

**SYNTHESES IN THE NAPHTHYRIDINE SERIES**

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by

**BARBARA M. FERRIER**

**A THESIS PRESENTED FOR THE DEGREE  
OF DOCTOR OF PHILOSOPHY.**

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I am happy to have this opportunity of thanking Dr. Neil Campbell for his guidance and friendly encouragement during this introduction to chemical research.

I am indebted to Dr. D.M.W. Anderson for the determination of infra-red spectra and to Miss D. Jeffreys, Mr. R. Norris and Mr. A. Robertson for help with some of the experimental work.

B.M.F.

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I N T R O D U C T I O N

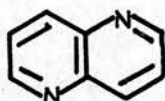


INTRODUCTION

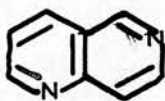
C.F.H. Allen (1) has reviewed the work done on the naphthyridines until 1950, and I have drawn extensively from his paper for the material for this introduction.

Naphthyridines are the bicyclic compounds obtained from the fusion of two pyridine rings, in such a way that neither nitrogen atom is common to both rings. They have been called pyridopyridines, benzodiazines and diazanaphthalenes, but the name naphthyridine is now favoured. It was suggested by Reissert (2) when he isolated the first example of the series in 1893, since he considered it to be a naphthalene analogue of pyridine.

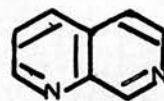
There are six possible isomeric naphthyridines:



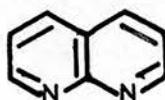
1,5-NAPHTHYRIDINE



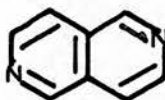
1,6-NAPHTHYRIDINE



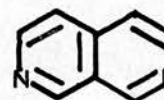
1,7-NAPHTHYRIDINE.



1,8-NAPHTHYRIDINE



2,6-NAPHTHYRIDINE



2,7-NAPHTHYRIDINE.

Of the six, only the 1,5 and 1,8 free bases have been isolated.

Naphthyridines have not proved to be readily accessible substances. Several factors contribute to this. The most obvious routes to their synthesis involve the use of simple pyridine derivatives as starting materials, many of which are still not easily obtained. The inertness of the pyridine ring towards electrophilic attack frequently makes the formation of a second ring by ring closure onto the first difficult or impossible. There has been only one authenticated claim to have isolated a naphthyridine derivative from a natural source. Ochiai (3) reports that he obtained a decahydro-1,6-naphthyridine from an alkaloid, matrin. This has not been proved.

A nitrogen atom in any ring system exerts an attractive inductive effect, which causes a lowering of the electron density at all other positions in the ring.

In conjugated systems there may also be a shift of electrons towards a nitrogen atom by a mesomeric effect.

In pyridine, positions 2 and 4 in the ring suffer from a lowering of electron density by a two stage

mesomeric shift of electrons:



In the naphthyridines similar effects may operate, but, as may be seen from the structural formulae, a two stage mesomeric shift to both nitrogen atoms can only take place with 1,5 and 1,8-naphthyridines:

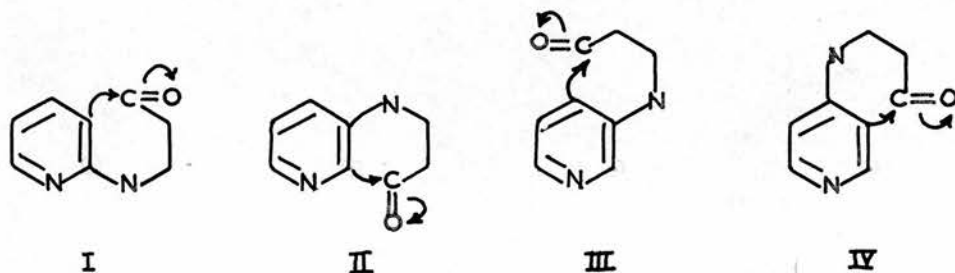


It may therefore be expected that the basic character of the molecule, in the case of the other four isomers, will be centred on one nitrogen atom in preference to the other.

If the classical syntheses of the quinoline nucleus, based on aniline, are applied to the monoaminopyridines, they would appear to give a route to the synthesis of 1,5, 1,6, 1,7 and 1,8-naphthyridines. A large part of the

research done on the naphthyridines has been based on such syntheses.

Cyclisation of intermediates from the condensation of aminopyridines with glycerol or acrolein (Skraup method), acetoacetic ester (Conrad-Limpach, Knorr), acetylacetone (Combes) and ethoxymethylenemalonic ester (E.M.M.E.) always involves carbon-carbon condensations of the ionic type, in which the pyridine ring acts as an electron donor and a C=O group as an electron acceptor. Since all carbon atoms in the pyridine ring have lower electron density than those in benzene, cyclisations of this type to give naphthyridines are always more difficult than the corresponding reaction in the quinoline series. The additional deactivation of the 2 and 4 positions by the process already described, makes the ease of cyclisation dependent on the position of the amino group relative to the ring nitrogen.

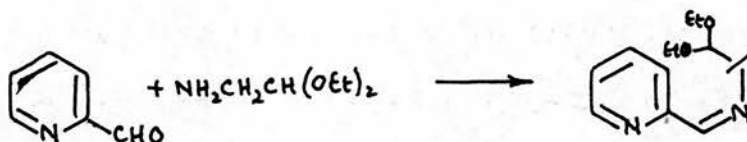


Of the two types of cyclisation possible from 3-aminopyridine derivatives (II, III), II normally occurs in preference to III, if position 2 in the ring is unsubstituted. This is in agreement with the calculated  $\bar{\pi}$  electron densities at these positions (2 : 0.849, 4 : 0.822). Conrad-Limpach and Knorr type intermediates do not cyclise under the usual conditions. 2- and 4-aminopyridine derivatives cyclise more easily as position 3 in the ring is the most reactive towards electrophilic reagents. In the majority of cases studied, cyclisation of 2-aminopyridine derivatives leads, not to 1,8-naphthyridines, but to pyridopyrimidines, ring closure having taken place through the ring nitrogen, which has a high electron density. When there is an electron repulsive substituent on position 6, it appears to activate position 3 in preference to position 1 and ring closure subsequently leads to 1,8-naphthyridine derivatives. 4-Aminopyridine derivatives cyclise to give 1,6-naphthyridines, but the Conrad-Limpach method is reported to have failed (4).

The application of the methods of synthesis used in the isoquinoline series to pyridine derivatives has proved less successful. Hart (5) has done work on the Pomeranz-Frisch synthesis applied to pyridine aldehydes. The



condensation of the aldehydes with aminoacetal gave Schiff's bases, which, however, could not be cyclised.



The physiological and therapeutic properties of naphthyridines have lately been under examination. Since many important bacteriocidal and therapeutic agents are pyridine derivatives, naphthyridine analogues have been prepared and tested. Albert and Hampton (6) prepared a series of hydroxynaphthyridines and compared them with 8-hydroxyquinoline, which has striking antibacterial properties. They found that the introduction of a second nitrogen atom into the ring system in all cases decreased the basic strength and hence the ability to chelate with metals, which is responsible for antibacterial activity.

Goldberg, Theobald and Williamson (7) prepared 2-butoxy - 8(4-diethylamino-1-methylbutylamino)1,5-

naphthyridine and found that it showed the same large suppressive activity as mepacrine against *P. gallinaceum* in chicks and *P. berghei* in mice.

Isolated naphthyridine derivatives have been reported to be tuberculostatic (8) and antimalarial (9).

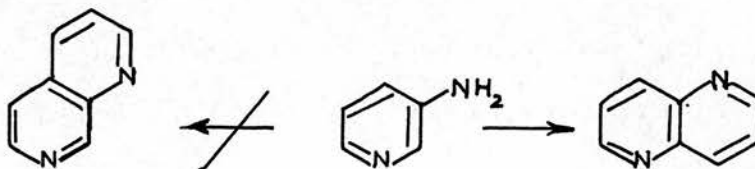
A large number of derivatives have been patented because of their disinfectant activity, but there have been no detailed reports of their application.

1,8 derivatives have also been reported as new cyanine dyes (10).

It seems unlikely, because of the relative expense of their preparation, that any of the derivatives so far examined will find any application on a commercial scale, unless they show more striking activity than has so far been observed.

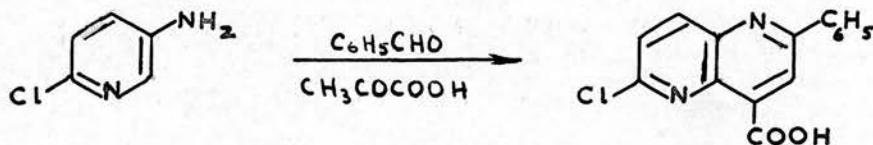
Synthesis of the 1,5-Naphthyridine Ring System.

3-Aminopyridine takes part in a Skraup synthesis to give the free base (11):



All cyclisation appears to take place through position 2, as none of the 1,7-naphthyridine, which would arise from ring closure at position 4, has been isolated from the reaction. Generally, when position 2 is blocked by a stable substituent, no cyclisation occurs, but Albert and Hampton (6) have found that 2-hydroxy-3-aminopyridine gives 8-hydroxy-1,7-naphthyridine when it is treated under modified Skraup conditions. However, when 2-chloro-3-aminopyridine is used the chlorine is eliminated and 1,5-naphthyridine results (12).

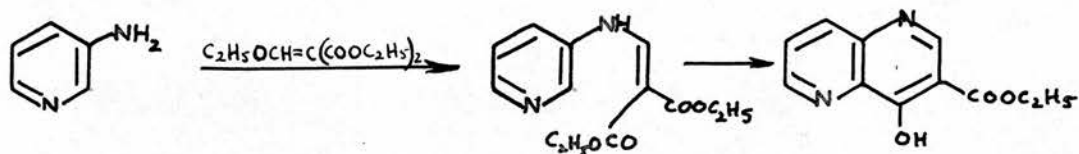
6-Chloro-2-phenyl-1,5-naphthyridine 4-carboxylic acid has been reported to be formed when Doebner's modification of Skraup's synthesis was applied to 5-amino-2-chloropyridine (13).



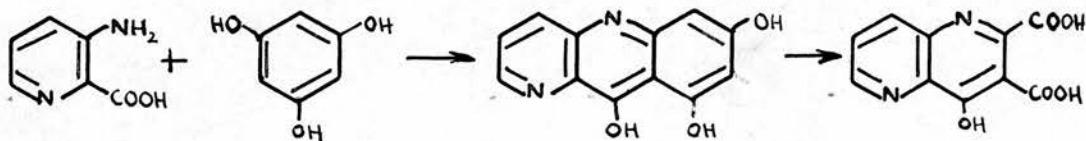
This has been questioned (14), because Skraup reactions on 5-amino-2-hydroxypyridine and on 5-amino-2-chloropyridine give the same product: 2-hydroxy-1,5-naphthyridine, the chlorine atom having undergone hydrolysis.



The E.M.M.E. quinoline synthesis, developed by Price and Roberts (15) has been applied to 3-aminopyridine. The intermediate obtained from the condensation of 3-aminopyridine and ethoxymethylenemalonic ester is cyclised by heating in a high boiling solvent (Dowtherm A)

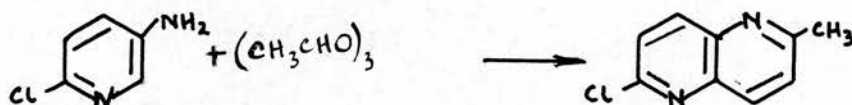


The structure of the ring system in 1,5-naphthyridine has been proved by another synthesis in which 3-aminopicolinic acid is condensed with phloroglucinol and the tricyclic system (7,9,10-trihydroxy-1,5-diazaanthracene) formed oxidised to 4-hydroxy-1,5-naphthyridine-2,3-dicarboxylic acid (11)

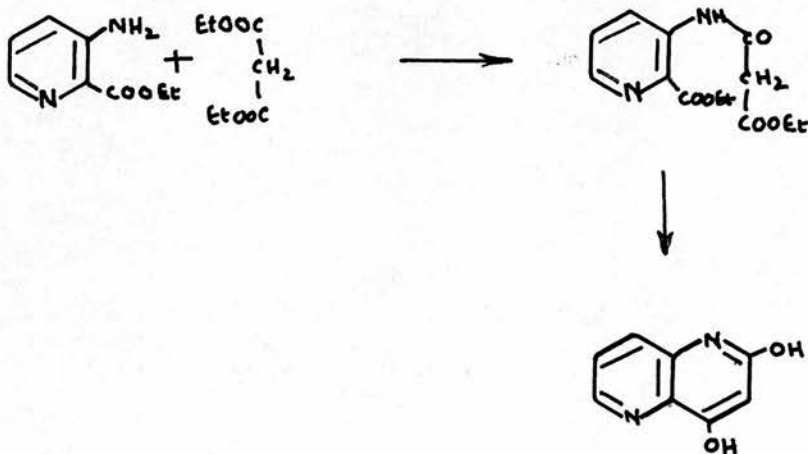


Takahashi and coworkers (16) have succeeded in preparing 2-chloro-6-methyl-1,5-naphthyridine from

2-chloro-5-aminopyridine and paraldehyde, in the presence of hydrogen chloride.

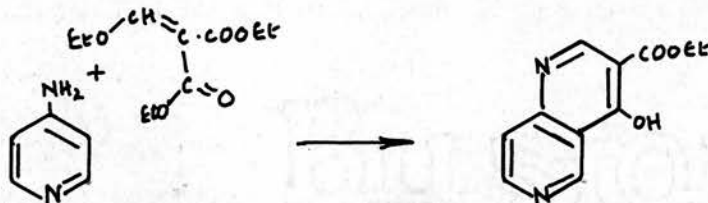


Oakes and Rydon (17) wished to study the relative reactivities of the two chlorine atoms in dichloro-naphthyridines. To prepare the necessary compound they first synthesised 2,4-dihydroxy-1,5-naphthyridine. They adapted a method used to prepare dihydroxyquinoline. Ethyl-3-aminopicolinate was condensed with malonic ester to give a substituted malonic ester. This underwent a Dieckmann cyclisation to give the dihydroxy compound.



Synthesis of the 1,6-Naphthyridine Ring System.

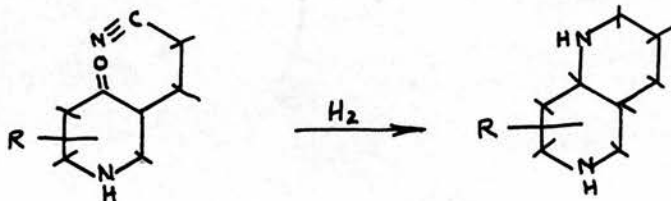
Although the usual Skraup and Conrad-Limpach type of reactions applied to 4-aminopyridine would appear to give the simplest route to this system, this has not always proved to be the case. 4-Aminopyridine and ethoxymethylenemalonic ester have been condensed to give 4-hydroxy-3-carbethoxy-1,6-naphthyridine ((4)) :



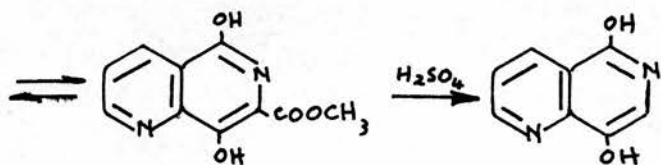
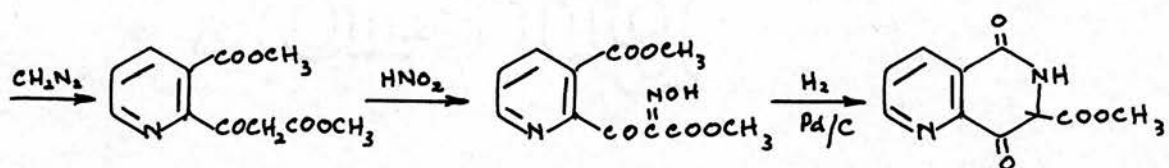
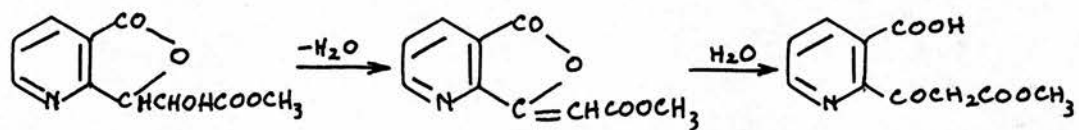
but many other similar syntheses have failed.

4-Aminopyridine and ethylacetoacetate do not condense to give a bicyclic system (4).

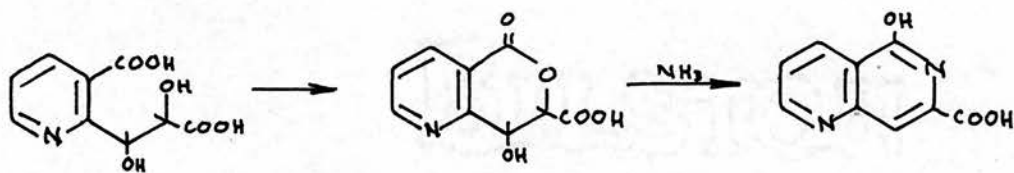
Decahydro-1,6-naphthyridines have been prepared by Nazarov and coworkers (19), by the hydrogenation, in the presence of Raney nickel, of substituted 5-(2-cyanoethyl)-4-piperidones:



Synthesis by Ochiai, Miyaki and Sato (3).



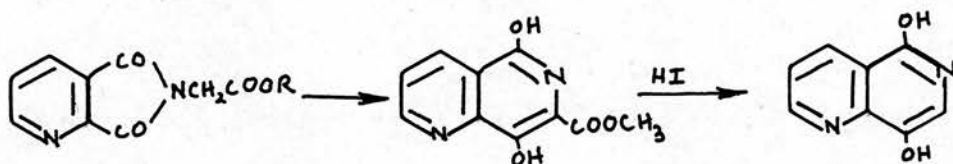
The first synthesis of the 1,6-naphthyridine nucleus was carried out by Rosenheim and Tafel in 1893 (20). Bamberger and Kitshelt (21) and Zincke (22) found that phenylglycerine carbonic acid, on heating with ammonia, gave isocarbostyryl 3-carboxylic acid. Rosenheim and Tafel claimed that an analogous reaction took place with pyridylglycerine carboxylic acid, to produce 5-hydroxy-1,6-naphthyridine-7-carboxylic acid:



This reaction is complex, and Ochiai and coworkers (3) have more recently undertaken a synthesis to establish the structure of the above compound. An outline of their synthesis is given on the facing page.

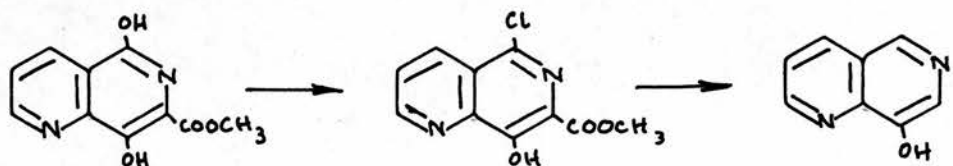
Gabriel and Colman (23) had found it possible to apply ring expansion reactions to phthalimidoacetic ester and cinchomeronylglycine ester. Fels (24) applied their reaction to quinolyglycine ester. In the presence of

sodium methoxide the imide ring undergoes expansion:



This rearrangement could give rise to a 1,7-naphthyridine derivative. That it does, in fact, give a 1,6 derivative was proved by Ochiai's synthesis (3), since the dihydroxy-naphthyridines formed by the two syntheses are identical.

The simplest 1,6-naphthyridine so far prepared is the 8-hydroxy compound. Albert and Hampton (25) repeated Fels' synthesis of 5,8-dihydroxy-7-carboxymethyl-1,6-naphthyridine and from it obtained the 5-chloro-8-hydroxy-7-carboxymethyl-1,6-naphthyridine by treatment with phosphorus oxychloride. This product, on heating with hydriodic acid, underwent hydrolysis, decarboxylation and reduction:

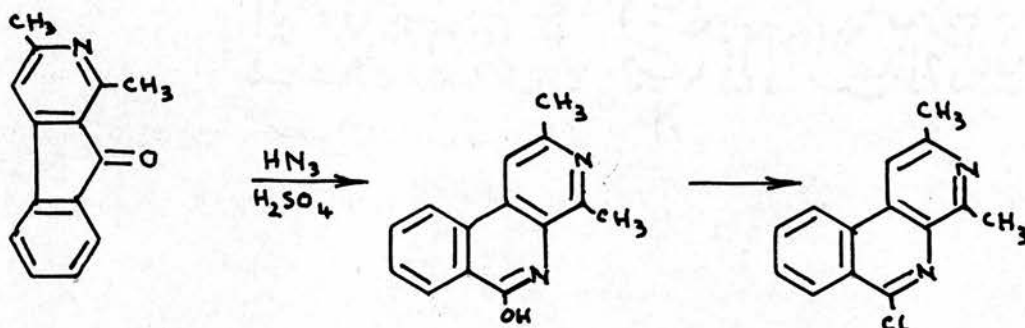




Synthesis of the 1,7-Naphthyridine Ring System.

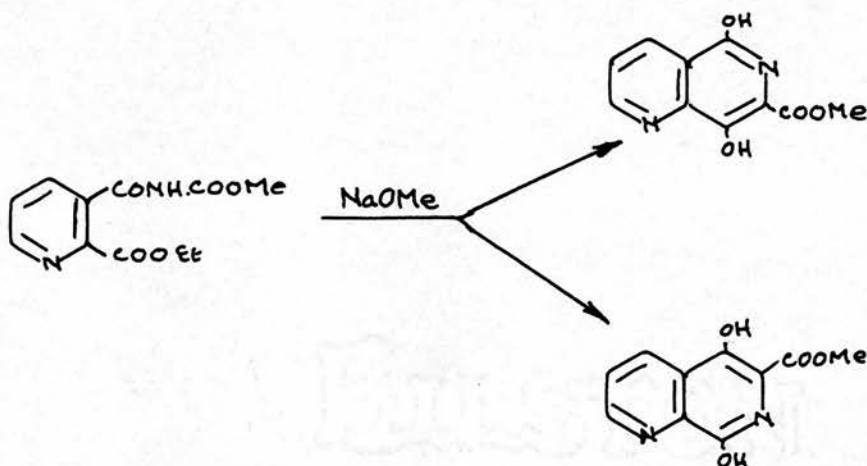
This is the group of compounds in which there has been the greatest recent development. Until 1945 no simple derivative was known.

Several workers (26, 27, 28, 29, 30, 31) had previously reported the ring enlargement undergone by azafluorenone derivatives when they are treated with Schmidt reagents. The hydrazoic acid treatment of 1,3-dimethyl-2-azafluorenone gives a lactam: 2-hydroxy-6,8-dimethyl-3,4-benzo-1,7-naphthyridine, which is converted by phosphorus oxychloride to the corresponding dichloro compound.



The first relatively simple derivative was prepared by Ochiai and coworkers (32). They obtained methyl-5,8-dihydroxy-1,7-naphthyridine-6-carboxylate along with

X methyl-5,8-dihydroxy-1,6-naphthyridine-7-carboxylate on treating the ethyl ester of N-(carboxymethyl) quinolin-3-amic acid with sodium methoxide:



Albert and Hampton (25) made an appreciable advance when they discovered that they could produce a bicyclic system arising from ring-closure of a derivative of 3-aminopyridine through position 4 in the pyridine ring.

Until this report, all 3-aminopyridine derivatives had cyclised through position 2, if it was unsubstituted, or not at all.

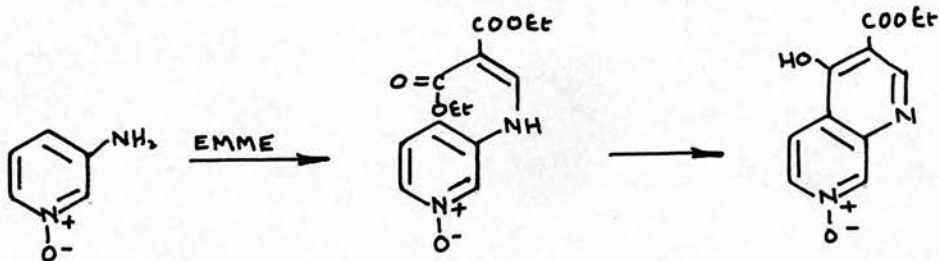
Albert and Hampton used modified Skraup conditions. When 3-amino-2-hydroxypyridine and glycerol were heated



with *m*-nitrobenzene-sulphonic acid, 8-hydroxy-1,7-naphthyridine was obtained.



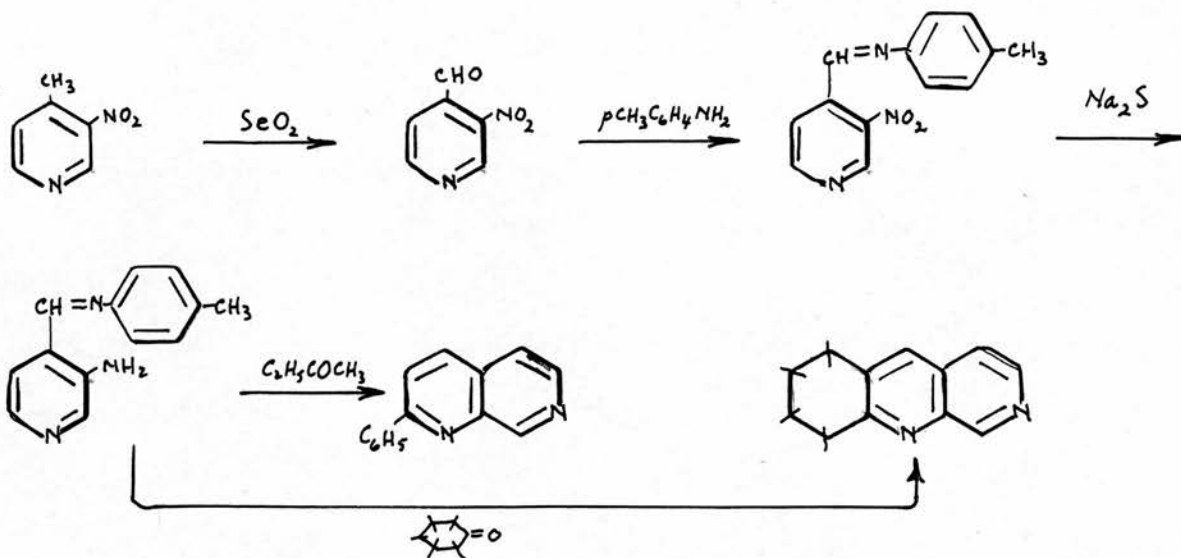
Two years later, Murray and Hauser (33) found that less violent conditions were needed to make cyclisations take place through position 4, when pyridine N-oxide derivatives were used. It had already been shown by many workers that the N-oxide group is a very strong para activating group.



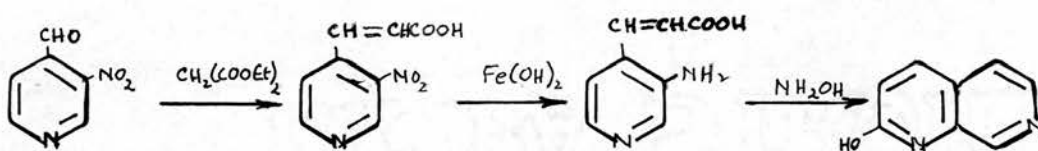
Baumgarten and Krieger (34) published details of three different synthetic approaches to 1,7-naphthyridine

Baumgarten and Krieger's Syntheses of 1,7-Naphthyridine Derivatives.

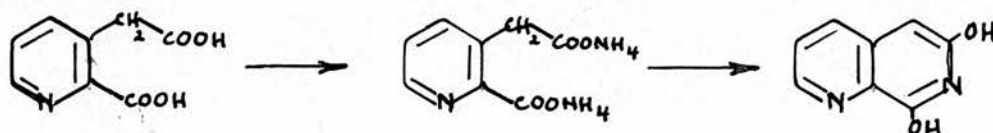
I



II



III



derivatives, all of which were modelled on quinoline or isoquinoline syntheses.

The first of their methods is, they suggest, applicable to the preparation of any substituted 1,7-naphthyridine. They have since published results illustrating its general applicability (35). It consists of the use of the Borsche modification of the Friedländer quinoline synthesis.

3-Nitroisonicotinaldehyde, obtained from the selenium dioxide oxidation of 3-nitro- $\gamma$ -picoline, was condensed with p-toluidine. After reduction of the nitro group, the product was treated with a carbonyl compound, when elimination of p-toluidine took place and a substituted 1,7-naphthyridine resulted. When acetophenone was used, 2-phenyl-1,7-naphthyridine was the product, and cyclohexanone gave 2,3-cyclohexyl-1,7-naphthyridine (see facing page).

Yields in this reaction are reported to be good.

In the second of Baumgarten and Krieger's methods, Chiozza's synthesis of carbostyryl from o-aminocinnamic acid was applied to the corresponding pyridine derivatives. 3-Nitroisonicotinaldehyde was condensed with malonic acid to give 3-nitro-4-pyridylacrylic acid. Ferrous

sulphate and ammonia reduced this to the corresponding amino compound. Hydrochloric acid and sulphuric acid failed to bring about ring-closure of this compound, but Posner's technique of refluxing in methanolic hydroxylamine gave a 30% yield of the bicyclic compound, 2-hydroxy-1,7-naphthyridine. (see facing page)

Meyer and Vittenet synthesised 1,3-dihydroxy-isoquinoline by fusion of the ammonium salt of homophthalic acid. Baumgarten and Krieger brought about their third synthesis of the 1,7-naphthyridine nucleus by applying this method to  $\beta$ -homoquinolinic acid. They obtained 6,8-dihydroxy-1,7-naphthyridine in 23% yield.

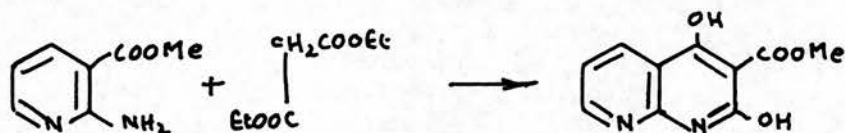
They also report failure to obtain bicyclic compounds from attempted condensations of 3-aminoisonicotinic acid and 2,6-dimethyl-3-aminoisonicotinic acid with malonic ester, ethylacetoacetate and methyl acetate under various conditions.

Gulland and Robinson (36) had already attempted such syntheses with 2-methyl-3-aminoisonicotinic acid and had attributed their failure to the steric effect of the methyl group on position 2. Baumgarten and Krieger's experiments show that other factors must operate.

Synthesis of the 1,8-Naphthyridine Ring System.

The fact that 2-aminopyridines can be easily prepared by the treatment of pyridine with sodium amide has given a good route to the synthesis of 1,8-naphthyridine derivatives. Although it is usual for derivatives of 2-aminopyridine to cyclise through the ring nitrogen atom to give pyridopyrimidines, an electron repelling substituent on position 6 activates position 3 in preference to position 1 and subsequent ring-closure gives rise to 1,8-naphthyridines. A reactive substituent on position 3 which can take part in condensation reactions can also give this result.

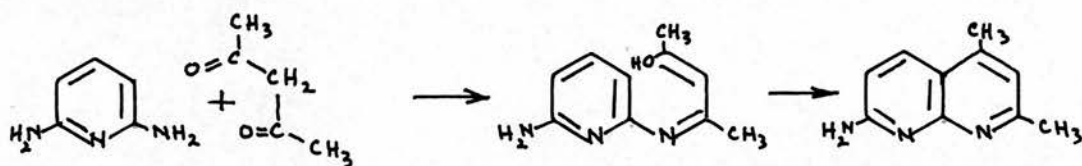
Methyl 2-aminonicotinate condenses with ethyl malonate, with ester exchange, to give methyl 2,4-dihydroxy-1,8-naphthyridine-3-carboxylate (37):



Lappin, Petersen and Wheeler (38) have studied the reactions of 6-substituted 2-aminopyridines and have found that 1,8-naphthyridines are produced in only a few

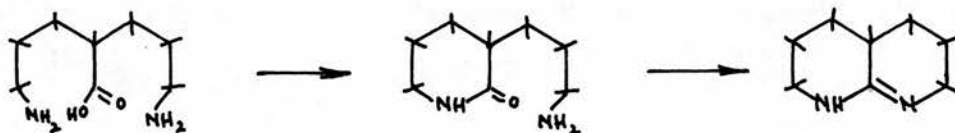
cases. Acetamido, ethoxy and amino substituents all gave good yields.

2,6-Diaminopyridine has been used to synthesise 7-amino-1,8-naphthyridines according to Knorr's procedure (39) (40) (41).



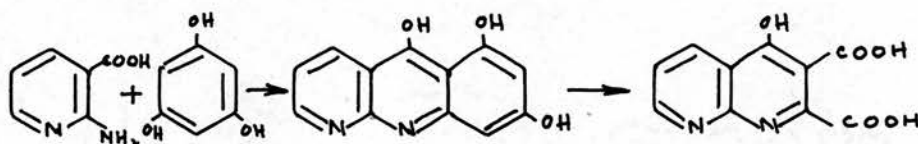
The intermediate anil has been isolated (42). Acetoacetic ester (43) (44) (45), benzoylacetic ester (46) (47), ethyl  $\alpha$ -ethoxalylpropionate (43) and ethoxymethylene-malonic ester (15) have all been used in condensations with 2,6-diaminopyridines to give various 1,8-naphthyridine derivatives.

Octahydro-1,8-naphthyridine has been prepared by heating the aliphatic substance di-( $\gamma$ -aminopropyl) acetic acid.  $\gamma$ -Aminopropylpiperidone has been isolated as an intermediate (2) (48).





The method of condensation of phloroglucinol and 3-aminopicolinic acid, which was used to establish the structure of the 1,5-naphthyridine ring system, can also be applied to the 1,8 isomer. Condensation of phloroglucinol and 2-aminonicotinic acid, followed by oxidation and decarboxylation gives 4-hydroxy-1,8-naphthyridine (49).



Recently these methods have yielded new derivatives, many of which have been patented as disinfectants. Work has also been done on sulphanilamides and (diethylamino) alkylamino derivatives with a view to the investigation of their physiological properties (32).

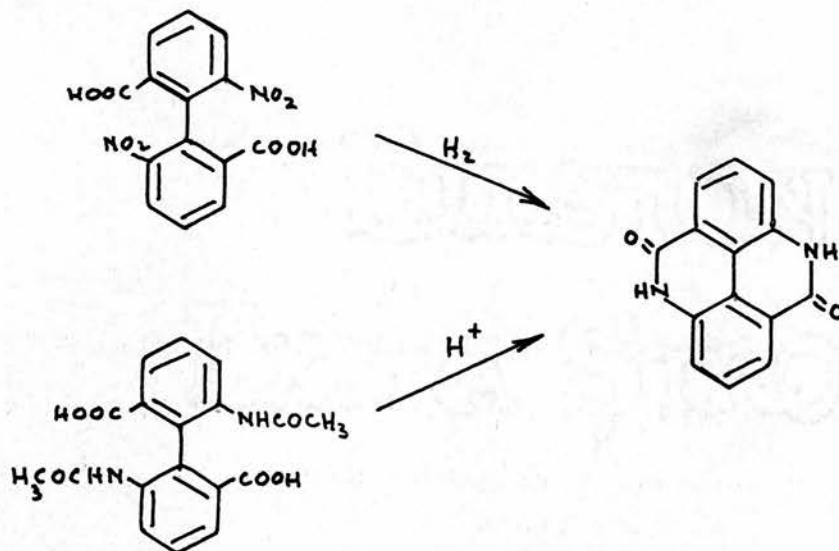
#### Synthesis of the 2,6-Naphthyridine Ring System.

There is no reported synthesis of 2,6-naphthyridine or of any simple derivative.

Some complex 2,6-naphthyridine derivatives have

been prepared, but they are more accurately classed in the ring systems of the diazapyrenes.

Kerner and Stubbings (59) obtained 5,10-diketo-4,5,9,10-tetrahydro-4,9-diazapyrene as a reduction product of a 6,6'-dinitrodiphenic acid. It is also produced on hydrolysis of 6,6'-diacetylaminodiphenic acid.



Various derivatives of this ring system were prepared from more highly substituted diphenic acids.

Lately, Mosby (60) has reported the preparation of the free base, 4,9-diazapyrene, from the cyclisation of



2,2'-diformaminobiphenyl by means of fused aluminium chloride.

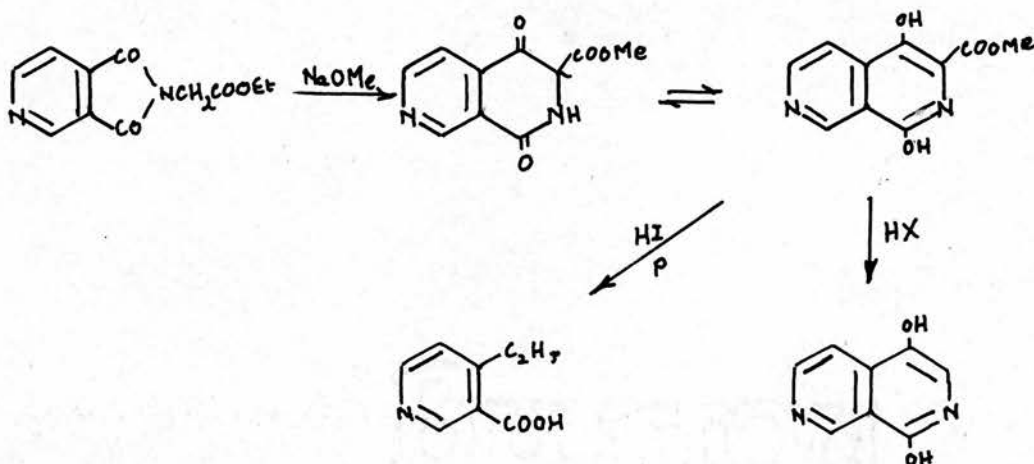


Synthesis of the 2,7-Naphthyridine Ring System.

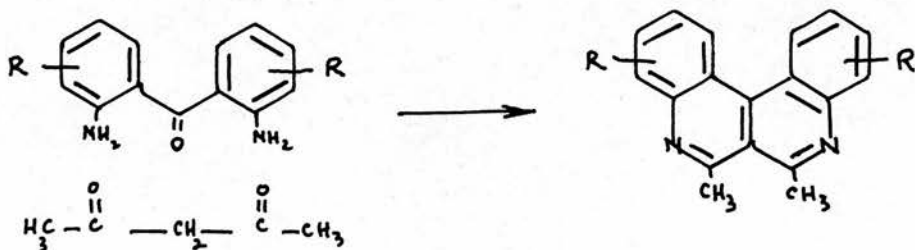
Gabriel and Colman (23) were the first to synthesise a 2,7-naphthyridine derivative. Their method of ring enlargement of phthalimidoacetic ester, which Fels applied to quinolyglycine ester, was used successfully by them in the treatment of cinchomeronylglycine ester with sodium methoxide. The methyl-1,4-dihydroxy-2,7-naphthyridine-3-carboxylate produced in the reaction can be hydrolysed and decarboxylated by hydrobromic or hydriodic acids.

The ring expansion was proved to have formed a 2,7- rather than a 2,6-naphthyridine by degradation of the

ester in a sealed tube, with hydriodic acid and red phosphorus. The 4-ethylnicotinic acid formed established the structure.



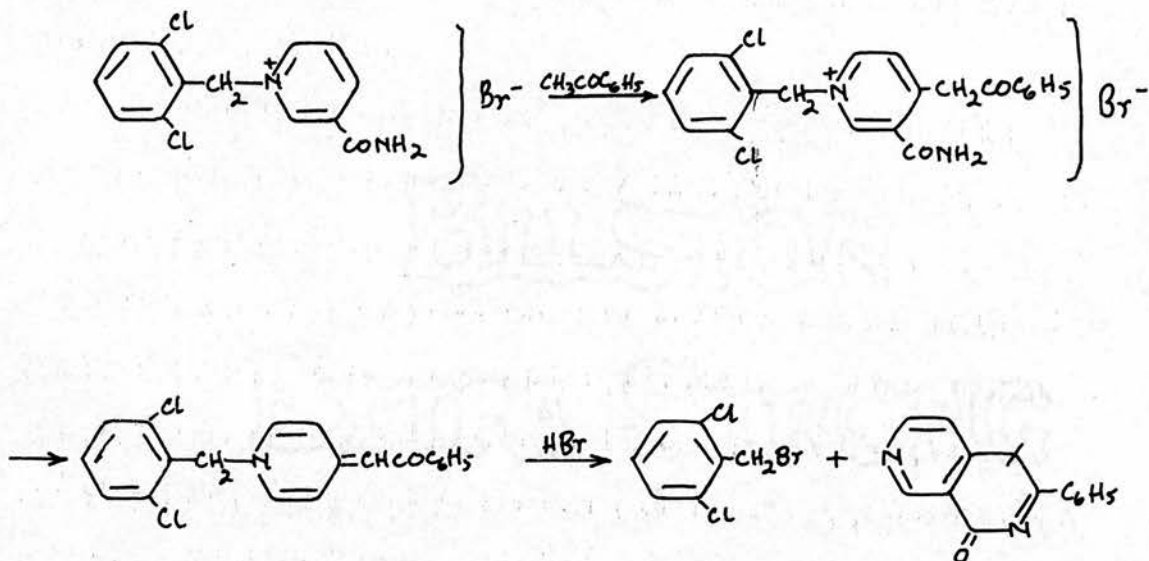
Some dibenzo-2,7-naphthyridines are known. They were obtained from the condensation of 2,2'-diamino-benzophenones and 1,3-diketones (50):



There have been some cases of syntheses, reported to be of 1,6-naphthyridines, which have recently been shown to have given the 2,7 isomers. Huff (51), Perlzweig (52), and Guisa and Nebbia (53) have all reported condensations using N-methyl-3-aminoformyl-pyridinium chloride, and have made the assumption that ring-closure takes place through position 2 to give a 1,6-naphthyridine.

Kröhnke and Ellegast (54) suggested that this assumption may not have been valid, on the basis of some work they did in which they found that condensations did take place at position 4 even when the usually favoured position 2 was unsubstituted. They prepared N[2,6-dichlorobenzyl]3-carbamido-4-phenacal-1,4-dihydropyridine by the condensation of N[2,6-dichlorobenzyl]3-carbamido-pyridinium bromide with acetophenone. The condensation was assumed to have taken place at position 4 because the product obtained from a similar condensation with N-[2,6-dichlorobenzyl]-pyridinium bromide was shown to be identical to a product obtained by Tschitschibabin from  $\gamma$ -picoline. They also give other evidence for believing that these condensations take place at this position.

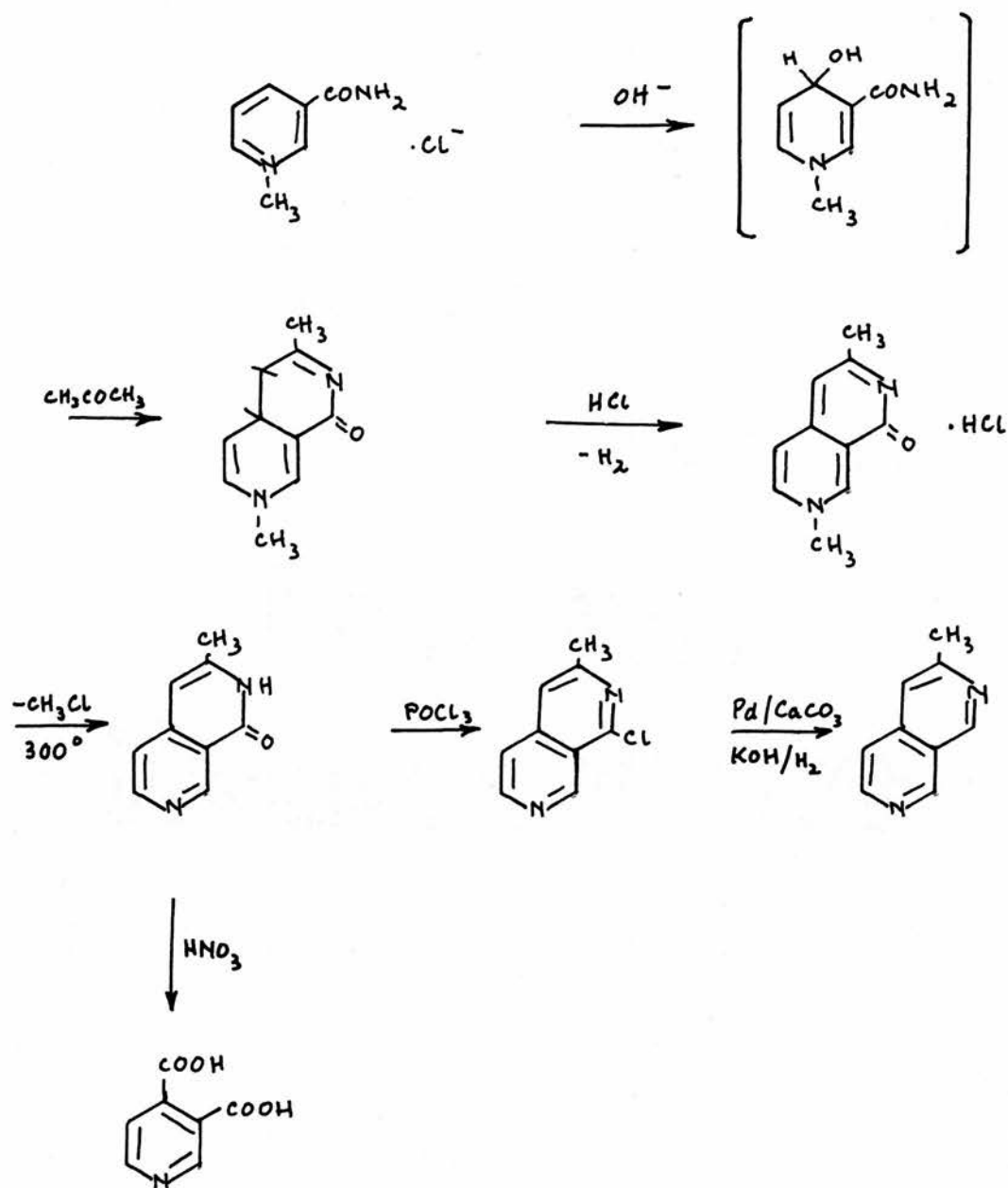
The N[2,6-dichlorobenzyl]3-carbamido-4-phenacal-1,4-dihydropyridine, on treatment with hydrobromic acid in a sealed tube at 180°, gave rise to a naphthyridine; postulated as a 2,7 derivative. This assumes that no migration of the group at position 4 has taken place.



This synthesis has not been fully established, but it seems extremely unlikely that the product is not a 2,7-naphthyridine derivative.

Further evidence for this view and final proof that the assumption made by Huff was not valid was given by Birkhofer and Kaiser (55). They repeated the condensation of N-methyl-3-aminoformylpyridinium chloride

Birkhofer and Kaiser's Synthesis (55).



with acetone done by Huff and proved that the product was 3,7-dimethyl-1-oxy-1,7-dihydro-2,7-naphthyridine hydrochloride, since on sublimation it loses methyl chloride and the product, 3-methyl-1-oxy-1,2-dihydro-2,7-naphthyridine, undergoes nitric acid oxidation to give cinchomeric acid (pyridine-3,4-dicarboxylic acid). They suggest that ring-closure takes place at position 4 because of the formation of an intermediate with a hydroxyl group on this position. The 3-methyl-1-oxy-1,2-dihydro-2,7-naphthyridine (3-methyl-1-hydroxy-2,7-naphthyridine) was treated with phosphorus oxychloride and the corresponding chloro compound thus obtained was catalytically dehalogenated to give 3-methyl-2,7-naphthyridine, the simplest derivative so far prepared. Various oxidative methods of removal of the methyl group all failed. (see facing page)

#### Properties of Naphthyridines.

The only two free bases so far isolated, 1,5 and 1,8-naphthyridines, have been found to be relatively low melting white solids, which show a certain degree of instability in air. The 3-methyl-2,7-naphthyridine obtained by Birkhofer and Kaiser (55) appeared to be extremely unstable.

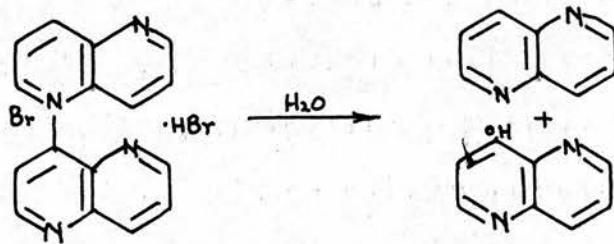
Very little work has been done on the properties of the free bases themselves.

Miyaki (56) found that hydrogenation of 1,5-naphthyridine, using Raney nickel or platinum oxide as catalysts, gave 1,2,3,4-tetrahydro-1,5-naphthyridine. Reduction of the second ring was brought about by sodium in alcohol.

In 1954, Hart (57) published the first paper to give a systematic study of the chemical properties of 1,5-naphthyridine.

It failed to undergo nitration under varying conditions.

On treatment with bromine in chloroform it formed the quaternary 1-(1,5-naphthyridin-4yl)-1,5-naphthyridinium bromide hydrobromide:





This, on hydrolysis in water at 100°, breaks down into 1,5-naphthyridine and 4-hydroxy-1,5-naphthyridine. Hart showed that the base undergoes the typical nucleophilic reaction of amination with sodium amide. 2-Amino-1,5-naphthyridine is formed, and this, on treatment with nitrous acid, gives 2-hydroxy-1,5-naphthyridine.

From the action of peracetic acid on the base both the mono and di-N-oxides can be isolated. Phosphoryl chloride transforms these into the 2-chloro and 2,6-dichloro-1,5-naphthyridines respectively; both of which undergo hydrolysis to the corresponding hydroxy compounds, and form anilino compounds on treatment with aniline.

The method employed by Albert and Royer (58) for removing active chlorine atoms from the acridine nucleus was used successfully with these chloro compounds. When they were condensed with p-toluenesulphonylhydrazide and the products treated with sodium hydroxide, 1,5-naphthyridine was produced. (see further page)

These reactions are typical of aromatic nitrogen heterocyclic systems, and although they have not been systematically studied in the cases of the isomeric naphthyridines, there are indications that they will take place in them all.



A reaction which has proved to be particularly useful in this series has been the replacement of hydroxyl groups by chlorine atoms by treatment with phosphorus oxychloride or phosphorus pentachloride. The hydroxy compounds are high melting and inactive, whereas the chloro compounds, if the chlorine atom is ortho or para to the ring nitrogen, are very reactive.

Many syntheses lead to hydroxynaphthyridines and the hydroxyl groups are usually most readily removed by replacing them with a chlorine atom and then removing the chlorine by catalytic hydrogenation. There have been isolated reports of hydroxyl groups being removed by zinc dust distillation.

Carboxylic acid groups are readily removed by heating. The method generally used is sublimation, the sublimate consisting of the decarboxylated material.

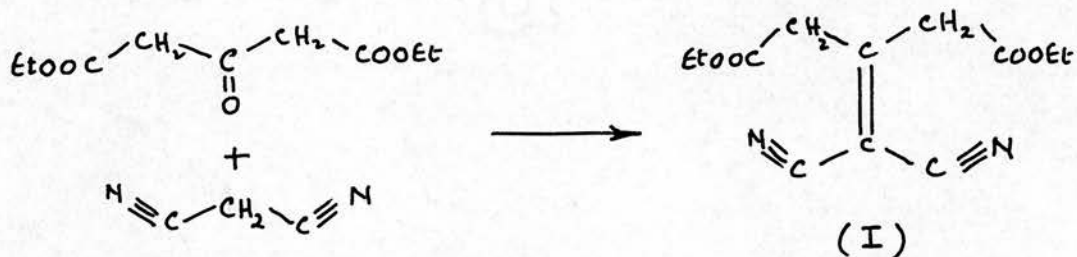
DISCUSSION OF RESULTS

Discussion of results.

I Synthesis of 2,7-naphthyridine derivatives.

The condensation of malononitrile with ketones (acetone, benzophenone, fluorenone) has been reported to take place in good yield when the reactants are allowed to stand in ethanol, in the presence of a basic catalyst. Potassium ethoxide, ammonia and diethylamine have all been used successfully (61).

If a similar condensation between malononitrile and diethyl acetone-dicarboxylate were successful, then the number and relative positions of the carbon and nitrogen atoms in the product would be those of a 2,7-naphthyridine derivative.

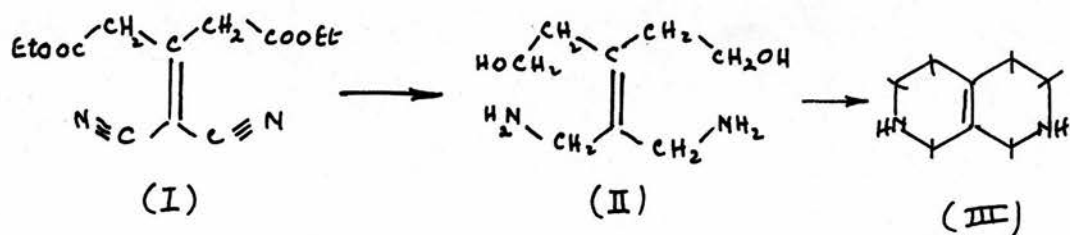


When molar proportions of malononitrile and diethyl acetone-dicarboxylate were allowed to stand in ethanol containing a little diethylamine, freshly distilled over sodium, until no free diethyl acetone-dicarboxylate could

be detected in a sample of the mixture (as its 2,4-dinitrophenylhydrazone), the colour of the solution became bright orange-red. Removal of the solvent left a dark red oil, which could not be distilled, even at pressures as low as 0.1 mm. Whenever the temperature was raised above 100°C. the oil blackened and gradually solidified, which indicated that extensive polymerisation was taking place.

Extraction of the solid material with boiling benzene gave a red solid which also appeared to be polymeric. Ether extraction gave a very small quantity of a yellow solid. This product was later obtained in larger quantities by another method and was proved to be the condensation product, 1,3-dicarbethoxyisopropylidene-malononitrile (I).

Since the oily condensation product was sensitive to heat and could therefore not be purified by distillation, an attempt was made to reduce it in its crude form to the corresponding amino-alcohol (II).

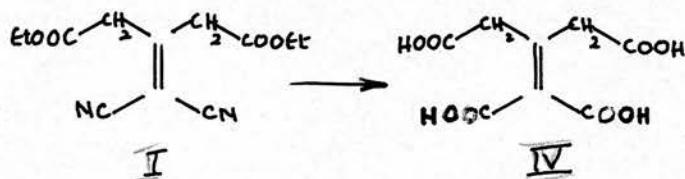


The reduction product would be a 1,5-aminoalcohol, which are reported to cyclise extremely readily (62). In this case the product of cyclisation would be the octahydro-2,7-naphthyridine (III). The oily material in ethereal solution was exhaustively dried and treated with lithium aluminium hydride. The colour of the solution changed from red to yellow, and the product, a yellow oil, gave positive tests for the presence of nitrogen, hydroxyl groups and amino groups. On this evidence it was assumed to be the desired aminoalcohol (II) and ring closing reagents were applied to it.

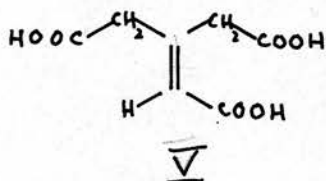
The oil obtained from treatment of the aminoalcohol in benzene solution with dry hydrogen chloride was found still to contain free amino groups showing that the material had not cyclised. When the oil from the reduction reaction was allowed to stand in concentrated sulphuric acid a very small quantity of a pale yellow solid was obtained. This material was found to be too unstable to be identified.

An attempt was now made to identify the product of the condensation by hydrolysing its ester and cyano groups. The tetracarboxylic acid which would be formed was expected

to be easier to isolate.



When the oil was hydrolysed with alkali and the solution made acid there was a vigorous evolution of carbon dioxide and a yellow oil separated, which was found to contain no nitrogen, no ester groups (Feigl's test (63)) and to be acidic in its reactions. From these results it appears that the alkali caused the hydrolysis of all four functional groups to carboxylic acid groups, at least one of which then decomposed. Since the product of such a hydrolysis would be a substituted methylene-malonic acid (IV) the most likely formula for the decarboxylation product would be (V).





As alkaline hydrolysis did not give a useful product, experiments were tried with acid.

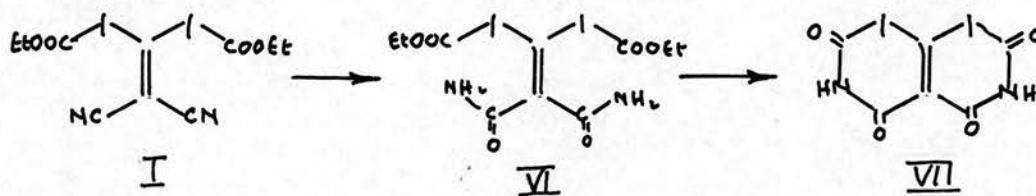
By means of 70% sulphuric acid nitriles add on water to form amides. When the red oil from the condensation was treated with cold 70% (by volume) sulphuric acid a very vigorous exothermic reaction took place. Dilution of the resultant yellow solution with water yielded a heavy, pale yellow precipitate. This solid was found to be insoluble in water, dilute acids, and all common organic solvents, and soluble in 2N sodium hydroxide solution. However, it was less soluble in sodium carbonate and ammonia solution. It thus appeared to be weakly acidic in character.

It did not melt below a temperature of 350°, and was found to contain nitrogen, but no sulphur. On exposure to air it darkened in colour.

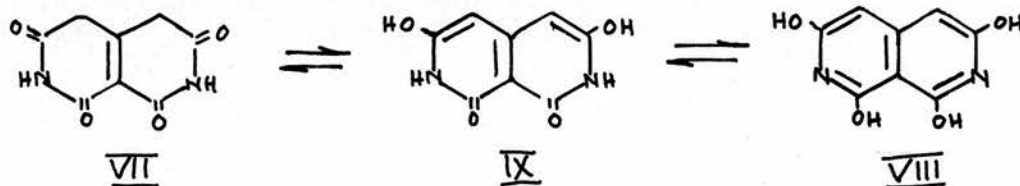
When this solid was dissolved in alkali the solution gradually developed a greenish-blue colour and a blue solid separated. This reaction seemed to be one of aerial oxidation since the colour was first seen on the liquid surface and vessel walls. This was confirmed by the fact that the addition of a solution of hydrogen peroxide to a fresh alkaline solution of the solid material caused the immediate formation of the blue solid.

This blue material was also found to be insoluble in organic liquids and in water, and not to melt below 350°C. When it was treated, in aqueous suspension, with acid it became red. The red solid was similarly high melting, insoluble and could be reconverted to the blue material by alkaline treatment.

Analysis of the product of acid hydrolysis, allowing for the fact that it could not be purified by recrystallisation, together with the information obtained from its solubility characteristics, suggested that it had been formed by partial hydrolysis of the cyano groups (VI) and subsequent elimination of ethyl alcohol to give a bicyclic system (VII):

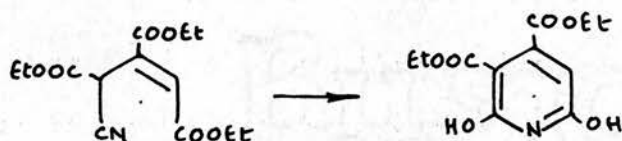


This substance can obviously be represented by several tautomeric forms, including:

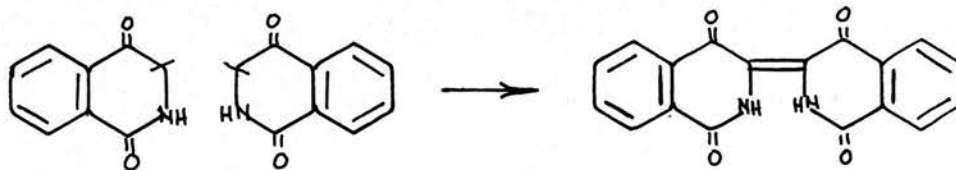


Formula VIII shows it to be 1,3,6,8-tetrahydroxy-2,7-naphthyridine. For simplicity it will be subsequently referred to as tetrahydroxynaphthyridine.

Rogerson and Thorpe (64) reported an analogous reaction when they found that treatment of ethyl  $\alpha$ -cyanoaconitate for 12 hours with concentrated sulphuric acid gave ethyl 2,6-dihydroxypyridine-4,5-dicarboxylate.

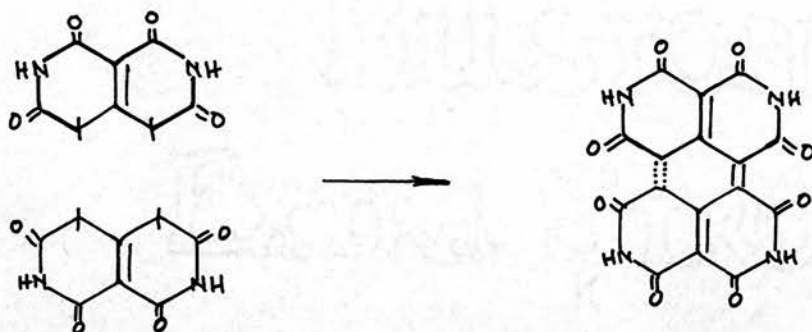


A survey of the literature showed that the substance postulated as tetrahydroxynaphthyridine had properties similar to some of those of 2,6-dihydroxypyridine and polyhydroxyquinolines and isoquinolines. They all have high melting points and are relatively insoluble in organic liquids. Gabriel and Colman (65) reported that 4-hydroxyisocarbestyryl gives the blue coloured substance, carbindigo, on serial oxidation:

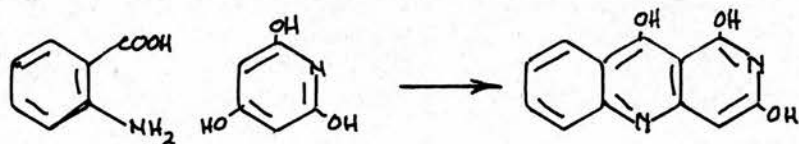


Errera (66) also found that 2,6-dihydroxypyridine gave blue "decomposition" products on treatment with bases, or on exposure to air.

By analogy with Gabriel and Colman's work, the blue solid formed when an alkaline solution of the tetrahydroxynaphthyridine is exposed to air may be a dimeric oxidation product, like carbindigo, in which oxidation has taken place at the methylene groups (imide structure VII):



Niementowski and Sucharda (67) prepared 4,5,7-trihydroxy-2,3-benzo-1,6-naphthyridine:



They found that this substance has a high melting point (370°) and is characterised by its insolubility. Its potassium salt was reported to become violet on drying in air and a red compound was obtained when a solution of the material in perhydrol was acidified.

Experiments were now made to prepare derivatives of the tetrahydroxynaphthyridine to establish its identity.

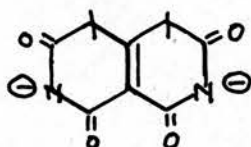
Acetylation procedures using acetic anhydride and sulphuric acid, and acetic anhydride and fused sodium acetate (67) gave slimy products which could not be crystallised. Niementowski's benzylation method was applied (67).

The solid in suspension in pyridine gradually dissolved when benzoyl chloride was added. A deliquescent solid was formed which went into solution. A stable solid was obtained from the reaction mixture by the addition of water. This solid was crystalline, but could not be recrystallised. The result of analysis of this compound (again allowing for the fact that it had not been recrystallised) was in reasonable agreement with the theoretical analysis of a dibenzoyl derivative of tetrahydroxynaphthyridine.



The Haworth and Hirst methylation method was applied to the substance. As this reaction is carried out in 20% sodium hydroxide solution, nitrogen gas was bubbled through the solution continuously to try to prevent the aerial oxidation which takes place in alkaline solution. No product could be isolated from the alkaline solution, but when it was acidified, ethyl acetate extraction gave a very small amount of a dark red oil. The colour of the solution, originally yellow, became green on exposure to air and reddish-brown on acidification. When the product was triturated with ether a grey solid was obtained.

It seems likely from the above facts that N-methylation took place under the Haworth and Hirst conditions, but the product was obtained in too small yield to be characterised. In alkaline solution the tetrahydroxynaphthyridine may exist in the ionised form:





This would cause preferential methylation at the negatively charged nitrogen atom. Arndt et al. (68) reported that N-methylation took place when they treated "2,4-dihydroxyquinoline", which exists as 4-hydroxycarbostryl, with dimethyl sulphate:



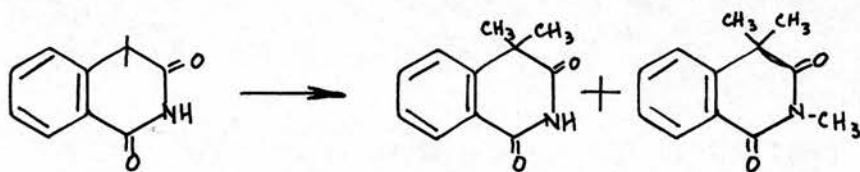
N-methylpyridone is reported to give a hydrochloride which turns red on exposure to light (69).

Garden and Thomsen (70) found that the best reagents for methylating polyhydroxynaphthoquinones are the Purdie reagents. Their conditions for the methylation of juglone were adapted and applied to the tetrahydroxynaphthyridine. A buff-coloured solid was obtained from the reaction. After recrystallisation from water it was found to have a wide melting point range and lack of homogeneity was suspected. It was run on paper chromatograms in several solvent systems and all showed a single fluorescent spot in ultra violet light. The papers were also photographed in ultra violet light and

again only one localised region of absorption was seen, so that it appeared that the wide melting point range was not due to lack of homogeneity.

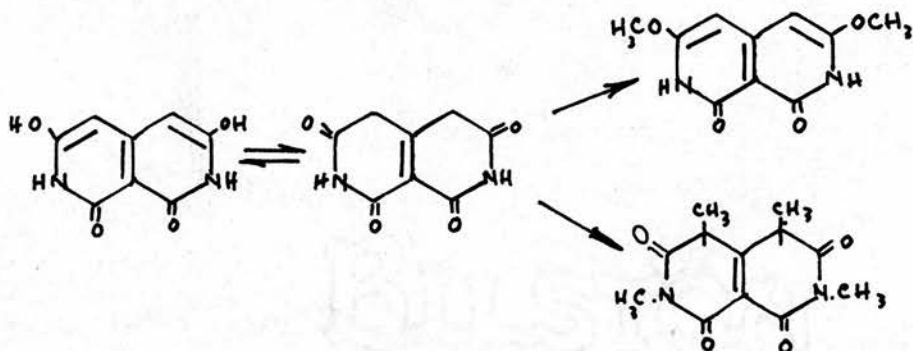
Determination of the extent of methylation by a volumetric method indicated that there were two methyl groups in the molecule which were removed in refluxing hydrogen iodide.

Gabriel (71) treated homophthalimide with methyl iodide, potassium hydroxide and methyl alcohol and obtained di- and trimethylated products. He suggested that these products arose from the formation of carbon-carbon and carbon-nitrogen bonds, since no methyl chloride was produced when they were treated with hydrogen chloride.



The presence of the potassium methoxide may have stabilised the molecule in the imide form and so the methylation conditions may not be comparable to those used on the tetrahydroxynaphthyridine. Analysis of the

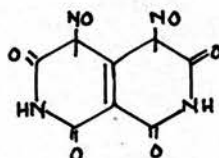
methylated product did not give completely satisfactory results for a dimethoxydihydroxynaphthyridine so that some nuclear methylation may have taken place.



When a solution of benzene diazonium chloride was added to a solution of tetrahydroxynaphthyridine in sodium hydroxide a bright orange precipitate was formed, showing the presence of a ring system which can exist in an aromatic form with an activated position available for coupling (positions 4 and 5).

R.C.F. Brown et al. (72) found that 4-hydroxyquinoline was difficult to characterise and they discovered that a nitroso derivative could be prepared satisfactorily. Their method was used to nitrosate the tetrahydroxynaphthyridine. Analysis of the yellow solid product

showed it to have the composition of a dinitrosotetrahydroxynaphthyridine:

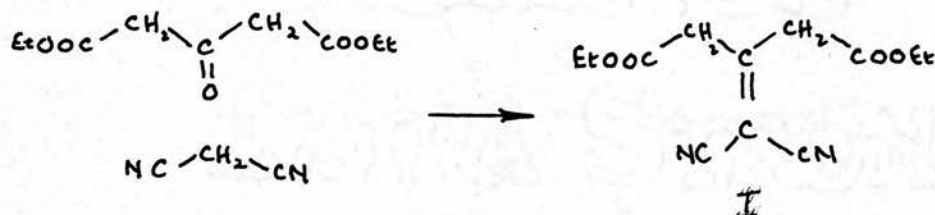


When the methylated product was treated under the same conditions no nitrosated compound was obtained. This result indicates that there is no longer the possibility of existence of an active methylene group in the molecule. This may be because *O*-methylation has taken place at positions 3 and 6 or because *C*-methylation of the type described by Gabriel has taken place at positions 4 and 5.

Since the evidence indicated that the product of the sulphuric acid treatment of the oil from the condensation of malononitrile and diethyl acetone-dicarboxylate was 1,3,6,8-tetrahydroxy-2,7-naphthyridine, further attempts were made to isolate the intermediate in a pure form.

The condensation was repeated and was allowed to stand for 19 days, compared with a maximum of 4 days in

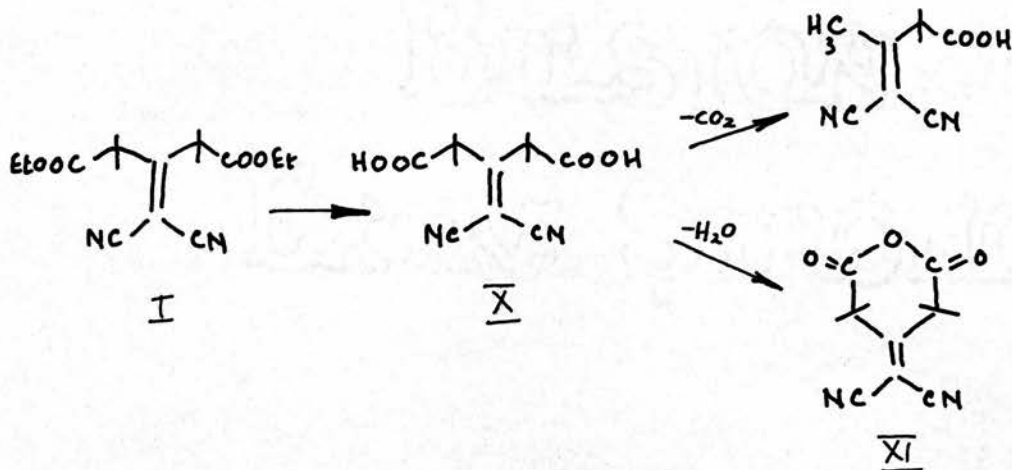
previous experiments. After this time the red colour of the solution showed a strong green fluorescence, and when the solvent was removed the residual oil gradually solidified. The solid product was proved to contain free ester groups and was found to be the same substance as that isolated from the polymeric residue left after attempted distillation, by ether extraction (see p. 32). Analysis showed the product to be the desired intermediate, dicarbethoxyisopropylidenemalononitrile (I).



Treatment of this solid with 70% sulphuric acid gave the same material as was obtained from the crude oil.

The intermediate ester is very soluble in sodium hydroxide, but no ammonia was produced even on refluxing with 20% sodium hydroxide solution for 1 hour. In the pure compound the nitrile groups thus appear to be very stable to alkaline hydrolysis. This is in contrast to the apparent ease of hydrolysis of the nitrile groups in the crude oil (see p. 34). When the alkaline hydrolysate

was acidified a solid was precipitated. This contained nitrogen and gave effervescence with sodium bicarbonate solution. It was found to melt, with evolution of gas at 165-175°, then to resolidify and finally melt at 220°. There seem to be two explanations of this behaviour. The hydrolysis product, the dicyanodicarboxylic acid (X) could either dehydrate to give the anhydride XI or decarboxylate to give the monocarboxylic acid:

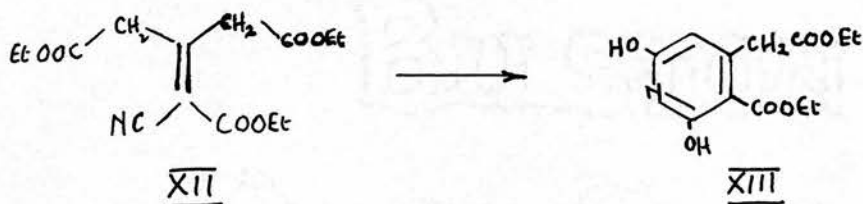


The former explanation seems to be preferable, since it would not be expected that the decarboxylated product would have a higher melting point than the original material.

Raha (73) condensed ethyl cyanoacetate and diethyl acetone-dicarboxylate using piperazine acetate as the catalyst. This condensation was found to take place

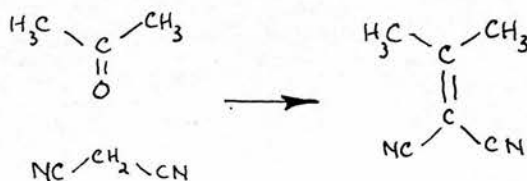


equally well with diethylamine as the catalyst. The crude product, (XII) a red oil, gave no solid on treatment with 70% sulphuric acid according to the method for the preparation of the tetrahydroxynaphthyridine, but when it was allowed to stand in concentrated sulphuric acid overnight the ring closed material, ethyl 3-(ethyl 2,6-dihydroxynicotinyl)-acetic ester, XIII, was obtained.



This result gives further evidence for the formation of the tetrahydroxynaphthyridine.

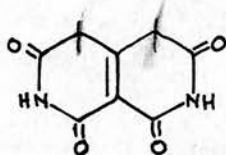
The ultra violet absorption spectrum of the intermediate ester (I) was compared with that of the product of the condensation of acetone and malononitrile, 1,1'-dimethyl-2,2'-dicyanoethylene:



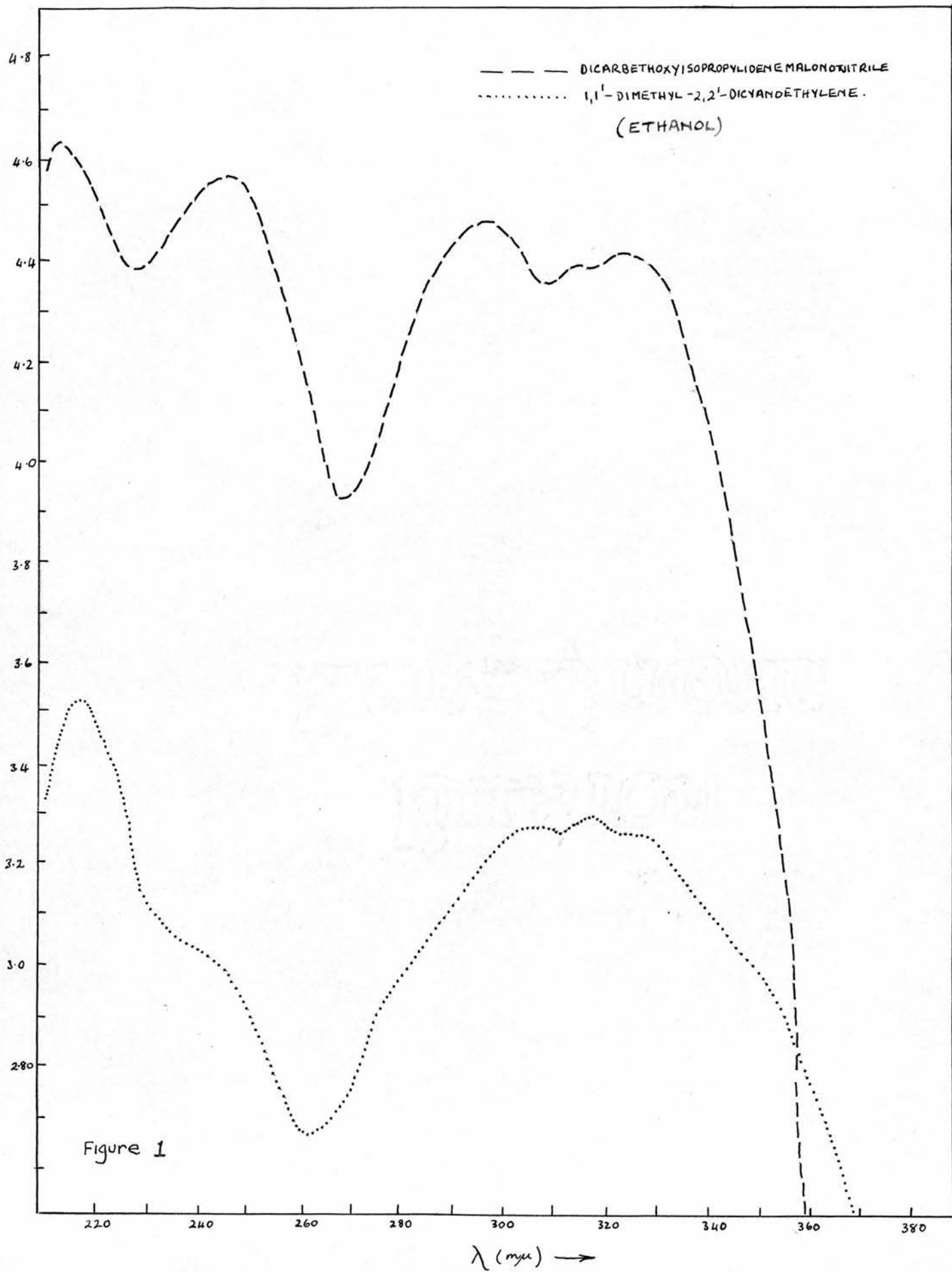
This compound had been prepared by Schenck and Finken (61) using potassium ethoxide as the catalyst; but repetition of this method was found unsatisfactory as it appeared to cause polymerisation. Diethylamine, however, catalysed the condensation successfully.

The spectra of the two substances were found to be similar in form, but the introduction of the carbethoxy groups was seen to have caused a marked increase in the intensity of absorption (see Fig. I).

Mason (74) claims that the infra red absorption spectrum of homophthalimide shows the absence of any hydroxyl group in the molecule. From this and other results he concludes that when hydroxyl groups are  $\alpha$  or  $\gamma$  to a heteroaromatic nitrogen atom the molecule exists in the quasiquinoid form, whereas hydroxyl groups  $\beta$  to the nitrogen atom are principally enolic in character. On this basis 1,3,6,8-tetrahydroxy-2,7-naphthyridine should exist as the di-imide:



VII



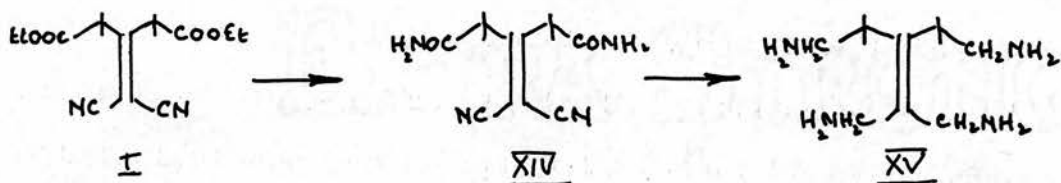
The infra red absorption spectrum of the material showed a strong C=O ( $1697\text{cm}^{-1}$ ) stretching frequency, but it was not possible to say that no hydroxyl groups are present since the N-H stretching frequency region, showing highly hydrogen bonded character is broad ( $3250-2500\text{cm}^{-1}$ ) and may mask any absorption due to the O-H group.

Attempts were now made to modify the 1,3-dicarbethoxy-isopropylidenemalononitrile (I) before hydrolysis and ring-closure in an effort to obtain a less intractable product.

When it was shaken in ethanolic solution in an atmosphere of hydrogen and in the presence of Adams' catalyst, there was no appreciable uptake of hydrogen, showing that the ethylenic double bond present is resistant to this method of reduction.

When the material was treated with bromine a bromine-containing product, which had arisen from the substitution of one atom of bromine in each molecule, was obtained. No addition of bromine occurred. This is in agreement with the general finding that bromine does not add on to an ethylenic double bond when both carbon atoms are fully substituted, particularly by groups which can interact electronically with the double bond.

The crude product from the condensation of malono-nitrile and diethyl acetone-dicarboxylate had already been reduced with lithium aluminium hydride, without satisfactory results. This experiment was not repeated on the purified product. An oil, smelling of peppermint, was obtained, but the yield was too low for the further application of this method. It was originally intended to try a similar reduction on the diamide (XIV). This was obtained from the diester by treatment with concentrated ammonia:



Reduction of this compound would give a 1,5-diamino compound (XV) of the type reported to ring close very readily to give piperidines. However, the introduction of another stage into the synthesis, with accompanying low yield (60%) seemed to offer no new hope of success and this approach was abandoned.

Some experiments were now done on the tetrahydro-naphthyridine to see whether the hydroxyl groups could be removed by direct reduction.

Hermanek and Trojanek (75) successfully reduced the comparable compound,  $\Delta$ -4,5-tetrahydrohomophthalimide to  $\Delta$ -6,7-octahydroisoquinoline.



They used lithium aluminium hydride and the Soxhlet extraction method, with tetrahydrofuran as solvent. Their method was applied to the tetrahydroxynaphthyridine, but weighing the solid after 24 hours showed that none had been dissolved.

The method of zinc dust distillation had been successfully applied by Sucharda (11) to the preparation of 1,5-naphthyridine from 4-hydroxy-1,5-naphthyridine. No product was obtained when the tetrahydroxynaphthyridine was heated to red heat with zinc dust or with a mixture of zinc dust and zinc chloride.

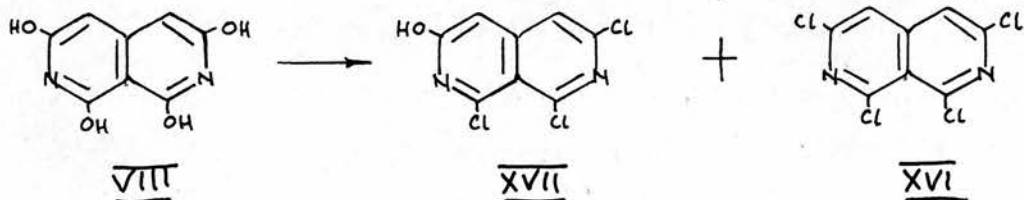
Only starting material was recovered when the naphthyridine derivative was treated with red phosphorus and iodine in refluxing acetic acid.





In the naphthyridine series it has been found that the most satisfactory method of removing hydroxyl groups from the nucleus is to replace the hydroxyl group by a chlorine atom and then reduce the chlorine catalytically. When the tetrahydroxynaphthyridine was refluxed with phosphorus oxychloride a solution was obtained but treatment of the oily product with water caused re-precipitation of the starting material.

Gabriel (76)(77) when working on homophthalimide and Prelog and Metzler (78) working with 4,5-cyclopenteno-2,6-dihydroxypyridine found that to replace the hydroxyl groups by chlorine atoms the compounds had to be treated with phosphorus oxychloride in sealed tubes at temperatures above 150°. The tetrahydroxynaphthyridine was treated in this way, and a yellow solid, consisting of two different products, was obtained. These products were shown by analysis to be 1,3,6,8-tetrachloronaphthyridine (XVI) and a trichloromonohydroxynaphthyridine (XVII).

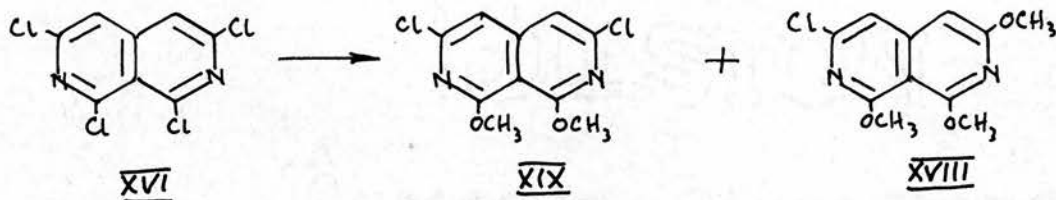


By analogy with 1,3-disubstituted isoquinolines in which the substituent on position 1 is more reactive than that on position 3, it is probable that the trichlorohydroxynaphthyridine will have the hydroxy group at position 3. Since this product, as well as the fully chlorinated compound, has been isolated it seems probable that dichlorodihydroxy and monochlorotrihydroxy derivatives will also be formed in the reaction. The increasing number of hydroxyl groups will, however, make them less soluble in organic solvents and thus more difficult to isolate from an aqueous solution.

It was found that increasing the length of heating during the reaction caused an increase in the amount of the tetrachloro compound formed, so it seems likely that heating for a short time will give significant amounts of the dihydroxy compound.

Attempts were now made to remove the chlorine atoms from the tetrachloronaphthyridine by catalytic hydrogenation. A solution of the tetrachloro compound in absolute methanol was hydrogenated in the presence of Raney nickel and sodium methoxide. The uptake of hydrogen was significantly less than that expected for the complete reduction of the chlorine atoms. Two solid products were obtained. One,

from analysis, appeared to be a trimethoxymonochloro-naphthyridine (XVIII) and the other was later found to be identical to dimethoxydichloronaphthyridine (XIX) prepared by another method. Although these products did not account for all the starting material or the uptake of hydrogen, no other product was isolated.



This result shows a parallel difference of the rates of reaction at the 4 substitution positions with those in the chlorination experiment.

As the conditions of this experiment gave rise to extensive solvolysis, hydrogenations were repeated under different conditions. All experiments were done in basic or buffered media since the replacement of the chlorine atoms would produce hydrogen chloride and it has been shown by many workers that the reduction of pyridine rings is catalysed by acid (83,84). 5% Ruthenium on charcoal in methanol containing excess sodium acetate, palladium hydroxide on calcium carbonate with excess solid calcium

carbonate in ether, palladium on calcium carbonate with excess solid calcium carbonate in benzene, platinum oxide in benzene, all failed as hydrogenating systems and the tetrachloronaphthyridine was recovered quantitatively in each case.

Gabriel found that the chlorine atoms in 1,3-dichloroisoquinoline, obtained from homophthalimide, could both be replaced by methoxyl groups on treatment with sodium methoxide and that the chlorine at position 1 was more readily replaced than the other. However, Prelog and Metzler (78) claim to have reduced 4,5-cyclopenteno-2,6-dichloropyridine to the free base by the Raney nickel/sodium methoxide hydrogenation.

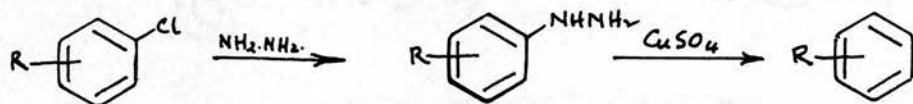
Gabriel found that he could reduce the chlorine atoms in 1,3-dichloroisoquinoline by heating with red phosphorus and hydrogen iodide in a sealed tube (76). When this method was applied to the tetrachloronaphthyridine a very small quantity of a white solid and an oil resulted. Neither oil nor solid gave a picrate and neither contained chlorine, but both were in too small quantity to be identified.

Haworth and Robinson (79) found that they could reduce one chlorine atom in 1,3-dichloroisoquinoline by treating it with hydrogen iodide and red phosphorus in refluxing

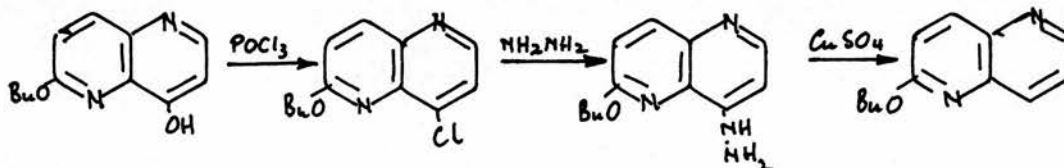
glacial acetic acid, a result obtained by Gabriel (76) by controlled heating with phosphorus and hydrogen iodide in a sealed tube.

When Haworth and Robinson's method was applied to the tetrachloronaphthyridine trichloromonohydroxynaphthyridine was obtained. This reaction mixture therefore has caused hydrolysis and not reduction. Seide reported a similar case of hydrolysis by hydrogen iodide (45).

Robert (80) successfully dehalogenated benzene derivatives by preparing the hydrazine and decomposing it with copper sulphate to give the dehalogenated product:



This method has been applied in the naphthyridine series by Goldberg, Theobald and Williamson (7) who carried out the following reactions:





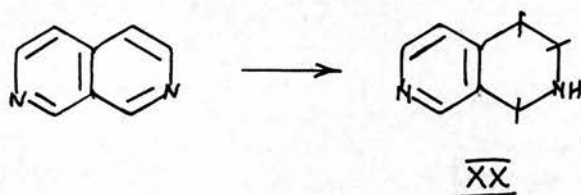
When a hot alcoholic solution of hydrazine hydrate was added to a boiling alcoholic solution of the tetrachloronaphthyridine a dark red colour developed immediately and on cooling a solid separated. This reaction shows the very great reactivity of at least one of the chlorine atoms since the formation of substituted hydrazines from chloro compounds frequently requires several hours of refluxing. The red solid, when filtered off and dried, gradually became black. This product did not melt below  $350^{\circ}$  and still contained chlorine. When an aqueous suspension of this solid was treated with a saturated solution of copper sulphate a gas was seen to be given off but no product could be obtained.

This immediate formation of a red colour with hydrazine hydrate has been shown to be a sensitive test for the tetrachloro-2,7-naphthyridine and it was used as a spray for chromatograms for the identification of tetrachloronaphthyridine spots.

Wibaut and Krooyman (81) catalytically dehalogenated 2,6-dichloro-3,4-dimethylpyridine using palladium chloride and hydrogenating in dry methanol containing solid potassium acetate as a buffer. When this method was



applied to the tetrachloronaphthyridine it was found that the uptake of hydrogen was greater than the calculated theoretical amount for the reduction of the four chlorine atoms. A small amount of oil was obtained from the reaction. Analysis of the picrate of this oil indicated that the compound was a tetrahydro-2,7-naphthyridine (XX). The acetic acid produced in the reaction appeared to have catalysed the reduction of one of the rings.



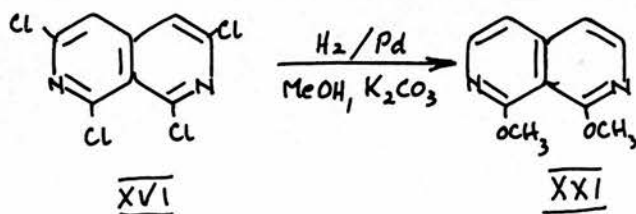
When the oil was purified by decomposition of its picrate it was found to darken on exposure to air. Neither a trinitrobenzene nor a methiodide derivative could be prepared from it.

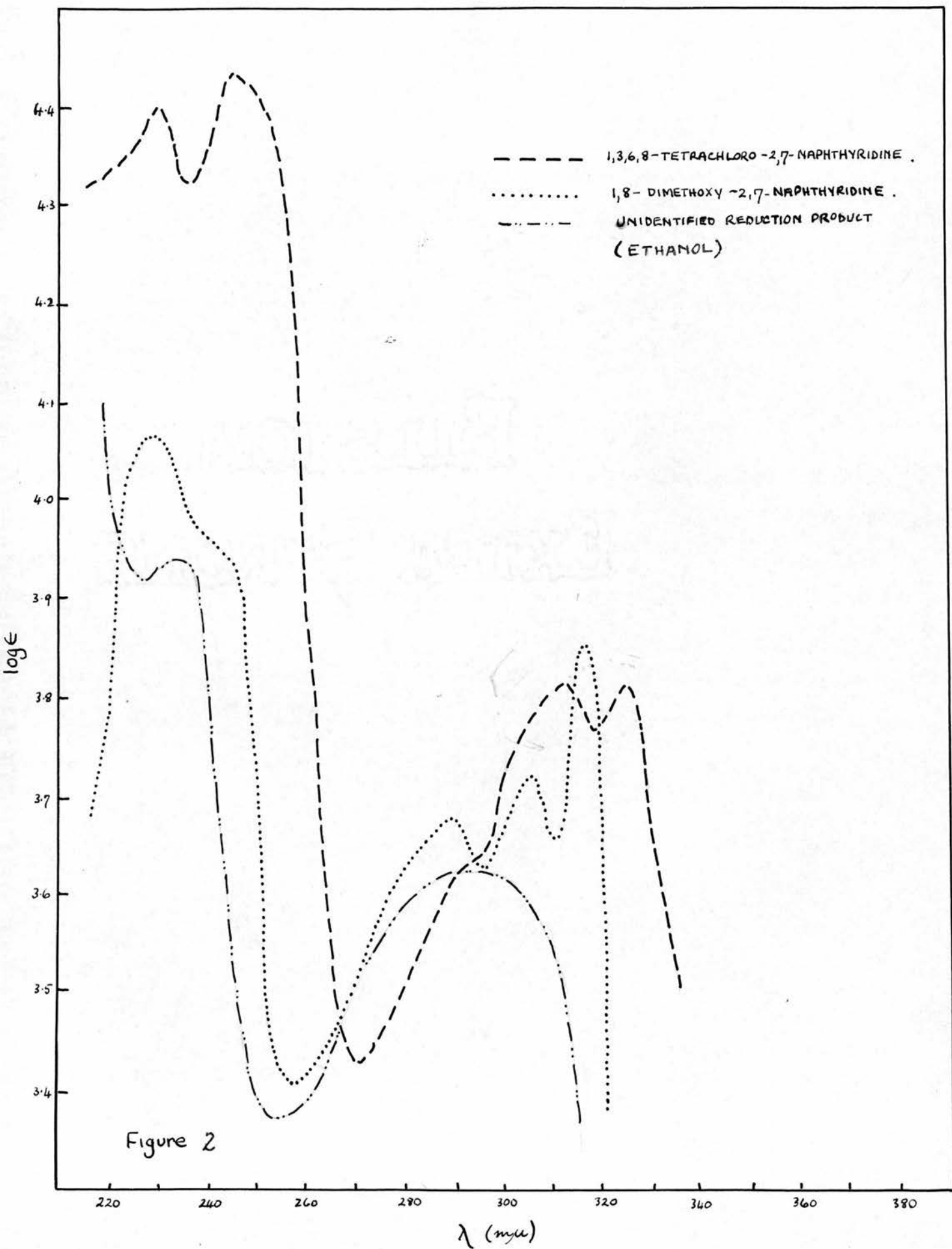
This hydrogenation experiment was repeated using excess solid potassium carbonate instead of potassium acetate, thus ensuring that acid conditions could not arise during the reaction. A very rapid uptake of hydrogen was observed until slightly more than the theoretical amount had been taken up. Three different

products were isolated. Two appeared from analysis to be dimethoxynaphthyridines and the other was the same tetrahydronaphthyridine as was obtained from the previous experiment.

Of the two solids which appeared to be dimethoxynaphthyridines the one which was higher melting was found to have an ultra violet absorption spectrum like that of the tetrachloronaphthyridine and also similar in type to quinoline and isoquinoline (see Fig. 2). It could therefore be identified as 1,8-dimethoxy-2,7-naphthyridine (XXI). Its infra red absorption spectrum showed the absence of any N-H group.

The other solid product was lower melting. When its picrate was prepared and examined it was found to melt at about 150°, then resolidify and remelt above 200°, showing that some change in the molecular or crystalline structure was occurring. The ultra violet absorption spectrum of this solid did not show the characteristic complex absorbing region near 300m $\mu$ , but showed a wide band at this wavelength (Fig. 2).





It appears from these results that solvolysis of two of the chlorine atoms make the other two more readily reducible. When no solvolysis can take place the four chlorine atoms seem to deactivate one another sufficiently to prevent hydrogenation, but when two are replaced by the activating methoxyl groups the remaining two are easily removed. Hardman and Partridge (82) report that they obtained an appreciable amount of 4-ethoxyquinoline, along with quinoline and tetrahydroquinoline from the catalytic hydrogenation of 2,4-dichloroquinoline by Raney nickel in ethanol and sodium hydroxide.

Attempts to dehalogenate the tetrachloronaphthyridine using the same conditions but in solvents which could not cause solvolysis, e.g. ether, benzene, ethyl acetate all failed, thus confirming that under these conditions replacement of two chlorine atoms is necessary before reduction of the others can take place.

The tetrachloronaphthyridine could be recrystallised from petrol or from aqueous methanol to give identical products. This means that solvolysis either does not take place very rapidly, or does not take place without a basic catalyst. This latter possibility is supported by the fact that when run on a paper chromatogram in acid

or neutral solvent systems the tetrachloro derivative runs unchanged as shown by the development of a red spot on spraying with dilute hydrazine hydrate solution.

When, however, it is run in a basic system no trace of the red colour develops when the chromatogram is sprayed.

Solutions of tetrachloronaphthyridine in methanol were treated with a little concentrated hydrochloric acid and with solid potassium carbonate. Unchanged material was recovered from the acid treated solution after standing for 7 days, by the addition of water. An untreated methanolic solution gives the same result. Whenever the potassium carbonate was added, however, the yellow methanolic solution became orange and after a few minutes a solid started to separate. It was shown by analysis to be a dichlorodimethoxynaphthyridine (XIX). This is presumably the compound which undergoes catalytic dehalogenation to give the dimethoxynaphthyridine. It does not give an immediate colour with hydrazine. The same compound was obtained when the tetrachloronaphthyridine was boiled with 50% aqueous methanol containing potassium carbonate, and not the dihydroxy compound as was expected. This appears to be due to the insolubility of the dimethoxydichloronaphthyridine in aqueous methanol.



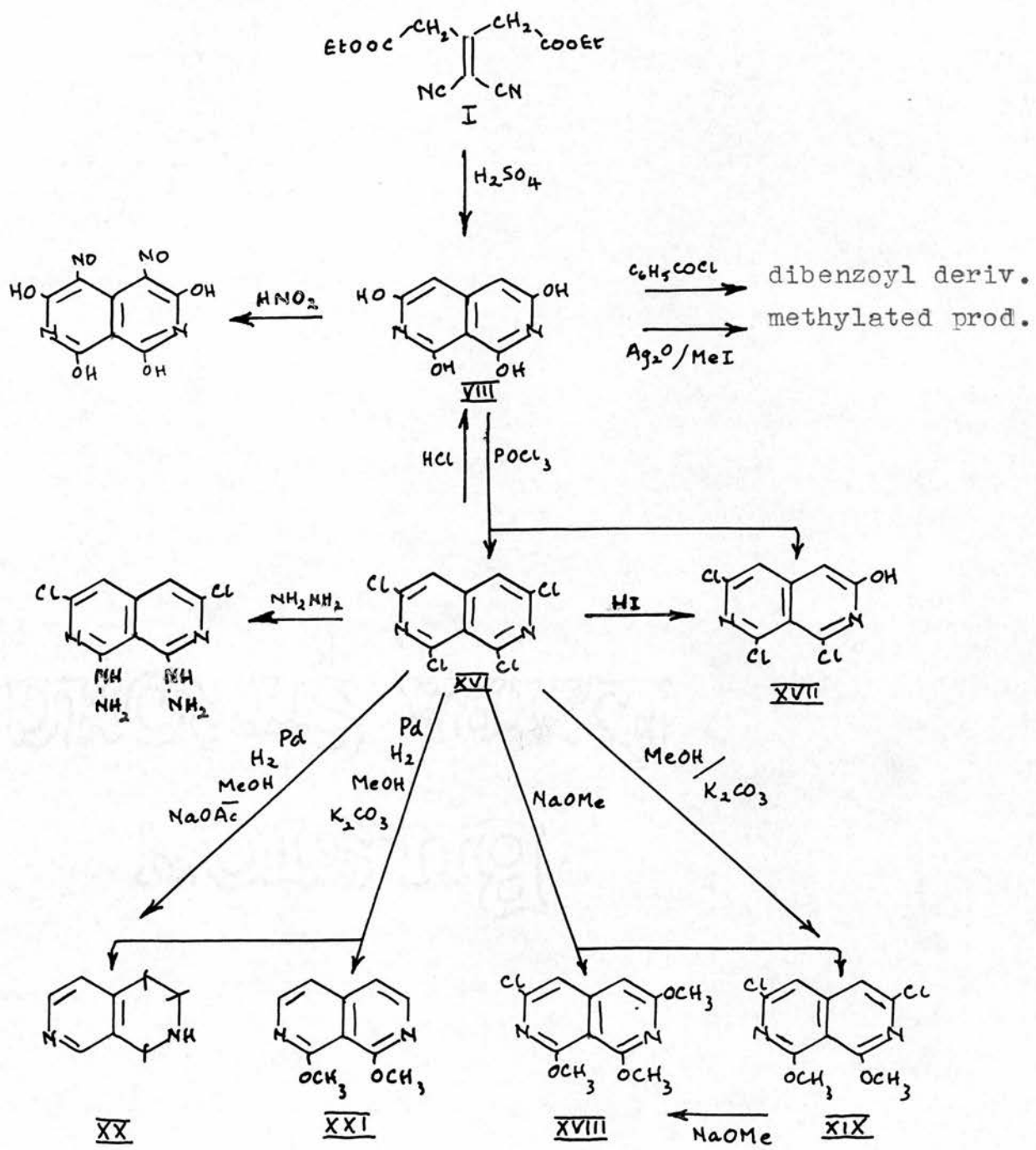
When the dimethoxydichloro-2,7-naphthyridine was refluxed with sodium methoxide a trimethoxymonochloro-2,7-naphthyridine was obtained. This is another example of the asymmetric reactions of 1,3,6,8-tetrasubstituted-2,7-naphthyridines.

Boiling 1,3,6,8-tetrachloro-2,7-naphthyridine in a dilute hydrochloric acid-dioxan mixture afforded a chlorine free solid, which, from its insolubility, high melting-point and blue oxidation product, appeared to be the tetrahydroxynaphthyridine.

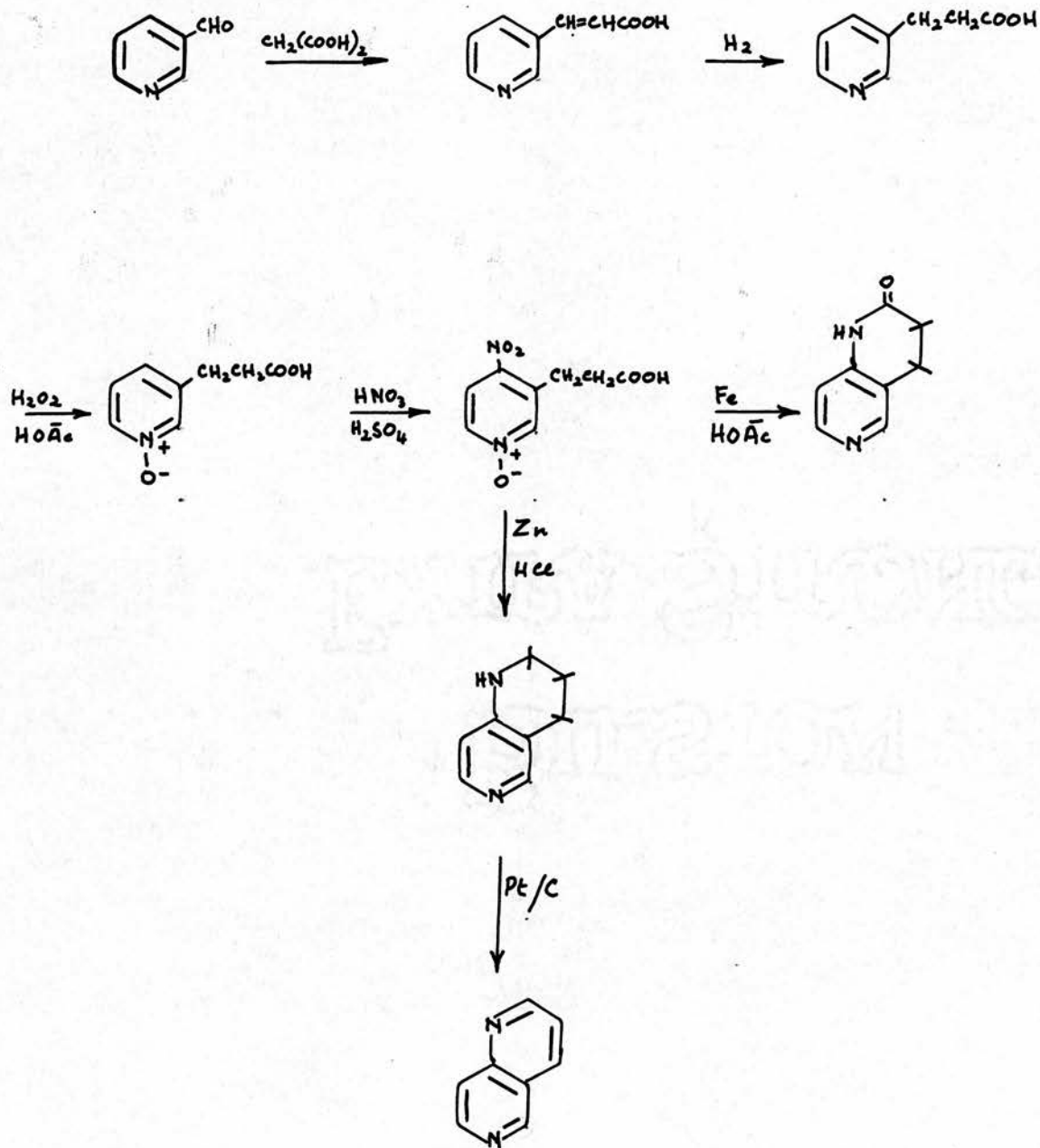
One of the most interesting results of this work is the illustration of the very rapid base catalysis of replacement reactions of 1,3,6,8-tetrachloro-2,7-naphthyridine. It is to be expected that the halogen atoms will readily undergo nucleophilic substitution by a bimolecular mechanism since both the hetero nitrogen atom in the ortho position and the chlorine atoms in meta positions, relative to each other, have an activating effect in nucleophilic replacement reactions. It is, however, surprising that the reactions should be base-catalysed since the mobility of such halogen atoms is usually increased by protonation (126, 127). The addition of hydrochloric acid had no catalytic effect on the methanolysis of 1,3,6,8-tetrachloro-2,7-naphthyridine.



## 2,7-Naphthyridine Derivatives.

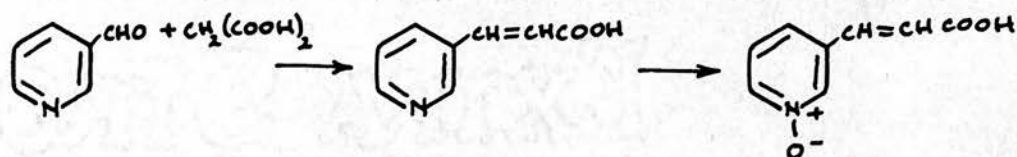


SYNTHESIS OF 1,6-NAPHTHYRIDINE.



## II. Synthesis of 1,6-Naphthyridine.

3-Pyridylacrylic acid, prepared according to Panizzon's method of condensing nicotinaldehyde with malonic acid (85), was treated with a mixture of acetic acid and perhydrol to form the N-oxide.



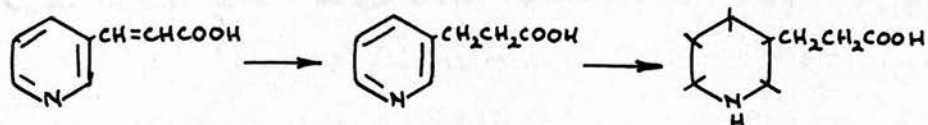
Attempts to nitrate this N-oxide with various proportions of fuming and concentrated nitric and sulphuric acids afforded only a small quantity of a brown oil. The results of analysis of the picrate of this oil could not be interpreted. It appears that the deactivating effect of the carboxylic acid group, conjugated to the ring by the double bond, has been sufficient to overcome the strongly para activating and directing N-oxide group.

In order to isolate the acid group from the ring the double bond in 3-pyridylacrylic acid was hydrogenated according to the method given by Dornow and Schacht (86) using platinum oxide as catalyst. This procedure was

found to give considerably lower yields of the 3-pyridylpropionic acid than the quantitative yields reported. Although the experiment was done several times no more than 35% recovery of the pyridylpropionic acid was made. The hydrogenation was done in aqueous solution, in which the pyridylacrylic acid is insoluble and the pyridylpropionic acid soluble. It was, therefore, convenient to continue the hydrogenation until no pyridylacrylic acid remained undissolved; by this time, considerably more than the theoretical amount of hydrogen had been taken up. A pale yellow oil was isolated from the mixture, as well as the propionic acid derivative.

From these results it appeared that before the pyridylacrylic acid could all be hydrogenated the pyridylpropionic acid formed underwent further reduction. In an attempt to curtail this secondary reaction the reduction technique was modified, by stopping the reaction at half hourly intervals, filtering off the unreacted starting material and catalyst from the aqueous solution of the product and resuspending them in water. In this way none of the pyridylpropionic acid was present in the hydrogenating conditions for longer than thirty minutes and the yield was raised to 65%. This proves that the oil obtained previously is a reduction product of the

pyridylpropionic acid. When a suspension of 3-pyridyl-acrylic acid in water was shaken in an atmosphere of hydrogen in the presence of Adams' catalyst until the uptake of hydrogen stopped, almost 4 moles of hydrogen had been absorbed for each mole of the acid. The only product was the same yellow oil, which gave a crystalline hydrochloride. Analysis of this solid showed the oil to be 3-piperidylpropionic acid.



King et al. (83) report the production of 2-piperidylpropionic acid in theoretical yield by the hydrogenation of 2-pyridylacrylic acid in acetic acid and at a hydrogen pressure of 3 atmospheres.

Pyridine bases poison platinum oxide as a catalyst, but the presence of acid in the solvent or acid groups in the substrate counteracts this. The acidity of the 3-pyridylacrylic acids appears to have been enough to overcome this effect.

The yield of the propionic acid could probably have been raised above 65% by more frequent removal of the



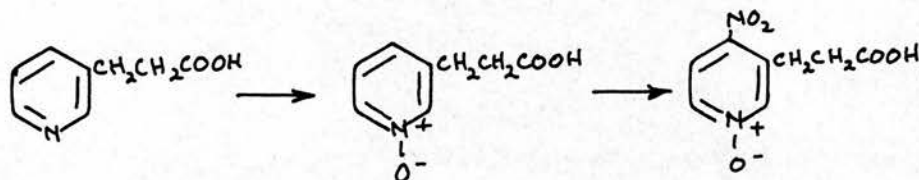
aqueous solution but it was found that the very large volume of water used in the whole reaction caused an accumulation of the very slightly soluble pyridylacrylic acid in the product, and mixtures of the two acids were difficult to separate.

Since this procedure was tedious, experiments were done with less strong hydrogenating catalysts. 5% Palladium on barium sulphate and 5% palladium hydroxide on calcium carbonate were both found to give none of the piperidylpropionic acid and up to 60% of the pyridylpropionic acid. Their application was limited by the length of time taken for the hydrogenation to occur, and by the fact that in all cases the uptake of hydrogen stopped before all the pyridylacrylic acid was reduced. Increasing the original amount of catalyst did not prevent this and the reaction could only be completed by the addition of fresh catalyst.

Loeffler (87) reported the successful reduction of 2-pyridylacrylic acid to 2-pyridylpropionic acid with sodium in alcohol. Although it did not seem likely to succeed since sodium in alcohol is a reagent used to reduce the pyridine ring, this method was applied to the 3-pyridylacrylic acid. Only oily material was recovered from the reaction.



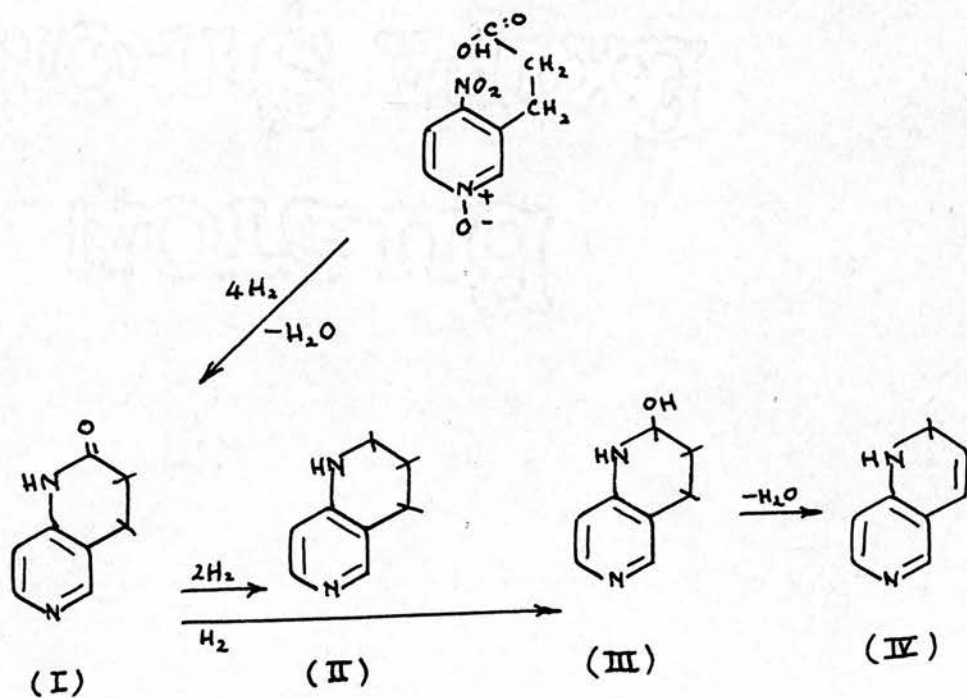
3-Pyridylpropionic acid was treated with acetic acid and perhydrol to form its N-oxide and this material was nitrated to give 4-nitro-3-pyridylpropionic acid N-oxide. It was found that the most successful nitrating mixture was one of fuming nitric and concentrated sulphuric acids. When fuming sulphuric acid was used only an oily product was obtained.



Attempts were now made to reduce 4-nitro-3-pyridylpropionic acid N-oxide to 4-amino-3-pyridylpropionic acid, which would contain carbon and nitrogen atoms in the correct number and relative positions to form a 1,6-naphthyridine derivative. Hydrogenation with Raney nickel as catalyst and reduction with ammonia and ferrous sulphate both failed to give any product. This, in the latter case, may be due to the difficulty of isolation of the resultant amino acid.

A reduction was now attempted in a strongly acid medium in the hope that the product would ring close and the resultant bicyclic compound would be more readily

isolated. The 4-nitro-3-pyridylpropionic acid N-oxide was dissolved in concentrated hydrochloric acid and treated with zinc dust until the yellow colour disappeared. The mixture was made strongly alkaline and the product was obtained either by ether extraction or, in better yield, by sublimation of the solid left after the solution of the zinc hydroxide in alkali. The product, a white solid, smelled strongly of crude acetamide. Analysis of this material showed that it did not contain oxygen as was expected from a simple ring-closure of the amino acid.



There are four possible products

- 2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridine (I)  
1,2,3,4-tetrahydro-1,6-naphthyridine (II)  
2-hydroxy-1,2,3,4-tetrahydro-1,6-naphthyridine (III)  
and 1,2-dihydro-1,6-naphthyridine (IV)

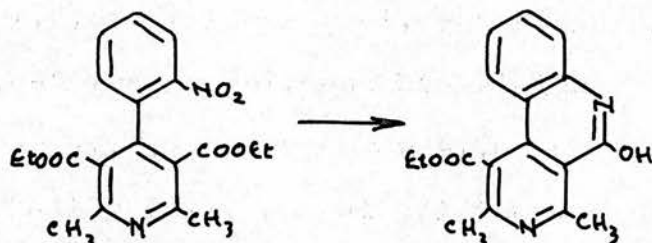
which may arise from the dehydration of III and subsequent isomerisation to give the conjugated system.

That the product is not I or III is indicated by the analysis and proved by its infra red absorption spectrum which shows the absence of any C=O or O-H stretching frequencies.

The analysis most closely fits II. It seems likely that this is the product since the reduction conditions were those of the Clemmensen reduction which reduces carbonyl groups to methylene groups. That IV is the product is unlikely since such a dihydro compound would be expected, on the basis of analogy with 1,2-dihydroquinoline, to be unstable and it is improbable that it would withstand sublimation.

Experiments were now made to prepare the tetrahydronaphthyridone (I). Petrow (88) succeeded in a similar reduction by using stannous chloride in acetic

and hydrochloric acids. Application of this method

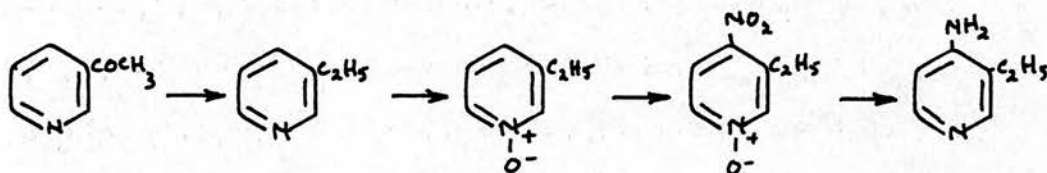


to the reduction of 4-nitro-3-pyridylpropionic acid N-oxide gave no isolable product.

When reduced iron powder and glacial acetic acid were used as reducing agents a product was obtained which was proved by analysis to be the required compound, 2-oxy-1,2,3,4-tetrahydro-1,6-naphthyridine (I).

The ultra violet absorption spectra of 1,2,3,4-tetrahydro-1,6-naphthyridine (II) and 2-oxy-1,2,3,4-tetrahydro-1,6-naphthyridine (I) were determined and compared with those of 4-aminopyridine, 4-acetaminopyridine and 4-amino-3-ethylpyridine. These three compounds were synthesised. 4-Aminopyridine was prepared by the method of Hertog and Overhoff (89) by the reduction of 4-nitropyridine N-oxide. The 4-aminopyridine thus formed was acetylated by means of acetic anhydride. 4-Amino-3-ethylpyridine had not been previously

prepared. It was obtained by the following route:



3-Acetylpyridine was reduced by the Huang-Minlon modification of the Wolff-Kisher method according to the directions of Fand and Lutomski (90). The ethylpyridine thus obtained was oxidised by glacial acetic acid and perhydro to give the corresponding N-oxide. This was identified by analysis of its picrate. The N-oxide was nitrated by a mixture of fuming nitric and concentrated sulphuric acids. The 4-nitro-3-ethylpyridine N-oxide was reduced by zinc dust and concentrated hydrochloric acid to give 4-amino-3-ethylpyridine. It was also reduced by catalytic hydrogenation in glacial acetic acid, using platinum oxide as catalyst. In both of these reduction methods a satisfactory yield could be obtained only if the product was isolated immediately, otherwise the yield was very low and the solid dark in colour.

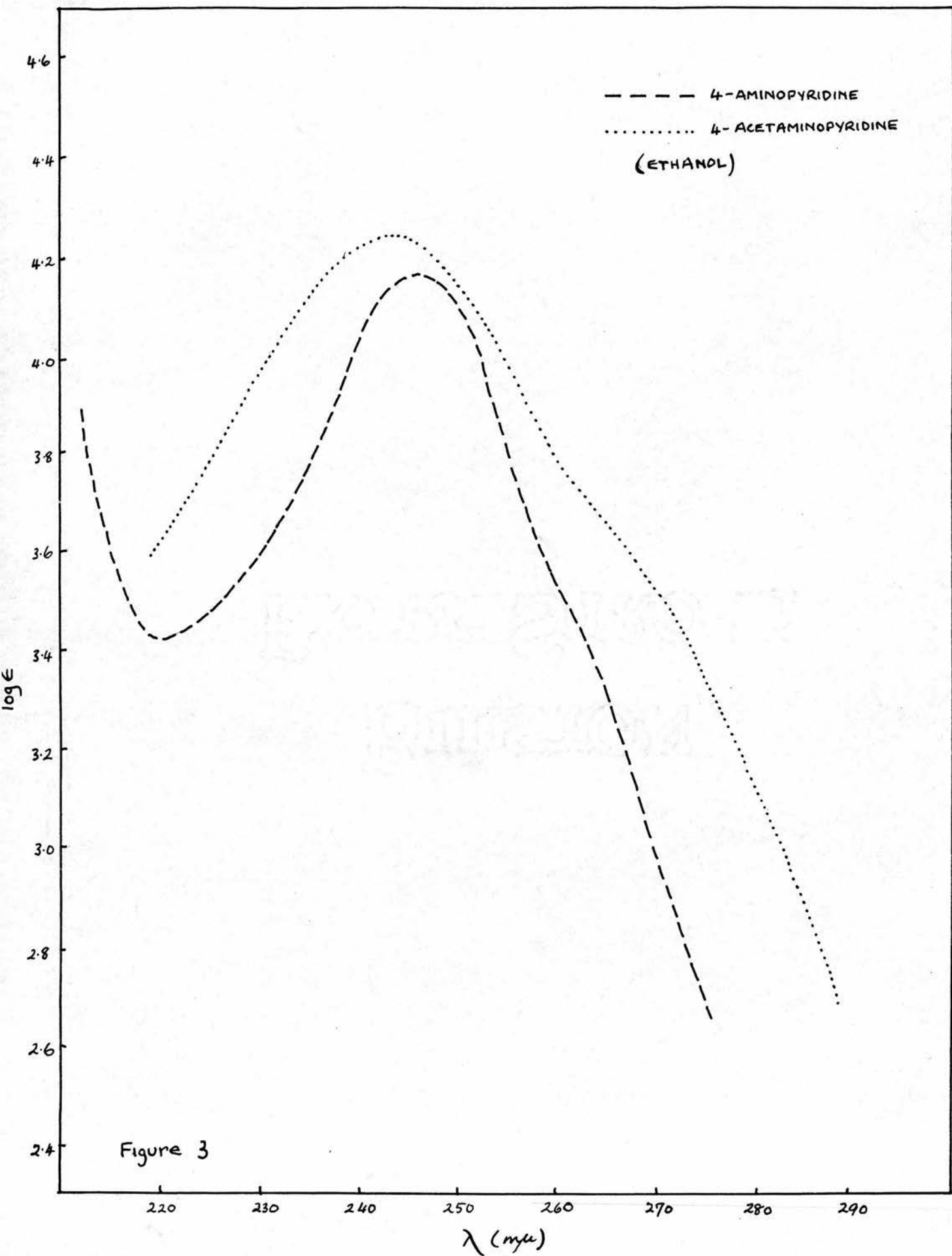
The ultra violet absorption spectra of 4-aminopyridine,



4-acetaminopyridine, 4-amino-3-ethylpyridine and 2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridine were all found to be of the simple pyridine derivative type, with one maximum in the region 240-260 $\mu$ . Since the spectra of 4-aminopyridine and 4-acetaminopyridine are similar (Fig. 3) it was expected that the spectrum of 1,2,3,4-tetrahydro-1,6-naphthyridine would resemble that of 2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridine and of 4-amino-3-ethylpyridine. It was found, however, that it is quite different in type (Fig. 4) with two maxima at 245 and 272 $\mu$ . Cairns, Sauer and Wilkinson (91) found that a compound which they prepared and characterised as 2-ethyl-3-methyl-4-aminopyridine or 2-amino-3-methyl-6-ethylpyridine had a similar spectrum (Fig. 5). When 1,2,3,4-tetrahydro-1,6-naphthyridine was treated with bromine, a bromine-containing compound, shown by analysis to have one atom of bromine in each molecule, was isolated. The bromine is most probably substituted in the saturated ring. This product had a spectrum which had reverted to the pyridine derivative type (Fig. 4).

Although it is surprising that the spectrum of tetrahydro-1,6-naphthyridine is unlike that of 4-amino-3-ethylpyridine no conclusions can safely be drawn from this.





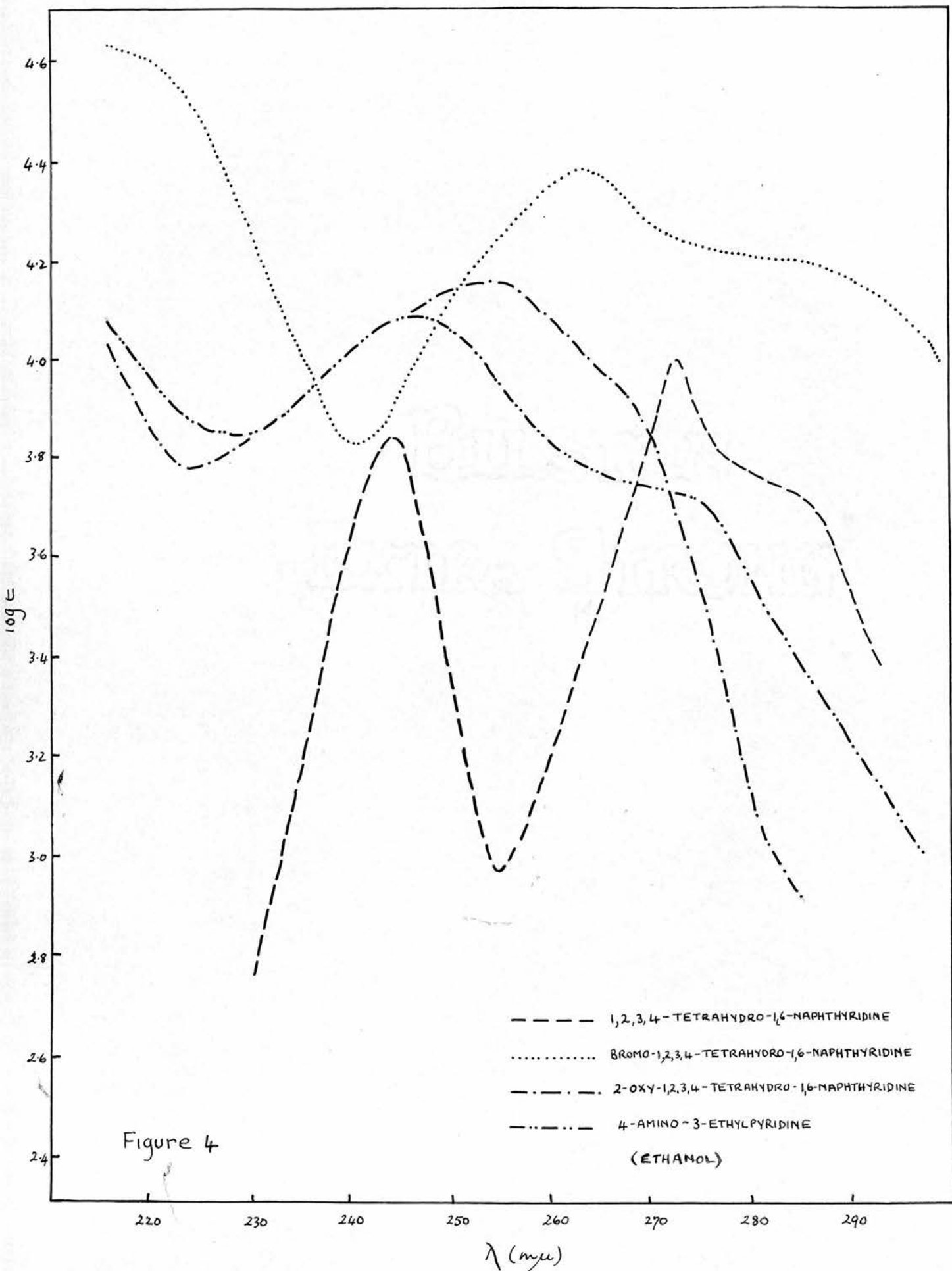
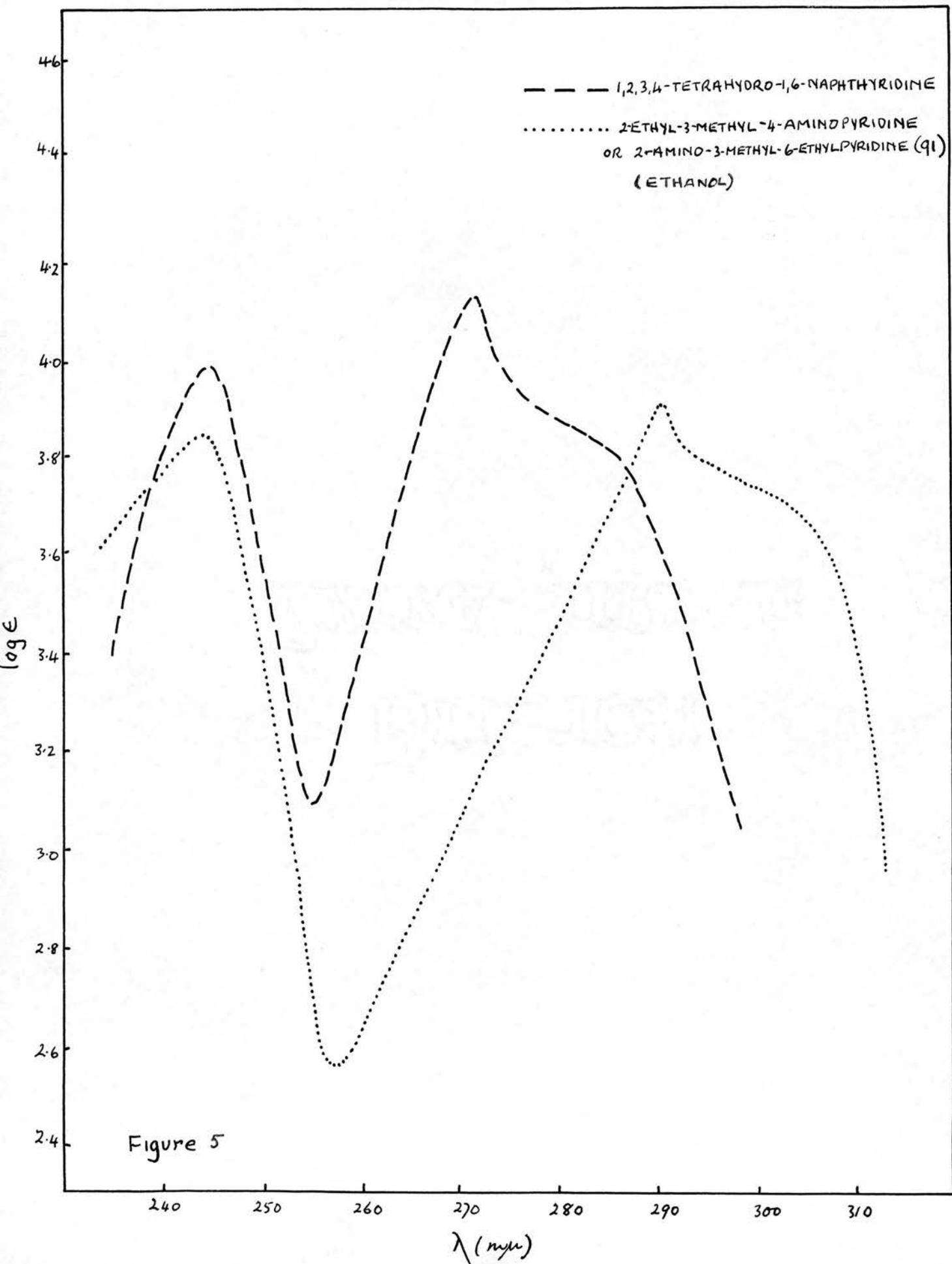


Figure 4



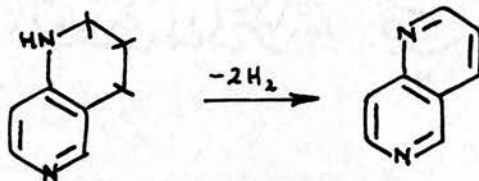
It is not impossible that a strongly chromophoric impurity may be present. 4-Amino-3-ethylpyridine has a spectrum like that of 4-aminopyridine which, although it resembles 2-aminopyridine in form, absorbs at considerably shorter wavelengths. Both the basicity and dipole moment of 4-aminopyridine are larger than the calculated values and this has been ascribed to a large contribution of the doubly charged form, which may also account for the difference in absorption.

The 1,2,3,4-tetrahydro-1,6-naphthyridine was now treated under dehydrogenating conditions. Boiling with chloranil in sulphur free xylene gave a mixture of products, all in small quantity. Treatment of the tetrahydro compound with platinum on charcoal gave a green oil which was purified by decomposition of its picrate. A colourless oil was obtained, which gradually crystallised. It was recrystallised from low boiling petrol ether to give fine white needles, m.p. 29-30°, with an even stronger mouse-like smell than the tetrahydro derivative. Analysis of the picrate of this compound indicated that it is 1,6-naphthyridine.

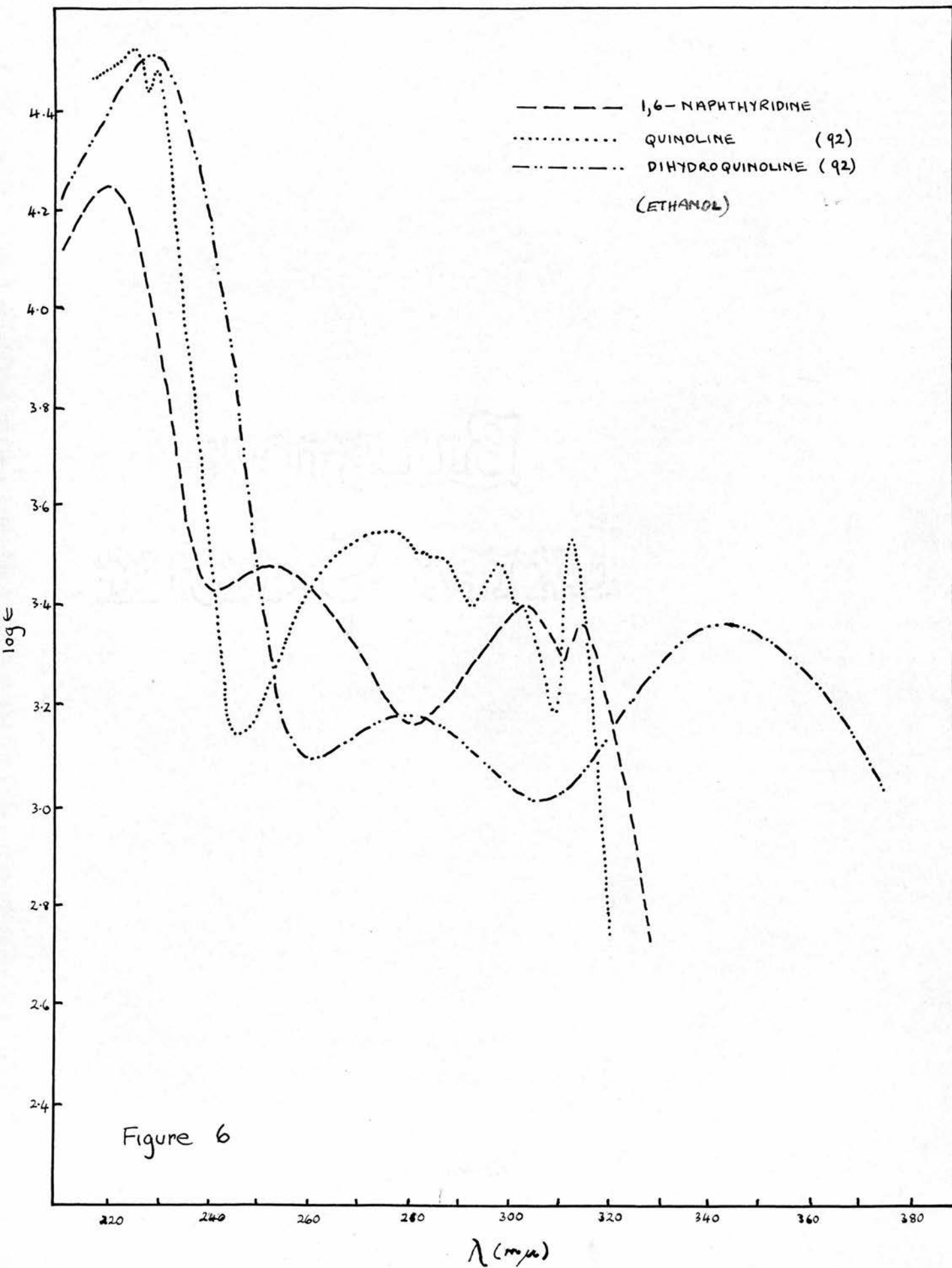
The dehydrogenation might have given the dihydro derivative, although this is unlikely since it was

effected at high temperatures and the dihydro compound would be expected to be unstable.

Further evidence that the product was 1,6-naphthyridine was obtained from its ultra violet absorption spectrum, which resembles those of quinoline, isoquinoline and the 2,7-naphthyridine derivatives already examined. It shows a complex absorption in the region 300-320 $\mu$ . At longer wavelengths the absorption falls off very rapidly (Fig.6). The spectrum of 1,2-dihydroquinoline shows a strongly absorbing region between 320 and 400 $\mu$  (92).







III. Synthesis of 5,10-dimethyl-4,9-diazapyrene.

Ockenden and Schofield (95) have reported the successful ring-closure of 2-formaminobiphenyl to give phenanthridine, by refluxing in nitrobenzene containing phosphorus oxychloride and anhydrous stannic chloride:



If a similar ring-closure were to take place with 2,2'-diformaminobiphenyl a diazapyrene would result:

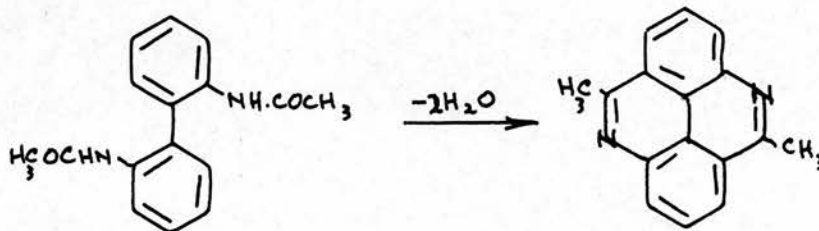


2,2'-Diformaminobiphenyl was prepared according to the method of Macrae and Tucker (96). 2,2'-Dinitrobiphenyl was reduced to 2,2'-diaminobiphenyl by suspending it in concentrated hydrochloric acid and treating it with granulated zinc. To obtain satisfactory results it was found necessary to use the dinitrobiphenyl in a very finely

divided form. The product with anhydrous formic acid gave 2,2'-diformaminobiphenyl. Ockenden and Schofield's ring-closure procedure resulted in heavy charring and after the nitrobenzene was removed by steam distillation the only product recovered was 2,2'-diaminobiphenyl. This was also the result when 2,2'-diacetaminobiphenyl, prepared according to the directions of Brady and McHugh (97) was treated under the same conditions.

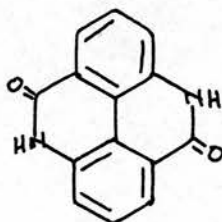
Attempted ring-closure by refluxing with phosphorus oxychloride and with phosphorus pentoxide in toluene also gave none of the tetracyclic compounds.

Fieser and Peters (98) have described the use of a melt of aluminium chloride and sodium chloride as a ring-closing agent. When 2,2'-diacetaminobiphenyl was added to such a melt the mixture became dark green in colour and a yellow solid was isolated. Analysis showed it to be the ring-closed compound, 5,10-dimethyl-4,9-diazapyrene.



Attempts were now made to oxidise this tetracyclic compound to the 2,6-naphthyridine-tetracarboxylic acid. When it was treated with acetic acid and chromic anhydride a very small amount of a purple solid which could not be crystallised was obtained. It showed a wide melting point range of 260-290° but no decarboxylation was observed. It also gave no effervescence with sodium bicarbonate solution.

9-Methylphenanthridine has been shown to have a very stable ring system. On oxidation with dichromate or permanganate in acid solution the 9,10(H)-phenanthridone is produced (31) and there is no report of easy disruption of the rings. It is possible that the oxidation of 5,10-dimethyl-4,9-diazapyrene has given similar results, in which case the purple product might have been the dione, 5,10-dioxy-4,5,9,10-tetrahydro-4,9-diazapyrene.



Fairfull et al. (99) prepared 5,10-diaryl-4,9-diazapyrenes by protecting one amine group in 2,2'-diaminobiphenyl by a phthaloyl group, acylating the other and ring-closing to the 9-phenanthridine derivative by the nitrobenzene, phosphorus oxychloride, stannic chloride method. The phthaloyl group was then hydrolysed off and the above stages repeated to give the diazapyrene derivative. They found that when 2,2'-diaminobiphenyl was treated under benzoylating and dehydrating conditions a dibenzodiazacycloheptatriene derivative was formed rather than a diazapyrene.



These rings are reported to be unstable and are therefore not likely to arise from the aluminium chloride, sodium chloride treatment.

Yields of dimethyldiazapyrene from diacetaminobiphenyl were low (20%) and the method was applied to the



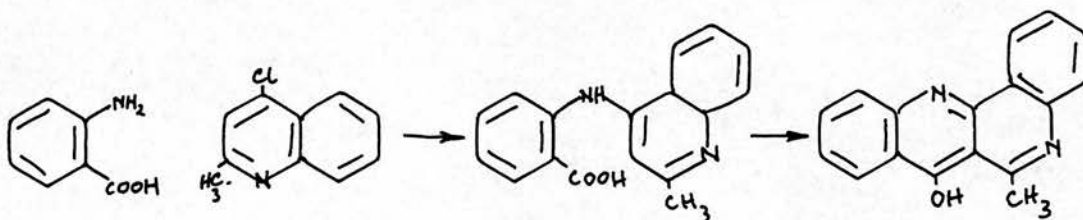
dibenzoylaminobiphenyl to find out whether this would give more of a tetracyclic compound. However, yields proved to be even lower.

By analogy with the phenanthridine ring system it appears unlikely that diazapyrene derivatives will be readily oxidised to naphthyridine derivatives.

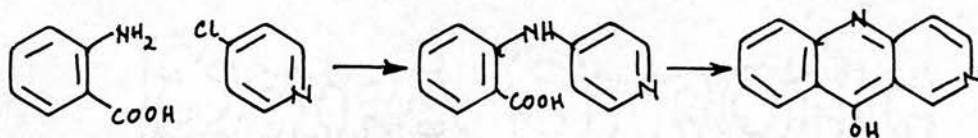
Since this work was completed Mosby (60) has published a successful synthesis of 5,10-dimethyl-4,9-diazapyrene by the method described here. He also used this method to synthesise 4,9-diazapyrene itself from 2,2'-diformamine-biphenyl.

IV. Synthesis of 4-hydroxy-2,3-benzo-1,6-naphthyridine.

Backeberg (100) has reported the following reactions, starting with the condensation of anthranilic acid with 4-chloroquinoline.



These reactions were repeated using anthranilic acid and 4-chloropyridine.



4-chloropyridine was prepared by treating 4-nitropyridine N-oxide with acetyl chloride (102) followed by reduction with iron powder in acetic acid (124). When the product was refluxed with anthranilic acid in acetic acid a solid product was obtained. Analysis of this compound showed it to be the hydrochloride of N-(4-pyridyl)anthranilic acid. Petrow (101) prepared N-(4-pyridyl)anthranilic acid

hydrochloride but reports failure to bring about ring-closure by unstated methods. Backeberg's cyclisation method of allowing the substituted anthranilic acid to stand over phosphorus pentoxide for several days failed.

The acid was esterified and the ester, identified by analysis of its picrate, was treated with concentrated sulphuric acid at 100°. No ring-closure took place and the sulphate of the acid was precipitated.

The hydrochloride of N-(4-pyridyl)anthranilic acid was treated with fused aluminium chloride and sodium chloride. Vigorous effervescence took place when the temperature of the mixture was raised to 240°. A solid product was isolated which did not cause effervescence in sodium bicarbonate solution and proved by analysis to be 4-hydroxy-2,3-benzo-1,6-naphthyridine.

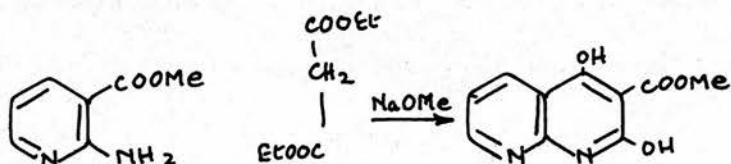
Attempts to oxidise this material to 4-hydroxy-1,6-naphthyridine-2,3-dicarboxylic acid using chromic anhydride gave no product. The acridine ring system is also very stable to oxidative breakdown.

5-Chloroacridine can be prepared by treatment of N-phenylanthranilic acid with phosphorus oxychloride (103). The chlorine atom is then removed by Albert's p-toluene sulphonylhydrazide method (58). When the hydrochloride of

N-pyridylanthranilic acid was treated in this way considerable charring took place and several products were obtained, all in too small quantity to be identified.

This synthesis was not pursued as yields at the ring-closure stage were low and subsequent oxidation of the benzene ring did not appear to be easy.

V. Koller (37) prepared a 1,8-naphthyridine derivative by condensing methyl 2-aminonicotinate with malonic ester:

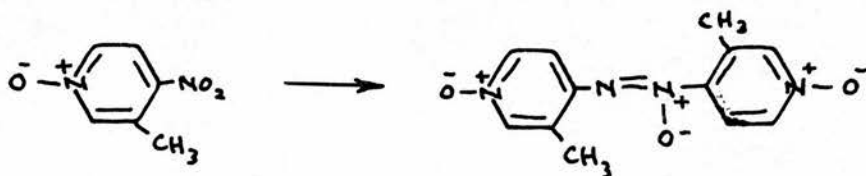


Baumgarten and Krieger (34) reported failure to condense 3-aminoisonicotinic acid with malonic ester, but experiments were now made to prepare methyl 4-aminonicotinate and to try Koller's synthesis with it. There are two methods reported for the synthesis of 4-aminonicotinic acid. Kirpal (105) obtained it by treatment of the monoamide of cinchomeric acid with the Hoffman reagents. Taylor and Crovetti (106) found that they got a better yield by the oxidation of 4-amino- $\beta$ -picoline.

4-Nitro- $\beta$ -picoline N-oxide was obtained by nitration of  $\beta$ -picoline N-oxide, and was then reduced by iron powder in glacial acetic acid. The yields of 4-amino- $\beta$ -picoline were found to be low and the product unstable. The low yields appeared to be partly due to the difficulty of extracting the ferrous hydroxide sludge. The reduction

was then attempted by catalytic hydrogenation. A theoretical uptake of hydrogen was observed to take place, but whenever the solution was exposed to air a pink colour developed, and the 4-amino- $\beta$ -picoline was again obtained in poor yield. The yield decreased with increasing time of standing before isolation.

A third reduction method was now attempted. Hydrazine hydrate in the presence of a catalyst has been reported to reduce nitro groups smoothly to the corresponding amine (107). A white solid separated when 4-nitro- $\beta$ -picoline N-oxide was treated in this way. When this was filtered off, with the catalyst the pale yellow filtrate darkened to orange and an orange solid separated. When the catalyst and white solid mixture was extracted with boiling ethanol an intensely yellow solution was obtained and the same orange solid was precipitated on cooling. Analysis of this compound showed it to be 4,4'-azoxy-3,3'-dimethylpyridine 1,1'-dioxide.

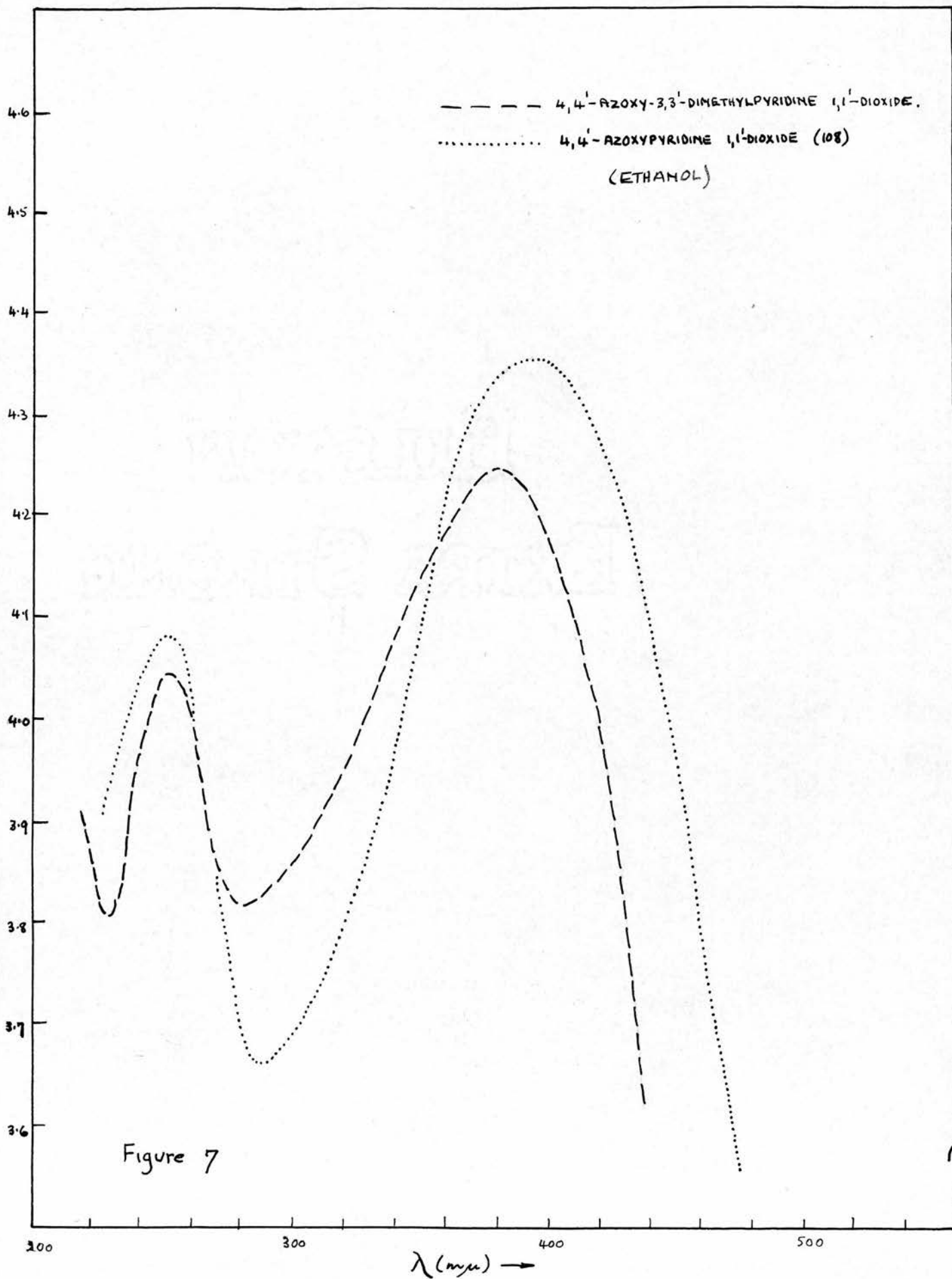




Ochiai and Katada (102) prepared 4,4'-azoxypyridine 1,1'-dioxide by reducing 4-nitropyridine N-oxide with zinc and acetic acid. Den Hertog (108) prepared the same compound by reducing 4-nitropyridine to 4,4'-azoxypyridine by arsenic trioxide and sodium hydroxide, and then forming the dioxide of this by means of perbenzoic acid. Reduction of 4-nitropyridine N-oxide in alkaline media usually gives rise to the azopyridine dioxide (102,108).

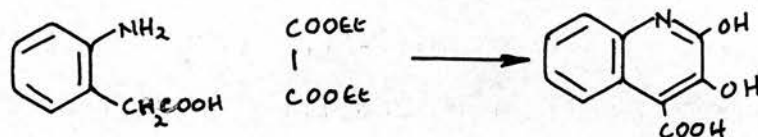
The ultra violet absorption spectrum of 4,4'-azoxy-3,3'-dimethylpyridine 1,1'-dioxide was compared with that of 4,4'-azoxypyridine 1,1'-dioxide (Hertog) and seen to be similar (Fig.7).

4-Amino- $\beta$ -picoline prepared by iron and acetic acid reduction of 4-nitro- $\beta$ -picoline N-oxide was acetylated and oxidised by potassium permanganate according to the method of Taylor and Croveti (106). The 4-aminonicotinic acid was esterified in methanolic hydrogen chloride and the ester was treated with ethyl malonate in alcoholic sodium ethoxide. A yellow solid formed in the reaction mixture. When this solid was dissolved in water a blue solid was precipitated. On acidification this solid became red. This shows parallel behaviour to the tetrahydroxy-2,7-naphthyridine already examined, giving some evidence that

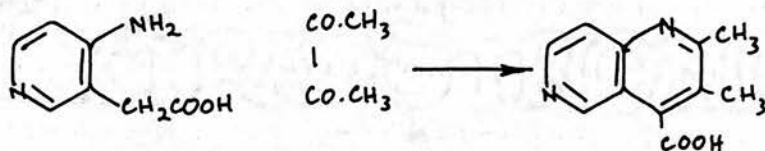


the naphthyridine derivative had been formed in the reaction, but was too unstable in alkaline conditions to be isolated. The difficulty in preparing 4-aminonicotinic acid in any quantity prevented further investigation of this.

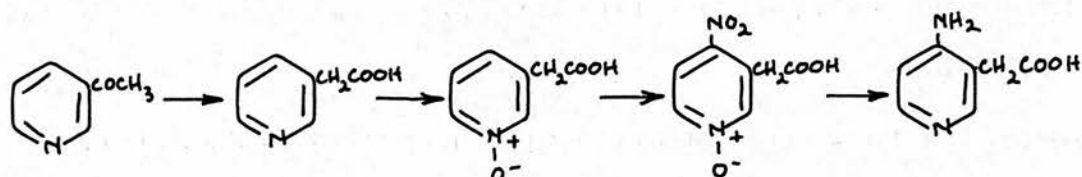
Wislicenus and Bubeck (109) condensed 2-aminophenylacetic acid with oxalic ester:



If a similar condensation took place between the pyridine analogue and diacetyl a 1,6-naphthyridine derivative would result.



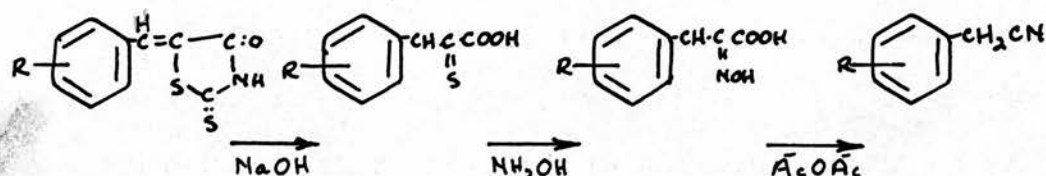
A proposed route to the starting material was as follows:



Schwenck and Papa (110) prepared 3-pyridylacetic acid from 3-acetylpyridine by a modified Willgerodt reaction in which the usual ammonium sulphide was replaced by sulphur and morpholine. When this procedure was attempted the thioacetmorpholide was obtained as described, but the decomposition of this did not give the required product. From their paper it appears that Schwenck and Papa were successful in distilling the ester from an acidic mixture.

Attempts were now made to prepare 3-pyridylacetonitrile, which could be used instead of 3-pyridylacetic acid in the proposed synthesis. Campbell and McKail (111) prepared substituted acetonitriles by condensing the lower aldehyde

with rhodanine and treating the product as follows:



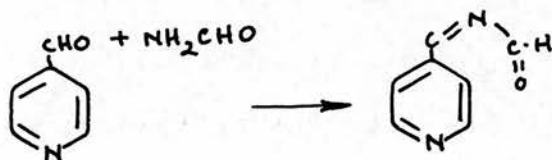
Each of the isomeric pyridine aldehydes was found to condense readily with rhodanine in acetic acid. The product was isolated in each case in theoretical yield. They did not have normal properties for such compounds. They were high melting and decomposed on melting. Since this work was completed, Allan, Allan and Thomson (112) have published a paper describing the preparation of these compounds. They ascribe their anomalous properties to intermolecular salt formation. They used ethanol and ammonia as the condensing medium and the yields obtained were lower.

The method given by Campbell and McKail for the preparation of the acetonitrile derivative was applied, without isolation of the intermediates, and failed to give the required products, and it appeared advisable to isolate the thio-acid. The thio-acid from 5-(2-pyridyl-methylene)rhodanine was obtained in low yield. The

4-pyridyl isomer gave a very unstable product and no product at all could be obtained from the 3-pyridyl isomer. Acid decomposition also failed due to the complete insolubility of the substances in ethanolic or dilute aqueous hydrogen chloride.

Baumgarten and Krieger (34) prepared 3-nitroisonicotinaldehyde by the selenium dioxide oxidation of 3-nitro- $\gamma$ -picoline and subsequently prepared a 1,7-naphthyridine derivative by condensing it with malonic acid. 4-Nitro- $\beta$ -picoline N-oxide was treated according to their method but the only product obtained was acid in reaction and appeared to be the nicotinic acid derivative.  $\beta$ -picoline is reported to be oxidised to nicotinic acid by selenium dioxide (113).

Benzaldehyde and p-nitrobenzaldehyde have been condensed with formamide to give benzylidene derivatives (114). If isonicotinaldehyde and formamide were to react in the same way the product might be a suitable starting material for the synthesis of 2,6-naphthyridine derivatives.





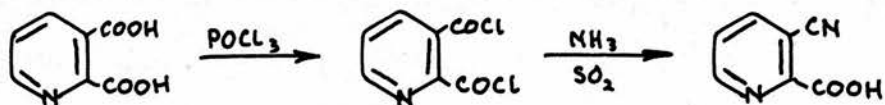
When isonicotinaldehyde and formamide were heated to  $120^{\circ}$  in the presence of a catalytic quantity of pyridine a vigorous exothermic reaction set in. The reaction proved to be a complex one. Three products were isolated. Isonicotinic acid, identified by chromatographic comparison with an authentic sample, was produced. The second product was a high melting solid which could not be characterised. It was basic in reactions, non-reducing, contained no amide or nitrile groups, was not hydrolysed by acid or alkali and gave a solid hydrochloride, picrate and 2,4-dinitrophenylhydrazine. The solid and its three solid derivatives were analysed, but the results could not be interpreted. From the analyses of the solid and its hydrochloride it appeared to have an empirical formula of  $C_{10}H_9N_2O$ . The third product, a yellow oil, was soluble in water, acid and alkali, and most organic solvents. No solid derivative could be readily prepared from it and it charred on attempted distillation. On standing it gradually precipitated isonicotinic acid.

4-Methylcarbostyryl-5,6-quinone was prepared by Holmes' method (115). Attempts to introduce a second nitrogen atom into this molecule by Schmidt reagents or by the formation of a monooxime both failed.

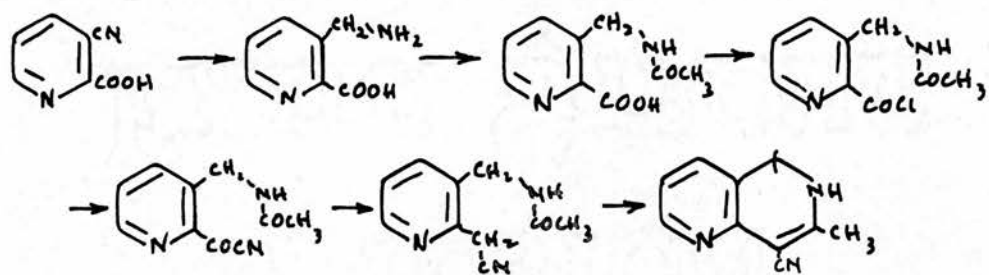
Kulisch (116) prepared quinoline in unstated yield by condensing *o*-toluidine with glyoxal. His method was repeated. If it gave a high yield it was intended to apply it to the pyridine analogue. No quinoline was ever detected in many repetitions and modifications of the experiment. Traces of *ortho* and *para*-nitrotoluenes and *p*-toluidine added as the most likely catalytic impurities in Kulisch's *o*-toluidine had no effect on the result, and this approach was abandoned.

Substituted azafluorenones have undergone ring-expansion with Schmidt reagents to give benzonaphthyridine derivatives ( 128 ). 7-Methoxy-1,3-dimethyl-2-azafluorene-9-one was prepared (117) and treated with hydrazoic acid in concentrated sulphuric acid and in trichloroacetic acid. Only unchanged material was recovered. Petrow (118) has reported similar failure with 7-nitro and 7-amino derivatives.

Scheiber and Knothe (119) carried out the following reactions, but reported no yields.

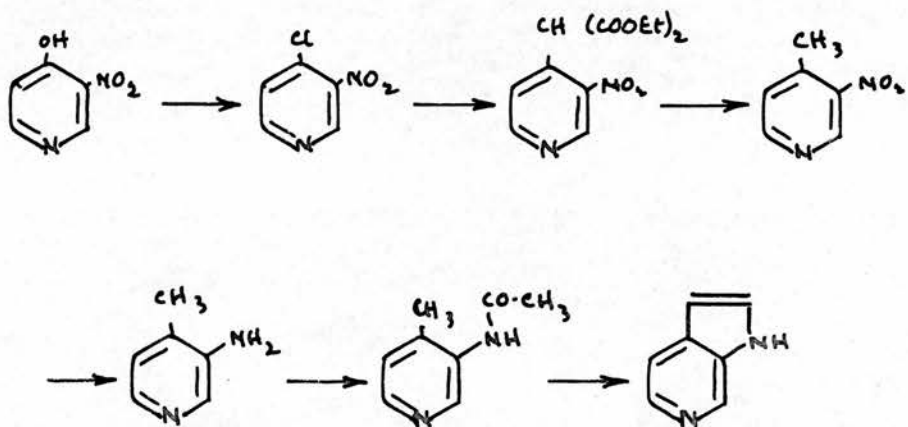


If this product could be obtained in reasonable yield then it could undergo further reaction.



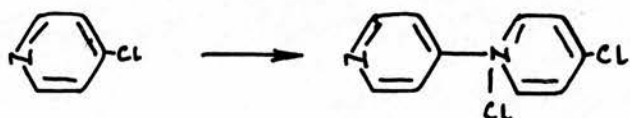
Scheiber and Knothe's preparation was repeated but yields were found to be relatively small, and mixtures of products, thought to be quinolinic acid and 2-cyano-nicotinic acid and 3-cyanopicolinic acid, were obtained.

Königs and Fulde (120) carried out the following series of reactions:

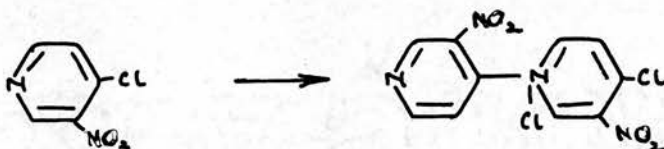


If their final product was easily prepared it might be possible to expand the 5-membered ring by treatment of the isolated double bond with diazomethane or diazoacetic

ester. This synthesis was found to fail at the stage of condensing 4-chloro-3-nitropyridine with malonic ester. Bremer (121) also has reported difficulty with this preparation. He found it preferable to condense 4-methoxy-3-nitropyridine with sodium malonic ester, thus eliminating the isolation of the unstable 4-chloro derivative. His procedure was applied. 4-Hydroxy-3-nitropyridine was treated with phosphorus pentachloride and phosphorus oxychloride and the mixture treated with dry methanol. None of the required compound was obtained, but an orange solid was isolated. This was high melting and explosive in an open flame. Wibaut and Broekman (122), describing the preparation of 4-chloropyridine from 4-hydroxypyridine, report that the isolation and storage of the chloro compound must be done in the cold or else the orange-red N-(4-pyridyl)4-chloropyridinium chloride is formed.

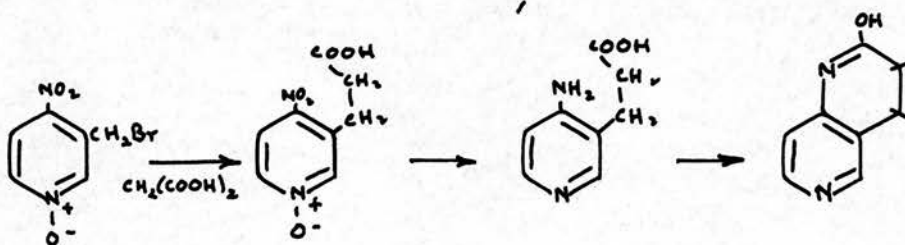


A similar reaction may have occurred in this case:



Analysis indicated that this was the structure of the product.

Attempts were now made to brominate 4-nitro- $\beta$ -picoline N-oxide to prepare the starting material for the following proposed synthesis:



Neither bromine nor N-bromosuccinimide in the presence of peroxide catalysts or in ultra violet light caused any bromination and the starting material was recovered unchanged.



VI.

The use of basic catalysts in the condensation of malononitrile with ketones.

Schenck and Finken (61) have reported on condensations of malononitrile with ketones using several basic catalysts but have not tested the general applicability of any of them. Since diethylamine had proved successful in the present work, experiments were made using it as a catalyst in the condensation of malononitrile and a variety of ketones.

Acetone and malononitrile in ethanol condensed almost immediately in the presence of diethylamine. Fluorenone and malononitrile in ethanol condensed within 30 minutes to give a quantitative yield of the product. Neither diethyl ketone nor dibenzyl ketone gave a solid product under these conditions, even on standing for several weeks. When the minimum quantity of ethanol was used, however, both of these ketones gave solid products.

The catalyst from these results appears to be generally applicable, but there are some limiting factors to its use. The solvent used must be miscible with water and yields are limited by their solubility in this solvent. If the time taken for the condensation is too long, polymerisation appears to occur extensively and thus lowers the yield.



It was found that morpholine was as effective as diethylamine in all cases. Diethylamine has the advantage that it can be readily removed, along with the solvent, by distillation at lower temperatures. It proved to be a successful catalyst in all condensations attempted; malononitrile with acetone, diethyl acetone-dicarboxylate, fluorenone, diethyl ketone, dibenzyl ketone and ethyl cyanoacetate with diethyl acetone-dicarboxylate.

## EXPERIMENTAL METHODS AND RESULTS

All melting-points were determined on a Kofler heating block and are uncorrected.

Analyses were done by Drs. Weiler and Strauss of Oxford.

Unless otherwise stated, solutions were dried over anhydrous sodium sulphate.

Ultra-violet absorption spectra were determined on a Unicam S.P.500 absorption spectrophotometer, and in ethanolic solution. The ethanol was prepared by boiling benzene-free ethanol under reflux with sodium (2 g./l.) for 4 hours and then distilling and storing it in dry conditions.

EXPERIMENTAL

I.

Condensation of malononitrile and diethyl acetone-dicarboxylate.

Malononitrile (1.1 g.) and diethyl acetone-dicarboxylate (3 g.) were dissolved in dry ethanol (25 ml.) containing 4 drops of diethylamine, distilled over sodium directly into the reaction mixture. The solution gradually developed an orange colour. After 4 hours a sample of the solution (1 ml.) was tested for the presence of diethyl acetone-dicarboxylate by treating it with 2,4-dinitrophenylhydrazine (Brady's method). A yellow precipitate of diethyl acetone-dicarboxylate-2,4-dinitrophenylhydrazone was formed. This was recrystallised from ethanol to give bright yellow plates; m.p. and mixed m.p. with authentic sample 83-84° (lit. 86-87° (125)). After 24 hours no free diethyl acetone-dicarboxylate could be detected in this way. The solution was allowed to stand for a further 24 hours, then the solvent and catalyst were removed by distillation at reduced pressure. A red oil was left. When this oil was heated to 100° at 0.1 mm. pressure (oil and mercury vapour pumps) it became dark in colour and solidified. This solid was ground in a mortar and extracted with boiling benzene. A red solid separated from the dark brown benzene solution on

cooling. It was recrystallised from benzene to give red elongated prisms; (0.02 g.) m.p. 197-199°. The benzene solution was evaporated and the residual brown oil and the original solid were extracted with ether. Evaporation of the green ethereal solution gave a brown oil. This was shaken in petrol ether (60-80°) (10 ml.) and the insoluble portion was dissolved in ethanol (2 ml.) To the brown alcoholic solution was added petrol ether (60-80°) (30 ml.). Pale yellow needles separated on standing at 0° overnight (0.008 g.) m.p. 157-162°.

Reduction of the crude condensation product.

A three-necked flask (1 l.) containing a slurry of lithium aluminium hydride (22.5 g.) in anhydrous ether (250 ml.) was fitted with a stirrer (mercury seal), dropping funnel and a 'Y' joint bearing a condenser and a gas inlet. The condenser and dropping funnel were protected by calcium chloride-soda lime tubes. The apparatus was swept out with nitrogen and a slow stream of nitrogen was bubbled through the mixture during the reaction. A solution of the crude oily condensation product (from 4.4 g. malononitrile) in ether (100 ml.) which had been dried over sodium sulphate (3 days) and potassium carbonate (4 days) was added from the dropping funnel at such a rate that gentle refluxing took place.

When the addition was complete (1 hour) the mixture was refluxed for a further 30 minutes and allowed to stand overnight. The excess lithium aluminium hydride was destroyed by the careful addition of water (ice cooling) and the ethereal layer was decanted. The aqueous layer was extracted with ether (100 ml.) and the combined ethereal solutions were dried and evaporated. The yellow oily residue was dissolved in 10 ml. dilute sulphuric acid and the insoluble material filtered off. The filtrate was made alkaline with ammonia and extracted with ethyl acetate (3 x 15 ml.). The yellow extract was dried and evaporated to give a yellow oil (1.2 g.). This oil contained nitrogen (Lassaigne test), hydroxyl groups (gas evolved with sodium) and amino groups (gas evolved with nitrous acid).

Attempted ring-closure of reduced product.

The oil obtained from the reduction (0.5 g.) was dissolved in dry benzene (10 ml.) through which dry hydrogen chloride was bubbled. A brown oil separated. The benzene suspension was shaken with saturated sodium acetate solution (10 ml.) when the oil went into solution in the benzene. Drying and evaporation of the benzene layer gave a brown oily residue, (0.32 g.), which still gave brisk effervescence with nitrous acid.



The reduction product (0.5 g.) was dissolved in concentrated sulphuric acid (5 ml.) and allowed to stand overnight. The dark brown solution was poured into water (15 ml.) and made alkaline with ammonia. Ethyl acetate extraction of this solution gave a yellow extract, which, on drying and evaporation, gave a deliquescent, pale yellow solid, in very small yield.

Alkaline hydrolysis of the crude condensation product.

The condensation product (1 g.) was dissolved in ethanol (10 ml.) and 10% sodium hydroxide solution (20 ml.). The mixture was refluxed for 30 minutes. Acidification with dilute hydrochloric acid caused a vigorous evolution of gas and a yellow oil separated. The ethanol was evaporated off and the suspension of the oil extracted with ethyl acetate to give a yellow-green fluorescent extract. Drying and evaporation of this gave a dark brownish-green oil (0.13 g.) which was soluble in alkali and insoluble in acid. It gave a negative result when tested for the presence of ester groups (Feigl (63)).

1,3,6,8-Tetrahydroxy-2,7-naphthyridine.

The crude product from the condensation of malononitrile and diethyl acetone-dicarboxylate (1 g.) was warmed gently with 70% (by volume) concentrated sulphuric acid (4 ml.)



until complete solution was obtained, when a vigorous exothermic reaction set in. When this reaction was complete (30 seconds) the yellow solution was boiled for a further 30 seconds, cooled and poured into water (15 ml.). A heavy, pale yellow precipitate was formed. This was filtered and washed thoroughly with water and then with alcohol. It was found to contain nitrogen but no sulphur (Lassaigne).

Yield 0.65 g. (84%) m.p. > 350°.

<u>Analysis</u>	Found:	C:48.9,	H:3.6,	N:13.2.
$C_8H_6N_2O_4$	requires:	C:49.5,	H:3.1,	N:14.4.

Tetrahydroxy-2,7-naphthyridine (0.1 g.) was dissolved in 2N sodium hydroxide solution (10 ml.). A blue solid separated on standing. The formation of this solid was accelerated by the addition of hydrogen peroxide solution. The solid could not be recrystallised. m.p. > 350°. When it was treated with hydrochloric acid it became red. The red solid was filtered off. It could not be recrystallised. m.p. > 350°.

Attempted acetylation of tetrahydroxy-2,7-naphthyridine.

Treatment of the tetrahydroxynaphthyridine with acetic anhydride containing a trace of concentrated sulphuric acid and with acetic anhydride containing fused sodium

acetate caused solution to take place. When the solutions were poured into water intractable products were obtained in each case.

Dibenzoyl derivative of 1,3,6,8-tetrahydroxy-2,7-naphthyridine.

Reference: (67)

To tetrahydroxynaphthyridine (0.1 g.) suspended in dry pyridine (10 ml.) was added dropwise benzoyl chloride (3 g.) with shaking and cooling. The naphthyridine derivative went into solution on the addition of the benzoyl chloride, and a deliquescent solid separated. Further addition of benzoyl chloride caused this to dissolve. The brown solution was allowed to stand for 30 minutes and was then carefully treated with water, with cooling. A buff coloured solid separated. This was filtered off, washed with dilute hydrochloric acid, sodium carbonate solution, water and alcohol. The solid could not be recrystallised.

Yield 0.03 g. m.p. 234-238°.

Analysis Found: C:66.4, H:3.7, N:6.14.

$C_{22}H_{14}N_2O_6$  requires: C:65.7, H:3.5, N:7.0.

Methylation of 1,3,6,8-tetrahydroxy-2,7-naphthyridine.

a) Tetrahydroxynaphthyridine (0.5 g.) was dissolved in 20% sodium hydroxide solution (100 ml.) through which nitrogen

was bubbled. The solution was refluxed gently while dimethyl sulphate (20 ml.) was added dropwise over 2 hours. The mixture was refluxed for a further 30 minutes. The original green colour of the solution, which had faded to yellow, was restored on exposure to air. Ether and ethyl acetate extractions of this solution yielded no product. The aqueous solution was acidified with dilute hydrochloric acid when the colour became reddish-brown. Ethyl acetate extraction of this solution gave a red oil which solidified on trituration with ether. This solid dissolved in hot ethanol to give a red solution from which a greenish-grey solid separated on cooling. This was very small in quantity and had a wide melting point range.

b) Reference: (70)

Tetrahydroxy-2,7-naphthyridine (1 g.) was finely ground, suspended in dry chloroform (25 ml.) and shaken with silver oxide (1 g.) and methyl iodide (1.5 ml.) for 1 hour. Two further additions of silver oxide (1 g.) and methyl iodide (1 ml.) were made hourly. The mixture was then shaken for 16 hours. The chloroform solution was filtered off and the residue extracted with 20 ml. chloroform. The combined red chloroform solutions were evaporated to give a red oil. This was dissolved in

boiling benzene (10 ml.) and refluxed for 5 minutes with charcoal (0.1 g.). The mixture was hot-filtered to give a red solution from which a buff-coloured solid separated on cooling. More of the solid was precipitated by the addition of petrol ether (40-60°). The solid was recrystallised from water to give off white cubic crystals. Yield 0.8 g. m.p. 190-200° (softens 170°)

This material was spotted onto chromatographic paper and run in the following solvents systems: ethyl acetate, pyridine, water; butanol, formic acid, water; butanol, ethanol, water. All chromatograms showed a single region of absorption in ultra violet light.

The extent of methylation was measured by refluxing the methylated material in hydrogen iodide, oxidising the liberated methyl iodide to iodate and estimating this by titrating the iodine liberated by it from potassium iodide with sodium thiosulphate solution. The results were calculated assuming that all methylation had taken place at the hydroxyl groups, and are expressed as the percentage of methoxyl groups in the molecule.

<u>Analysis</u>	Found:	C:54.4, H:5.8, N:10.72, OCH <sub>3</sub> :26.2
C <sub>10</sub> H <sub>10</sub> N <sub>2</sub> O <sub>4</sub> (dimethoxy) requires:		C:54.0, H:4.5, N:12.6, OCH <sub>3</sub> :27.9
C <sub>12</sub> H <sub>14</sub> N <sub>2</sub> O <sub>4</sub> (tetramethoxy) requires:		C:57.6, H:5.6, N:11.2, OCH <sub>3</sub> :49.6



Coupling reaction of 1,3,6,8-tetrahydroxy-2,7-naphthyridine.

Tetrahydroxynaphthyridine (0.1 g.) was dissolved in 2N sodium hydroxide solution (10 ml.) and cooled in an ice bath. To this was added an ice-cold solution of benzene-diazonium chloride. A bright orange precipitate formed immediately.

Dinitroso-1,3,6,8-tetrahydroxy-2,7-naphthyridine.

Reference: (72)

To a solution of tetrahydroxynaphthyridine (0.1 g.) in 2N sodium hydroxide solution (10 ml.) at 0° was added solid sodium nitrite (0.5 g.). This mixture was kept at 0° while dilute hydrochloric acid was added gradually, with stirring, until the solution was acid. A yellow solid separated. It was filtered off and washed with water and alcohol. It could not be recrystallised.

Yield 0.03 g. m.p. > 350°

Analysis Found: N:21.8.

$C_8H_6N_4O_6$  requires: N:22.2.

When the methylated tetrahydroxynaphthyridine was treated in the same way no solid was obtained.

Dicarbethoxyisopropylidene malonitrile.

Malonitrile and diethyl acetone-dicarboxylate were condensed as before but the mixture was allowed to stand

for 19 days. The red solution showed a green fluorescence. When the solvent was distilled off (reduced pressure) and the syrup allowed to stand overnight a solid separated. The mixture was triturated with benzene, which dissolved the oil. The solid was filtered off, washed with benzene and recrystallised from benzene to give pale yellow needles, which gave a positive Feigl test for ester groups.

Yield 62% m.p. 166°.

Analysis Found: C:57.1, H:5.6, N:11.3, M.W.:237.

$C_{12}H_{14}N_2O_4$  requires: C:57.6, H:5.6, N:11.2, M.W.:250.

Treatment of this solid with 70% sulphuric acid gave the tetrahydroxynaphthyridine.

Alkaline hydrolysis of dicarbethoxyisopropylidenemalononitrile.

Dicarbethoxyisopropylidenemalononitrile (0.2 g.) was refluxed with 20% sodium hydroxide solution (15 ml.) for 1 hour. No ammonia was detected. The solution was made acid with dilute sulphuric acid, and on cooling a solid separated. This was recrystallised from water to give shining white needles, which were found to contain nitrogen but no ester groups.

Yield 0.11 g. m.p. 165-175° with evolution of gas, followed by solidification and final melting ~ 220°.



Ethyl 3-(ethyl 2,6-dihydroxynicotinyl)acetic ester.

Ethyl cyanoacetate (2.5 g.), diethyl acetone-dicarboxylate (4 g.) and diethylamine (freshly distilled over sodium) (6 drops) were allowed to stand in dry ethanol (10 ml.) for 7 days. The colourless solution became orange. The alcohol was distilled off on a water bath and the water and unreacted starting materials were distilled on an oil bath at 150° (8 mm pressure). The residue was a red oil.

Yield 3.2 g.

The crude condensation product (1 g.) was dissolved in concentrated sulphuric acid (6 ml.) and allowed to stand overnight. The orange solution was poured into water (20 ml.) and a solid separated. This was recrystallised from ethanol to give sheaves of orange-yellow needles.

Yield 0.45 g. (28% overall) m.p. 176.5°.

Analysis Found: C:53.0, H:5.7, N:5.3.

$C_{12}H_{15}NO_6$  requires: C:53.5, H:5.6, N:5.2.

1,1'-Dimethyl-2,2'-dicyanoethylene.

The method of Schenck and Finken (61) of condensing malononitrile and acetone using potassium ethoxide as the catalyst was found to give a high melting product, not mentioned by Schenck and Finken, in high yield.

Malononitrile (1 g.), acetone (2 ml.) and diethylamine (freshly distilled over sodium) (4 drops) were dissolved in dry ethanol (6 ml.). Heat was evolved and the solution became yellow. After 10 minutes a solid started to separate. This was filtered off after 1 hour and recrystallised from ethanol to give shining, white prisms.

Yield 1.2 g. (75%) m.p. 172-173°.

Attempted hydrogenation of dicarbethoxyisopropylidene-malononitrile.

Dicarbethoxyisopropylidenemalononitrile (1 g.) was dissolved in ethanol (25 ml.) and was shaken with Adams' catalyst (50 mg.) in an atmosphere of hydrogen. After 24 hours no hydrogen had been taken up.

Attempted addition of bromine to dicarbethoxyisopropylidene-malononitrile.

A solution of bromine in carbon tetrachloride was added to a solution of dicarbethoxyisopropylidenemalononitrile (0.5 g.) in ethanol (10 ml.) until the bromine was no longer decolorised. The solvent was then evaporated off and fumes of hydrogen bromide were noted. The solid residue was recrystallised from benzene to give shining, white

plates, m.p. 173°.

<u>Analysis</u>	Found:	C:43.9,	H:4.1,	N:8.8,	Br:23.4.
$C_{12}H_{13}N_2O_4Br$	requires:	C:43.8,	H:3.9,	N:8.5,	Br:24.3.

Reduction of dicarbethoxyisopropylidenemalononitrile.

Dicarbethoxyisopropylidenemalononitrile (0.25 g.) suspended in anhydrous ether (15 ml.) was treated with small portions of lithium aluminium hydride until 0.22 g. had been added. The mixture was then refluxed gently for 1 hour. The excess hydride was destroyed by the addition of ethyl acetate and the mixture filtered through a sintered glass funnel. The yellow filtrate was evaporated to dryness and the residue extracted with ether. Drying and evaporation of the ethereal solution gave a pale yellow oil with a faint smell of peppermint (0.007 g.).

Dicarbonylamidoisopropylidenemalononitrile.

Dicarbethoxyisopropylidenemalononitrile (0.11 g.) was shaken with concentrated ammonia solution (10 ml.) until it had all dissolved. The solution was allowed to stand overnight in which time a precipitate of white needles had formed. This solid no longer gave a positive Feigl ester test and gave off ammonia on warming with sodium hydroxide solution.

Yield 0.55 g. (65%) m.p. 241-242°.

Attempted reduction of 1,3,6,8-tetrahydroxy-2,7-naphthyridine.

a) With lithium aluminium hydride.

Reference: (75)

Lithium aluminium hydride (2.5 g.) in dry tetrahydrofuran (100 ml.) was refluxed for 24 hours through a Soxhlet containing tetrahydroxy-2,7-naphthyridine (1 g.). The residual tetrahydroxynaphthyridine was dried and weighed (0.97 g.).

b) With zinc dust and zinc chloride.

Tetrahydroxynaphthyridine (0.5 g.) was mixed with zinc dust (0.5 g.) in a hard glass test tube. This mixture was covered with a layer of zinc dust (1 g.) and heated to red heat for 30 minutes. No product could be extracted. A similar result was obtained when equal parts of anhydrous zinc chloride were added to the zinc dust.

c) With red phosphorus and iodine.

Red phosphorus (3 g.) and iodine (1 g.) were allowed to stand in glacial acetic acid (50 ml.) for 1 hour. Then tetrahydroxynaphthyridine (1 g.) and water (1 ml.) were added and the mixture was refluxed for 4 hours. It was filtered and poured into water (100 ml.) containing sodium bisulphite (4.5 g.). A buff-coloured solid separated. This, from its insolubility, high melting point and blue aerial oxidation product, appeared to be starting material.



Attempted replacement of hydroxyl groups by chlorine atoms in tetrahydroxynaphthyridine.

Tetrahydroxynaphthyridine (0.75 g.) was ground finely and refluxed for 1 hour with phosphorus oxychloride (40 ml.). The excess phosphorus oxychloride was distilled off (reduced pressure) and a reddish-brown oil was left. Treatment of this oil with water or methanol caused evolution of heat and precipitation of a high melting, insoluble solid.

1,3,6,8-Tetrachloro-2,7-naphthyridine.

Tetrahydroxynaphthyridine (1 g.) and phosphorus oxychloride (10 ml.) were heated in a Carius tube in an oven at 180° for 24 hours. The dark brown solution was poured onto crushed ice (150 g.) and made alkaline with solid potassium carbonate. The mixture was extracted with ether (3 x 100 ml.). The yellow ethereal solution was dried and evaporated to give a yellow solid (0.7 g.), which was extracted with boiling petrol ether (80-100°) (3 x 10 ml.). The volume of the petrol solution was halved by distillation at reduced pressure and the residual solution was allowed to stand overnight at 0°. A yellow solid was precipitated. This recrystallised from aqueous alcohol in yellow needles.

Yield        0.5 g.    (36%)    m.p. 157-161°.

Analysis        Found:    C:36.0,    H:1.0,    N:10.65,    Cl:52.3.

$C_8H_2N_2Cl_4$  requires:    C:35.8,    H:0.7,    N:10.4,    Cl:53.0.



Trichloromonohydroxy-2,7-naphthyridine.

The residue from the petrol ether extraction of the solid obtained from the treatment of tetrahydroxynaphthyridine with phosphorus oxychloride was recrystallised from benzene and then sublimed onto a cold finger (reduced pressure) to give off-white needles.

Yield 0.1 g. (8%) m.p. 295° (rapid heating).

Analysis Found: C:39.0, H:1.4, N:12.0, Cl:42.5.

$C_8H_3N_2OCl_3$  requires: C:38.4, H:1.2, N:11.2, Cl:42.7.

When the heating of the tetrahydroxynaphthyridine and phosphorus oxychloride was altered to 220° for 36 hours, the yield of tetrachloronaphthyridine rose to 52% and that of trichloromonohydroxynaphthyridine fell to a trace.

Attempted reduction of 1,3,6,8-tetrachloro-2,7-naphthyridine.

a) By catalytic hydrogenation with Raney nickel.

Reference: (78)

Tetrachloronaphthyridine (0.8 g.) was dissolved in dry methyl alcohol (100 ml.) containing sodium (2 g.). This solution was shaken with Raney nickel (2 g.) in an atmosphere of hydrogen. 145 ml. hydrogen was absorbed (theoretical uptake for replacement of 4 chlorine atoms: 266 ml.). The catalyst was filtered off and the filtrate was evaporated to

dryness. The solid residue was dissolved in water (20 ml.) and the solution was extracted with ether (3 x 15 ml.). The yellow ethereal solution was dried and evaporated to give a yellowish solid, which recrystallised from aqueous alcohol in shining, pale yellow needles.

Yield 0.3 g. m.p. 143-147°

Analysis Found: C:49.9, H:4.0, N:10.55, Cl:20.8, OCH<sub>3</sub>:32.4.  
C<sub>11</sub>H<sub>11</sub>N<sub>2</sub>O<sub>3</sub>Cl requires: C:51.4, H:4.3, N:11.00, Cl:13.9, OCH<sub>3</sub>:36.5.

The Raney nickel was extracted with ether and a white solid was obtained. This was recrystallised from aqueous alcohol to give white plates, which contained chlorine (Beilstein).

Yield 0.005 g. m.p. 154-157°.

This was later identified with dimethoxydichloro-2,7-naphthyridine (p.120).

From the analysis results of the first product it appears to be trimethoxymonochloronaphthyridine contaminated with dimethoxydichloronaphthyridine.

b) By catalytic hydrogenation with various catalysts.

Tetrachloronaphthyridine (0.5 g.) was shaken in an atmosphere of hydrogen under the following conditions: in dry methanol (25 ml.) containing 5% ruthenium on charcoal (100 mg.)

and fused sodium acetate (2 g.); in dry ether (50 ml.) containing 5% palladium hydroxide on calcium carbonate (250 mg.) and solid anhydrous calcium carbonate (2 g.); in dry benzene (50 ml.) containing 5% palladium hydroxide on calcium carbonate (250 mg.) and solid calcium carbonate (2 g.); in dry benzene (50 ml.) containing platinum oxide (50 mg.) and fused sodium acetate (2 g.); in dry ethyl acetate (25 ml.) containing platinum oxide (50 mg.) and fused sodium acetate (2 g.). No uptake of hydrogen was observed in any of these experiments and the substrate was recovered quantitatively by filtration of the catalyst and inorganic material and evaporation of the filtrate.

c) By red phosphorus and hydrogen iodide.

Reference: (76)

Tetrachloronaphthyridine (0.25 g.), red phosphorus (0.5 g.) and hydrogen iodide (d. 1.7) (4.1 ml.) were heated in a Carius tube at 250° for 5 hours. The contents of the tube were poured into water (15 ml.) and the iodine destroyed by sodium thiosulphate. The solution was made alkaline with sodium hydroxide solution and continuously extracted with ether. Evaporation of the ethereal solution gave a small amount of an oil. This was dissolved in hot ethanol (0.5 ml.). On cooling a solid separated. This was recrystallised from alcohol to give off-white blades.

Yield 0.004 g. m.p. 114-120°.

Evaporation of the ethanolic filtrate gave an oil (0.002 g.). Neither oil nor solid gave a picrate in ethanol. A Beilstein test indicated the absence of chlorine, but the quantities were too small for this test to be conclusive. Both products had a pungent, isoquinoline-like smell.

d) By red phosphorus and hydrogen iodide in acetic acid.

Reference: (79)

Tetrachloronaphthyridine (0.56 g.), red phosphorus (0.3 g.) and hydrogen iodide (d. 1.7) (2 ml.) were boiled under reflux in glacial acetic acid (8 ml.) for 12 hours. The phosphorus was filtered off and the solution poured into water (20 ml.). The iodine was destroyed by sodium thiosulphate solution and the resultant yellow solution made alkaline with solid potassium carbonate and extracted with ethyl acetate. A very small quantity of solid was obtained on evaporation of the extract. It was sublimed to give pale yellow needles.

Yield 0.005 g. m.p. and mixed m.p. with trichloromono-hydroxynaphthyridine 295° (rapid heating).

e) By decomposition of the hydrazine derivative.

To a boiling solution of tetrachloro-2,7-naphthyridine (0.5 g.) in ethanol (15 ml.) was added a solution of 95% hydrazine hydrate (2 g.) in ethanol (10 ml.). A dark red

colour developed immediately. The mixture was boiled under reflux for 15 minutes, cooled and filtered. The dark red precipitate became black on drying. This solid was found to contain chlorine (Lassaigne) m.p.  $350^{\circ}$ . It was suspended in water (20 ml.) at  $80^{\circ}$  and treated with saturated copper sulphate solution until no more gas was evolved. No product could be isolated from this mixture by extraction with ether, ethyl acetate, or chloroform.

1,2,3,4-Tetrahydro-2,7-naphthyridine.

Reference: (81).

Tetrachloronaphthyridine (0.46 g.), fused potassium acetate (1 g.) and palladium chloride (0.2 g.) in dry methanol (40 ml.) were shaken in an atmosphere of hydrogen for 12 hours. 190 ml. hydrogen was absorbed (theoretical uptake for reduction of 4 chlorine atoms: 154 ml.). The catalyst and inorganic material were filtered off and the yellow fluorescent solution was evaporated to dryness. The oily residue smelled strongly of acetic acid. It was dissolved in water (15 ml.), the solution made alkaline with solid potassium carbonate and extracted with ethyl acetate. Drying and evaporation of the extract gave a yellow oil (0.044 g.). A picrate was prepared (ethanol). It was



recrystallised from water to give orange-yellow elongated prisms, m.p. 248-50°, with apparent loss of solvent of crystallisation.

Analysis Found: C:39.6, H:3.2, N:17.6  
 $C_8H_{10}N_2 \cdot (C_6H_3N_3O_7)_2 \cdot H_2O$  requires: C:39.3, H:3.6, N:18.4.

The picrate was dissolved in concentrated ammonia solution and the solution extracted with benzene. The benzene solution was dried and evaporated to give a brown oil (0.03 g.) which rapidly darkened on exposure to air.

Attempted preparation of a trinitrobenzene derivative and a methiodide gave no solid products.

1,8-Dimethoxy-2,7-naphthyridine.

Tetrachloronaphthyridine (0.36 g.), palladium chloride (0.2 g.) and anhydrous potassium carbonate (1 g.) in dry methanol (25 ml.) were shaken in an atmosphere of hydrogen. After 1 hour 141 ml. hydrogen had been absorbed and the uptake stopped (theoretical uptake for reduction of 4 chlorine atoms: 120 ml.). The inorganic material was filtered off and the yellow methanolic solution evaporated to dryness. The residue was dissolved in water (3 ml.) and extracted with ether (4 x 5 ml.). Drying and evaporation of the ethereal solution gave a yellow oil which gradually crystallised.

Yield of crude product 0.119 g.

The solid was dissolved in the minimum quantity of hot methanol (2 drops). On cooling, fine, pale yellow needles were formed. This was recrystallised from water to give white needles.

Yield 14 mg. m.p. 108-110°.

Analysis Found: C:63.6, H:5.8, N:14.3.

$C_{10}H_{10}N_2O_2$  requires: C:63.2, H:5.3, N:14.7.

This dimethoxynaphthyridine gave a picrate from benzene of short yellow blades m.p. 148-150°.

The methanolic filtrate was evaporated to give an oil in which some solid formed on standing. This mixture was extracted with boiling petrol ether (40-60°). On cooling the extract an oil separated. The solution was decanted from this and kept at 0° overnight. A white solid separated.

Yield 0.016 g. m.p. 44-51°.

Analysis Found: C:64.4, H:5.2.

$C_{10}H_{10}N_2O_2$  requires: C:63.2, H:5.3.

A picrate was prepared from this material (benzene) m.p. 150° followed by solidification and final melting 260°.

Mixed m.p. with picrate from first dimethoxy-  
naphthyridine 132-137°.

Analysis Found: C:50.2, H:3.3, N:16.6.

$C_{10}H_{10}N_2O_2 \cdot C_6H_3N_3O_7$  requires: C:45.8, H:3.1, N:16.7.

$C_{16}H_{13}O_9N_5$

The constitution of this compound remains unknown.

The oil from the petrol ether was dissolved in ethanol (2 ml.) and was treated with a boiling ethanolic solution of picric acid. The yellow precipitate was recrystallised from water. m.p. and mixed m.p. with picrate of tetrahydronaphthyridine 248-250°.

When hydrogenations of tetrachloronaphthyridine were attempted under the same conditions, but replacing methanol by ethyl acetate, benzene or ether, no uptake of hydrogen took place and the substrate was recovered quantitatively.

Tetrachloronaphthyridine recrystallised from petrol ether and tetrachloronaphthyridine recrystallised from aqueous alcohol were "spotted" onto chromatographic paper and run in solvent systems of butanol, formic acid, water and butanol, ethanol, water. The papers were dried and sprayed with a 10% alcoholic solution of 95% hydrazine hydrate. The two samples of tetrachloronaphthyridine were seen to be identical by the development of similar red

spots in both solvent systems. When prepared papers were run in pyridine, ethyl acetate, water, only a yellow streak developed on spraying with hydrazine hydrate.

Tetrachloronaphthyridine (0.1 g.) was dissolved in methyl alcohol (5 ml.). The solution was allowed to stand for 7 days. Water (10 ml.) was added and the tetrachloronaphthyridine was precipitated unchanged. This experiment was repeated with the addition of concentrated hydrochloric acid (0.25 ml.) to the solution. The same result was obtained.

3,6-Dichloro-1,8-dimethoxy-2,7-naphthyridine.

Tetrachloronaphthyridine (0.1 g.) was dissolved in dry methanol (5 ml.) and anhydrous potassium carbonate (0.1 g.) was added to the solution. The colour of the solution immediately changed from yellow to orange and after 5 minutes a solid separated. After 1 hour this solid was filtered off and recrystallised from methanol to give off-white, fine needles. The addition of water to the methanolic solution caused further precipitation. The sample for analysis was taken from the original precipitate, recrystallised from methanol.

Yield 0.04 g. (41%) m.p. 155-157°.

<u>Analysis</u>	Found:	C:46.6,	H:3.2,	Cl:26.8.
$C_{10}H_8N_2O_2Cl_2$	requires:	C:46.3,	H:3.1,	Cl:27.4.

This compound does not give an immediate colouration with hydrazine.

Tetrachloronaphthyridine (0.1 g.) was refluxed for 1 hour with methanol (5 ml.) and 10% aqueous potassium carbonate solution (5 ml.). On cooling, 3,6-dichloro-1,8-dimethoxynaphthyridine was precipitated (0.08 g.) (82%).

Monochlorotrimethoxy-2,7-naphthyridine.

Dichlorodimethoxy-2,7-naphthyridine (0.1 g.) was boiled under reflux in dry methanol (10 ml.) containing sodium (0.2 g.). On cooling a white solid separated. It was recrystallised from methanol to give white needles.

Yield 0,048g. (48%) m.p. 151-152°.

mixed m.p. with starting material 135-145°.

Analysis Found: C:49.6, H:3.8, N:10.95, Cl:22.3.

$C_{11}H_{12}N_2O_3Cl$  requires: C:51.4, H:4.3, N:11.0, Cl:20.8.

11

13.9

Hydrolysis of 1,3,6,8-tetrachloro-2,7-naphthyridine.

Tetrachloro-2,7-naphthyridine (0.1 g.) was boiled under reflux for 3 hours in 5N hydrochloric acid (4 ml.) and dioxan (3 ml.). The solution was poured into water (10 ml.), brought to pH 7 with sodium carbonate, and continuously extracted with ethyl acetate. A very small quantity of insoluble material was obtained. m.p. > 350°. When it was dissolved in alkali and treated with hydrogen peroxide, a blue colour developed.



II

3-Pyridylacrylic acid.

Reference: (85)

3-Pyridal (5.3 g.), malonic acid (5.2 g.), pyridine (4 g.) and piperidine (1 drop) were heated on a boiling water bath until all evolution of gas had stopped and the mixture had solidified. Heating was continued for a further 2 hours. Water (20 ml.) was added and the mixture filtered. The solid was recrystallised from aqueous alcohol.

Yield 5.8 g. (74%) m.p. 234-5° (lit. 233°).

3-Pyridylacrylic acid N-oxide.

3-Pyridylacrylic acid (1 g.), 100 vol. hydrogen peroxide (5 ml.) and glacial acetic acid (25 ml.) were heated at 100° for 3 hours. The volume of the mixture was reduced to 10 ml. by distillation on a boiling water bath (reduced pressure). Water (10 ml.) was added and the volume again reduced. A solid separated. This was recrystallised from water to give buff-coloured blades.

Yield 0.83 g. (75%) m.p. 286°.

Analysis Found: C:58.4, H:4.3, N:8.6.

$C_8H_7NO_3$  requires: C:58.2, H:4.2, N:8.5.

Attempted nitration of 3-pyridylacrylic acid N-oxide.

3-Pyridylacrylic acid N-oxide (0.5 g.), fuming nitric acid (7.5 ml.) and concentrated sulphuric acid (10 ml.) were boiled under reflux for 2 hours. The solution was poured onto crushed ice (50 g.) and brought to pH 5 with ammonia solution. No product could be extracted from this solution with ether or ethyl acetate. The solution was evaporated to dryness on a water bath and the residue was extracted with ethanol. Evaporation of the ethanolic solution gave a brown oil. A picrate of this oil was prepared (ethanol) to give yellow plates m.p. 272°.

Analysis Found: C:28.3, H:2.8, N:22.2.

The constitution of this compound remains unknown.

3-Pyridylpropionic acid.

Reference: (85)

3-Pyridylacrylic acid (4.5 g.) and platinum oxide (0.5 g.) in water (100 ml.) were shaken in an atmosphere of hydrogen until complete solution was obtained (4 hours). The catalyst was filtered off and the solution concentrated by distillation (reduced pressure) until a solid separated. The solid was recrystallised from alcohol to give off-white cubic crystals.

Yield 1.57 g. (35%) m.p. 161-162°.

When the aqueous solution was evaporated to dryness a yellow oil was left.

This experiment was repeated. After 30 minutes the catalyst and undissolved acrylic acid were filtered off, resuspended in water (100 ml.) and again shaken in hydrogen. This was repeated until all the pyridylacrylic acid had been reduced. The product was isolated from the combined aqueous solutions as before.

Yield 2.92 g. (65%).

3-Pyridylacrylic acid (1.5 g.) and 5% palladium on barium sulphate (0.3 g.) in water (50 ml.) were shaken in hydrogen until no more hydrogen was taken up (7.5 hours). The amount of hydrogen absorbed was 192 ml. (Theoretical uptake for reduction of double bond: 225 ml.).

Yield of 3-pyridylpropionic acid: 0.97 g. (65%).

No oil was obtained when the aqueous solution was evaporated to dryness.

This experiment was repeated with 5% palladium hydroxide on calcium carbonate. Similar results were obtained.

#### 3-Piperidylpropionic acid.

3-Pyridylacrylic acid (1 g.) and platinum oxide (0.1 g.) in water (50 ml.) were shaken in an atmosphere of hydrogen

until no further uptake of hydrogen was observed. The total uptake was 600 ml. (4 moles). The catalyst was removed and the solution evaporated to dryness. The yellow oily residue was dissolved in boiling ethanol (15 ml.) and concentrated hydrochloric acid was added (1 ml.). On cooling a solid separated. It was recrystallised from ethanol to give shining white blades.

Yield 1.1 g. (85%) m.p. 225°.

<u>Analysis</u>	Found:	C:49.4,	H:8.6,	N:6.75,	Cl:17.0.
$C_8H_{16}NO_2Cl$	requires:	C:49.6,	H:8.3,	N:7.2,	Cl:18.3.

Attempted reduction of 3-pyridylacrylic acid with sodium and alcohol.

Reference: (87)

To 3-Pyridylacrylic acid (2 g.) in absolute ethanol (25 ml.) was added sodium (8 g.). Ethanol was added until the sodium was completely dissolved. After cooling, the solution was diluted with an equal volume of water, made acid with dilute hydrochloric acid and evaporated to dryness. The residue was extracted with boiling ethanol. Evaporation of alcoholic solution gave a yellow oil.

3-Pyridylpropionic acid N-oxide.

3-Pyridylpropionic acid (1 g.), 100 volume hydrogen

peroxide (5 ml.) and glacial acetic acid (25 ml.) were heated on a boiling water bath for 3 hours. The volume of the solution was reduced to 10 ml. by distillation (reduced pressure), water was added (25 ml.) and the volume again reduced. This was repeated until a solid separated. It was recrystallised from ethanol to give buff prisms.

Yield 0.8 g. (73%) m.p. 144-153°.

Analysis Found: C:56.6, H:5.2, N:8.8.

$C_8H_9NO_3$  requires: C:57.5, H:5.4, N:8.4.

4-Nitro-3-pyridylpropionic acid N-oxide.

3-Pyridylpropionic N-oxide (0.5 g.), fuming nitric acid (7.5 ml.) and 30% fuming sulphuric acid (10 ml.) were refluxed for 4 hours. The mixture was poured onto crushed ice (50 g.) and brought to pH 5 with solid sodium carbonate. No product could be extracted from the orange solution. It was evaporated to dryness and extracted with boiling alcohol. Evaporation of the extract gave a yellow oil.

3-Pyridylpropionic acid N-oxide (0.5 g.), fuming nitric acid (10 ml.) and concentrated sulphuric acid (10 ml.) were boiled under reflux for 1 hour. The solution was poured onto crushed ice (50 g.), brought to



pH 5 with ammonia solution and continuously extracted with ethyl acetate. The yellow ethyl acetate solution was dried and evaporated to give a yellow solid which was recrystallised from alcohol to give pale yellow plates.

Yield 0.36 g. (57%) m.p. 169-171°.

Analysis Found: C:45.2, H:3.1, N:12.8.

$C_8H_8N_2O_5$  requires: C:45.3, H:3.8, N:13.2.

Attempted reduction of 4-nitro-3-pyridylpropionic acid N-oxide.

a) By Raney nickel catalysed hydrogenation.

4-Nitro-3-pyridylpropionic acid N-oxide (0.25 g.) in aqueous alcohol (10 ml.  $H_2O$ , 40 ml. ethanol) was shaken with Raney nickel (1 g.) in hydrogen. 15 ml. hydrogen was taken up in 10 minutes and then no further absorption was observed. The catalyst was filtered off and the solution concentrated to 5 ml. when a solid separated. This was found to be starting material (0.21 g.).

b) By ammonia and ferrous sulphate.

4-Nitro-3-pyridylpropionic acid N-oxide (0.2 g.) was dissolved in concentrated ammonia solution (5 ml.). A solution of 50% ferrous sulphate (15 ml.) was added and the mixture boiled for 15 minutes, brought to pH 5 with

dilute hydrochloric acid and extracted with ether and ethyl acetate. No product was obtained.

1,2,3,4-Tetrahydro-1,6-naphthyridine.

4-Nitro-3-pyridylpropionic acid N-oxide (0.3 g.) was dissolved in concentrated hydrochloric acid (5 ml.). Zinc dust was added in small portions, with shaking and warming until the yellow colour of the solution had disappeared (0.75 g.). The mixture was then boiled for 2 minutes with more zinc dust (0.25 g.), then cooled and made strongly alkaline with sodium hydroxide solution. Half of this mixture was extracted with ether. Drying and evaporation of the ether gave a white solid, which was recrystallised from benzene to give white prisms.

Yield 0.054 g. (57%) m.p. 161°.

The second half of the mixture was filtered through a sintered glass funnel. The solid was dried and sublimed onto a cold finger (reduced pressure). It was recrystallised from benzene to give white prisms.

Yield 0.067 g. (71%) m.p. 161°.

<u>Analysis</u>	Found:	C:70.5,	H:7.3,	N:20.0.
		C:71.4,	H:7.4,	
$C_8H_{10}N_2$	requires:	C:71.6,	H:7.5,	N:20.9.

The picrate of this material was prepared (ethanol). It was recrystallised from ethanol to give orange-yellow blades. m.p. 175°.

<u>Analysis</u>	Found:	N:18.9.
$C_8H_{10}N_2 + C_6H_5N_3O_7$ requires:		N:19.3.

1,2,3,4-Tetrahydro-1,6-naphthyridine-2-one.

Reference: (88)

4-Nitro-3-pyridylpropionic acid N-oxide (0.2 g.) and stannous chloride (1 g.) in acetic acid (2.5 ml.) and concentrated hydrochloric acid (2 ml.) were boiled under reflux for 30 minutes and then kept at 0° for 2 days. No complex salt separated and no product could be extracted.

4-Nitro-3-pyridylpropionic acid N-oxide (0.3 g.) reduced iron powder (0.5 g.) and glacial acetic acid (6 ml.) were heated on a boiling water bath for 30 minutes. The mixture was poured into water (20 ml.) and filtered. The filtrate was made slightly alkaline with ammonia solution and extracted with ethyl acetate. The extract was dried and evaporated to give a white solid, which was recrystallised from benzene to give white needles.

Yield 0.05 g. (24%) m.p. 208°.

<u>Analysis</u>	Found:	C:64.8,	H:5.8,	N:19.7.
$C_8H_8N_2O$ requires:		C:64.9,	H:5.4,	N:18.9.

Pyridine N-oxide.

Reference: (124)

Pyridine (32 g.), 100 volume hydrogen peroxide (150 ml.) and glacial acetic acid (150 ml.) were kept for 24 hours at 50°. The solution was then distilled at 100° and 20 mm pressure. A yellow oily residue was left.

4-Nitropyridine N-oxide.

Reference: (124)

The residue from the oxidation of pyridine was dissolved in concentrated sulphuric acid (80 ml.) and this solution was added to a mixture of fuming nitric acid (120 ml.) and concentrated sulphuric acid (80 ml.). The solution was heated to 90° and kept at this temperature for 1½ hours. It was then poured onto crushed ice (500 g.) and brought to pH 5 with dilute sodium hydroxide. The solution was continuously extracted with ether (30 hours). The yellow solid product was recrystallised from ethanol to give yellow prisms.

Yield 30 g. (53% overall) m.p. 159-60°.

4-Aminopyridine.

Reference: (89)

4-Nitropyridine N-oxide (3 g.) and reduced iron powder (6.6 g.) were heated with glacial acetic acid (90 ml.) at 100° for 1 hour. The mixture was diluted with twice its volume of water and made strongly alkaline with sodium hydroxide solution. Continuous extraction with ether gave a white solid which was recrystallised from toluene to give shining white blades.

Yield 0.75 g. (37%) m.p. 162° (lit. 159°).

4-Acetaminopyridine.

4-Aminopyridine (0.2 g.) and acetic anhydride (0.5 ml.) were boiled for 1 minute. The solution was diluted with water (3 ml.), made alkaline with sodium carbonate, and ether extracted. The white solid obtained was recrystallised from water to give white needles. m.p. 128°.

3-Ethylpyridine.

Reference: (90)

3-Acetylpyridine (9.68 g.), 85% hydrazine hydrate (10.8 g.) and potassium hydroxide pellets (9.0 g.) were added to diethylene glycol (40 ml.). The mixture was heated for 1 hour at 110-125°, with stirring. The reflux condenser was changed for distillation and the temperature was



raised to 185-190° over ½ hour and kept at this temperature for 2 hours. The distillate was extracted with ether. The ethereal solution was dried over potassium carbonate and evaporated. The faintly yellow liquid residue was identified as 3-ethylpyridine by preparation of its picrate from alcohol. It was recrystallised from alcohol to give bright yellow plates. m.p. 128-129° (lit. 129-130°).

Yield of ethylpyridine 6 g. (70%).

#### 3-Ethylpyridine N-oxide.

3-Ethylpyridine (3 g.) was boiled under reflux for 30 minutes with 100 volume hydrogen peroxide (30 ml.) and glacial acetic acid (30 ml.). The mixture was distilled on a boiling water bath (reduced pressure). When no more liquid distilled water was added (25 ml.) and the distillation was repeated. This was repeated three times. The yellow liquid residue was dissolved in chloroform (50 ml.) and shaken with an aqueous paste of potassium carbonate. The chloroform layer was dried and evaporated. A yellow liquid was left.

#### 4-Nitro-3-ethylpyridine N-oxide.

3-Ethylpyridine N-oxide (from 3 g. ethylpyridine)

was heated at 100° for 3 hours with fuming nitric acid (10 ml.) and concentrated sulphuric acid (12.5 ml.). The cooled mixture was poured onto crushed ice (100 g.) and the solution made alkaline with sodium carbonate. A yellow oil separated. It was extracted with ethyl acetate. The extract was dried and evaporated to give a yellow solid, which was recrystallised from a large volume of petrol ether (40-60°) to give pale, lemon-yellow needles.

Yield 1.4 g. (30% overall) m.p. 63-64°.

A quantity of tarry material was left.

<u>Analysis</u>	Found:	C:49.9,	H:4.8,	N:16.6.
$C_7H_8N_2O_3$	requires:	C:50.0,	H:4.8,	N:16.7.

4-Amino-3-ethylpyridine.

a) 4-Nitro-3-ethylpyridine N-oxide (0.38 g.) was dissolved in glacial acetic acid (30 ml.) and hydrogenated in the presence of platinum oxide (0.02 g.). 220 ml. hydrogen (theor.) was taken up in 1 hour, and the yellow solution had become colourless. The solution was diluted with an equal volume of water, made alkaline with sodium carbonate, and extracted with ether. The ethereal solution developed a red colour on standing. Evaporation gave a

yellow oil which crystallised from benzene-petrol ether (40-60°) to give a felt of fine, white needles.

Yield 0.004 g. (14%) m.p. 42-43°.

Picrate (alcohol) recrystallised from water to give shining yellow blades, m.p. 202-203°.

b) 4-Nitro-3-ethylpyridine N-oxide (0.1 g.) was dissolved in 50% (by volume) hydrochloric acid (10 ml.) and treated with zinc dust (0.25 g.) added in small portions. The solution was boiled for 5 minutes, made alkaline with sodium hydroxide and extracted with ether. The ethereal solution was dried and evaporated to give a pale yellow oil, from which 4-amino-3-ethylpyridine was extracted as above. The picrate was prepared and analysed.

<u>Analysis</u>	Found:	C:44.9,	H:3.8,	N:20.7.
$C_7H_{10}N_2 + C_6H_3N_3O_7$	requires:	C:44.4,	H:3.7,	N:19.9.

Bromo-1,2,3,4-tetrahydro-1,6-naphthyridine.

Tetrahydronaphthyridine (0.02 g.) was dissolved in acetic acid (1 ml.) and treated with a 10% solution of bromine in acetic acid (1 ml.). The mixture was allowed to stand for 2 hours, then diluted with twice its volume of water and made alkaline with ammonia solution. A solid

formed which was extracted with ether. The ethereal solution was dried and evaporated to give a white solid in very small quantity. It was recrystallised from water to give off-white blades, m.p. 110-112°. The picrate of this compound was prepared from ethanol, and analysed. m.p. 180-184°.

<u>Analysis</u>	Found:	Br:16.35.
$C_8H_9N_2Br + C_6H_5N_3O_7$ requires:		Br:18.1.

Attempted dehydrogenation of 1,2,3,4-tetrahydro-1,6-naphthyridine.

Tetrahydronaphthyridine (0.14 g.) and chloranil (0.23 g.) were boiled under reflux for 16 hours in sulphur free xylene (5 ml.). Some of the tetrahydronaphthyridine sublimed unchanged onto the condenser walls. The solution was decanted from a deposit of black solid and washed with sodium hydroxide solution until no purple colour formed in the alkaline layer. The xylene was distilled off (reduced pressure) leaving a reddish-brown residue which was insoluble in polar solvents but very soluble in benzene. A benzene solution (2 ml.) of this material was run on a small alumina column (20 x 1 cm.) and eluted with benzene. Several bands separated.

They were eluted and the solutions evaporated. All residues were found to be oily and very small in volume.

1,6-naphthyridine.

1,2,3,4-Tetrahydro-1,6-naphthyridine (0.03 g.) was put in a small hard glass tube (2 x 1/4") and covered with platinum on carbon (13 1/2% platinum) (0.025 g.). The tube was heated in a glycerol bath at 220-230° for 2 hours. The contents were extracted with alcohol to give a greenish-yellow fluorescent solution, giving on evaporation a yellow oil, which gradually crystallised. This product in alcohol (2 ml.) with a boiling solution of picric acid (0.03 g.) in alcohol (2 ml.) gave a yellow solid. It recrystallised from water in bright yellow blades, m.p. 211°.

<u>Analysis</u>	Found:	N:19.1.
$C_8H_6N_2 + C_6H_3N_3O_7$	requires:	N:19.5.

The picrate was dissolved in concentrated ammonia solution (2 ml.) and this was extracted with benzene. The benzene solution was dried and evaporated to give a pale yellow oil, which gradually crystallised. It was extracted with boiling petrol ether (40-60°). On cooling, the petrol solution was decanted off from this and cooled in a salt-ice bath. White needles separated. Yield 0.003 g. (10%) m.p. 29-30°.



III.

2,2'-Diaminobiphenyl.

Reference: (96)

2,2'-Dinitrobiphenyl (20 g.) was dissolved in boiling ethanol (200 ml.) and precipitated in a fine state by the addition of water (300 ml.) to the hot solution. This material was dissolved in concentrated hydrochloric acid (200 ml.) and heated with stirring on a boiling water bath with granulated tin (100 g.) until solution was complete (3 hours). The mixture was cooled, made strongly alkaline with 10% sodium hydroxide solution and extracted with ether. The ethereal solution was extracted with dilute hydrochloric acid. The yellow aqueous layer was made alkaline with ammonia solution and the oil which separated extracted with ether. The extract was washed with water, dried over sodium carbonate and evaporated to give a pale brown oil, which solidified to give a buff-coloured solid. This crystallised from aqueous alcohol in fine white prisms.

Yield 8 g. (52%) m.p. 76-78° (lit. 81°).

2,2'-Diformaminobiphenyl.

2,2'-Diaminobiphenyl (1 g.) was boiled with anhydrous

formic acid (1 g.) for 3 hours. The solution was poured into water (5 ml.) and allowed to stand overnight, when buff crystals formed. The solid crystallised from alcohol in buff-coloured prisms.

Yield 1.3 g. (theor.) m.p. 136° (lit. 137°).

Attempted ring-closure of 2,2'-diformaminobiphenyl.

Reference: (95).

2,2'-Diformaminobiphenyl (1 g.), anhydrous stannic chloride (0.65 g.), phosphorus oxychloride (6 ml.) and nitrobenzene (12 ml.) were boiled for 4 hours. The black mixture was poured into water (20 ml.) and the nitrobenzene was steam-distilled to leave a brown solution and a black tarry residue. The mixture was filtered and the filtrate made alkaline with ammonia solution, when a buff solid was precipitated. The solid was extracted with ether. Evaporation of the ethereal solution gave 2,2'-diaminobiphenyl.

2,2'-Diacetaminobiphenyl.

Reference: (97)

2,2'-Diaminobiphenyl (2 g.), acetic anhydride (2.2 ml.), acetic acid (5 ml.) and concentrated sulphuric acid (1 drop) were boiled under reflux for 2 hours. The solution was

poured into water (10 ml.) and no precipitate was formed (cf. lit.). The volume of the solution was reduced by distillation at reduced pressure and the solid residue was recrystallised from benzene to give buff-coloured blades.

Yield 2 g. (69%) m.p. 161°.

Attempted ring-closure of 2,2'-diacetaminobiphenyl.

The procedure described above was applied. 2,2'-Diaminobiphenyl was again the only product isolated.

2,2'-Diacetaminobiphenyl (1 g.) and phosphorus oxychloride (4 g.) were boiled for 1 hour. The phosphorus oxychloride was distilled off and the dark brown residue dissolved in dilute hydrochloric acid (10 ml.). This solution gave no product on extraction with ether. It was made alkaline with ammonia and the precipitate which separated was extracted with ether. Evaporation of the ether solution gave a yellow residue, which, dissolved in benzene and run on an alumina column (18 x 1 cm.), was seen to consist of several components. All were found to be very small in quantity.

2,2'-Diacetaminobiphenyl (0.25 g.) was boiled for 1 hour with phosphorus pentoxide (2 g.) in dry toluene (15 ml.). The hot toluene solution was filtered from the tarry residue and on cooling 2,2'-diaminobiphenyl separated.

5,10-Dimethyl-4,9-diazapyrene.

2,2'-Diacetaminobiphenyl (0.24 g.) was added in small portions to a melt of anhydrous aluminium chloride (2.5 g.) and sodium chloride (0.5 g.). The mixture was kept at 140-160° for 30 minutes and was then poured into water (20 ml.). The red solution was filtered off from the black residue and extracted with ether. The yellow ethereal solution was dried and evaporated to give a yellow solid residue which was recrystallised from alcohol to give a felt of shining yellow needles.

Yield 0.037 g. (19%) m.p. 258-260° (subl.)  
(rapid heating)

<u>Analysis</u>	Found:	C:81.4,	H:5.3,	N:11.7.
$C_{16}H_{12}N_2$	requires:	C:82.7,	H:5.2,	N:12.1.

Attempted oxidation of 5,10-dimethyl-4,9-diazapyrene.

Dimethyldiazapyrene (0.032 g.) was added to glacial acetic acid (2.5 ml.), water (1 ml.) and chromic anhydride (0.4 g.). The mixture was boiled for 50 minutes. The

green solution was diluted with an equal volume of water made alkaline with ammonia and extracted with ether. Evaporation of the extract gave a purple solid (2 mg.) m.p. 260-290°. It dissolved in sodium bicarbonate solution without evolution of carbon dioxide.

2,2'-Dibenzoylaminobiphenyl.

2,2'-Diaminobiphenyl (0.3 g.) was shaken with benzoyl chloride (0.5 ml.) in 10% sodium hydroxide solution (10 ml.) until an oil separated. This solidified and was recrystallised from ethanol to give buff-coloured prisms.

Yield 0.5 g. (78%) m.p. 184-6° (lit. 191°).

Ring-closure of 2,2'-dibenzoylaminobiphenyl.

2,2'-Dibenzoylaminobiphenyl (0.1 g.) was added in portions to a melt of aluminium chloride (1 g.) and sodium chloride (0.2 g.). The temperature of the mixture was kept at 200-220° for 15 minutes. It was then poured into water (10 ml.) and extracted with ether. The extract was dried and evaporated to give a yellow oil and a buff solid. The oil was dissolved in alcohol and the solid filtered off (1 mg.). It was found to consist of blades, m.p. 310-314°. (lit. 320-321° (99)).



IV.

4-Chloropyridine N-oxide.

Reference: (102)

4-Nitropyridine N-oxide (3.5 g.) was heated on a water bath at 50° with acetyl chloride (17.5 ml.) until the mixture solidified. Ice-water (50 ml.) was added carefully, the solution made alkaline with sodium carbonate and extracted with chloroform. The extract was dried over potassium carbonate and evaporated. The residue was recrystallised from acetone to give white prisms.

Yield 1.8 g. (55%) m.p. 169°.

4-Chloropyridine.

4-Chloropyridine N-oxide (1 g.) was heated at 100° for 1 hour with reduced iron powder (0.5 g.) and glacial acetic acid (3 ml.). The brown solution was diluted with water (10 ml.) and made alkaline with sodium carbonate. The product was co-distilled (reduced pressure) with water. The distillate was extracted with ether and the extract dried and evaporated to give a pale yellow liquid. A picrate of fine yellow needles was prepared (water) m.p. 140-142°.

Yield of 4-chloropyridine 0.7 g. (87%).

N-(4-pyridyl)anthranilic acid hydrochloride.

4-Chloropyridine (1 g.) and anthranilic acid (1.2 g.) were boiled under reflux with glacial acetic acid (10 ml.) for 2 hours. The red solution was allowed to stand overnight, when a solid separated. This was recrystallised from glacial acetic acid to give pale yellow elongated prisms.

Yield 1.4 g. (64%) m.p. 260-270° (evolution of gas).

<u>Analysis</u>	Found:	C:57.5,	H:4.6,	N:10.2,	Cl:14.5.
$C_{12}H_{11}N_2O_2$ Cl	requires:	C:57.5,	H:4.4,	N:11.2,	Cl:14.2.

This material gave a picrate (alcohol) of yellow needles, m.p. 236-248° (dec.).

Attempted ring-closure of N-(4-pyridyl)anthranilic acid hydrochloride.

4-Pyridylanthranilic acid hydrochloride was allowed to stand over phosphorus pentoxide in a vacuum desiccator for 3 days. No change occurred.

Ethyl N-(4-pyridyl)anthranilic ester.

N-(4-pyridyl)anthranilic acid hydrochloride (1 g.) was boiled under reflux with ethanol which had been saturated with dry hydrogen chloride (40 ml.). The alcohol

was distilled off and the residue dissolved in water (10 ml.). The solution was made alkaline with potassium hydroxide solution and extracted with ether. Drying and evaporation of the ethereal solution gave a yellow oil, which yielded a picrate (alcohol), which was recrystallised from water to give bright yellow needles, m.p. 211-212°.

<u>Analysis</u>	Found:	N:14.0.
$C_{14}H_{14}N_2O_2 + C_6H_3N_3O_7$	requires:	N:14.9.

The oil gave a positive Feigl ester test.

Yield of ester 0.62 g. (64%)  $n_D^{13}$  1.6766.

Attempted ring-closure of ethyl N-(4-pyridyl)anthranilic ester.

Ethyl 4-pyridylanthranilic ester (0.5 g.) was heated with concentrated sulphuric acid (10 ml.) at 120° for 30 minutes. The solution was poured into water (25 ml.). A solid separated. It was recrystallised from dilute sulphuric acid to give shining white blades, m.p. > 350°. This solid decarboxylated on strong heating and dissolved in water to give free sulphate ions.

4-Hydroxy-2,3-benzo-1,6-naphthyridine.

N-(4-Pyridyl)anthranilic acid hydrochloride (0.5 g.) was added in portions to a melt of anhydrous aluminium

chloride (2.5 g.) and sodium chloride (0.5 g.) at 160°. The temperature was raised to 240° over 10 minutes when the colour of the melt became dark brown. It was poured into water (25 ml.), made strongly alkaline with sodium hydroxide solution, and extracted with ethyl acetate. The extract was washed with water, dried and evaporated to give a pale yellow residue, which was recrystallised from water to give pale yellow needles.

Yield 0.08 g. (21%) m.p. 339° (dec.).

Analysis Found: C:71.7, H:3.9, N:13.3.

$C_{12}H_8N_2O$  requires: C:73.5, H:4.1, N:14.3.

Attempted oxidation of 4-hydroxy-2,3-benzo-1,6-naphthyridine.

To a solution of 4-hydroxy-2,3-benzo-1,6-naphthyridine (0.03 g.) in glacial acetic acid (1 ml.) was added a solution of chromic anhydride (0.4 g.) in acetic acid (1.5 ml.) and water (1 ml.). The mixture was boiled under reflux for 1 hour, cooled and diluted with an equal volume of water. A solid separated. It was recrystallised from water to give fine yellow needles, m.p. > 350°. A hot aqueous solution of this was treated with concentrated ammonia solution (1 ml.). On cooling a precipitate of the starting material was formed.

V.

$\beta$ -Picoline N-oxide.

Reference: (125)

$\beta$ -Picoline (46.6 g.), glacial acetic acid (300 ml.) and 100 volume hydrogen peroxide (50 ml.) were heated for 3 hours at 70-80°. Hydrogen peroxide (35 ml.) was added and the heating continued for 9 hours. The solution was concentrated to 100 ml. by distillation (reduced pressure). Water (100 ml.) was added and the volume again reduced to 100 ml. The residue was taken up in chloroform (250 ml.) and shaken with an aqueous paste of potassium carbonate. The chloroform layer was dried and evaporated to give a yellow oil. The oil was distilled and the fraction boiling at 146-149° at 15 mm pressure was collected. It solidified and was kept in a dessicator.

Yield 42 g. (77%).

A picrate of this material was prepared (ethanol). It was recrystallised from ethanol to give shining yellow needles, m.p. 140-141° (lit. 138-139°).

$\beta$ -Nitro- $\beta$ -picoline N-oxide.

Reference: (106)

$\beta$ -Picoline N-oxide (10 g.) was added to a cooled (5°)



mixture of fuming nitric acid (27.5 ml.) and concentrated sulphuric acid (35 ml.). The solution was kept at 100-105° for 1 hour, cooled, poured onto crushed ice (200 g.) and brought to pH 2-3 with sodium carbonate. After standing overnight the precipitated product was extracted with chloroform. When the chloroform solution was dried and evaporated a yellow solid was left. It was recrystallised from acetone and then from water.

Yield 7.3 g. (44%) m.p. 137-8° (lit. 136-7°).

4-Amino-β-picoline.

a) Reference: (106)

4-Nitro-β-picoline N-oxide (10 g.) was dissolved in glacial acetic acid (300 ml.) and stirred with reduced iron powder (30 g.) for 2 hours at 100°. The mixture was poured into water (500 ml.) brought to pH 10-11 with sodium hydroxide solution and extracted with ether. The ethereal solution was dried and evaporated, and the 4-amino-β-picoline recrystallised from petrol ether (100-120°). The product darkened on standing.

Yield 1.4 g. (20%) m.p. 108°.

b) 4-Nitro-β-picoline N-oxide (1.75 g.) was shaken with platinum oxide (0.05 g.) in 10% acetic acid solution (100 ml.)

in an atmosphere of hydrogen. 1050 ml. hydrogen was taken up in 4 hours (theoretical uptake: 1024 ml.). The catalyst was filtered off, the solution made alkaline with sodium hydroxide solution and extracted with ether. The ethereal solution was dried and evaporated and the 4-amino- $\beta$ -picoline recrystallised as before.

Yield 0.4 g. (35%).

4,4'-Azoxy-3,3'-dimethylpyridine 1,1'-dioxide.

4-Nitro- $\beta$ -picoline N-oxide (1 g.) was dissolved in ethanol (40 ml.) containing hydrazine hydrate (2 g.) and platinum on charcoal (13%) (0.5 g.) was added gradually. There was a vigorous evolution of gas and a white solid separated. After 1 hour the mixture was refluxed with a further 0.1 g. catalyst and filtered. The filtrate became orange and an orange solid separated. The residue from the filtration was extracted with boiling ethanol and the same orange solid was precipitated from the ethanolic solution on cooling. It was recrystallised from ethanol to give fine orange needles.

Yield 0.82 g. (97%) m.p. 265° (dec.).

<u>Analysis</u>	Found:	C:55.5,	H:5.4,	N:20.9.
$C_{12}H_{12}N_4O_3$	requires:	C:55.4,	H:4.6,	N:21.5.

4-Aminonicotinic Acid.

Reference: (106)

4-Amino- $\beta$ -picoline (1 g.) was boiled under reflux for 20 minutes with acetic anhydride (5 ml.). The excess anhydride was distilled off (reduced pressure) to give a brown oil which was dissolved in hot benzene. This solution was concentrated to small volume when a solid separated. This solid was dissolved in water (150 ml.). The solution was warmed to 70° and potassium permanganate (2.5 g) was added. The mixture was stirred vigorously at 70° for 6 hours. The manganese dioxide was filtered off and extracted with hot water (3 x 20 ml.). The combined aqueous solutions were evaporated to dryness and the solid residue dissolved in water (5 ml.). The pH of this solution was adjusted to 2-3 with concentrated hydrochloric acid and boiled for 15 minutes. The pH was adjusted to 5 with concentrated ammonia and on standing overnight a solid separated.

Yield 0.6 g. (45%) m.p. 325°(dec.).

Methyl 4-aminonicotinic ester.

4-Aminonicotinic acid (0.5 g.) was suspended in dry methanol (15 ml.) through which dry hydrogen chloride was

bubbled for 1 hour. The mixture was boiled under reflux for a further 2 hours. The alcohol was distilled off; the solid residue dissolved in water (5 ml.) and the solution made slightly alkaline by the addition of sodium hydroxide solution. The solution was extracted with chloroform. Drying and evaporation of the chloroform extract gave a white solid product, 0.2 g. (36%) m.p. 173°.

Condensation of methyl 4-aminonicotinic ester and ethyl malonate.

Reference: (104)

Methyl 4-aminonicotinic ester (0.2 g.) and ethyl malonate (0.2 g.) were added to a solution of sodium (0.03 g.) in dry ethanol (1 ml.). The mixture was heated in a sealed tube at 140° for 7 hours. The contents of the tube became yellow and solidified. The solid was filtered off, washed with benzene and dried. It was then dissolved in water (0.5 ml.) and a blue solid separated on standing. On acidification with dilute hydrochloric acid this solid became red. Neither melted below 350°.

Attempted preparation of methyl 3-pyridylacetic ester.

Reference: (110)

3-Acetylpyridine (30 g.), sulphur (13 g.) and morpholine

(37.5 g.) were boiled under reflux for 6 hours. The solution was poured onto crushed ice (100 g.) and allowed to stand overnight. The separated solid was washed with water and recrystallised from ethanol. 22.2 g.

This thioacetmorpholide was boiled with 50% aqueous ethanol (100 ml.) and 50% sodium hydroxide solution (20 ml.) for 8 hours. The solution was evaporated to dryness (reduced pressure); the residue taken up in dry methanol (150 ml.) and saturated with dry hydrogen chloride. The mixture was boiled for 1 hour and the methanol evaporated off. The residue was distilled. No liquid distilled. The residue was dissolved in water (50 ml.); the solution made alkaline with ammonia and extracted with ethyl acetate. No product was obtained. This report (110) does not indicate how long the alkaline breakdown of the thioacetmorpholide takes and appears to have omitted an essential stage (making solution alkaline before isolation of the ester).

Condensation of pyridine aldehydes with rhodanine.

Pyridine aldehyde (10.7 g.), rhodanine (13.3 g.) and fused sodium acetate (26.6 g.) were boiled under reflux in glacial acetic acid (50 ml.) for 30 minutes. The mixture



became yellow and solidified. The solid was recrystallised.

Pyridine 2-aldehyde: the product was recrystallised from glacial acetic acid to give yellow needles.

Yield: theor. m.p. 265° dec.

Analysis Found: C:48.9, H:3.1, N:12.7.

$C_9H_6N_2OS_2$  requires: C:48.6, H:2.7, N:12.6.

Pyridine 3-aldehyde: the product was recrystallised from glacial acetic acid to give yellow needles.

Yield: theor. m.p. 300° (dec.).

Analysis Found: C:49.1, H:3.1, N:12.6.

$C_9H_6N_2OS_2$  requires: C:48.6, H:2.7, N:12.6.

Pyridine 4-aldehyde: the product was recrystallised from 50% concentrated ammonia solution to give yellow needles.

Yield: theor. m.p. 330° (dec.).

Analysis Found: C:48.9, H:2.9, N:12.5, S:28.7.

$C_9H_6N_2OS_2$  requires: C:48.6, H:2.7, N:12.6, S:28.8.

These condensations were repeated without the use of sodium acetate. Similar results were obtained.

Decomposition of 5-pyridylmethylenerrhodanine.

Reference: (111)

5-(2-Pyridylmethylene)rhodanine (2 g.) was boiled in

ethanol (50 ml.) containing sodium hydroxide (1.5 g.) until a clear solution was obtained (1 1/2 hours). To this was added a solution of hydroxylamine prepared by dissolving hydroxylamine hydrochloride (2 g.) in water (4 ml.), and adding a solution of sodium hydroxide (1.15 g.) in ethanol (10 ml.) and filtering off the sodium chloride. The mixture was neutralised with dilute hydrochloric acid and boiled under reflux until hydrogen sulphide was no longer evolved (2 hours). The alcohol was distilled off and the oily brown residue dissolved in dilute sodium hydroxide solution. The solution was brought to pH 5 with hydrochloric acid and extracted with ethyl acetate. Only a very small quantity of oily material was extracted.

Attempts to prepare the 2,4-dinitrophenylhydrazone of the thio acid without isolating it (on the acidified alcoholic solution) gave no product.

Similar results were obtained with the isomeric 5-pyridylmethylenerrhodanines.

#### 2-Pyridylthiopyruvic acid.

5-(2-Pyridylmethylene)rhodanine (1 g.) was stirred in 8% sodium hydroxide solution (10 ml.) at 50° until solution was complete. The brown solution was cooled in an ice-bath

and rapidly titrated with dilute hydrochloric acid. An orange precipitate formed. It was recrystallised from ethanol containing a few drops of water to give brown needles.

Yield 0.02 g. (2.5%) m.p. 136° (dec.).

Analysis Found: S:17.3.

$C_8H_7NO_2S$  requires: S:17.7.

This compound was found to be unstable and decomposed, with evolution of gas, on standing in air.

The experiment was repeated with 5-(3-pyridylmethylene)rhodanine. No solid was obtained. From 5-(4-pyridylmethylene)rhodanine a small amount of a very unstable solid was isolated.

Attempted oxidation of 4-nitro- $\beta$ -picoline N-oxide.

4-Nitro- $\beta$ -picoline N-oxide (2 g.) in refluxing xylene (20 ml.) was treated with selenium dioxide (1.6 g.) in small portions. The mixture was boiled for 4 hours. The liquid was decanted off from the solid deposit and extracted with dilute hydrochloric acid. No product was obtained. It was extracted with ammonia solution. The yellow ammonia solution was evaporated to dryness. The residue was taken up in water (1 ml.) and acidified. A very small amount of

solid was precipitated. This solid dissolved in sodium bicarbonate solution, with effervescence.

Condensation of isonicotinaldehyde and formamide.

Isonicotinaldehyde (10 g.), formamide (8.5 g.) and pyridine (2 drops) were heated to 120°. An exothermic reaction took place. When this was complete (15 minutes) the temperature was maintained at 100° for 1½ hours. A solid separated during this time. It was filtered off from the dark red viscous liquid, and washed with acetone. It was recrystallised from water to give white prisms. This material was spotted onto chromatographic paper beside a spot of authentic isonicotinic acid, and the paper was run in ethyl acetate:pyridine:water. It was dried and sprayed with an acid developer (1 part ½% potassium iodate solution:1part 1% potassium iodide and 0.4% starch solution). Identical blue spots developed. The viscous filtrate was dissolved in water (20 ml.) to give a red solution which precipitated a yellow solid on standing. This solid was recrystallised from aqueous alcohol to give small yellow prisms.

Yield 1.75 g. m.p. > 350°.

Analysis Found: C:72.2, H:5.0, N:16.4.

A hydrochloride of this material was prepared by adding a few drops of concentrated hydrochloric acid to a hot ethanolic solution. It consisted of yellow plates m.p. 220° (dec.).

Analysis Found: C:50.5, H:4.5, N:12.7, Cl:25.85.

This corresponds to the formula  $C_{10}H_9N_2O \cdot 2HCl$ .

$C_{10}H_9N_2O$  requires: C:69.4, H:5.2, N:16.4.

These two analyses indicate that the solid has the empirical formula  $C_{10}H_9N_2O$ .

A picrate of the solid was prepared (ethanol). It consisted of yellow plates, m.p. 250° (dec.).

When it was recrystallised from water the melting point was raised to 315°.

Analysis Found: C:44.45, H:2.9, N:9.4.

A 2,4-dinitrophenylhydrazone of the solid was prepared (Brady's method). Whenever a solution of 2,4-dinitrophenylhydrazine was added to an ethanolic solution of the solid a precipitate was formed. This was filtered off and found to be very deliquescent. When dilute sulphuric acid was added to the filtrate a solid separated. It was recrystallised from 50% acetic acid to give orange needles. m.p. 122-3°.

Analysis Found: C:46.4, H:4.3, N:21.1.



The aqueous solution from which this solid separated was extracted with ethyl acetate. Drying and evaporation of the extract gave a yellow oil. On standing for 7 days isonicotinic acid separated. The oil was neutral in reaction. It did not give a solid picrate or hydrochloride and charred on attempted distillation.

From 10.5 g. isonicotinaldehyde yields were:  
isonicotinic acid:3g., solid product:1.75g., oil:4.5g.

4-Methylcarbostyryl 5,6-quinone.

Reference: (115)

6-Methoxy-4-methylcarbostyryl was prepared by the condensation of p-anisidine and ethyl acetoacetate. It was hydrolysed to 6-hydroxy-4-methylcarbostyryl by hydrobromic acid and oxidised to the quinone by chromic oxide.

Yield 10% (overall).

Treatment of 4-methylcarbostyryl 5,6-quinone with Schmidt reagents.

4-Methylcarbostyryl 5,6-quinone (1 g.) was dissolved in concentrated sulphuric acid (10 ml.) at 50°. Sodium azide (0.86 g.) was added in small portions over 1 hour. The mixture was kept at 50° for 1 ½ hours and then poured into water (20 ml.) when a red precipitate separated. The

precipitate was filtered off and found to be very tarry. It was run in alcohol-benzene on a short alumina column (16 x 1 cm.). Several bands separated. All products were small in quantity and oily.

Attempted preparation of 4-methylcarbostyryl 5,6-quinone monooxime.

Reference: (123)

4-Methylcarbostyryl 5,6-quinone (1 g.) and hydroxylamine hydrochloride (6 g.) were boiled under reflux in dry pyridine (30 ml.) for 68 hours. The pyridine was distilled off and the solid residue dissolved in alcohol-benzene and run on an alumina column (20 g.). Several bands separated. Elution of these bands gave products which were very small in quantity.

Similar results were obtained when the time of boiling was reduced to 4 hours.

Attempted preparation of quinoline.

Reference: (116)

Glyoxal was depolymerised by distilling over phosphorus-pentoxide (reduced pressure). The monomer was condensed at  $-80^{\circ}$  and was immediately dissolved (10 g.) in o-toluidine (25 g.). 30% Aqueous sodium hydroxide (10 ml.) was added and the mixture heated in a sealed bottle at  $150^{\circ}$  for  $1\frac{1}{2}$  hours.

A black tar had formed and there was no detectable smell of quinoline, and none could be isolated (as its zinc chloride complex) from an ether extract.

The experimental conditions were modified with respect to time, temperature and catalytic quantities of ortho and para nitrotoluene and p-toluidine were added but no quinoline was ever detected.

7-Methoxy-1,3-dimethyl-2-azafluorenone.

Reference: (117)

This compound was prepared by the condensation of  $\beta$ -aminocrotonic acid, p-anisaldehyde and ethyl acetoacetate.

Treatment of 7-methoxy-1,3-dimethyl-2-azafluorenone with Schmidt reagents.

7-Methoxy-1,3-dimethyl-2-azafluorenone (0.2 g.) was dissolved in concentrated sulphuric acid (2 ml.). To the mechanically stirred mixture was added sodium azide (0.1 g.) in portions over 1 hour. Stirring was continued for 2 hours and the mixture was allowed to stand for 2 days at room temperature. The solution was poured into water (10 ml.) and a solid separated. This was dissolved in hot water and treated with sodium hydroxide solution. A solid separated, which was shown from its melting point and

mixed melting point to be the original fluorenone derivative. m.p. 126°.

The experiment was repeated using trichloroacetic acid as solvent and the reaction was carried out at 60°. The same result was obtained.

Attempted preparation of 3-cyanonicotinic acid.

Reference: (119)

Quinolinic acid was prepared by the nitric acid oxidation of 8-hydroxyquinoline (86). The di-acid chloride was prepared by treatment of the acid with phosphorus pentachloride. A stream of dry air bubbled through the reaction mixture to displace the hydrogen chloride improved the yield. The solid precipitated when the acid chloride was treated with ammonia was dissolved in sodium hydroxide solution through which was bubbled sulphur dioxide. The solid which formed had a wide melting point range. It decarboxylated  $\sim 180^\circ$  to give a solid which melted with further decarboxylation  $\sim 225^\circ$ . The yield of the crude product was 1 g. (11% overall).

Attempted preparation of 4-(3-nitropyridyl)malonic ester.

Reference: (120)

4-Hydroxy-3-nitropyridine was prepared by the nitration

of 4-hydroxypyridine with fuming nitric acid (d. 1.5) and fuming sulphuric acid (63%  $\text{SO}_3$ ). 4-Chloro-3-hydroxypyridine was prepared from this by treatment with phosphorus pentachloride. Condensation of this with sodium malonic ester failed to give the desired product.

Attempted preparation of 4-methoxy-3-nitropyridine.

Reference: (121)

4-Hydroxy-3-nitropyridine was treated with phosphorus pentachloride and the crude product shaken with dry methanol. The solid which separated was not the hydrochloride of 4-methoxy-3-nitropyridine. It was dissolved in hot water and the solution made alkaline with sodium carbonate. An orange solid separated on cooling. It was recrystallised from water to give orange needles. m.p.  $> 350^\circ$ .

<u>Analysis</u>	Found:	N:16.8.
$\text{C}_{10}\text{H}_6\text{N}_4\text{O}_4\text{Cl}_2\text{H}_2\text{O}$ requires:		N:16.7.

Attempted bromination of 4-nitro- $\beta$ -picoline N-oxide.

4-Nitro- $\beta$ -picoline N-oxide (0.5 g.) was dissolved in boiling carbon tetrachloride (50 ml.). A solution of bromine (1 g.) in carbon tetrachloride (10 ml.) was added and the mixture boiled under reflux for 1 hour. On cooling and evaporation starting material was recovered quantitatively.



The same result was obtained when the heating was done in ultra violet light (silica vessel) or in the presence of benzoyl peroxide.

4-Nitro- $\beta$ -picoline N-oxide (1.5 g.), N-bromosuccinimide (1.7 g.) and benzoyl peroxide (0.05 g.) were heated in boiling dry carbon tetrachloride (50 ml.) for 20 hours. No succinimide was formed.

VI.

Condensations of ketones with malononitrile, using diethylamine as catalyst.

Acetone and malononitrile were condensed as reported (p.108).

Diethyl acetone dicarboxylate were condensed as reported (p.105).

Fluorenone (2.7 g.) and malononitrile (1 g.) in absolute ethanol (20 ml.) containing diethylamine (4 drops) gave a precipitate of the condensation product in 5 minutes. It was filtered off after 30 minutes and recrystallised from glacial acetic acid.

Yield: theor.            m.p.  $234^{\circ}$  (cf.  $217^{\circ}$  lit.(64)).

Diethyl ketone (0.43 g.), malononitrile (0.33 g.) and diethylamine (2 drops) were allowed to stand in absolute ethanol (2 ml.) for 4 days at  $0^{\circ}$ . After this time the

solution had become dark brown and a solid separated. It was recrystallised from aqueous alcohol to give white needles.

Yield: 0.06 g. (10%) m.p. 160-161°.

<u>Analysis</u>	Found:	C:72.5,	H:7.7,	N:19.5.
$C_8H_{10}N_2$	requires:	C:71.6,	H:7.4,	N:20.9.

Dibenzyl ketone (1.5 g.), malononitrile (0.5 g.) and diethylamine (2 drops) were dissolved in absolute ethanol and kept at 0° overnight. The mixture became orange and a solid separated. It was recrystallised from aqueous alcohol to give white plates.

Yield: 1.15 g. (66%) m.p. 49.5°.

<u>Analysis</u>	Found:	C:82.0,	H:5.1,	N:10.8.
$C_{18}H_{14}N_2$	requires:	C:83.7,	H:5.4,	N:10.8.

In all cases the catalyst was distilled over sodium directly into the reaction mixture.

Morpholine was found to be equally effective as a catalyst.

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# ABSTRACT OF THESIS

Name of Candidate Barbara M. Ferrier  
Degree Doctor of Philosophy Date May 1958  
Title of Thesis Syntheses in the Naphthyridine Series

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Diethyl acetone-dicarboxylate and malononitrile in ethanol, containing a catalytic quantity of diethylamine, condensed to give dicarbethoxyisopropylidenemalononitrile, which on treatment with 70% (by volume) sulphuric acid ring-closed to give 1,3,6,8-tetrahydroxy-2,7-naphthyridine. Two products were isolated when this compound was treated with phosphorus oxychloride at 200°. They were identified as 1,3,6,8-tetrachloro-2,7-naphthyridine and a trichloromonohydroxy-2,7-naphthyridine. Treatment of the tetrachloro derivative with sodium methoxide gave a mixture of a monochlorotrimethoxy-2,7-naphthyridine and a dichlorodimethoxy-2,7-naphthyridine. The latter was also produced when potassium carbonate was added to a methanolic solution of 1,3,6,8-tetrachloro-2,7-naphthyridine. The monochlorotrimethoxy compound was obtained from this by treatment with sodium methoxide. Catalytic dehalogenation of the tetrachloronaphthyridine was found to be possible only when initial solvolysis of two of the chlorine atoms could occur. 1,8-dimethoxy-2,7-naphthyridine and a tetrahydro-2,7-naphthyridine were obtained. The ultra-violet absorption spectra of the tetrachloro and dimethoxy derivatives were found to be similar to those of quinoline and isoquinoline. One of the most interesting results of this work is the illustration of the base catalysis of replacement reactions of the tetrachloro compound. Such halogen atoms usually undergo acid catalysed replacement.

3-Pyridylacrylic acid, prepared by the condensation of 3-pyridal and malonic acid, was hydrogenated to give 3-pyridylpropionic acid. The N-oxide of this compound was prepared and nitrated to give 4-nitro-3-pyridylpropionic acid N-oxide. Reduction of this compound by iron





and acetic acid gave 1,2,3,4-tetrahydro-1,6-naphthyridin-2-one. Zinc and hydrochloric acid reduction gave 1,2,3,4-tetrahydro-1,6-naphthyridine. This compound was dehydrogenated by platinum on charcoal to give 1,6-naphthyridine. The ultra-violet absorption spectrum of this was found to be like those of quinoline and the 2,7-naphthyridine derivatives already determined.

5,10-Dimethyl-4,9-diazapyrene was obtained when 2,2'-diacetaminobiphenyl was heated in a melt of aluminium chloride and sodium chloride. The tetracyclic ring system appeared to be resistant to oxidative breakdown.

N-(4-Pyridyl)anthranilic acid hydrochloride was obtained by the condensation of 4-chloropyridine and anthranilic acid. It ring-closed on treatment with fused aluminium chloride and sodium chloride to give 4-hydroxy-2,3-benzo-1,6-naphthyridine, which was recovered unchanged when attempts were made to oxidise the benzene ring.

Diethylamine and morpholine were found to be effective catalysts in the condensation of malononitrile with a variety of ketones.