%).

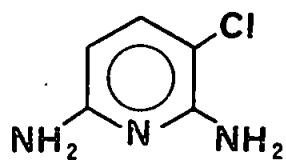
Infra-red (KBr) 3230, 2920, 1608, 1590, 1410, 1282, 963, 798, 770, 618 cm^{-1}

N.M.R.τ ($(CD_3)_2SO$) -1.93 (1H diffuse NH), 1.68(1H dd 6-H J_{56} 4Hz J_{46} 2Hz), 2.91(1 dd 4-H J_{54} $6H_2$ J_{64} 2Hz), 2.53(1H s 2-H), 2.88(1H dd 5-H J_{45} 5Hz J_{65} 5Hz), 7.69(3H's s CH_3).

Mass Spec m/e 164(92), 149(100), 122(15.4), 71(34.6%).

2,6-diaminopyridine in the Gassman reaction
(preparation of 2,6-diamino-3,5-dichloropyridine and 3-chloro-2,6-diamino-pyridine)





To a stirred solution of finely powdered 2,6-diaminopyridine (27.25 grams 0.25 M) in dichloromethane (750 cm^3) at -65°C was added dropwise with stirring a solution of tertiary butyl hypochlorite (55.5 grams 0.52 M) in dichloromethane (125 cm^3) at -65°C. The mixture was stirred for 0.9 hour and then methylthiopropan-2-one ethylene ketal (74.04 grams 0.5 M) at -65°C was added and the stirring continued for 1 hour. A solution of sodium methoxide (30.0 grams 0.52 M) in methanol (125 cm^3) at -65°C was added and the solution stirred for 3 hours and then allowed to warm to room temperature. Distilled water (750 cm^3) was added and a grey solid came down. This was filtered off and dried at the pump. The solid was warmed with dichloromethane (500 cm^3) and filtered and dried at the pump. The washing was combined with the dichloromethane separated from the aqueous layer formed previously. The aqueous layer was extracted with dichloromethane

(4 x 500 cm^3) and the combined dichloromethane washings and extracts were dried over anhydrous sodium sulphate. After filtration the extracts were evaporated to dryness to yield an oil.

The crude sulphinilimine was refluxed in a solution of potassium tertiary butoxide (56.0 grams 0.5 M) in tertiary butanol (27.50 cm^3) for 7.5 hours. The solvent was removed on a rotary evaporator and distilled water (1 litre) was added. The resulting solution was extracted with diethyl ether (4 x 800 cm^3). The combined extracts were evaporated to dryness and the resulting oil was stirred with hydrochloric acid (1.5 litres 1 molar) and diethyl ether (1.25 litres) for 24 hours at room temperature. The diethyl ether was separated off and the aqueous layer adjusted to Ph 9 - 10 with aqueous sodium hydroxide solution (10% w/v) and extracted with diethyl ether (4 x 1 litre).

The combined extracts were dried over anhydrous sodium sulphate, filtered and evaporated to dryness to yield a brown oil. T.L.C. (toluene: acetone 2:1 silica gel) showed it to consist of a complicated mixture containing some of the product isolated previously (yellow/grey to Ehrlichs reagent) together with one other major product (yellow/grey to Ehrlichs reagent) together with 5 other products in small amounts. The oil was subjected to preparative T.L.C. under the conditions above. 3-chloro-2,6-diaminopyridine was separated (1.6 grams (4.5%)) as a light yellow solid of melting point 150°C - 152°C.

Infra-red (KBr)	3430, 3350, 3180, 2925, 2858, 1633, 1592, 1460, 1355, 1296, 794 cm^{-1}.
N.M.R. δ ($(CD_3)_2SO$)	2.88(1H d 4-H J_{54} 8Hz), 4.32(1H d 5-H J_{45} 8Hz), 4.44(4H's m 2,6-NH_2's).
Mass Spec m/e	145(54.3), 143(100), 116(17.4), 114(43.5), 81(19.6).
Elemental Analysis	Theory: C=41.8 H=4.2 N=29.2 Cl=24.8%
	Found: C=41.6 H=4.0 N=29.5 Cl=24.9%

The grey solid filtered off earlier was recrystallised from glacial

acetic acid after charcoal treatment to give white crystals of 3,5-dichloro-2,6-diaminopyridine which after drying at 110°C melted at 211°C - 212°C. The yield was 31.7 grams (71.4%).

Infra-red (KBr)	3458, 3408, 3310, 1620, 1457, 1295, 1226, 1020, 900, 739 cm^{-1}.
N.M.R. τ ($(CD_3)_2SO$)	2.64(1H s 4-H), 4.14(4H' s 2,6-NH_2's)
Mass Spec m/e	181(15.0), 179(85.0), 177(100), 152(16.3), 150(27.5), 142(18.7), 115(18.7), 88(8.8%)
Elemental Analysis	Theory C=33.7 H=2.8 N=23.6 Cl=39.9%
	Found C=33.9 H=2.8 N=23.6 Cl=39.7%

Attempted Gassman reaction on 2,6-diaminopyridine using N-chlorosuccinimide

To a stirred solution on N-chlorosuccinimide (5.6 grams 45 m mol) in dichloromethane (150 cm^3) at -45°C (freezing methyl cyanide) was added dropwise a solution of methylthioethan-2-one dimethyl acetal (5.4 grams 40 m mol) in dichloromethane (20 cm^3) at -45°C. After the addition was complete the mixture was stirred for 2 hours at -45°C. Ground 2,6-diaminopyridine (2.2 grams 20 m mol) suspended in dichloromethane (20 cm^3) was added. And the reaction mixture stirred for 1.5 hours at -45°C. A white solid was formed. Sodium methoxide (5.4 grams 100 m mol) in methanol (40 cm^3) was added and the mixture stirred for 3 hours and then the solution was allowed to stand overnight. Distilled water (60 cm^3) was added and the aqueous layer was separated and extracted with dichloromethane (2 x 40 cm^3) The combined extracts were dried over anhydrous sodium sulphate, filtered and evaporated to dryness to give an oil. The oil was refluxed in a solution of potassium tertiary butoxide (4.8 grams 50 m mol) in tertiary butanol (240 cm^3) for 2.5 hours. The solvent was removed on a rotary evaporator and water (80 cm^3) was added. The solution was extracted with chloroform (3 x 100 cm^3) and the combined extracts evaporated to dryness to give an oil. The oil was heated with hydrochloric acid (80 cm^3 1 molar) and chloroform (20 cm^3) on a steam bath for 2 days. The aqueous layer was separated and basified to Ph 9 - 10 with aqueous sodium hydroxide solution (10% w/v).

A brown solid came down and this was filtered off.

T.L.C. (toluene: acetone 2:1 silica gel) on this solid showed it to consist essentially of a single substance R_f 0.01 red colour to Ehrlich's reagent with minor impurities.

The melting point of the solid was >360°C yet it was organic (burnt with luminous flame and left no residue). It was insoluble in a whole range of organic solvents and was insoluble in hydrochloric acid. Attempts at purification by preparative T.L.C. were not successful. The infra-red spectra consisted of diffuse peaks and indicated some aromatic character together with the presence of an amino group.

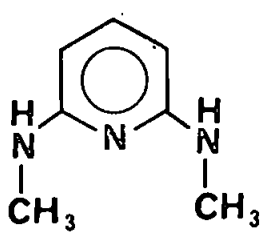
An attempted Gassman reaction on 2-amino-5-nitropyridine

To a stirred solution of 2-amino-5-nitropyridine (2.8 grams 20 m mol) in dichloromethane (100 cm^3) at -15°C was added dropwise a solution of tertiary butyl hypochlorite (2.2 grams 20 m mol) in dichloromethane (10 cm^3) at -15°C and the mixture stirred at -15°C for 0.7 hour. A solution of methylthioethan-2-one dimethyl acetal (2.72 grams 20 m mol) in dichloromethane (10 cm^3) at -15°C was added and the mixture stirred at -15°C for 0.9 hour. A solution of sodium methoxide (2.1 grams 38.7 m mol) in methanol (20 cm^3) at -15°C was added and the mixture stirred for 2 hours at -15°C and then allowed to reach room temperature. Distilled water (30 cm^3) was added and the mixture filtered, 2-amino-5-nitropyridine (0.3 grams) was recovered. The aqueous layer was separated and extracted with dichloromethane (3 x 40 cm^3). The combined extracts were dried over anhydrous sodium sulphate, filtered and evaporated to dryness to yield an oily red solid. This solid was refluxed in a solution of potassium tertiary butoxide (2.25 grams 20 m mol) in tertiary butanol (120 cm^3) for 14 hours. The solvent was removed on a rotary evaporator and water (50 cm^3) was added. This solution was extracted with diethyl ether (4 x 60 cm^3) and the combined extracts evaporated to dryness to yield a red solid. This was

stirred with hydrochloric acid (60 cm^3 1 molar) for 2 days and then the solution was neutralised with aqueous sodium hydroxide solution (10% w/v) and the resulting suspension extracted with diethyl ether (4 x 60 cm^3). After drying over anhydrous sodium sulphate and filtration the extracts were evaporated to dryness to yield a brown-yellow solid. This was 2-amino-5-nitropyridine (2.0 grams). The total amount of recovered substrate was 2.3 grams (82%).

The above experiment was repeared using exactly the same conditions except that it was carried out at 20°C and that methylthiopropan-2-one ethylene ketal (2.96 grams 20 m mol) was used. 2-Amino-5-nitropyridine (2.0 grams 71.4%) was recovered.

Preparation of 2,6-di-(methylamino)-pyridine

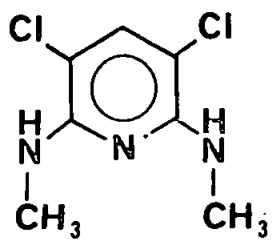


The method is a modification of Brenstein et al's[10].

A mixture of 2,6-dibromopyridine (30.4 grams 0.128 M) and an aqueous solution of methylamine (25% w/w 128 cm^3) was heated in a large stainless steel bomb for 24 hours at 185°C - 195°C. The cooled yellow reaction mixture was diluted with distilled water (320 cm^3) and made strongly alkaline with aqueous potassium hydroxide solution (40% w/v). The mixture was extracted with diethyl ether (4 x 240 cm^3) and the combined extracts were dried over anhydrous potassium carbonate and evaporated to dryness after filtration. The residue was vacuum distilled and the fraction boiling at 142°C at 3 mm of mercury was collected. The product weighed 9.0 grams (41% lit[10] 59.0%) and melted at 67°C - 70°C (lit[10] 70°C - 71°C). The material was used without any further purification.

Infra-red (KBr) 3390, 3060, 1600, 1465, 1443, 1368, 768, 700, 542 cm^{-1}.

A Gassman reaction on 2,6-di-(methylamine)-pyridine
(Preparation of 3,5-di-chloro-2,6-di-(methylamino)-pyridine)

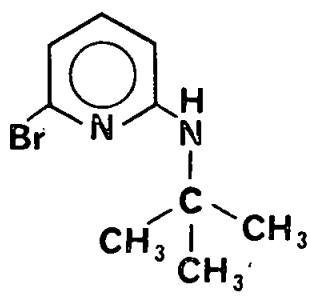


To a stirred solution of 2,6-di-(methylamino)-pyridine (3.42 grams 25 m mol) in dichloromethane (78 cm^3) at -65°C was added dropwise a solution of tertiary butyl hypochlorite (5.5 grams 50 m mol) in dichloromethane (12.5 cm^3) at -65°C. The reaction mixture was stirred for 1 hour at -65°C. Methylthio-propan-2-one ethylene ketal (7.4 grams 50 m mol) at -65°C was added and the solution stirred for a further hour. The mixture was allowed to warm to room temperature and rotary evaporated to dryness. The resulting oily solid was refluxed in a solution of potassium tertiary butoxide (11.2 grams 100 m mol) in tertiary butanol (275 cm^3) for 7.5 hours. The solvent was removed on a rotary evaporator and distilled water (180 cm^3) was added. The resulting solution was then extracted with diethyl ether (4 x 150 cm^3) and the combined extracts were evaporated to dryness and the resulting oil was stirred with hydrochloric acid (300 cm^3 1 molar) and diethyl ether (200 cm^3) for 2 days at room temperature. The aqueous layer was separated and basified to pH 9 - 10 with aqueous sodium hydroxide solution (10% w/v).

The resulting suspension was extracted with diethyl ether (4 x 500 cm^3) and the combined extracts were dried over anhydrous sodium sulphate, filtered and evaporated to yield a dark brown oily crystalline solid. T.L.C. (toluene: acetone 2:1 silica gel) showed it to consist mainly of a product at R_f 0.92 giving a dark grey colour to Ehrlichs reagent. The solid was subjected to column chromatography (silica gel 60°C - 80°C petroleum ether/ toluene. This gave 3,5-dichloro-2,6-di-(methylamino)-pyridine. The product was recrystallised from 40°C - 60°C petroleum ether to give white crystals (1 gram 19.1%) of melting point 102°C - 104°C. The crystals and the material left on the column were very sensitive to heat and light and air.

Infra-red (KBr)	3460, 3420, 3385, 2935, 1595, 1572, 1508, 1390, 1270, 1250, 1020, 896, 740 cm^{-1}.
N.M.R.τ($(CD_3)_2SO$)	2.69(1H s 4-H), 3.88(2H's m 2-NH's), 7.16(6H's d CH_3's)
Mass Spec m/e	207(64.9), 205(100), 190(15.6), 179(41.6), 170(15.6), 114(15.6%).

Preparation of 2-N-tertiarybutylamino-6-bromopyridine



A mixture of 2,6-dibromopyridine (16 grams 0.068 M) and tertiary butylamine (51.3 grams 0.7 M) and water (40 cm^3) was heated at 185°C - 195°C for 2 days in a stainless steel bomb. The cooled reaction mixture was diluted with distilled water (200 cm^3) and made strongly alkaline with aqueous potassium hydroxide solution (40% w/v). The mixture was then extracted with diethyl ether (4 x 150 cm^3) and the combined extracts were dried over anhydrous potassium carbonate, filtered and evaporated to dryness. The residue was vacuum distilled and the fraction boiling at 143°C at 7 mm or mercury collected. This gave 2-N-tertiarybutylamino-6-bromopyridine (7.5 grams 48.3%) as a syrupy liquid.

Infra-red (NaCl liquid cell)	3418, 2970, 1593, 1496, 1450, 1437, 1229, 1160, 1128, 980, 773 cm^{-1}.
N.M.R.τ($(CD_3)_2SO$)	2.78(1H dd 4-H J_{34} 6Hz J_{54} 7Hz), 3.43(1Hd 5-H J_{45} 5Hz), 3.58(1H d 3-H J_{43} 6Hz), 8.68 (9H's s CH_3's) 5.08(1H diffuse NH)
Mass Spec m/e	230(21.4), 228(21.4), 215(78.6), 213(81.5), 174(57.2), 172(60.0), 93(100), 66(21.4), 57(48.6%).

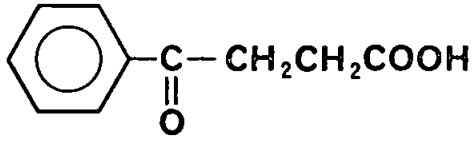
Attempted Gassman reaction on 2-N-tertiarybutylamino-6-bromopyridine

To a stirred solution of 2-N-tertiarybutylamino-6-bromopyridine (4.6 grams 20 m mol) in dichloromethane (100 cm^3) at -15°C was added dropwise

a solution of tertiary butyl hypochlorite (2.2 grams 20 m mol) in dichloromethane (10 cm^3) at -15°C and the mixture was stirred for 0.7 hour. A solution of methylthioethan-2-one dimethyl acetal (2.72 grams 20 m mol) in dichloromethane (10 cm^3) at -15°C was added and the mixture stirred for 0.9 hour. The mixture was allowed to warm to room temperature and evaporated to dryness. The resultant oily solid obtained was refluxed for 6 hours in a solution of potassium tertiary butoxide (4.5 grams 40 m mol) in tertiary butanol (120 cm^3). The solvent was rotary evaporated off and distilled water (50 cm^3) was added. The resultant solution was extracted with diethyl ether (5 x 100 cm^3) and the combined extracts were evaporated to dryness. The residue was stirred with hydrochloric acid (60 cm^3 1 molar) for 2 days and the solution was basified to pH 9 - 10 with aqueous sodium hydroxide (10% w/v). The resulting solution was extracted with diethyl ether (4 x 100 cm^3) and the combined extracts were dried over anhydrous sodium sulphate, filtered and evaporated to dryness. The resulting oil was subjected to column chromatography to yield, after purification by vacuum distillation, 2-N-tertiarybutylamino-6- bromopyridine (4.2 grams 91.5%).

DERIVATIVES OF KNOWN SYSTEMS

Preparation of β-benzoylpropanoic acid



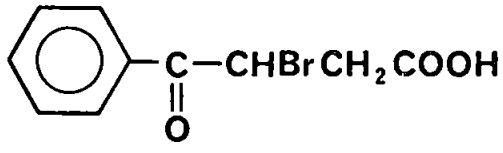
The method is that of Somerville and Allen[50].

Succinic anhydride (34 grams 0.34 M) and benzene (175 grams 2.25 M) were placed in a reaction vessel (1 litre) fitted with 2 reflux condensers, a dropping funnel and a vibromix stirrer. The mixture was agitated and powdered anhydrous aluminium chloride (100 grams 0.75 M) was added. Large quantities of hydrogen chloride were evolved and the mixture was refluxed for 0.5 hour. The vessel was then cooled to 0°C and cold water (150 cm^3)

was added slowly with stirring followed by concentrated hydrochloric acid (50 cm^3). The benzene was then removed by steam distillation. The hot mixture was transferred to a round bottomed flask (1 litre) and allowed to cool and then chilled to 0^oC. The solution was filtered and the retained solid was washed with hydrochloric acid (25% w/v 100 cm^3). The crude acid was dissolved in aqueous sodium carbonate solution (15% w/v 250 cm^3) and the solution boiled for 0.25 hour. The solution was filtered and the retained aluminium hydroxide washed with boiling water (50 cm^3). The filtrate was charcoal treated and cooled to 50^oC - 60^oC and carefully acidified with concentrated hydrochloric acid (65 cm^3). After cooling to 0^oC the white crystalline solid was filtered off and dried at 40^oC - 60^oC. This yielded β-benzoylpropanoic acid (52.0 grams 86.5% lit^{50} 77 - 82%) of melting point 116^oC - 118^oC (lit^{50} 116^oC). The product was used without further purification.

Infra-red (KBr) 3000, 1688, 1599, 1450, 1404, 1350, 1240, 1174, 768, 692 cm^{-1}.

Preparation of β-bromo-β-benzoylpropanoic acid



The method is a modification of that of Knott[51].

β-Benzoylpropanoic acid (41.5 grams 0.28 M) was dissolved in chloroform (1.25 litre) and the solution heated to boiling and bromine (40 grams 0.5 M) was added in small quantities with stirring. After the addition was completed the solution was stirred for 0.25 hour. The solution was washed with water (4 x 500 cm^3) and then dried over anhydrous sodium sulphate. After filtration the solution was evaporated to dryness to yield a white solid. The solid was recrystallised from benzene after charcoal treatment. This yielded product (34.7 grams 58.4%) of melting point 125^oC - 127^oC (lit^{56} 126^oC).

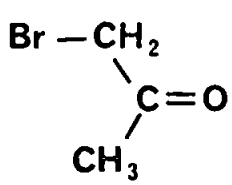
Infra-red (KBr) 3070, 3010, 1718, 1680, 1597, 1450, 1403, 1314, 1242, 1185, 943, 713, 688, 640 cm^{-1}.

The product was used without any further purification.

Attempted preparation of 2,3,7-triphenyl-1H-imidazo[1,2-a]pyrrolo[3,2-e]pyridine-8-acetic acid

2,3-Diphenyl-6-amino-1H-pyrrolo[2,3-b]pyridine (4.8 grams 0.017 M), β-benzoyl-β-bromopropanoic acid (4.6 grams 0.017 M), sodium bicarbonate (3.2 grams 0.04 M), ethanol (60 cm^3) and water (10 cm^3) were placed in a round bottomed flask (100 cm^3) fitted with a reflux condenser and refluxed for 1 hour. The mixture was filtered from the tarry residue and poured into water (150 cm^3). A yellow tarry solid came down. The suspension was extracted with diethyl ether (200 cm^3) and chloroform (200 cm^3). The solutions after drying over anhydrous sodium sulphate and filtering were charcoal treated and evaporated to dryness to yield tarry solids. These were taken up in ethanol, treated with charcoal and recrystallised from ethanol/water. This yielded 2,3-diphenyl-6-amino-1H-pyrrolo[2,3-b]pyridine (4.05 grams 84.3%) No acid was recovered but a large amount of black tar was recovered from the mother liquor.

Preparation of bromopropan-2-one



The method is that of Levene[52]. Into a reaction vessel (1.5 litre) fitted with a reflux condenser, a dropping funnel, a thermometer and a stirrer and surrounded by a water-bath was placed water (550 cm^3), propan-2-one (167 cm^3) and glacial acetic acid (124 cm^3). Bromine (118 cm^3) was added over 1 hour with stirring to the heated (65°C) reaction mixture and the mixture maintained at 65°C until the solution had decolourised. The solution was diluted with water (267 cm^3) and cooled to 10°C. Anhydrous sodium carbonate (333 grams) was then added until the solution was neutral

to congo red. The oil that separated was separated from the aqueous layer and dried over anhydrous calcium chloride. The oil was vacuum distilled and the fraction boiling at 38°C - 48°C at 10 mm of mercury collected. This gave 118 grams (40.2 lit[52] 43 - 44%) of product. The product was used without further purification.

Attempted preparation of 2,7-dimethyl-1H-imidazo[1,2-a]pyrrolo[3,2-e] pyridine

Bromopropan-2-one (2.05 grams 0.015 M), 2-methyl-6-amino-1H-pyrrolo [2,3-b]pyridine (2.0 grams 0.0125 M) ethanol (10 cm^3), water (5 cm^3) and sodium hydrogen carbonate (1.1 grams) were refluxed together for 1 hour. The solution was cooled and ammonia solution (5 cm^3 5 molar) and water then added. A black tar separated. Attempts at purification of this tar by column chromatography (acidic alumina) and recrystallisation were not successful.

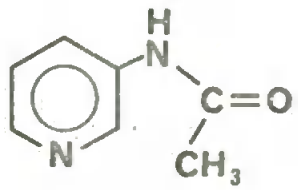
A melt reaction was then attempted as follows:-

A mixture of 2-methyl-6-amino-1H-pyrrolo[2,3-b]pyridine (1.47 grams 0.01 M) and a bromopropan-2-one (1.5 grams 0.0107 M) was stirred at 120°C for 0.2 hour and then at 180°C for 0.2 hour. The melt was cooled, pulverised and dissolved in hot ethanol (50 cm^3). The resulting solution was basified by aqueous sodium hydroxide solution (10% w/v) and poured into water (100 cm^3). A brown tarry solid came down, on filtration and exposure to light and air this material rapidly darkened. Attempts to purify this material by crystallisation and column chromatography (acidic alumina) were not successful.

The above two experiemnts were repeated using chloropropan-2-one in the same molar amounts. Again black polymeric material was obtained but some product was detected in the crude product by T.L.C. (toluene: acetone 2:1 silica gel) as a pink spot to Ehrlichs reagent R_f 0.09 but its presence was only in small amounts (3.4%)* and attempts to separate this by column chromatography (acidic alumina) were not successful.

* Estimated by chromoscan of TLC plate.

Preparation of 3-acetylaminopyridine



The method is that of Vogel[53] for aniline.

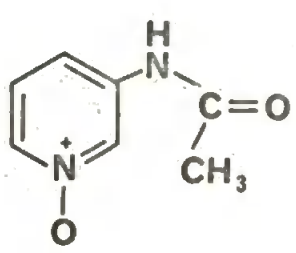
In a round bottomed flask (500 cm^3) fitted with a reflux condenser was placed 3-aminopyridine (18.8 grams 0.2 M), acetic anhydride (19.9 grams 0.195 M), acetic acid (20 cm^3) and zinc dust (1.0 gram). The mixture was refluxed for 0.5 hour. The hot liquid was poured onto crushed ice (100 grams) with stirring and neutralised with solid sodium carbonate. A heavy white precipitate came down, this was filtered off and recrystallised from water. This yielded 19.3 grams (71.0%) of product of melting point 130°C - 131°C (lit[57] 130°C - 133°C).

Infra-red (KBr) 2980, 1689, 1584, 1552, 1482, 1423, 1293, 1054, 1021 820, 710, 628, 605, 548 cm^{-1}.

N.M.R.τ ($(CD_3)_2SO$) -0.20(1H diffuse NH), 1.27(1H d 2-H J_{42} 3Hz), 1.75 (1H dd 6-H J_{56} 5Hz J_{46} 2Hz), 1.95(1H m 4-H), 2.70 (1H dd 5-H J_{65} 4Hz J_{45} 5Hz), 7.93 (3H's s CH_3).

Mass Spec m/e 136(32.6), 94(100), 67(21.8), 43(32.6%).

Preparation of 3-acetylaminopyridine-N-oxide



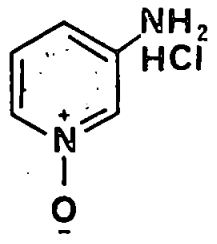
This is based on the method of Jaffe' and Doak[54].

3-Acetylaminopyridine (30.0 grams 0.22 M) was dissolved in glacial acetic acid (150 cm^3) in a round bottomed flask (500 cm^3) fitted with a stirrer and dropping funnel and placed in a water-bath. Hydrogen peroxide (25 cm^3 35% w/v aqueous solution) was added with stirring and the mixture was heated at 70°C - 80°C for 3 hours. After this time hydrogen peroxide (17.5 cm^3 35% w/v) was again added (0.85 M in total) and the mixture kept

stirred at 70°C - 80°C for a further 17 hours. The solution was evaporated to dryness leaving a brown oil which after titration with diethyl ether gave a yellow brown solid. The material was extracted with hot chloroform and the solid obtained by evaporating the extracts, recrystallised from propan-2-one with charcoal treatment. This gave the product as white crystals 15.2 grams (45.4% lit[54] 26.0%) of melting point 205°C - 207°C (lit[54] 215.5°C - 216.5°C).

Infra-red (KBr)	3430, 3010, 1680, 1622, 1590, 1570, 1489, 1419, 1373, 1312, 1154, 979, 860, 802, 780, 678, 556 cm^{-1}.
N.M.R. $\tau((CD_3)_2SO)$	-0.28(1H diffuse NH), 1.29(1H m 4-H), 2.05(1H m 5-H), 2.63(1H d 2-H), 2.63(1H d 6-H), 7.94(1H s CH_3).
Mass Spec. m/e	152(2.0), 136(26.0), 94(100), 67(28.0), 43(44.0%).

Preparation of 3-aminopyridine-N-oxide hydrochloride

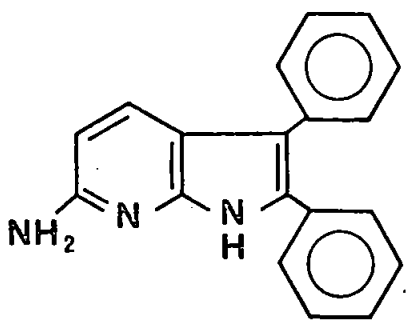


This is the method of Jaffé and Doak[54]. 3-Acetylaminopyridine-N-oxide (11.0 grams 0.1 M) was heated with aqueous sodium hydroxide solution (100 cm^3 10% w/v) in a flask (250 cm^3) on a steam-bath for 1 hour. The solution was neutralised to pH 6.3 with concentrated hydrochloric acid and evaporated to dryness under vacuum. The residue was extracted with absolute ethanol and the solution was treated with charcoal and filtered. A few drops of concentrated hydrochloric acid were added and the slight precipitate of salt was filtered off. The solution was evaporated to dryness and the residue recrystallised from ethanol/diethyl ether. This yielded 9.8 grams (92.0%). This material was used without any further purification as it appeared to be extremely heat, light and air sensitive.

Attempted Bischler reaction using 3-aminopyridine-N-one hydrochloride

3-Aminopyridine-N-oxide hydrochloride (3.7 grams 0.025 M) and 2-hydroxycyclohexanone (3 grams 0.028 M) in toluene (100 cm^3) were refluxed in a Dean and Stark apparatus for 20 hours. The hot toluene solution was decanted free from the tarry, residue and cooled. A tarry solid was obtained. T.L.C. (toluene: acetone 2:1 silica gel) on this and the residue showed them to consist of starting materials. 3-amino-Pyridine-N-oxide hydrochloride (2.0 grams 72.8%) was obtained on recrystallisation of the tarry solids from ethanol/diethyl ether. A large amount of 2-hydroxycyclohexanone was indicated along with dark material of low R_f by T.L.C. in the mother liquor.

Preparation of 2,3-diphenyl-6-amino-1H-pyrrolo[2,3-b]pyridine



The method is based on that of Bernstein et al[10].

2,6-diaminopyridine (16.4 grams 0.15 M) and concentrated hydrochloric acid (9 cm^3 0.1 M) were heated to dryness. To the stirred residue obtained benzoin (21.3 grams 0.1 M) was added and the mixture heated and stirred at 180°C - 190°C for 1 hour. The melt was cooled, pulverised and suspended in hydrochloric acid (50% v/v 100 cm^3). The insoluble residue was filtered off and suspended in ammonia solution (100 cm^3 5 molar) overnight. The crude product was filtered off and crystallised from glacial acetic acid with charcoal treatment. The crystals were filtered off and washed with a little aqueous ethanol. This gave product 23.6 grams (82.8% lit[10] 87.0%) of melting point 236°C - 238°C (lit[10] 234.5°C - 235.5°C).

The product was used without further purification.

Attempted Bischler reaction using 2-chlorocyclopentanone

2,3-Diphenyl-6-amino-1H-pyrrolo[2,3-b]pyridine (5.7 grams 0.02 M) was suspended in a solution of sodium hydrogen carbonate (2.3 grams) in ethanol (50 cm^3) and water (10 cm^3). To this was added 2-chlorocyclopentanone and the mixture was refluxed for 1 hour. A yellow precipitate was formed, which was filtered off and dissolved in ethanol and charcoal treated. The product was recrystallised from ethanol/water and was found to be 2,3-diphenyl-6-amino-1H-pyrrolo[2,3-b]pyridine (1.6 grams 28.6%). The mother liquor was examined by T.L.C. (2:1 toluene: acetone silica gel) and was shown to consist of 7 components and substrate a large amount of material occuring at a low R_f. The infra-red of this material showed it to have a similar spectrum to 2,3-diphenyl-6-amino-1H-pyrrolo[2,3-b]pyridine.

Attempted Bischler reaction using 3-hydroxypiperid-2-one

A solution of 2,6-diaminopyridine (1.55 grams 0.015 M), 3-hydroxypiperid-2-one (1.75 grams 0.016 M) and, hydrochloric acid (10% v/v 5 cm^3) in toluene (150 cm^3) was refluxed in a Dean and Stark apparatus for 18 hours. The hot toluene solution was decanted from the tarry residue and the residue extracted with hot toluene (150 cm^3). The combined extracts were evaporated to yield a buff coloured solid which was recrystallised from ethyl acetate after charcoal treatment. This yielded 3-hydroxypiperid-2-one

The tarry residue was shown by T.L.C. (2:1 toluene: acetone silica gel) to contain mainly 2,6-diaminopyridine.

A melt reaction was attempted as follows:-

2,6-Diaminopyridine (1.55 grams 0.015 M) and concentrated hydrochloric acid (1 cm^3) were heated to dryness. 3-Hydroxypiperid-2-one (1.75 grams 0.015 M) was then added and the melt was heated with stirring at 130°C - 140°C for 0.5 hour and at 180°C - 190°C for 0.5 hour. The melt was cooled, pulverised and stirred with excess hydrochloric acid (1 molar) for 1 hour. The solution was filtered and the residue stirred with excess ammonia

solution (5 molar) for 1 hour. The solution was filtered and the retained precipitate was shown by T.L.C. to consist of 3 components. An attempt was made to recrystallise this from glacial acetic acid but a black solid rapidly formed that was insoluble in a range of solvents and the solution went very dark. T.L.C. on the solid and solution showed dark material at very low R_f's.

Attempted bromination of 2,3-diphenyl-7-methoxy-1H- imidazo[1,2-a]pyrrolo [3,2-e]pyridine

A solution of bromine (2.4 grams) in chloroform (5 cm^3) was prepared and chilled in an ice-bath. 0.5 cm^3 of this solution was added over a period of 0.2 hour to a solution of 2,3-diphenyl-7-methoxy-1H-imidazo[1,2-a]pyrrolo [3,2-e]pyridine (0.47 grams 0.0015 M) in chloroform (5 cm^3) kept below 5°C. The mixture was allowed to stand for 0.2 hours and then stirred with hydrochloric acid (2.5 cm^3 2.5 molar) for 0.2 hour and cooled in ice. The based was precipitated with ammonium hydroxide solution (10 cm^3 5 molar) and extracted with chloroform (50 cm^3). The combined extracts were dried over anhydrous sodium sulphate and evaporated to dryness. T.L.C. (toluene: acetone 2:1 silica gel) showed the residue to consist of 7 components. Attempts at purifying the residue by crystallisation, preparative T.L.C., column chromatography, and sublimation were unsuccessful.

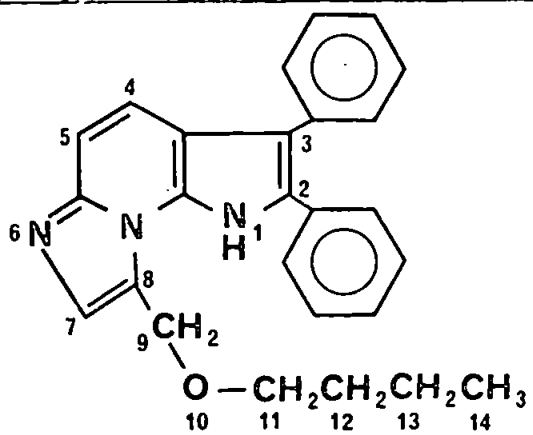
Attempted Mannich reaction in n-butanol on 2,3-diphenyl-1H-imidazo[1,2-a] pyrrolo[3,2-e]pyridine

A solution of 2,3-diphenyl-1H-imidazo[1,2-a]pyrrolo[3,2-c]pyridine (0.96 grams 0.0031 M), hydrochloric acid (0.003 M 1 cm^3 30% v/v), and paraformaldehyde (0.1 grams 0.003 M) in n-butanol (15 cm^3) was refluxed for 0.75 hour. The solution was cooled and ammonia (6 cm^3 2 molar) was added. The light brown precipitate which formed was filtered off and dried at the pump. T.L.C. showed this to consist of substrate which weighed after drying at 100°C 0.9 grams (93.8%). No Mannich base was detected.

REVIEW OF SPECTRA

Preparation of 2,3-Diphenyl-8-n-butoxymethyl-1H-imidazo[1,2-a]pyrrolo [3,2-e]pyridine

Exchange reaction between 2,3-diphenyl-8-dimethylaminomethyl-1H-imidazo [1,2-a]pyrrolo[3,2-e]pyridine and n-butanol



2,3-Diphenyl-8-dimethylaminomethyl-1H-imidazo[1,2-a]pyrrolo[3,2-e]pyridine hydrochloride[0.27 gram 0.67 M Mol] was refluxed in n butanol (10 cm^3) for 0.75 hour. The solid dissolved to form a yellow solution. The solution was cooled and ammonia solution (2 cm^3 2 molar) was added. A cloudy white solid was precipitated. The precipitate was extracted with diethyl ether (2 x 25 cm^3) and the combined extracts were were washed with water (25 cm^3) and dried over anhydrous sodium sulphate. The extracts after filtration were evaporated to dryness to yield an oil which on titration with ether gave a white solid. This was dried at 110°C and gave product 0.025 grams (10.0%) of melting point 304°C - 306°C.

Infra red (KBr)	2930, 1630, 1603, 1580, 1465, 1442, 770, 700 cm^{-1}.
NMR $\gamma((CD_3)_2SO)$	-1.4(1H m NH), 2.72(10H m phenylprotons, 4-H, 5-H, 6-H), 2.99(5H m phenylprotons) 4.19(2H m 9-CH_2), 8.75(6H m 11, 12, 13-CH_2's), 9.45(3H's m CH_3).
Mass Spec m/e	395(17.1), 337(7.9), 323(23.7) 322(43.5), 321(100) 320(31.6), 160(5.3), 74(18.4), 60(27.7), 89(22.4) 56(98.9), 55(32.9%).

Elemental Analysis Theory C=79.0 H=6.3 N=10.6 O=4.1%

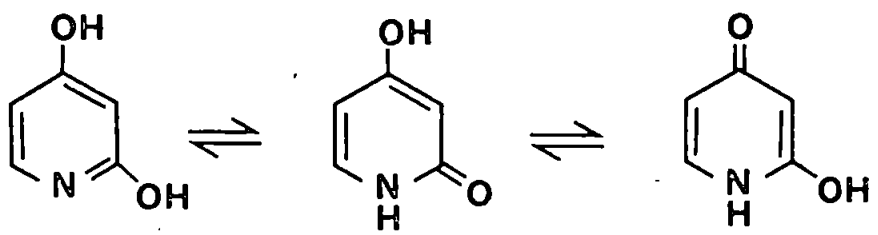
Found C=79.4 H=6.0 N=10.3 O=4.3%.

INRFA-RED SPECTRA

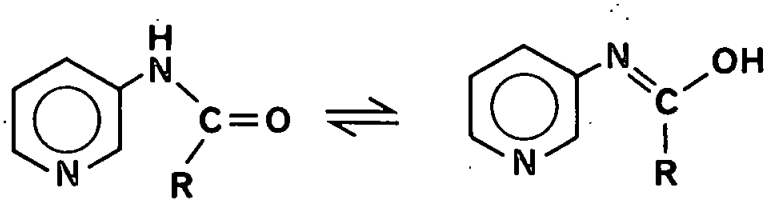
The infra-red spectra were recorded on a Perkin-Elmer 357 infra-red spectrophotometer, as a KBr disc or in NaCl cells.

Pyridine derivatives

All the pyridine derivatives synthesised showed the characteristic pyridine ring C-H vibrations (750 - 800 cm^{-1}). 2,4-dihyroxypyridines showed a characteristic broad band assigned to hydrogen bonded NH stretching around the 3000 - 3200 cm^{-1} region, together with a band assigned to C = O stretching around the 1650 cm^{-1} region. This is due to the existence of the forms shown below:-



They also show a broad band centred on 3490 cm^{-1} due to hydrogen bonded OH stretching. Compounds such as 3-acetylaminopyridine show a weak broad band centred at 3440 cm^{-1} assigned to hydrogen bonded OH stretching. This arises from equilibria of the type shown below:-



All other derivatives showed bands characteristic of the groups attached to the ring.

Pyrrolopyridines

These systems showed a broad band assigned to hydrogen bonded NH stretching in the region 3,000 - 3,200 cm^{-1}. Together with bands associated with the pyridine ring (750 - 800 cm^{-1}). All derivatives of this system showed bands, characteristic of the groups attached to the ring.

Dipyrrolopyridines

The 1H,7H,-dipyrrolo[2,3-b:3',2'-e]pyridine derivatives showed a characteristic strong sharp peak at about 3450 ± 25 cm^{-1}, assigned to the non hydrogen bonded NH stretching vibration. A broad band in the region 2850 - 3250 cm^{-1} is assigned to the hydrogen bonded NH stretching vibration. Again a strong peak assigned to pyridine ring C-H vibration is observed in the region 750 - 820 cm^{-1}.

The 1H,6H-dipyrrolo[2,3-b:2',3'-d]pyridine system shows a series of bands in the region 3000 - 3200 cm^{-1} assigned to the non hydrogen bonded and hydrogen bonded NH stretching vibrations. Again a strong band assigned to the pyridine ring C-H vibration is observed in the region 750 - 850 cm^{-1}.

Imidazopyrrolopyridines

The 1H-imidazo[1,2-a]pyrrolo[3,2-e]pyridine system gave broad bands in the region 2500 - 3200 cm^{-1} assigned to the hydrogen bonded NH stretching vibration. In contrast to the 1H,7H-dipyrrolo[2,3-b:3',2'-e]pyridine system no sharp peak due to the non hydrogen bonded form was present. A series of strong bands assigned to the pyridine ring C-H vibration is observed in the region 750 - 800 cm^{-1}. The fact that a series of bands are observed reflects the greater number of possible pyridine C-H vibration in the 1H-imidazo[3,2-e]pyridine system compared to the 1H,7H-dipyrrolo [2,3-b:3',2'-e]pyridine system.

Other Ring Systems

The 5,6,7,8,9,15,16,17,18,19,20-undecahydrodibenz[b,h]-N-hydropyrido [2,3-e]pyrido[2,3-k][1,4,7,10]tetra-azacyclododecine ring system shows a strong sharp peak at 3230 cm^{-1} assigned to the non hydrogen bonded NH stretching vibration. A broad band in the region 3350 - 3450 cm^{-1} is assigned to the hydrogen bonded NH stretching vibration. The rest of the spectrum showed the characteristic CH_2, CH, C-N and C-C vibrations but it is of interest to note that the characteristic strong bands due to pyridine ring C-H vibrations are very weak. This may indicate an involvement of the pyridine ring electrons in the system.

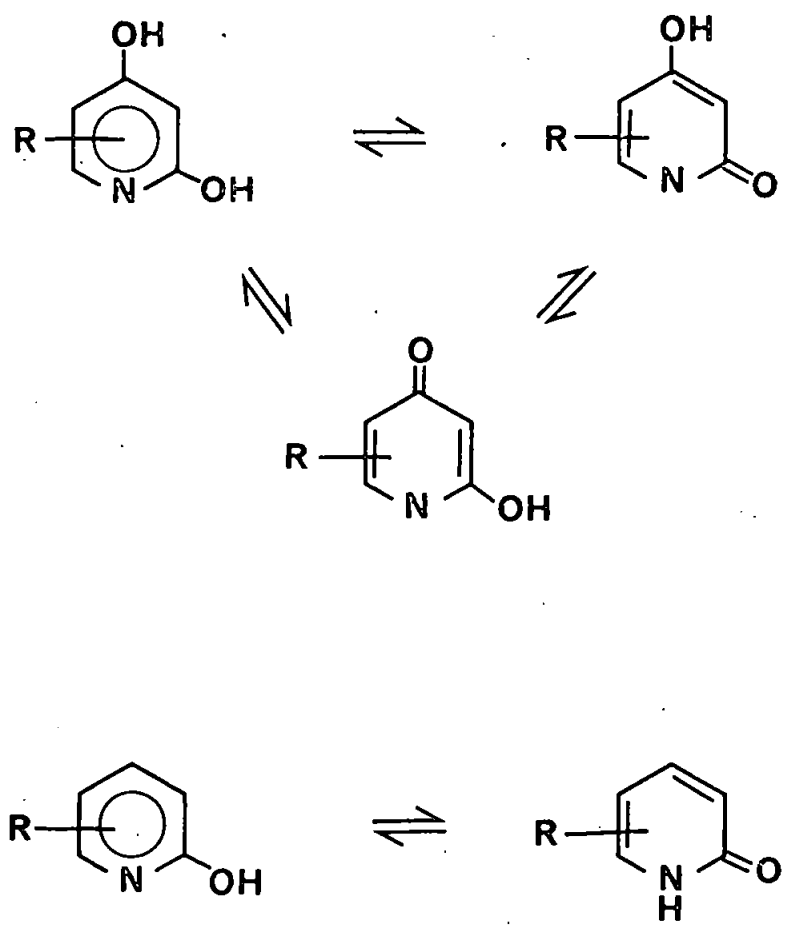
The 6,7,8,9 -tetrahydropyrido[3,4-b]quinoxaline system showed no bands that could be assigned to NH stretching vibrations. The rest of the spectrum showed the characteristic CH, CH_2, C-N and C-C, vibrations but here there were strong bands in the region 800 - 900 cm^{-1} assigned to the pyridine CH vibrations.

N.M.R. SPECTRA

The N.M.R. spectra were recorded at 60 MHz on a Perkin-Elmer R12B spectrometer using the solvents stated in the practical section for individual compounds.

Pyridine derivatives

A number of previously unrecorded spectra were obtained. 3 substituted pyridines showed 2,4; 2,5; 4,5 and 4,6 proton couplings in line with values found for similar 3-substituted pyridine derivatives. No 2,6 proton coupling was observed. 2,4 substituted pyridines showed 3,5, 3,6 and 5,6 proton couplings. 2-Hydroxy and 2,4 dihydroxypyridines showed a diffuse signal below 0.0τ due to NH protons and no signal due to hydroxyl protons. This is due to the tautomeric forms shown below:-



On integration the signals show almost complete conversion to the amide form as the NH signal integrates for nearly one proton.

2,6 substituted pyridines showed strong 3,4 and 4,5 proton coupling and a weak 3,5 proton coupling.

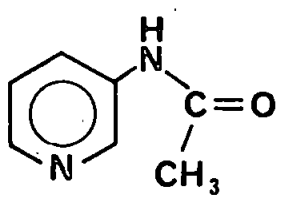
2,4,6 substituted pyridines showed only very small 3,5 proton coupling.

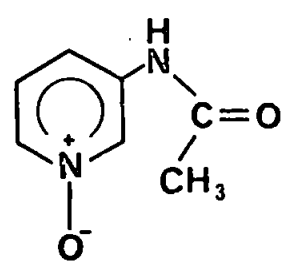
2,4,5 substituted pyridines showed no 3,6 proton coupling at all.

2,3,5 substituted pyridines showed 4,6 proton coupling to a small extent.

2,3,6 substituted pyridines showed a strong 4,5 proton coupling.

The spectrum of 3-acetylaminopyridine-N-oxide is of some interest when compared with the spectrum of 3-acetylaminopyridine. The pyridine-N-oxide spectra is shown in figure I and the pyridine derivative shown in figure 2





For 3-acetylaminopyridine the 2-H signal occurs at 1.27τ and is a doublet split by the 4-H proton. The 6-H signal occurs at 1.75τ and is a doublet of doublets and is split by the 5-H and 4-H protons. The 4H signal occurs at 1.95τ and is a doublet of doublet of doublets and is split by the 5-H, 6-H and 2-H protons. The 5-H signal occurs at 2.70τ and is a doublet of doublets and is split by the 4 and 6 protons.

FIGURE I

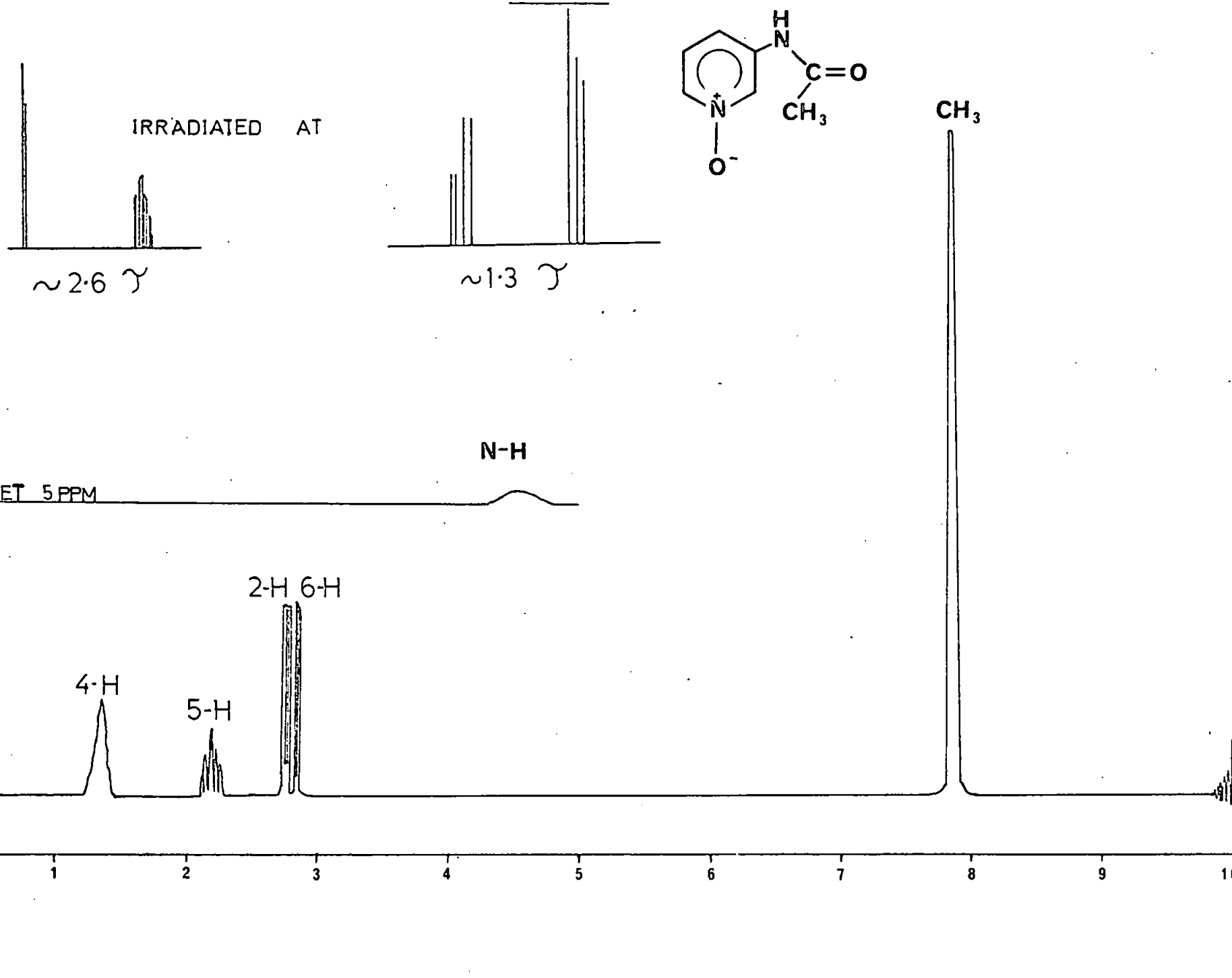
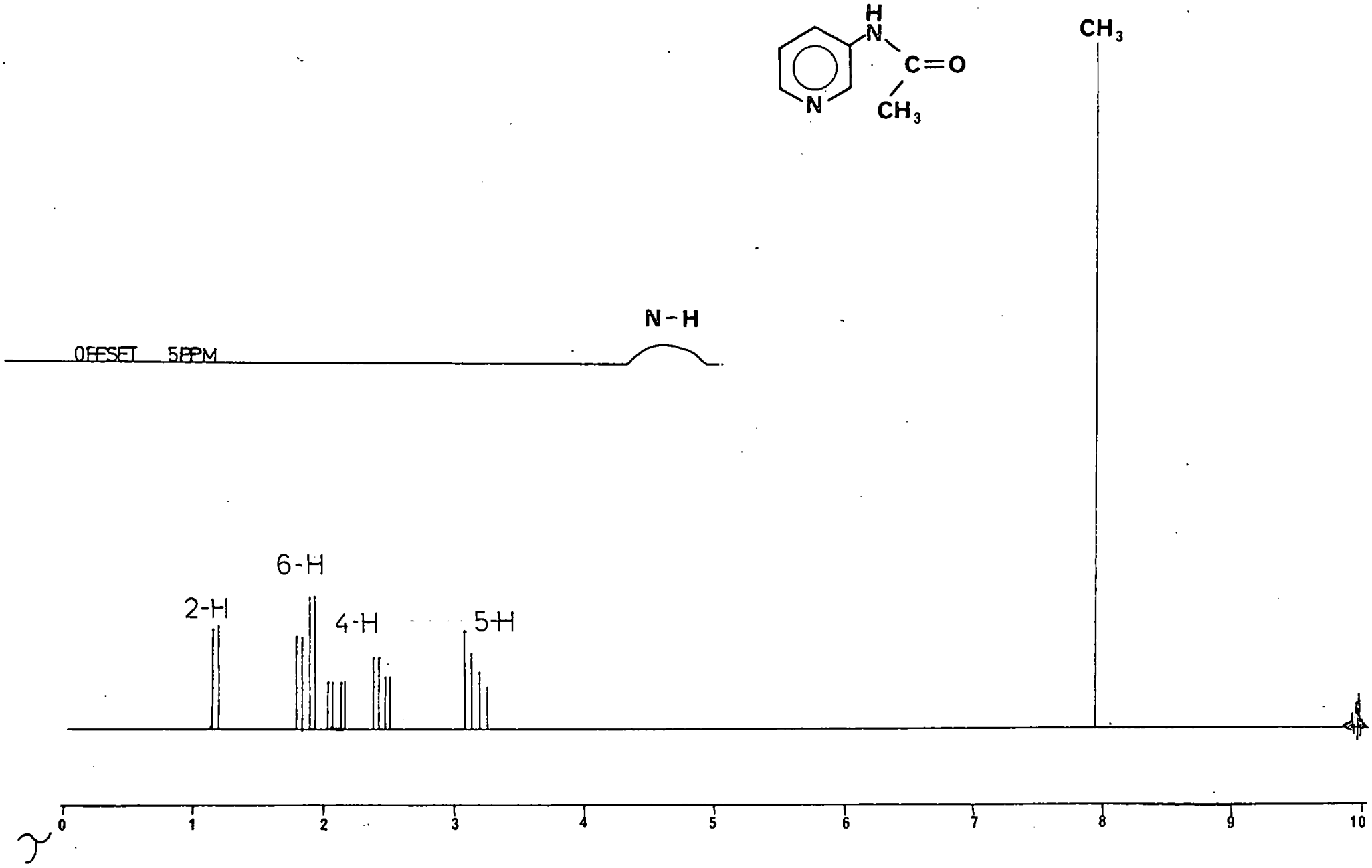

IRRADIATED AT
~2·6 τ
~1·3 τ
H
N
C=O
CH3
N+
O-
CH3
N-H
OFFSET 5 PPM
2-H 6-H
4-H
5-H
τ
0
1
2
3
4
5
6
7
8
9
10

FIGURE 2



For 3-acetylaminopyridine-N-oxide the 4-H signal occurs at 1.29τ as a multiplet. When the signal occuring at 2.60τ is irradiated the 4-H signal is resolved as a doublet coupled with the 5 proton. The 5-H signal occurs at 2.05τ as a multiplet, when the signal occuring at 1.30τ is irradiated this occurs as a doublet of doublets coupled with the 2 and 6 protons. When the signal occuring at 2.60τ is irradiated it occurs as a slightly diffuse doublet coupled with the 4 proton. The 2-H signal occurs at 2.63τ as a doublet coupled with the 4 proton when the 4-H signal is irradiated this doublet decays to a singlet. The 6-H signal occurs at 2.68τ as a doublet coupled with the 5-H proton.

This indicates that the 4-position is considerably deshielded in the pyridine-N-oxide compared to the pyridine derivative. The shifting downfield of the 5 position signal and the shifting upfield of the 2 and 6 position signals indicates a general shift of electrons towards the pyridine nitrogen.

Pyrrolopyridines

The NH proton of these systems appears as a broad peak below 0.0τ For 1H-pyrrolo[2,3-b]pyridines the 2 proton appears as a singlet, no splitting due to 1,2 coupling was observed. No derivatives unsubstituted in the 3-position were synthesised. The other protons of the ring system give signals similar to that of pyridine but shifted upfield.

For 1H-pyrrolo[3,2-b]pyridine the only derivatives synthesised were substituted in the 2 and 3 positions.

The NH proton appears as a diffuse signal below 0.0τ The 5-H, 6-H and 7-H signals occur as a doublet of doublets coupled with each other at 1.70, 2.35, 2.97τ respectively.

Dipyrrolopyridines

For 1H, 7H -dipyrrolo[2,3-b; 3',2'-e]pyridine the NH protons appear as a broad peak below 0.0τ The 4 proton appears as a singlet at 1.80τ no fine splitting of this signal could be detected. τ values will vary with substituents.

For the 1H, 4H -dipyrrolo[2,3-b; 2,3-d]pyridine system the NH protons appear as a very broad peak below 0.0τ. The 7 position was substituted in the derivative made so no information was obtained about the signal of the proton in the position.

Imidazopyrrolopyridines

The NH proton of the 1H imidazo[1,2-a]pyrrolo[3,2-e]pyridine system appears as a broad peak below 0.0τ. The derivatives made of this system had phenyl groups in the 2 and 3 positions and consequently the ring proton signal were masked and were not characterised.

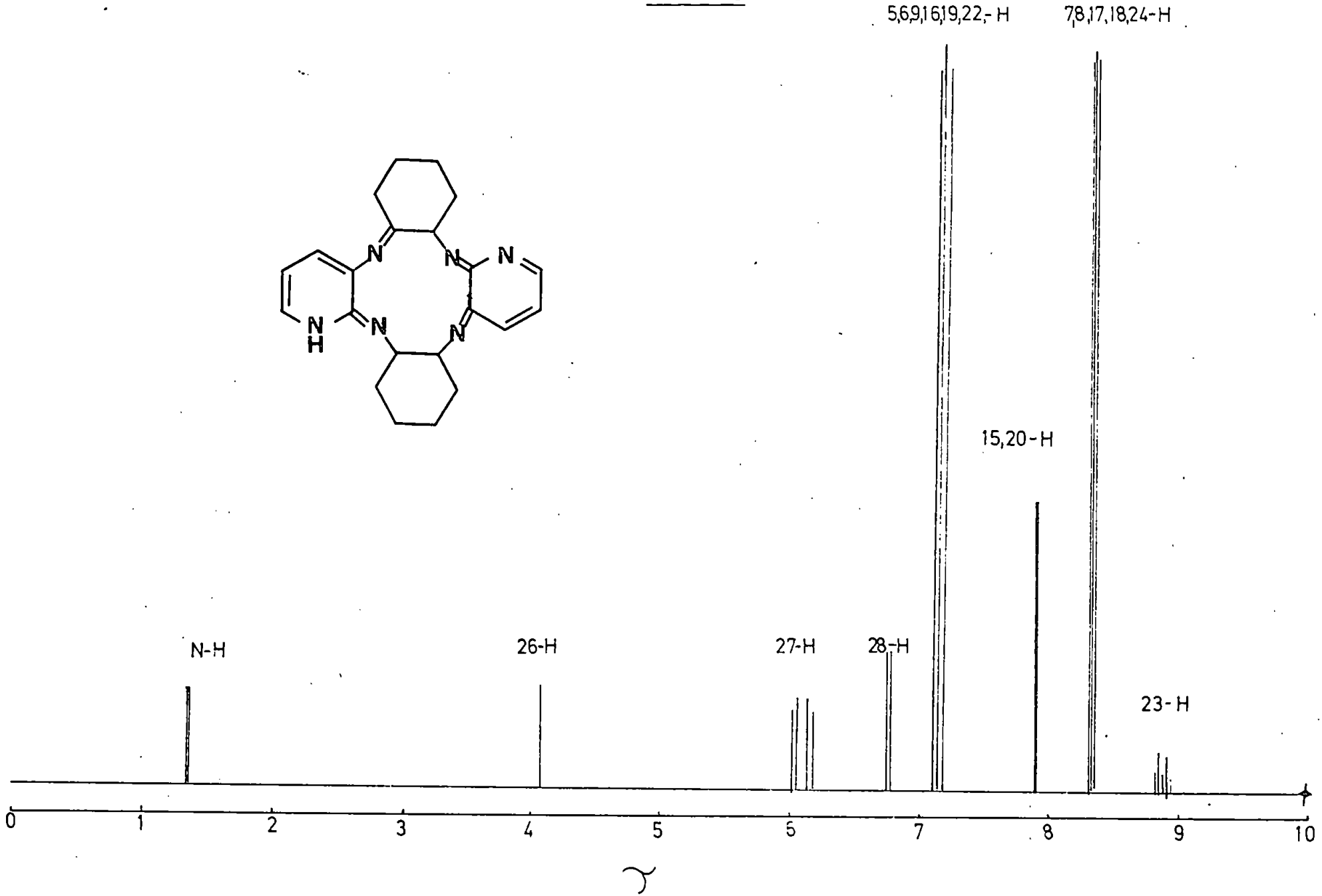
Other ring systems

The 6,7,8,9 -tetrahydropyrido[3,4-b] quinoxaline system shows the 12 proton as a singlet at 0.69τ, no fine splitting could be detected. The 14 and 13 protons occur as doublets coupled with each other at 1.28 and 2.15τ respectively. The 6 and 9 CH_2's occur as a multiplet at 6.91τ and the 7 and 8 CH_2's occur as a multiplet at 8.04τ.

The spectra of the 5,6,7,8,9,15,16,17,18,19,20-undecahydrodibenzo [b,h]-N-hydropyrido[2,3-e]pyrido[2,3-k][1,4,7,10]tetra-azacyclododecine. system was run at 220 MH_z by courtesy of P.C.M.U. The spectrum is interpreted as showing a NH signal at 1.38τ. The 26 proton appears as a singlet at 4.02τ. The 27 proton appears at 6.13τ as a doublet of doublets and the 28 proton appears as a doublet at 6.62τ. The 5,6,9, 16, 19, and 22 protons appear as a multiplet centred on 7.18τ. The 15 and 20 protons appear as a singlet at 7.87τ. The 7,8,17,18 and 24 protons appear as a multiplet centred at 8.27τ. The 23 proton appears as a multiplet centre at 8.60τ.

The spectrum is shown in figure 3. The spectrum when run in triflouroacetic acid becomes diffuse and alters indicating major conformational changes. The spectrum is interesting due to the unexpected absence of aromatic protons denoting complete loss of aromaticity of the pyridine rings.

FIGURE 3

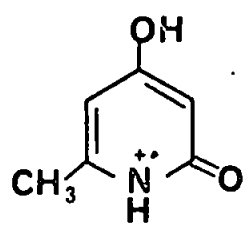

5,6,9,16,19,22,- H
7,8,17,18,24-H
15,20-H
N-H
26-H
27-H
28-H
23-H
0
1
2
3
4
5
6
7
8
9
10
τ

MASS SPECTRA

The mass spectra were recorded on a Perkin-Elmer Hitachi RMU6 spectrometer. Metastable peaks, where found were used to confirm any fragmentation suggested below.

Pyridine derivatives

A number of previously unrecorded spectra were obtained. 2,4 -dihydroxy-pyridines seem to involve cleavage of the pyridine ring rather than loss of the groups substituted on the ring. If we consider the spectrum of 2,4 -dihydroxy-6-methylpyridine (figure 4) we can see that the first main peak is due to the loss of carbon monoxide, this indicates the presence of a carbonyl group in the ring. The fragmentation of 2,4 -dihydroxy-6-methyl-pyridine is as shown below:

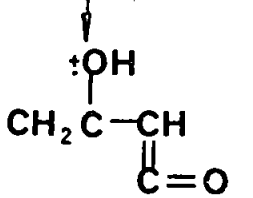


(100%)
125

$\xrightarrow[M^* \ 74{\cdot}1]{-CO}$ $C_5H_7\dot{N}O$

97 (16·9%)

$-CH_3CN$

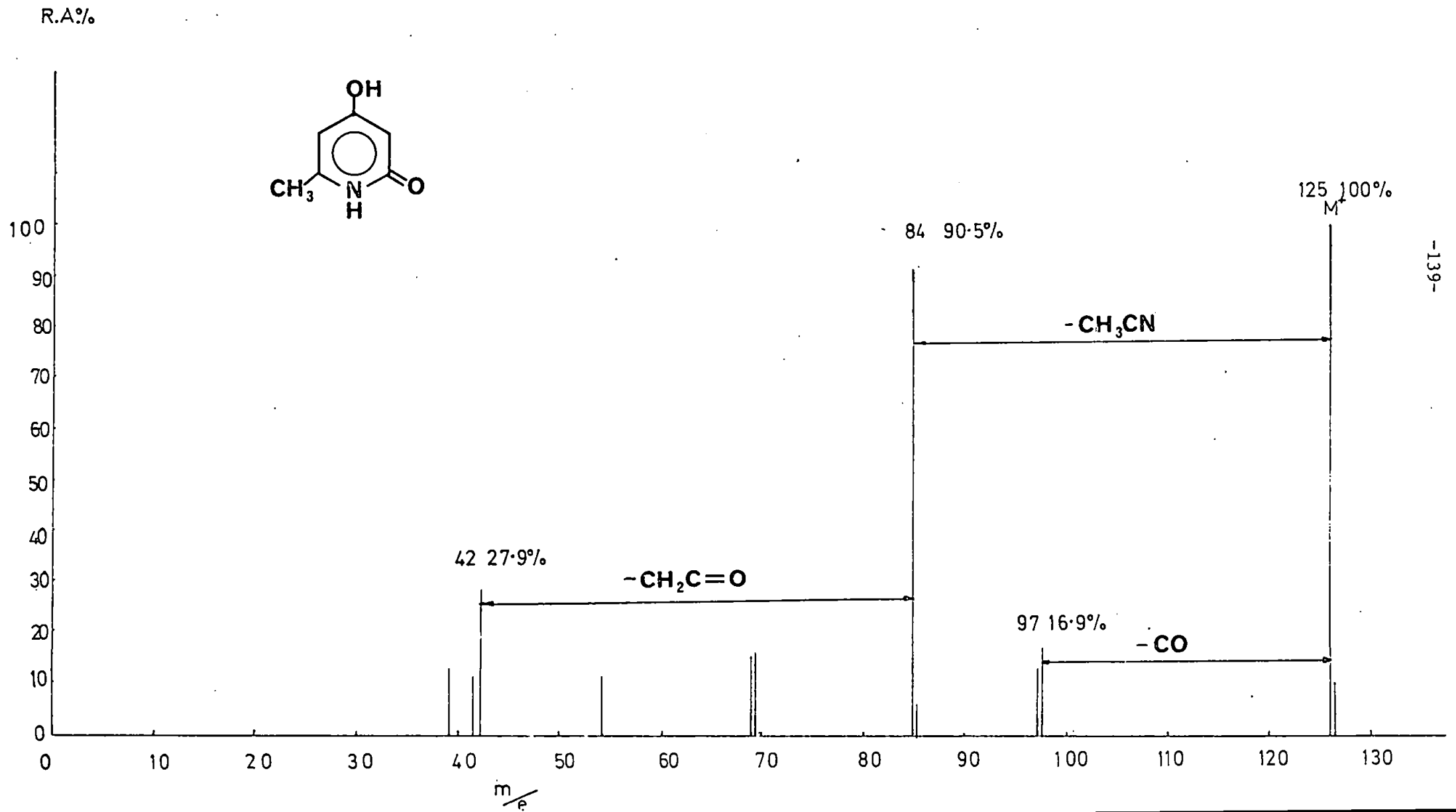


$\xrightarrow[M^* \ 21{\cdot}0]{CH_2=C=O}$ $CH_2=C=O$

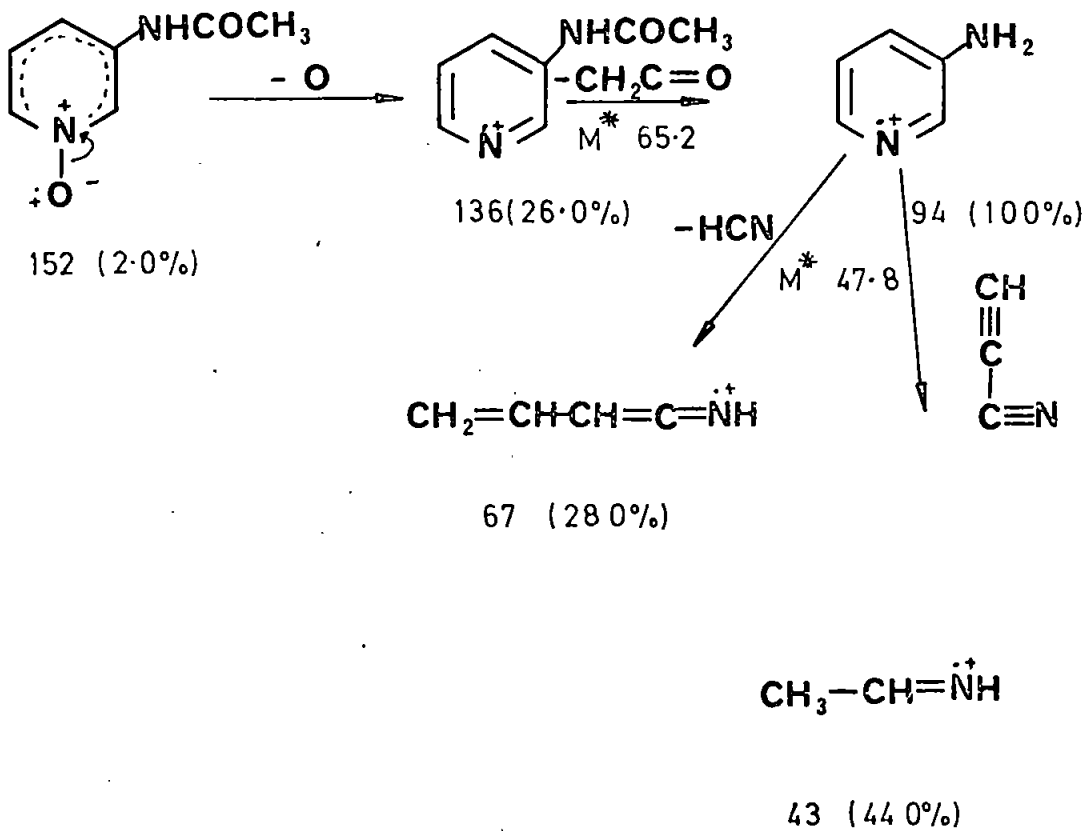
42 (27·9%)

84 (93·5%)

FIGURE 4

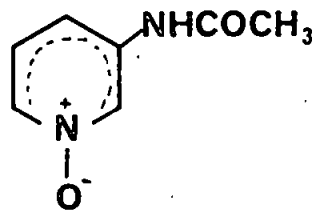

R.A.%
OH
CH3
N
H
O
125 100%
M+
84 90·5%
-CH3CN
42 27·9%
-CH2C=O
97 16·9%
-CO
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
80
90
100
110
120
130
m/e

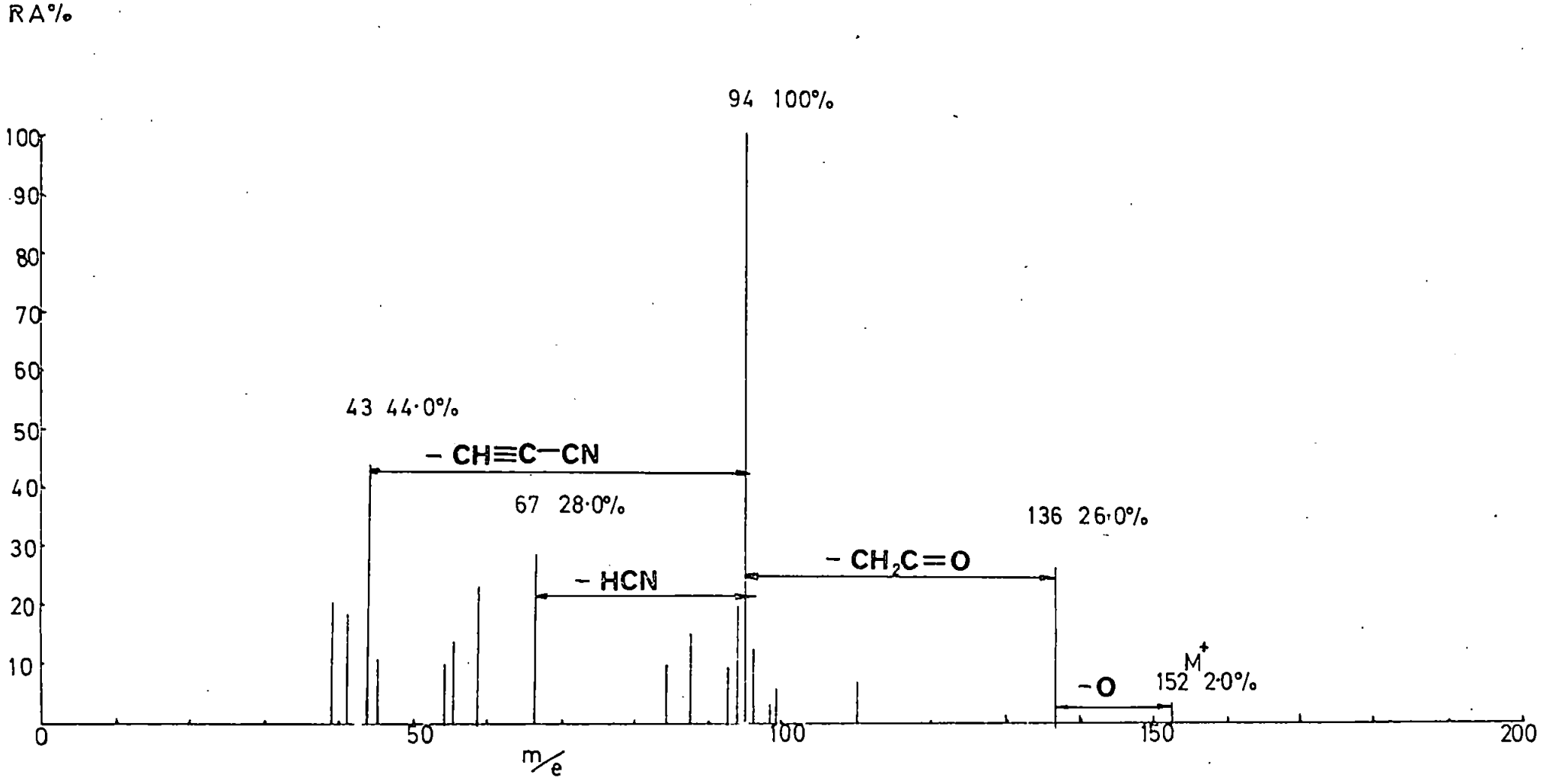
The spectrum of the 3-acetylaminopyridine-N-oxide (figure 5) involves the initial loss of an oxygen atom followed by loss of the acetyl group to give 3-aminopyridine. This is the same process that occurs with 3-acetylaminopyridine. The breakdown of the 3-aminopyridine then involves cleavage of the pyridine ring with the elimination of hydrogen cyanide. The formation of the N-oxide does not seem to affect the mass spectra. The fragmentation occurs as follows:



Other N-substituted aminopyridines fragment in a similar manner to the above although the most abundant ions in the spectra sometimes result from the breakdown of the N-substituent themselves (e.g. 3-tosyl-aminopyridine).

FIGURE 5

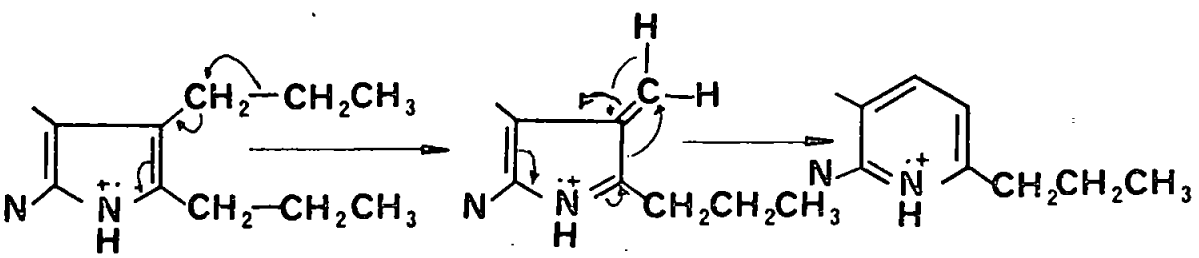

NHCOCH3
N+
O-

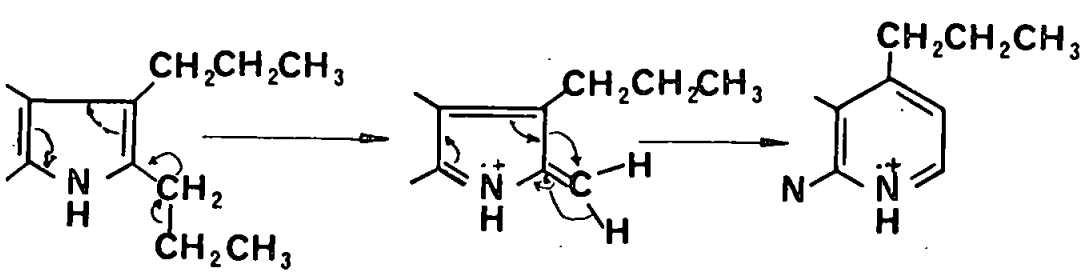

RA%
94 100%
43 44·0%
– CH≡C–CN
67 28·0%
– HCN
136 26·0%
– CH2C=O
– O
M+ 152 2·0%
100
90
80
70
60
50
40
30
20
10
0
50
100
150
200
m/e

Other substituted pyridines exhibited the types of fragmentations that would be expected of the substituents on the pyridine ring.

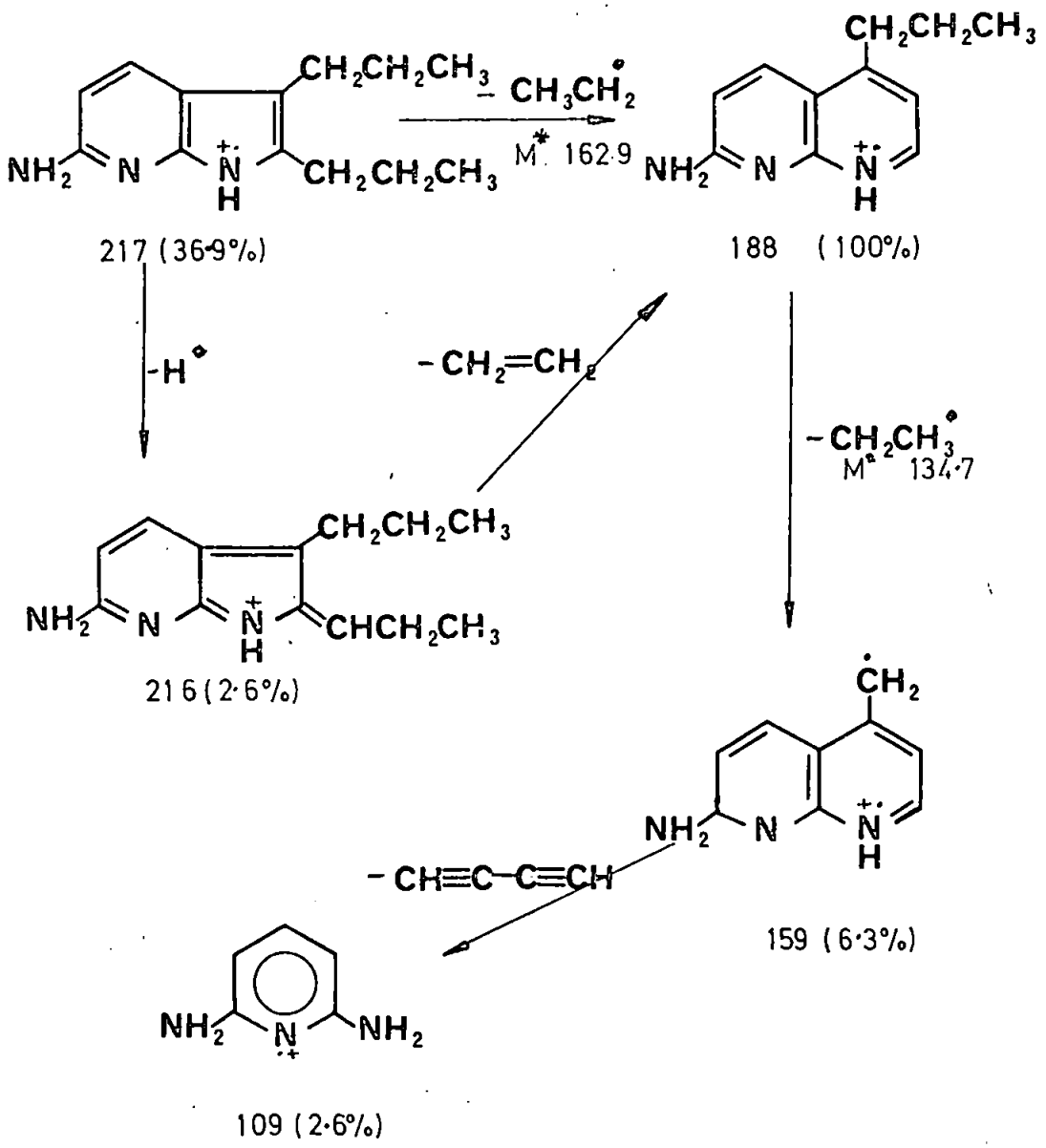
Pyrrolopyridines

For 1H-pyrrolo[2,3-b]pyridines, the spectra vary depending on the nature of the substituent. The fragmentation accompanying the 2,3 -diphenyl derivative was by initial loss of C_6H_5-CN from the molecular ion. However the abundance of this ion was relatively low reflecting the stabilising effect of the phenyl groups. The 2,3-di-n-propyl derivative however fragments by a different mechanism. On study of the spectrum (figure 6) it can be seen that the initial cleavage occurs by α cleavage of the alkyl groups, i.e. the formation of a M-C_2H_5 ion. This cleavage may be followed by ring expansion to give pyrrolonaphthyridinium ions as shown below:-



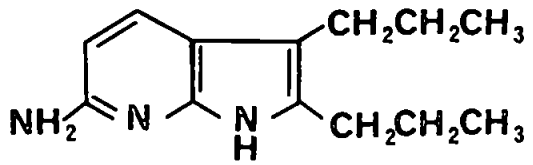


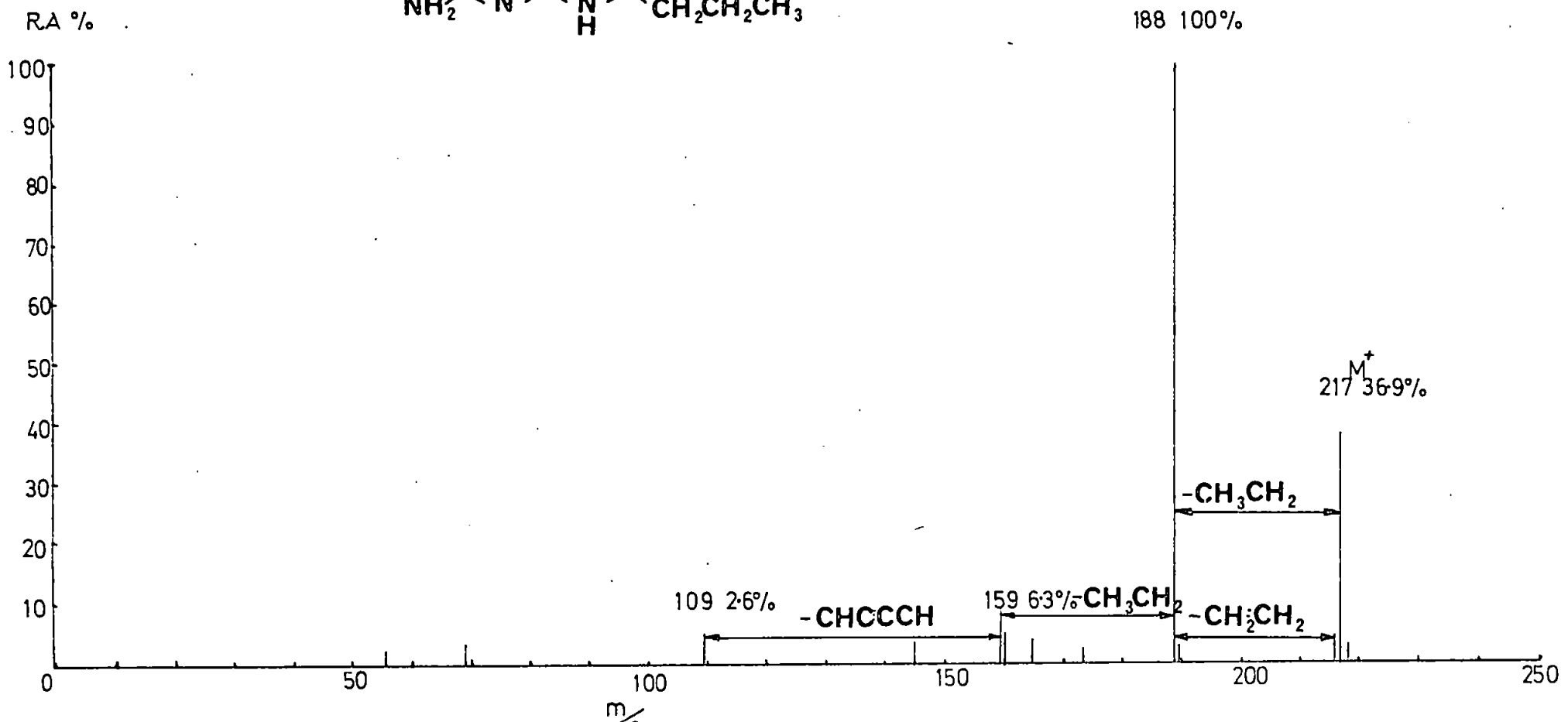
This type of fragmentation is important in the spectra of indoles[58] and has been found in other 1H-pyrrolo[2,3-b]pyridine derivatives[59]. The fragmentation is thought to follow the following scheme:



It can be seen that the competing reaction of α cleavage of a hydrogen atom is not favoured.

FIGURE 6


$CH_2CH_2CH_3$
NH_2
N
N
H
$CH_2CH_2CH_3$


R.A %
100
90
80
70
60
50
40
30
20
10
0
50
100
150
200
250
m/
188 100%
217 M^+ 36·9%
$-CH_3CH_2$
109 2·6%
$-CHCCCH$
159 6·3%
$-CH_3CH_2$
$-CH_2CH_2$

The spectra of the 1H-pyrrolo[3,2-b]pyridine system are similar to the 1H-pyrrolo[2,3-b]pyridine system again involving enlarging of the pyrrole ring.

Dipyrrolopyridines

The derivatives of the 1H,7H-dipyrrolo[2,3-b; 3′,2′-e]pyridine system have been shown by Ward[3] to give similar fragmentations as the monopyrrolopyridines although he shows that for a 2,3,5,6 tetraethyl derivative there is no expansion of the pyrrole rings. The spectrum (figure 7) of 1,2,3,4,5,7,8,9,10,11-decahydropyrido[2,3-b: 6,5,-b]diindole also shows this phenomena, no fragmentations arising from ring expansion being detected. The breakdown of 1,2,3,4,5,7,8,9,10,11 -decahydropyrido-[2,3-b; 6,5-b]diindole occurs as follows:

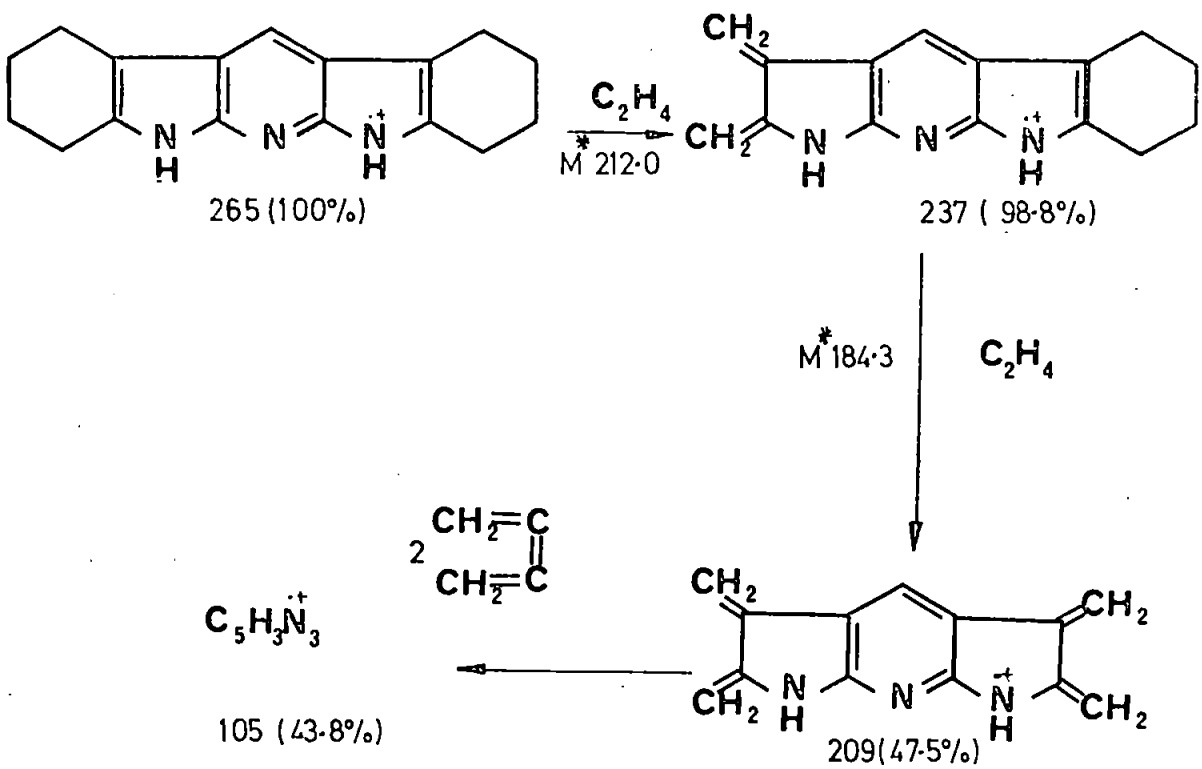
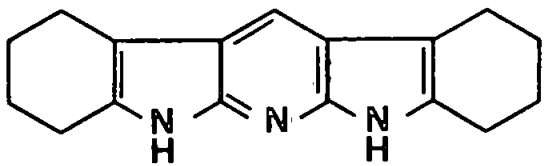
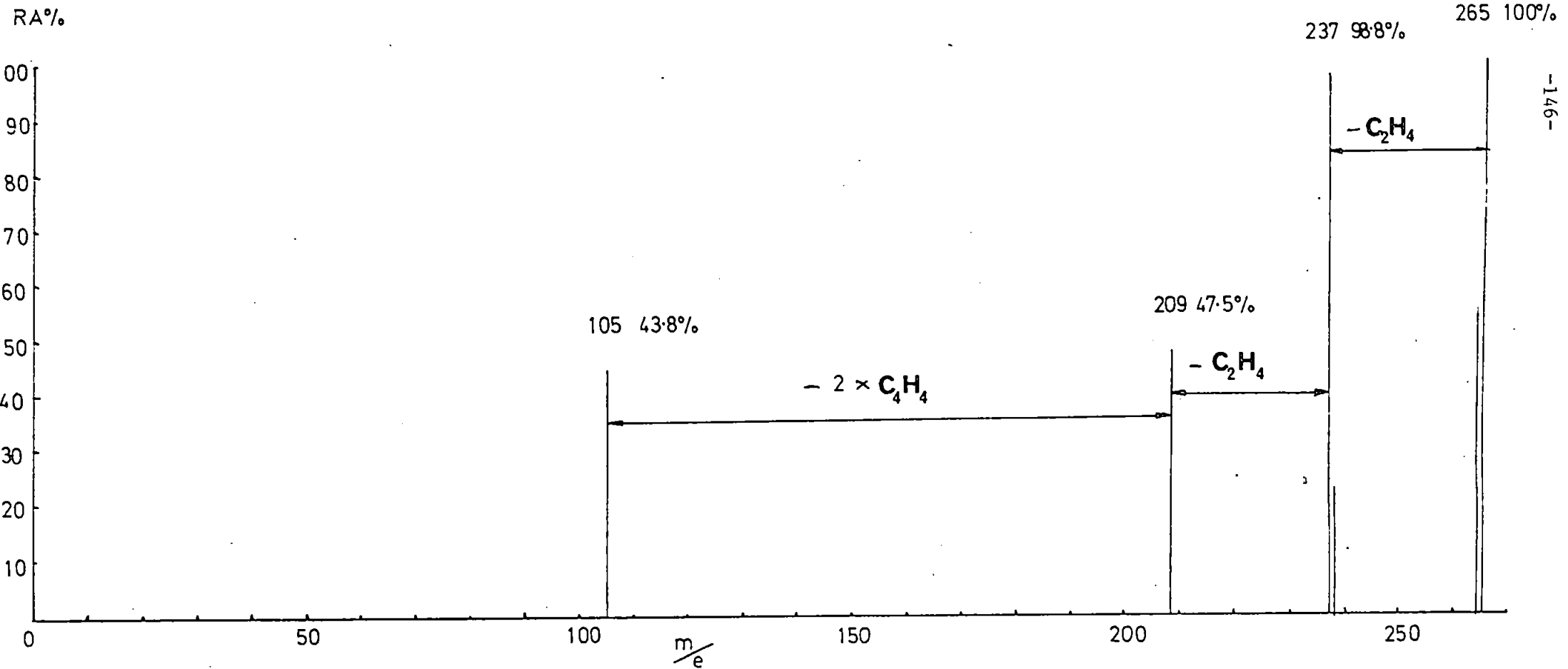


FIGURE 7


N
H
N
N
H


RA%
00
90
80
70
60
50
40
30
20
10
0
50
100
150
200
250
m/e
105 43·8%
237 98·8%
265 100%
209 47·5%
– 2 × C4H4
– C2H4
– C2H4

The 1H,4H-dipyrrolo[2,3-b;2',3'-d]pyridine system also shows the same tendancy of not expanding the pyrrole ring. The spectrum (figure 8) of 1,2,3,4,5,8,9,10,11,12-decahydro-7-methylpyrido[2,3-b:4',5'-b']diindole gives no indication of ring expansion but by stepwise loss of ethene suggests no change in ring size. The fragmentation is thought to occur as follows:-

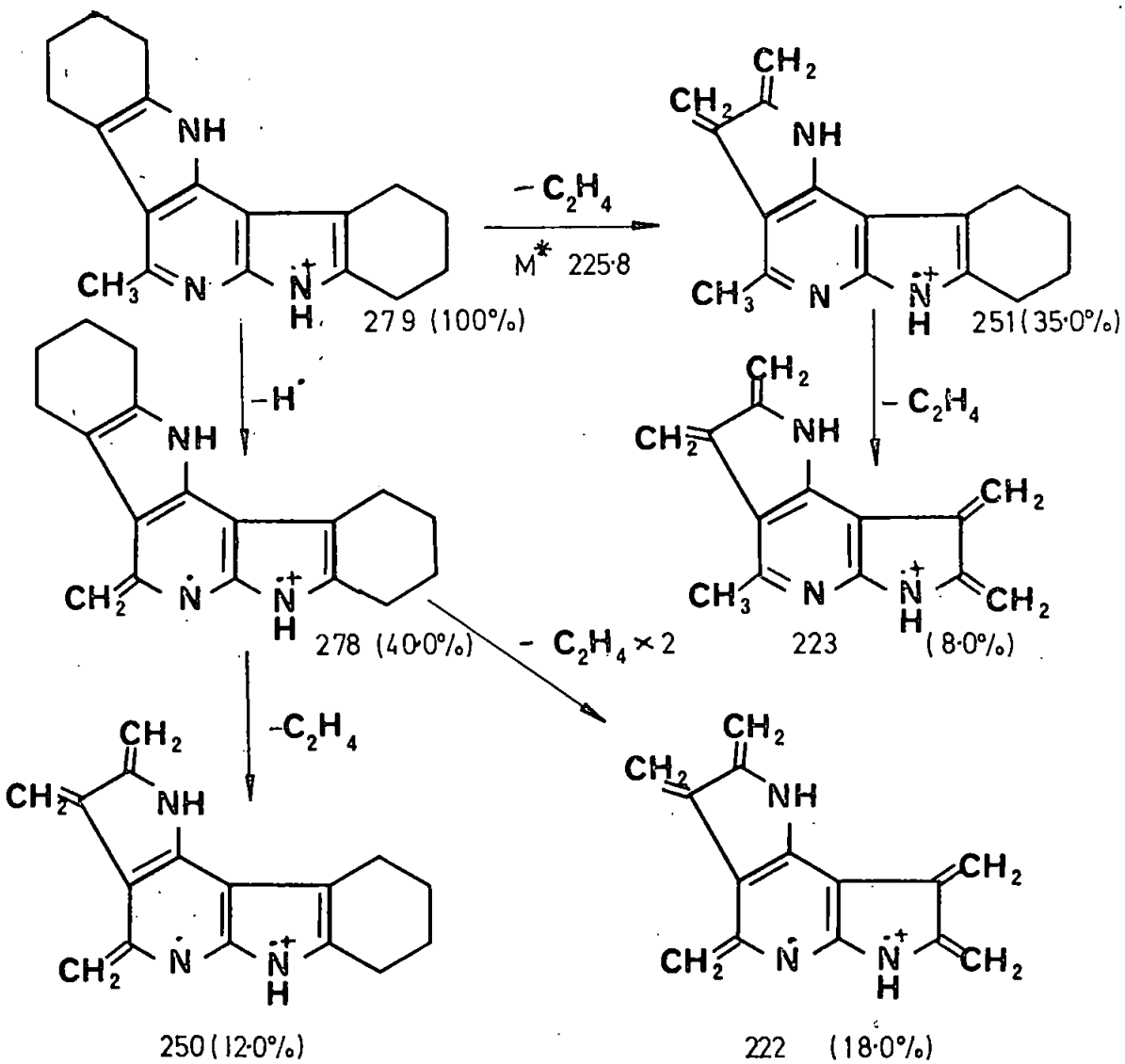
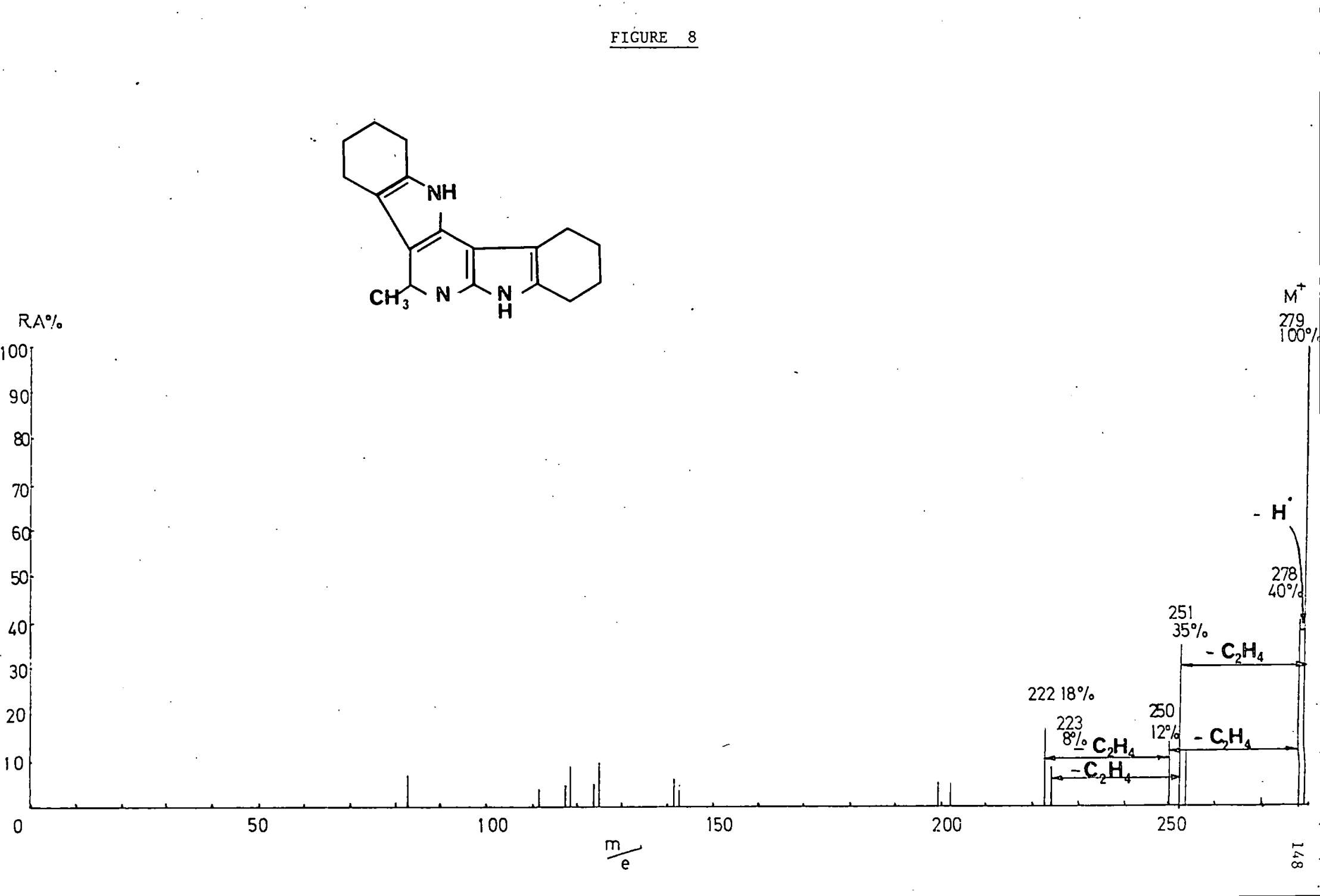


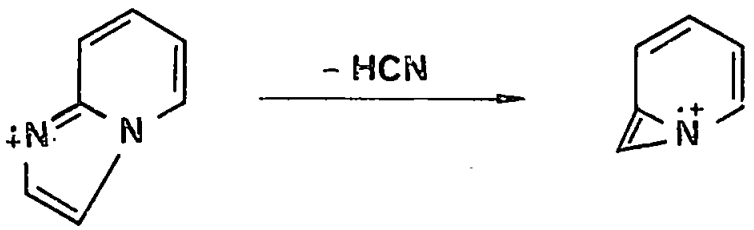
FIGURE 8


NH
CH3
N
N
H
RA%
100
90
80
70
60
50
40
30
20
10
0
50
100
150
200
250
m/e
M+
279
100%
- H·
278
40%
251
35%
- C2H4
222 18%
223
8%
C2H4
- C2H4
250
12%
- C2H4
148

Imidazopyrrolopyridines

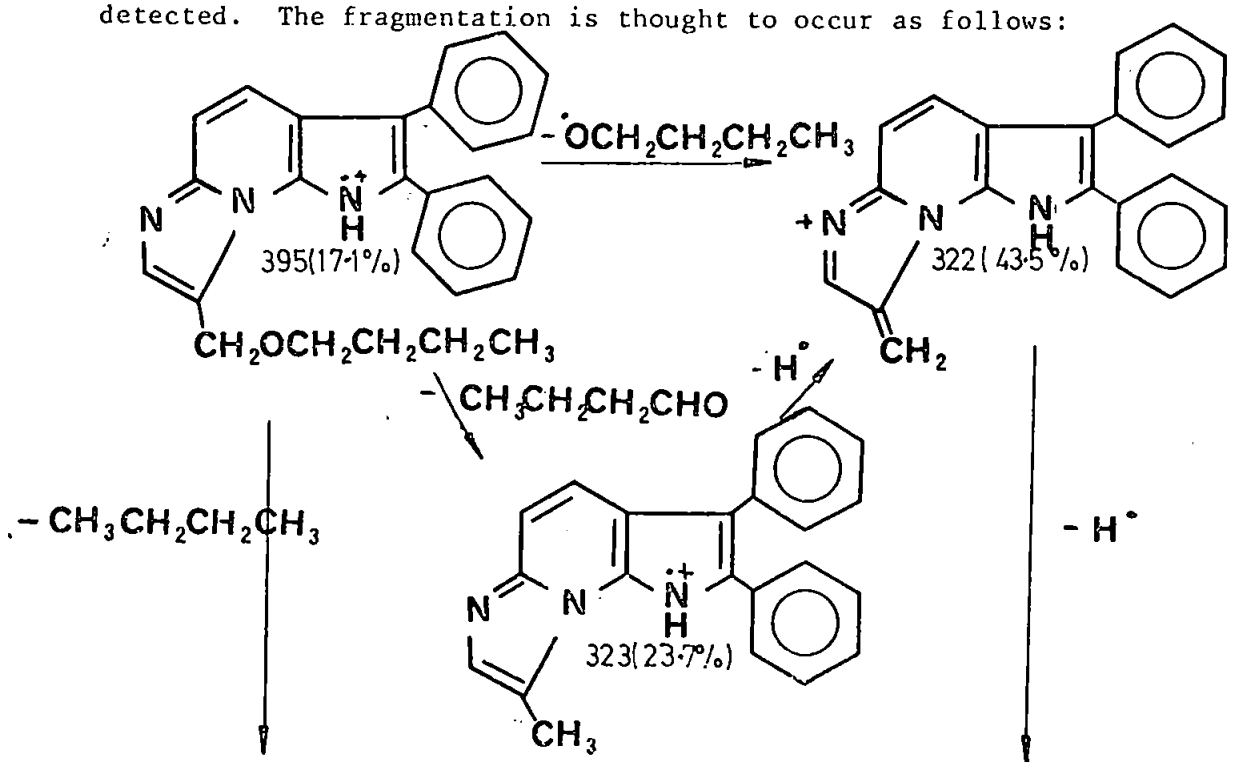
In the 1H-imidazo[1,2-a]pyrrolo[3,2-e]pyridine system initial fragmentation may occur at the pyrrolo or imidazo rings. The mass spectra of imidazo[1,2-a]pyridines have been recorded and analysed.[60]

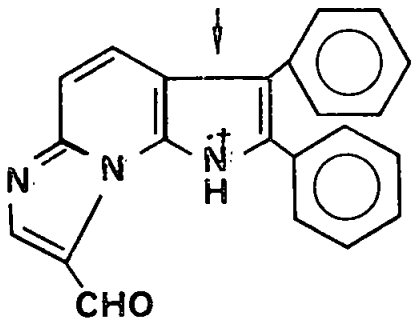
These compounds undergo initial fragmentation at the imidazo ring by loss of HCN:-



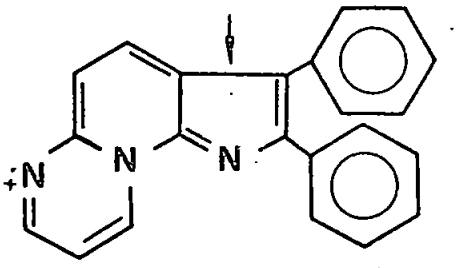
Ward[3] showed that for the 1H-imidazo[1,2-a]pyrrolo[3,2-e]pyridine system the pyrrole ring was the most fragile and ruptured or was expanded depending on the substituents on it.

For 2,3 -diphenyl-8-(n-butoxymethyl)-1H-imidazo[1,2-a]pyrrolo [3,2-b]pyridine however this does not seem to be true. The spectrum (figure 9) shows that after initial loss of the N-butoxy group there seems to be ring expansion of the imidazo ring to give the stable pyrimidino[1,2-a]pyrrolo[3,2-e]pyridine ring system. No ions due to loss of phenylcyanide, expected from rupture of the pyrrole ring, were detected. The fragmentation is thought to occur as follows:





337(7·9%)



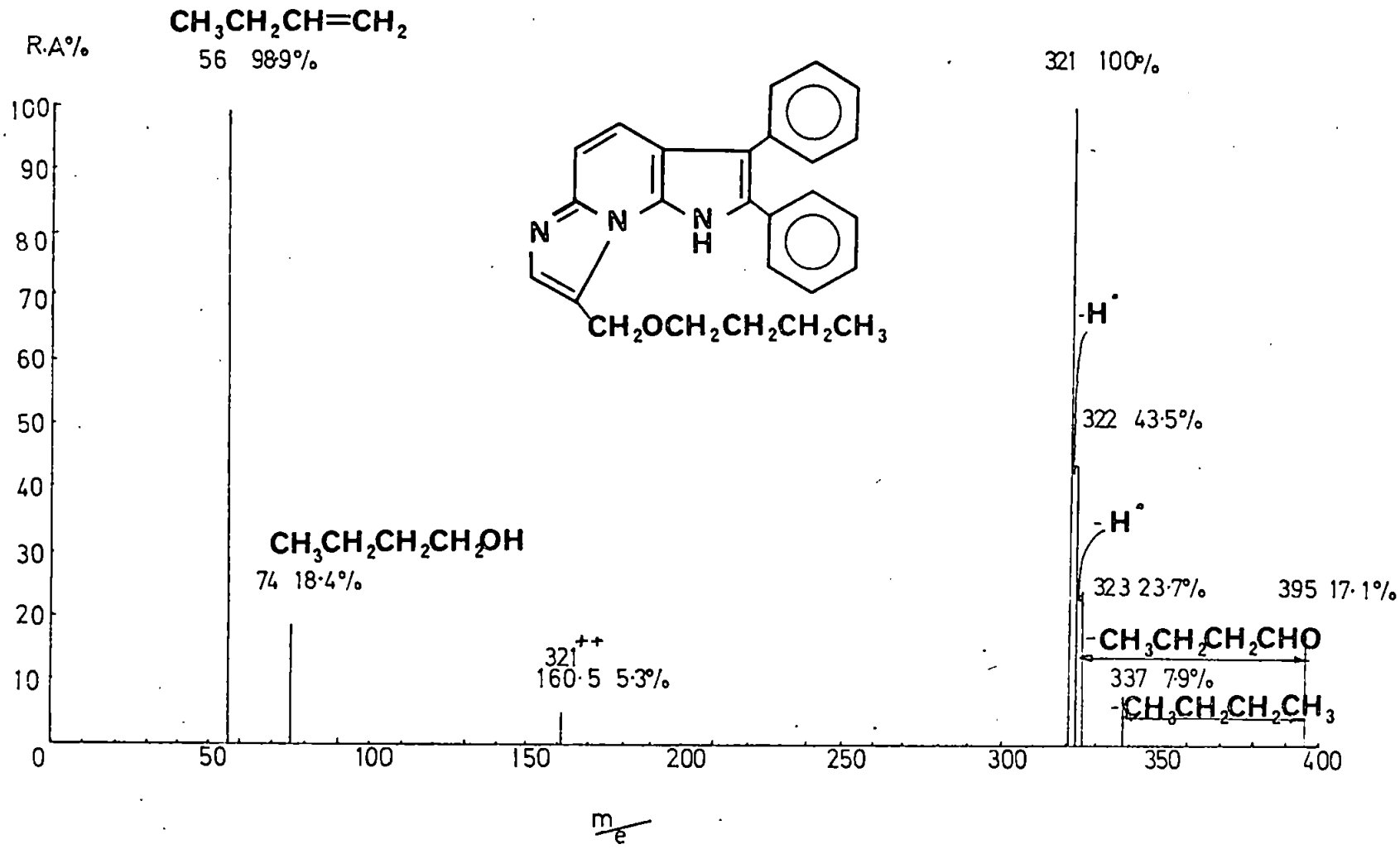
321 (100%)

An ion at 160.5 due to 321^{++} was detected. No ions due to break-down of 321 were detected in any quantity. This reflects the stability of the pyrimidino[1,2-a]pyrrolo[3,2-3]pyridine system.

Other ring systems

The spectrum (figure 10) of the 6,7,8,9 -tetrahydropyrido[3,4-b] quinoxaline ring system shows that the cyclohexyl ring is the first to be attacked with the loss of $CH_3^{\bullet}$. This fragmentation is followed by further rupturing of the cyclohexyl and break-down of the pyrazine ring. The fragmentations are thought to be as follows:

FIGURE 9


R.A%
CH3CH2CH=CH2
56 98·9%
321 100%
CH2OCH2CH2CH2CH3
-H·
322 43·5%
-H·
323 23·7%
395 17·1%
-CH3CH2CH2CHO
337 7·9%
-CH3CH2CH2CH3
CH3CH2CH2CH2OH
74 18·4%
321++
160·5 5·3%
100
90
80
70
60
50
40
30
20
10
0
50
100
150
200
250
300
350
400
m/e

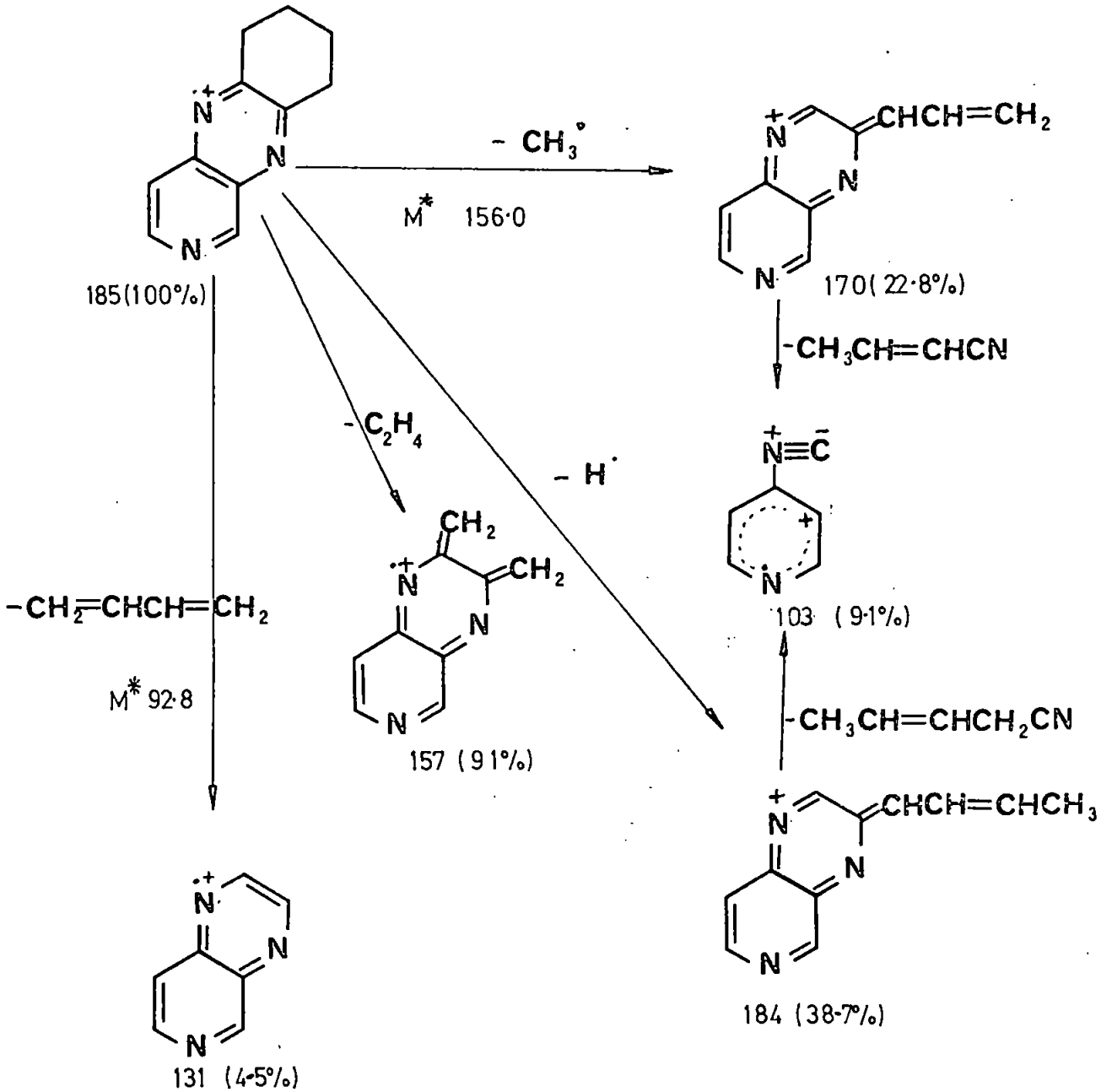
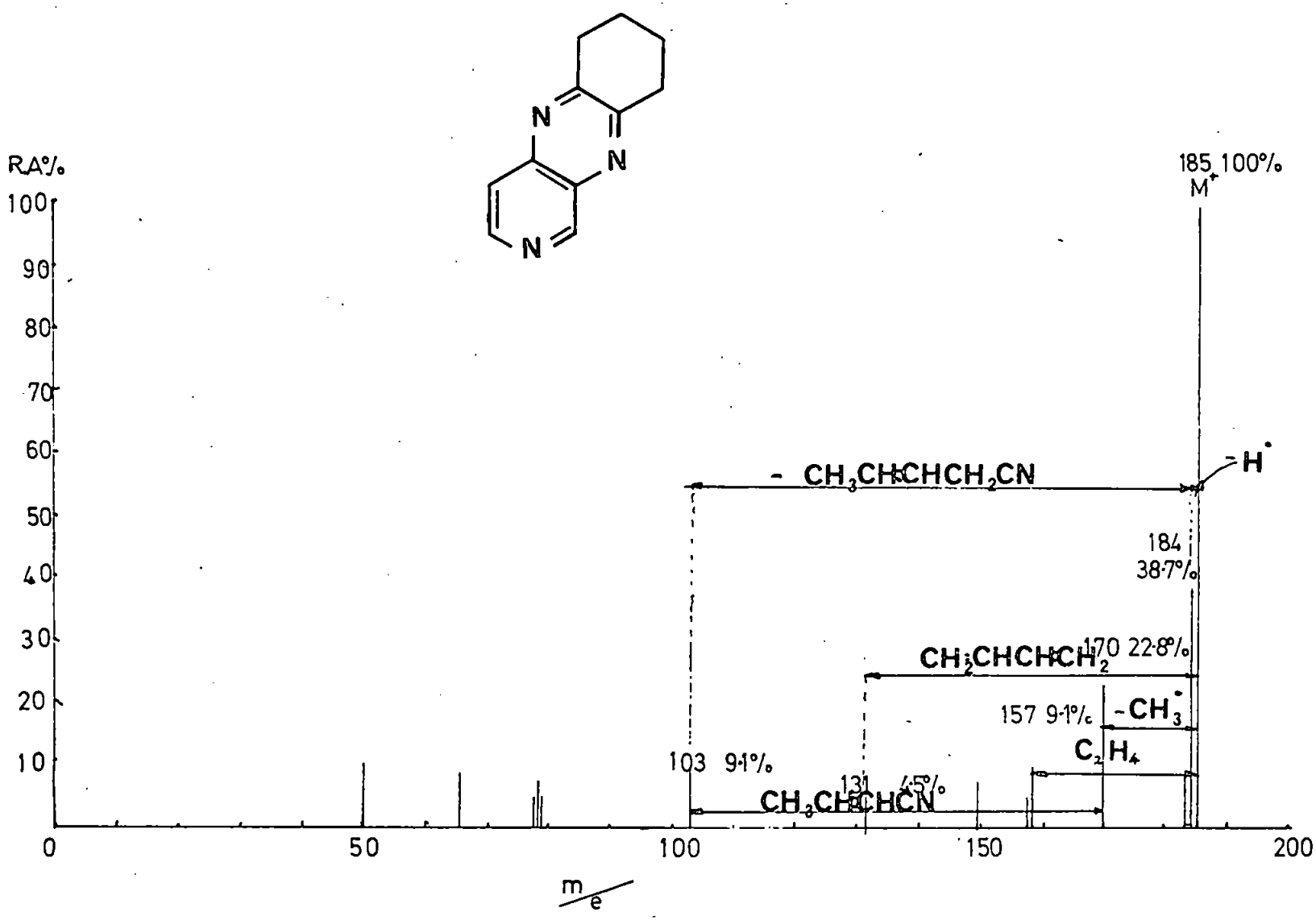

- CH3°
M* 156·0
185(100%)
170(22·8%)
-CH3CH=CHCN
-C2H4
- H·
-CH2=CHCH=CH2
M* 92·8
103 (9·1%)
157 (91%)
-CH3CH=CHCH2CN
184 (38·7%)
131 (4·5%)

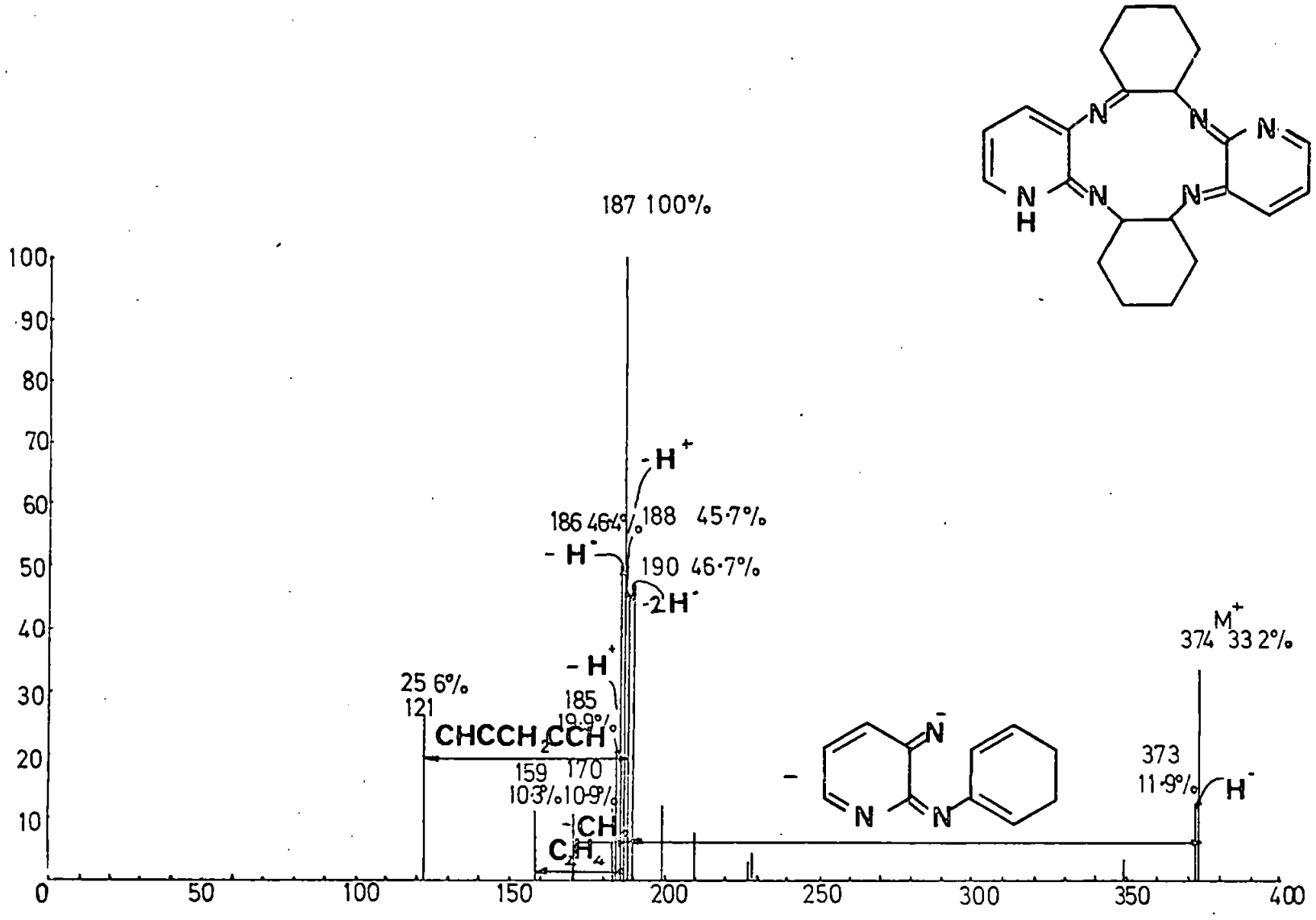
FIGURE 10

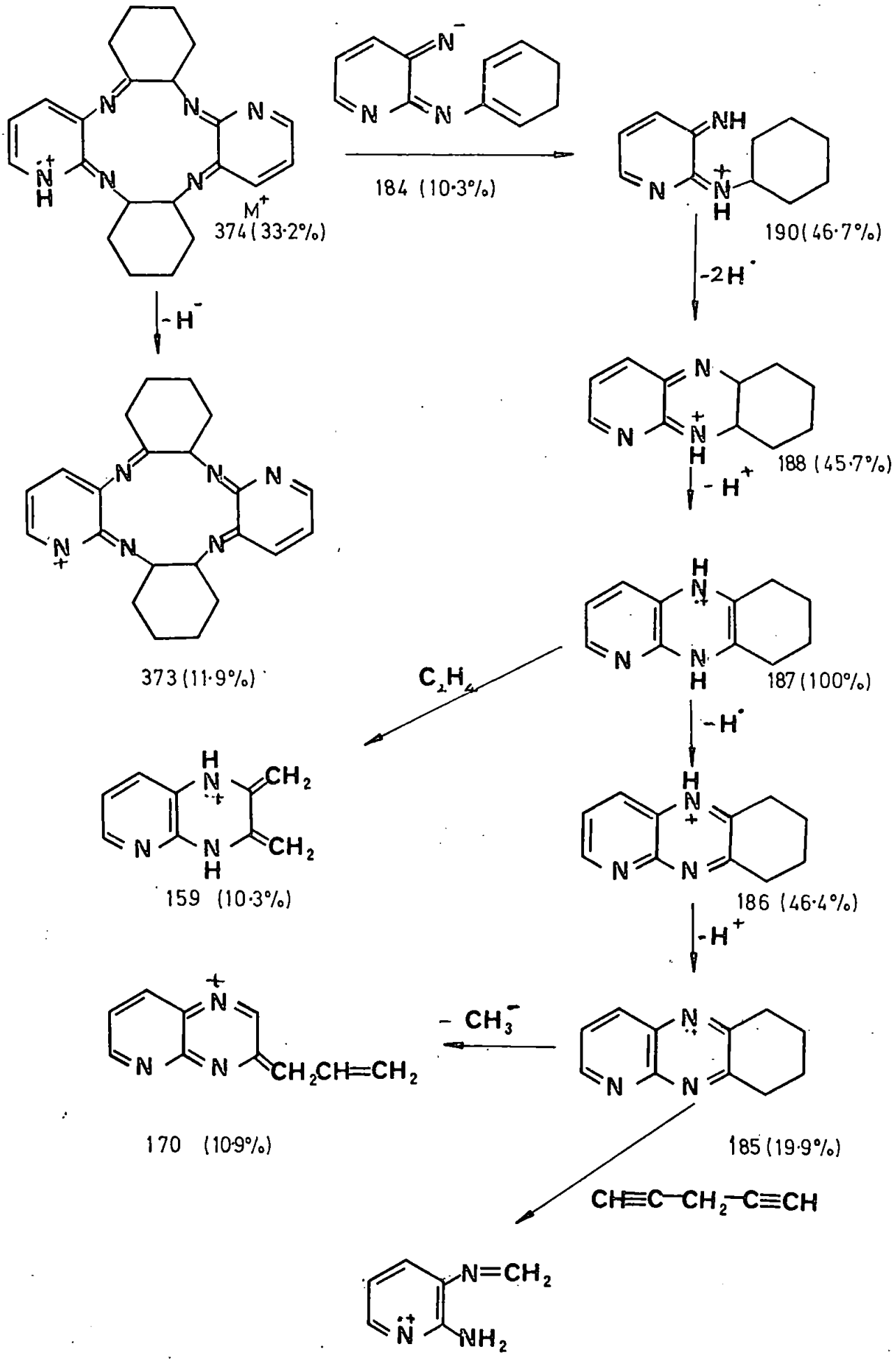

RA%
100
90
80
70
60
50
40
30
20
10
0
50
100
150
200
m/e
185 100%
M+
- CH3CH=CHCH2CN
- H•
184
38·7%
CH2=CHCH=CH2
170 22·8%
157 9·1%
- CH3•
C2H4
103 9·1%
131 4·5%
CH3CH=CHCN

The 5,6,7,8,9,15,16,17,18,19,20-undecahydrodibenzo[b,h]-N-hydro-Pyrido[2,3-e]pyrido[2,3-k][1,4,7,10]tetra-azacyclododecine had an accurate mass of 374.22212 established on the molecular ion. $C_{22}H_{26}N_6$ requires 374.22188.

The major fragmentation shown by the spectrum (Figure 11) is a splitting of the molecule in half. The resultant 5,6,7,8-tetrahydropyrido [2,3-b] quinoxaline loses CH_3 in a similar manner to 6,7,8,9 -tetrapyrido [3,4-b] quinoxaline. As an alternative to this step ruptures of the pyrazine ring may occur. The fragmentations are thought to occur as follows:-

FIGURE 11


187 100%
-H+
186 46·4%
188 45·7%
-H·
190 46·7%
-2H·
-H+
M+
374 33·2%
25·6%
121
185
19·9%
CHCCH2CCH
159
10·3%
170
10·9%
-CH2
C2H4
373
11·9%
H·
100
90
80
70
60
50
40
30
20
10
0
50
100
150
200
250
300
350
400


M+
374 (33·2%)
184 (10·3%)
190 (46·7%)
-2H·
188 (45·7%)
-H+
-H⁻
373 (11·9%)
C2H4
187 (100%)
-H·
159 (10·3%)
186 (46·4%)
-H+
-CH3⁻
170 (10·9%)
185 (19·9%)
CH≡C-CH2-C≡CH
121 (25·6%)

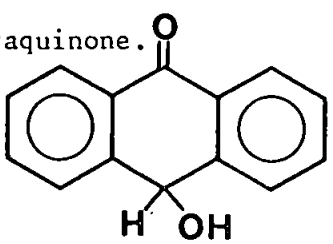
CONCLUSIONS AND SUGGESTIONS FOR FURTHER WORK

The preparation of dipyrrolopyridines has proved a difficult synthetic problem. Reactions which have shown wide applicability in other fields have failed to lead directly to these systems.

Thus the Gassman reaction[44] using methylthiopropan-2-one ethylene ketal on 2,6-diaminopyridine failed to undergo dicyclisation but gave the novel 2,6-diamino-3,5-dichloro and 2,6-diamino-3-chloropyridines.

The applicability of the Bischler reaction was extended to 2,4-diaminopyridines and the novel 1H,4H-dipyrrolo[2,3-b; 2′,3′-d] pyridine system was produced. However attempts to extend the reaction to other diaminopyridines met with no success, but a number of interesting ring systems were produced. The chemistry of these derivatives and the new ring systems themselves warrants further investigation especially the spectroscopic data on 5,6,7,8,9,16,17,18,19,20-undecahydrodibenzo[b,b]-N-hydropyrido[2,3-e]pyrido[2,3,-b][1,4,7,10]tetra-azacyclododecine. This could be clarified by reacting under solvent Bischler conditions 2,3-diaminopyridine with 3-hydroxybutan-2-one. The product providing it has a similar structure should give readily interpretable N.M.R. spectra.

Some novel derivatives of the 1H-pyrrolo[2,3-b]pyridine, 1H,7H-dipyrrolo[2,3-b;3 , 2 -e]pyridine and 1H-imidazo[1,2-a]pyrrolo[3,2-e] pyridine systems were synthesised. The yields obtained gave an interesting insight into the balance between electronic and steric considerations in determining the efficiency of the reaction. This could be further elucidated by comparing the yields obtained by reacting with 2,6-diaminopyridine under Bischler conditions with benzoin and compounds where the keto and hydroxyl groups are locked in space e.g. the keto form of 9,10-dihydroanthraquinone.



which may be prepared by the method of Meyer[61].

Here the electronic effects of the phenyl group on the hydroxyl group should approximate to that of benzoin.

Some work has been done on the chemistry of the dipyrrolopyridines and has been mainly directed in clarifying some of Wards[3] work however as the aims of this project were synthetic not a great deal of time was spent in this area of study. This may well prove a fruitful field especially when one considers the reactions of substituents on the ring systems and any possible change in biological activity that these reactions may bring about.

A large number of derivatives could be produced simply by using ring substituted benzoin derivatives. These could be used for kinetic studies of the reaction which could yield information about the structure of the transition state. A number of α-hydroxyketones could be made available for use in the synthesis of dipyrrolopyridine systems by use of the dithiane synthesis[62] and related reactions[63], the thallium derivatives of substituted alkynes[64] and by use of the acyloin synthesis[65]. The range of available halogeno ketones could be extended by the use of chromyl chloride on substituted alkenes[66]. Hopefully the biological activity of these different derivatives could give information on the maximum biological activity possible of the dipyrrolopyridine systems.

As the aim of this project was to produce new systems and not a plethora of new derivatives no work has been done in this field but it could well form the basis of a future project on the reaction.

The work on the Gassman reaction proved to be very difficult indeed, from a relatively simple reaction the necessary modifications turned it into a relatively long and tedious reaction involving considerable time in work up and in the latter stages of the work the use of high pressures and temperatures to obtain the necessary substrates. Some novel pyridine derivatives together with a novel derivative of the 1H-pyrrolo[3,2-b] pyridine system were obtained. Some knowledge was gained about the

N-chlorination of aminopyridines together with the mechanism of the N-chloramines rearrangement in pyridines.

The attractiveness of this reaction is that is could produce the unsubstituted parent dipyrrolopyridines by reduction of the S-alkyl group. The relative reactivities of the various positions toward electrophilic attack could then be studied and hence a better understanding of the chemistry of the systems. The scope for forming biologically active derivatives is considerably expanded if the unsubstituted systems are available. Whilst a considerable amount of effort has gone into developing this synthesis and a lot of knowledge has been gained, there is still work left to be completed. The synthesis still does not enable dipyrrolopyridines to be produced and the next step would be to try the halogen alkylthioketone ethylene ketal complex on 2,6 and N-substituted 2,6-diaminopyridines. If this meets with no success then as the 2,6-diaminopyridines are electron rich compared to the aminopyridines the original synthesis of Gassman[6] should be tried. The slow stage of the reaction could be the nucleophilic attack of the sulphur atom of the thioketone on the amino nitrogen of the aminopyridine, increase of the electron density at the sulphur atom by substitution of groups such as tertiary butyl should speed up this attack. There is of course, the yet untried field of attempting this reaction on other diaminopyridines and on amino imidazo[1,2-a] and pyrrolo[2,3-b]pyridines.

All these points could form the basis for further research.

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