STUDIES IN THE TRIAZANAPHTHALENE AND TRIAZAPHENANTHRENE SERIES

By

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The author is indebted to the Joint Education Committee for Derby and District College of Technology for the award of a Research Assistantship.

STATEMENT

The experimental work described in this thesis has been carried out by the author under the direction of Dr. S.H.Harvey in the chemical laboratories of Derby and District College of Technology between April 1961 and July 1964.

Brian N. Biddle

NOTES

The conventions and nomenclature used in this thesis are intended to correspond with those adopted by the Chemical Society.

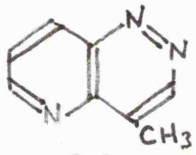
All melting points in this thesis are uncorrected.

The analyses were carried out by Drs. Weiler and Strauss of Oxford.

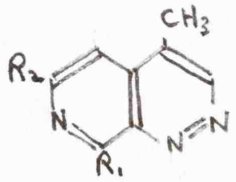
A summary of the work described has been published in the Journal of the Chemical Society in a paper - Triazaphenanthrenes. Part VI. Further Observations on the Widman-Stoermer and Borsche Reactions.
A copy of the paper is submitted together with this thesis.

ABSTRACT

The original work described in this thesis consists of attempts to extend the Widman-Stoermer and Borsche cinnoline syntheses to the preparation of a number of derivatives of the hitherto unreported 1,2,5- and 1,2,7-triazanaphthalenes, (I) and (II), and 1,2,9- and 3,4,8-triazaphehanthrenes, (III) and (IV).



(I)



(II)

(III)

(IV)

The application of the Widman-Stoermer reaction to the preparation of the 4-methyltriazanaphthalenes (I) and (II; $R_1=R_2=H$; $R_1=R_2=CH_3$; $R_1=CH_3, R_2=C_6H_5$) met with only limited success, probably due to the inhibiting effect of heterocyclic nuclei on the reaction. However, a synthetic route to 4-methyl-1,2,7-triazanaphthalene was developed, and in this case the reactivity of the methyl group was established.

Attempts were made to extend the Borsche reaction to the ring closure of diazotised 2-acetyl-3-aminopyridine,

4-acetyl-3-aminopyridine and 3-acetyl-2-aminopyridine but in no case was a product resulting from cyclisation obtained.

The preparation of the triazaphenanthrenes, (III) and (IV) was more successful. The 1,2,9-triazaphenanthrenes (III; $R_1=CH_3, R_2=H$; $R_1=C_6H_5, R_2=H$; $R_1=C_6H_5, R_2=CH_3$) were all obtained. The beneficial effect of aryl nuclei on the reaction was illustrated by the excellent yield of the 4-phenyl compound. 1-Methyl-3,4,8-triazaphenanthrene (IV) was also prepared in fair overall yield.

A modified Borsche reaction in alkali gave 4-hydroxy-3-methyl-10-phenyl-1,2,9-triazaphenanthrene (III; $R_1=OH, R_2=CH_3$) in good yield. The 4-hydroxy compound was converted via the 4-chloro compound (III; $R_1=Cl, R_2=CH_3$) to the amino compound (III; $R_1=NH_2, R_2=CH_3$).

CONTENTS

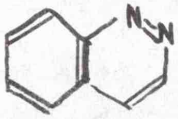
PART III — TRIAZAPHENANTHRENES — Page

PART I

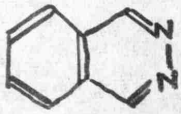
HISTORICAL SURVEY

(1) SYNTHESIS OF CINNOLINES

Of the four binuclear heterocycles having two nitrogen atoms in the same ring, cinnoline (1) is the least well known.



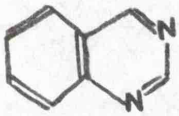
(I)



(II)

Cinnoline

Phthalazine



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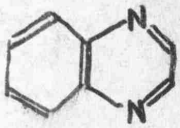


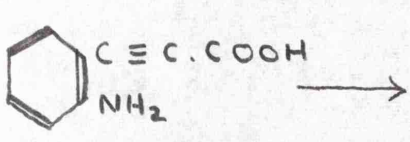
(IV)

Quinazoline

Quinoxaline

A number of reviews of cinnoline chemistry[1;2;3;4] have appeared in the literature.

The first cinnoline derivative to be described, 4-hydroxy-cinnoline-3-carboxylic acid (VI), was prepared in 1883 by v. Richter[5] by cyclisation of the diazotised o-aminophenylpropiolic acid (V).



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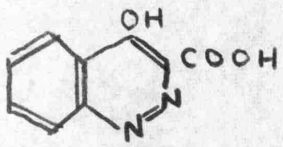
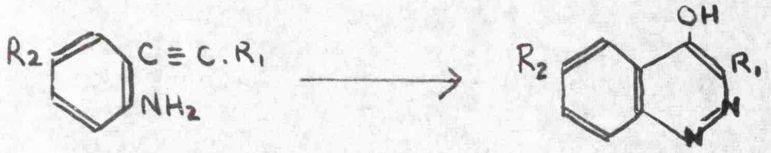


(VI)

There are three general methods for cinnoline synthesis, all of which involve cyclisation of an aryl diazonium compound containing an unsaturated group in the ortho-position.

(a) v. Richter method.

In his original synthesis, v. Richter[5] claimed an almost quantitative yield of the cinnoline (VI). Repetition of this work[6,7] gave much less satisfactory results, but the method has been extended by Schofield[7,8] to the cyclisation of a number of diazotised o-aminoarylacetylenes and tolans;



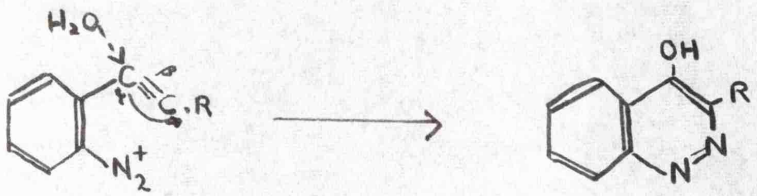
(VII) (VIII)

R_1 = COOH ; R_2 = H ; CH_3O ; Cl.

R_1 = H ; R_2 = H ; CH_3O ; Cl.

R_1 = C_6H_5 ; R_2 = H.

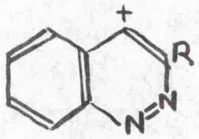
No quantitative data is available for any of the cinnoline syntheses but reasonable mechanisms have been proposed. In the v. Richter reaction it seems likely that intramolecular coordination of the diazonium cation with the anionoid β-carbon atom of the acetylenic group occurs with simultaneous introduction of hydroxyl at the α-carbon, as indicated below:



(IX) (X)

An alternative suggestion, which is not greatly different, is

that ring formation occurs first, as shown below (XI), followed by the attack of solvent.

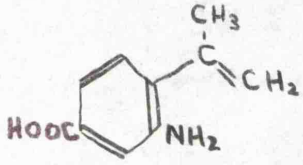


(XI)

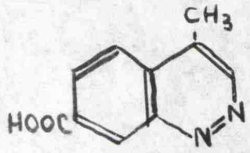
A quite different formulation, which involves hydration of the acetylenic link as the first stage, seems unlikely[6].

(b) Widman-Stoermer method.

In the year following v. Richter's discovery, Widman[9] prepared 4-methylcinnoline-7-carboxylic acid (XIII) by diazotisation of 1-methyl-1-(2'-amino-4'-carboxyphenyl)-ethylene:

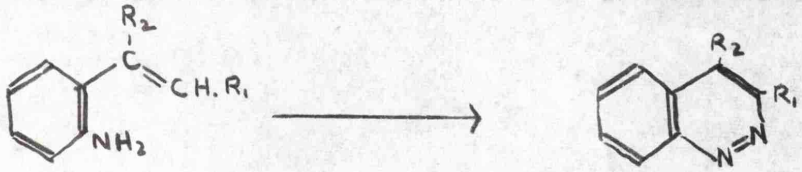


(XII)



(XIII)

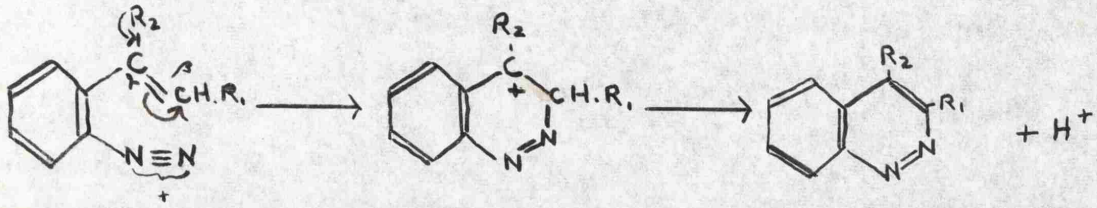
The reaction was rediscovered by Stoermer and his co-workers[10,11] and more recently it has been extended by Simpson and Schofield[12,13,14] to the synthesis of a wide variety of 4-aryl, 3,4-diaryl and 4-alkyl-cinnolines (XV) by the cyclisation of o-aminophenylethylenes (XIV).



(XIV) (XV)

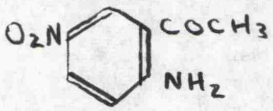
The mechanism of the reaction, discussed in greater detail in

Part II, probably follows the ionic route given below, involving cyclisation between the diazonium cation and the anionoid β-carbon atom of the ethylenic group.



(c) Borsche method.

This method, which has proved to be the most widely used of the cinnoline syntheses, was discovered in 1941 by Borsche and Herbert[15]. They found that diazotised 5-nitro-2-aminoacetophenone (XVI) slowly cyclised on standing to give 6-nitro-4-hydroxycinnoline (XVII).



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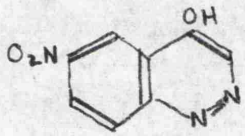
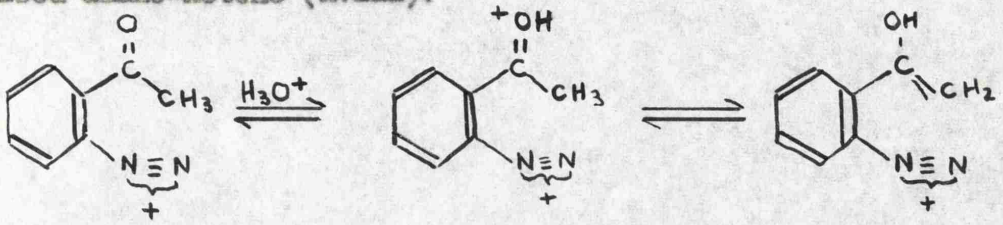


(XVII)

The reaction has been thoroughly explored, especially by Simpson, Schofield and their co-workers[7,13,16]. In general it was found that cyclisation was favoured by electron-withdrawing substituents at C_3 and C_5 in the 2-aminoacetophenones. In the absence of such substituents the cyclisation was found to be strongly dependent on the acidity of the solution and often diazotisation in concentrated hydrochloric acid was recommended.

The mechanism of the reaction is discussed again in Part II.

It is probably similar to the v. Richter and Borsche reactions, assuming that the reaction occurs through the enol form (XIX) of the diazotised amino-ketone (XVIII).

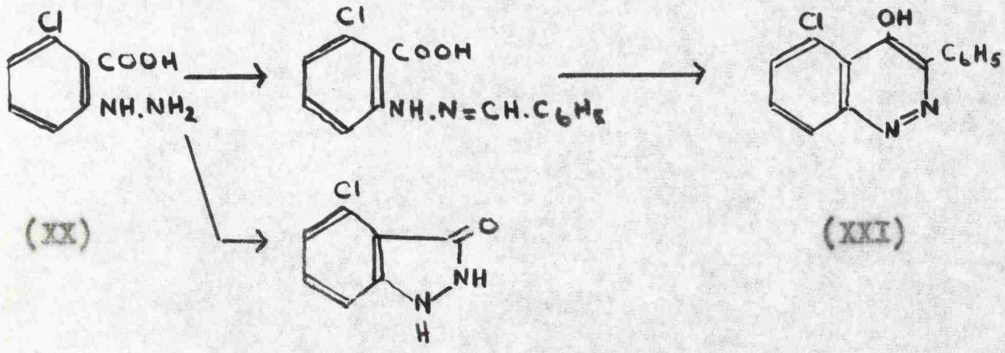


(XVIII) (XIX)

Other syntheses of cinnoline derivatives.

A number of other cinnoline syntheses has been reported but none of these has the generality of the three foregoing methods.

(a) Cyclisation of o-substituted hydrazines. Pfannstiel and Janecke[18] found that 6-chloro-2-hydrazinobenzoic acid (XX) yielded 5-chloro-3-phenyl-4-hydroxycinnoline (XXI) when treated with benzaldehyde. The yield was low because 4-chloroindazole (XXII) predominated and the reaction has found no further application.

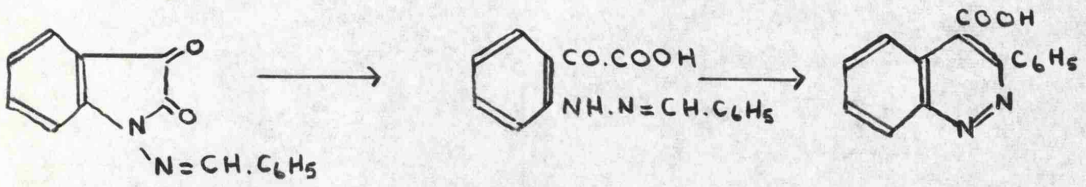


(XX) (XXI)

(XXII)

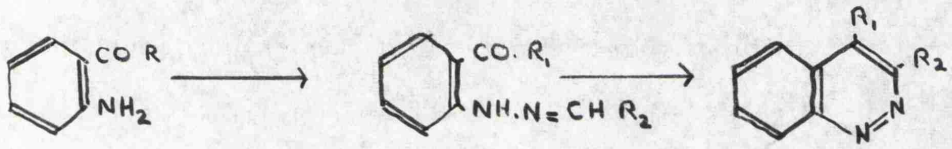
Another similar cinnoline formation, due to Stolle and Becker,[19]

involves the reaction of N-benzylideneaminoisatin (XXIII) with alkali. 3-Phenylcinnoline-4-carboxylic acid (XXV) was reported as a product of the cyclisation of the intermediate (XXIV).



(XXIII) (XXIV) (XXV)

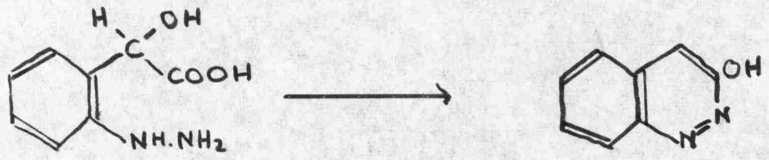
More recently the Stolle-Becker synthesis has been re-examined by Baumgarten and his co-workers[20,21] and a number of cinnoline syntheses have been developed, conforming to the general scheme given below:



(XXVI) (XXVII)

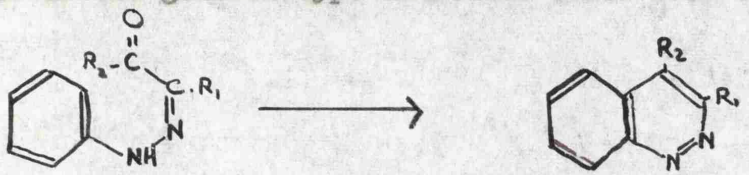
For example, Baumgarten and de Brunner[20] obtained nitroformaldehyde-o-acylphenylhydrazones (XXVI; R_1 = H, CH_3; R_2 = NO_2) by treatment of diazotised o-aminobenzaldehyde and o-aminoacetophenone with nitromethane and cyclised these to 3-nitrocinnolines (XXVII; R_1 = H, CH_3; R_2 = NO_2).

A further application of this type is the satisfactory cyclisation of o-hydrazinomandelic acids (XXVIII) to 3-hydroxycinnolines (XXIX) by Alford and Simpson[22].



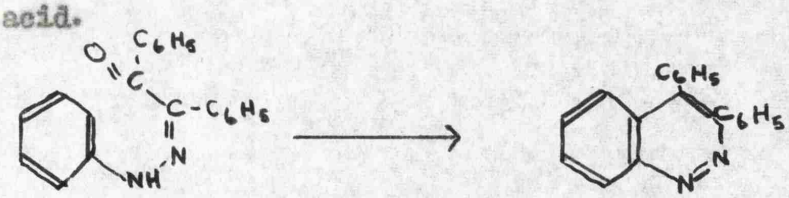
(XXVIII) (XXIX)

(b) Cyclisation of arylhydrazones and related compounds. A number of syntheses of the general type indicated below has been achieved:



(XXX) (XXXI)

The cyclisation of monophenylhydrazones of certain diketones, such as benzil or cyclohexanediones, has been realised by Moore[23] and Leonard, Boyd and Herbrandson[24]. 3,4-Diphenylcinnoline (XXXIII) was obtained in 75% yield by cyclisation of benzil monophenylhydrazone (XXXII) in sulphuric acid.

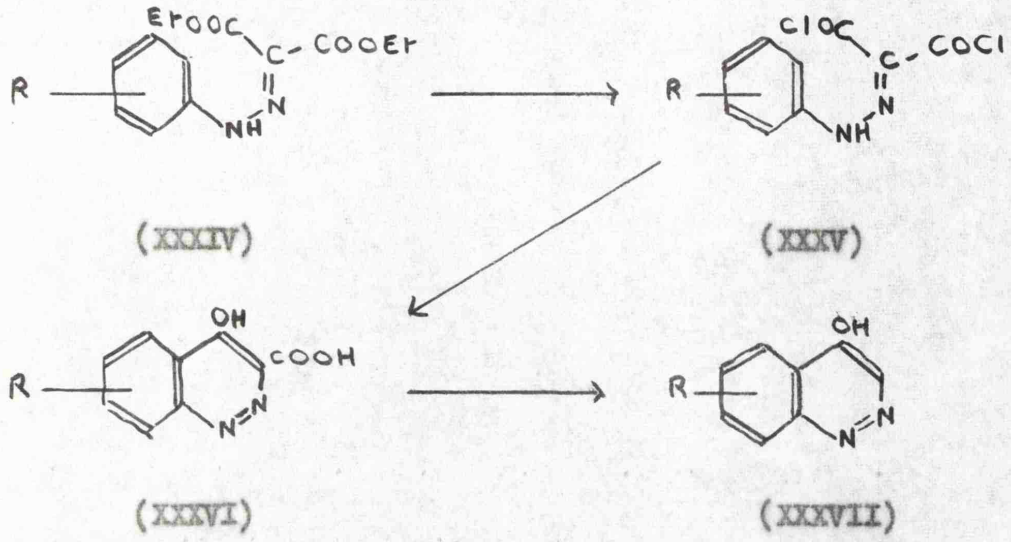


(XXXII) (XXXIII)

The reaction proved to be of very limited application.

A second and more recent cinnoline synthesis of the same type by Washbourn[25] is based on the cyclisation of the readily accessible mesoxalyl chloride phenylhydrazones (XXXV) to 4-hydroxycinnoline-3-carboxylic acids (XXXVI). The intermediate diesters (XXXIV) were obtained by condensation between diethyl malonate and diazotised

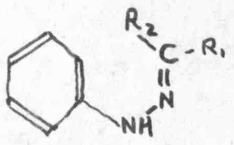
aromatic amines and were converted via the dicarboxylic acids, to the diacid chloride (XXXV).



(XXXIV) (XXXV)

(XXXVI) (XXXVII)

The reaction has provided a useful alternative to a variety of 4-hydroxycinnolines (XXXVII). The authors report, however, that attempts to extend the method to a number of phenylhydrazones of type (XXXVIII) were unsuccessful

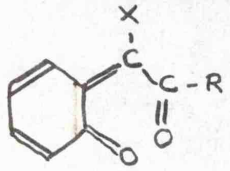


(XXXVIII)

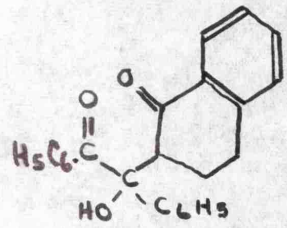
R_1 = COCl; R_2 = COOEt, H, CN or NO_2

(c) Condensation of diketones with hydrazines. Several applications of the well-known pyridazine synthesis from dicarbonyl compounds and hydrazines have been reported. The method has not been applied to the preparation of simple cinnoline derivatives from o-quinonoid compounds of type (XXXIX), although some polycyclic compounds have been prepared by this method. Allen and van Allen[26] have synthesised the benzo-cinnoline (XLII) by reaction of the

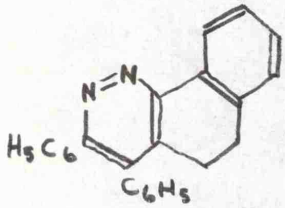
intermediate (XL) with hydrazine, followed by dehydrogenation of the resulting dihydrocinnoline (XLI).



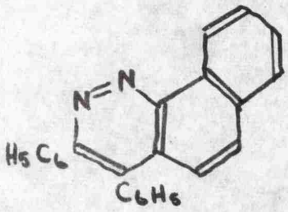
(XXXIX)



(XL)



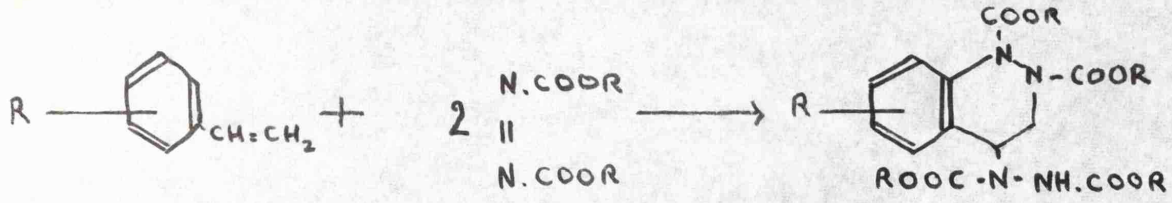
(XLI)



(XLII)

The same basic method has been extended to the synthesis of hydrogenated cinnolines from derivatives of cyclohexanone.[26,27,28]

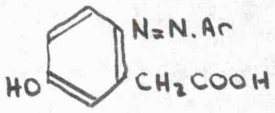
(d) Miscellaneous methods. Derivatives of cinnoline have been prepared by Alder and Niklas,[29] using a modification of the Diels-Alder pyridazine synthesis. The addition of azodicarboxylic esters (XLIV) to styrene derivatives (XLIII) gave the reduced cinnolines (XLV).



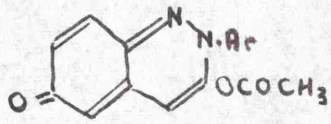
(XLIII) (XLIV) (XLV)

In 1948, Kornfeld[30] reported a new cinnoline synthesis based on the cyclisation of azo-compounds. The reaction of diazotised aromatic amines with m-hydroxyphenylacetic acid gave the azo-compounds (XLVI) which, on cyclisation with acetic anhydride, afforded the

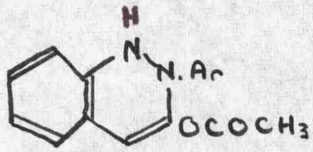
cinnoline (XLVII). Reduction with zinc in acetic acid gave 3-acetoxy-2-aryl-6-hydroxy-1,2-dihydrocinnolines (XLVIII).



(XLVI)



(XLVII)



(XLVIII)

No further applications of this synthesis have appeared in the literature.

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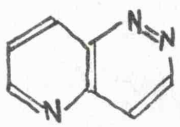
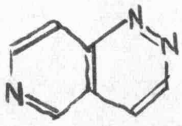
(2) TRIAZANAPHTHALENES

Of the fourteen possible triazanaphthalenes having no nitrogen atom common to both rings, derivatives of all have been reported in the literature, except the four pyrido-pyridazines (I, II, III, IV):



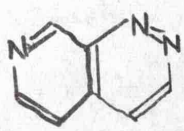
1,2,5

(I)



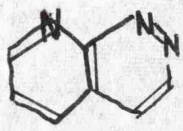
1,2,6

(II)



1,2,7

(III)



1,2,8

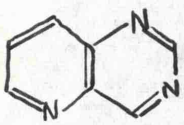
(IV)

Since these systems are related to cinnoline, obvious methods for the preparation of some of their derivatives might make use of the cinnoline syntheses described in the previous section, starting with o-aminoketones or o-aminoethylenes in the pyridine series. Unfortunately, in the case of the triazanaphthalenes (II) and (IV) the methods are limited by the difficulties involved in the diazotisation of 2- and 4-aminopyridines. Alternative routes would be based on cyclisations of amino-derivatives of pyridazine, such as the Skraup reaction. It appears from the literature that none of these routes has been attempted.

This review describes briefly the preparation of derivatives of the remaining triazanaphthalenes. The nomenclature used is according to the Stelzner system.

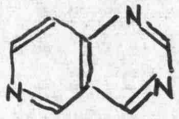
1,3,5-, 1,3,6-, 1,3,7-, and 1,3,8-Triazanaphthalenes.

The four pyrido-pyrimidines (V, VI, VII, VIII) have received more attention than any other triazanaphthalenes.



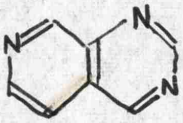
1,3,5

(V)



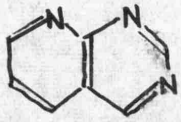
1,3,6

(VI)



1,3,7

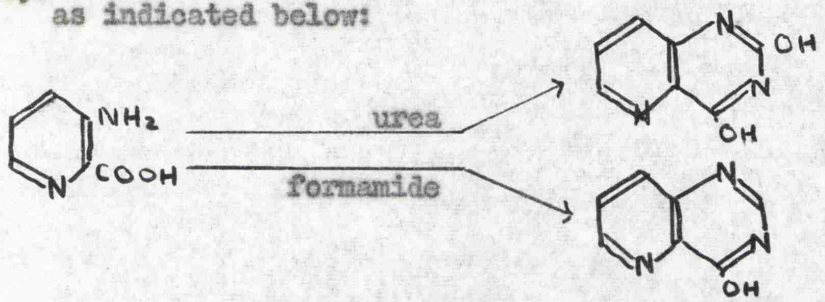
(VII)



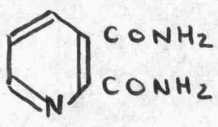
1,3,8

(VIII)

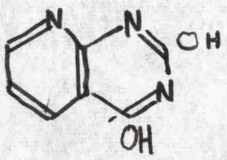
They are usually readily accessible via the van Niementowski reaction[1]. The fusion of o-amino acids of pyridine with urea, formamide or acetamide yields the hydroxy derivatives of the appropriate triazanaphthalene. For example, a variety of substituted 1,3,5-triazanaphthalenes have been prepared from 3-aminopicolinic acid,[2,3,4,5] as indicated below:



Similarly, the reaction has been used to prepare hydroxy derivatives of 1,3,7-triazanaphthalenes[6,7] and 1,3,8-triazanaphthalenes.[4,8,9] Some of the latter have also been prepared by application of the Hofmann reaction to pyridine amides.[10] Thus, alkaline hypobromite acts on quinoline amide (IX) to give 2,4-dihydroxy-1,3,8-triazanaphthalene (X):

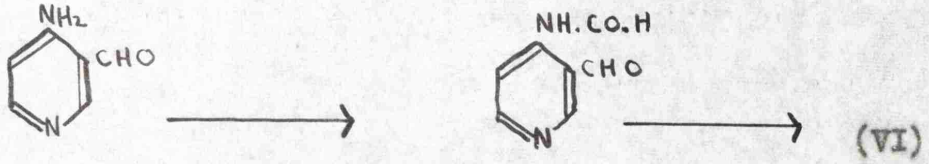


(IX)



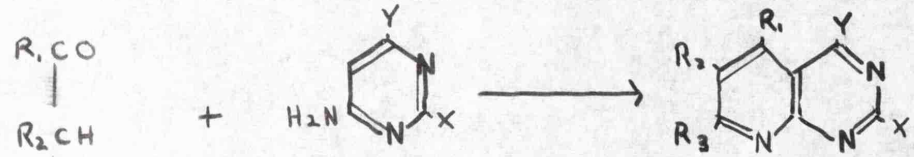
(X)

Armerego[7] has prepared the parent bases of all four pyrido-pyrimidines for studies in covalent hydration and has found that the alkaline decomposition of the 4-N-toluene-p-sulphonylhydrazides was successful, except in the case of 1,3,6-triazanaphthalene (VI). He has used an alternative route to this compound based on the ring closure of o-formamidopyridine-3-aldehyde (XII).



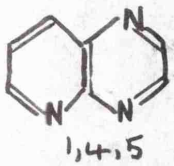
(XI) (XII)

The difficulty of obtaining the necessary pyridine amino-acids has led Robins and Hitchings[11] to develop an alternative synthetic route to a number of 1,3,8-triazanaphthalenes (XV) by condensing 4-aminopyrimidines (XIV) with 1,3-diketones (XIII) and other carbonyl compounds.

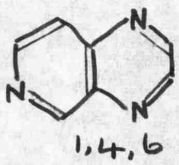


(XIII) (XIV) (XV)

1,4,5- and 1,4,6-Triazanaphthalenes



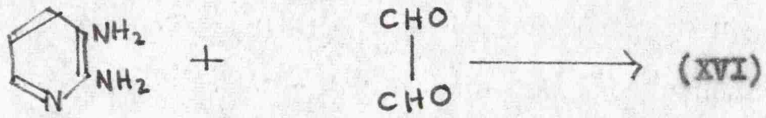
(XVI)



(XVII)

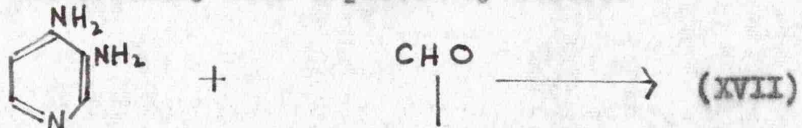
A number of derivatives of the two pyrido-pyrazines (XVI, XVII) has been prepared and the parent bases are known, but there is little published work relating to them. The usual method of preparation has been based on the well-known quinoxaline synthesis, involving condensation of the appropriate o-diamines with 1,2-diketones.

Derivatives of 1,4,5-triazanaphthalene were first reported by Tschitschibabin and Kirsanow[12] and more recently by Petrow,[13] Bernstein[14] and Lappin and Slezak,[15] all using the method indicated above. The parent base itself was prepared in poor yield by reaction between the diamine (XVIII) and glyoxal.[13]



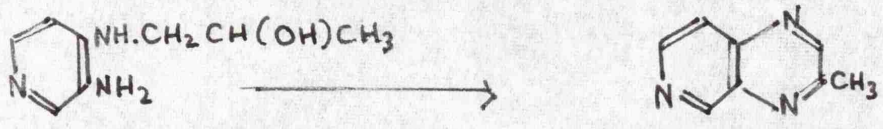
(XVIII)

The 1,4,6-triazanaphthalenes have received even less attention. The first reported preparation was by Koenigs[16] who synthesised the parent base by reaction between the o-diamine (XIX) and glyoxal. This method has recently been improved by Albert.[17]



(XIX)

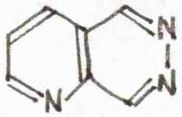
An alternative synthesis of interest is the unambiguous preparation of 3-methyl-1,4,6-triazanaphthalene (XXI) by Hepworth and Tittensor,[18] based on the cyclisation of the intermediate (XX).



(XX)

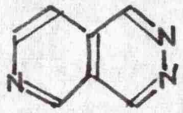
(XXI)

2,3,5- and 2,3,6-Triazanaphthalenes.



2,3,5

(XXII)

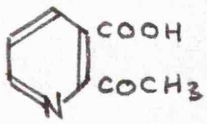


2,3,6

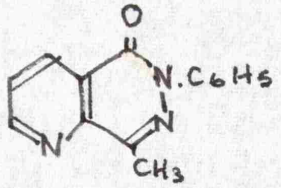
(XXIII)

A number of derivatives of the two pyrido pyridazines (XXII, XXIII) is known but no detailed study of these systems has been made. The methods which have been used for the preparation of these compounds are based on the synthesis of phthalazines by condensation of o-aldehydo- or o-keto acids with hydrazine or its derivatives.

The first example of a substituted 2,3,5-triazanaphthalene was reported by Rosenheim and Tafel[19] in 1893. The condensation of 2-acetyl-nicotinic acid (XXIV) with phenylhydrazine gave 1-keto-4-methyl-2-phenyl-2,3,5-triazanaphthalene (XXV).

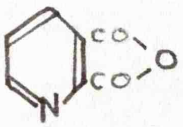


(XXIV)

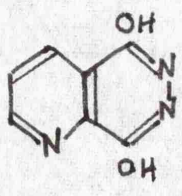


(XXV)

The condensation of quinolinic anhydride (XXVI) with hydrazine under various conditions[20,21,22] gives 1,4-dihydroxy-2,3,5-triazanaphthalene (XXVII).

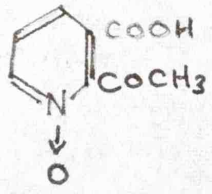


(XXVI)

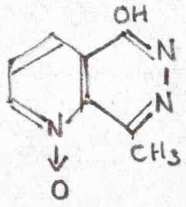


(XXVII)

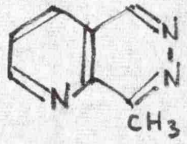
Armerego[23] has recently prepared 4-methyl-2,3,5-triazanaphthalene (XXX), by the same basic method, starting with 2-acetylnicotinic acid-1-oxide[24] (XXVIII).



(XXVIII)



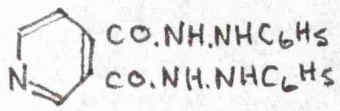
(XXIX)



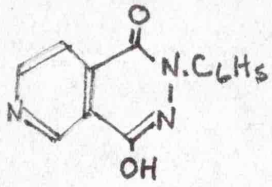
(XXX)

The intermediate hydroxy-compound (XXIX) was obtained by reaction of the N-oxide with hydrazine hydrate and was then converted to the 4-methyl-compound (XXX) via the chloro-derivative.

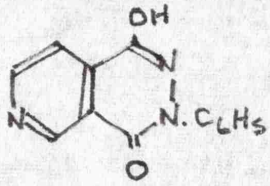
There is little published work on 2,3,6-triazanaphthalene (XXIII). The N-phenyl-derivative of 1,4-dihydroxy-2,3,6-triazanaphthalene (XXXI or XXXII) was reported by Strache[25] in 1890. It was obtained by heating the diphenylhydrazide (XXXIII) of cinchomeronic acid.



(XXXIII)

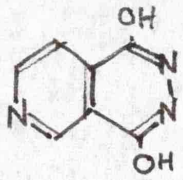


(XXXI)



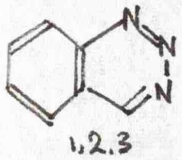
(XXXII)

Condensation of cinchomeronic acid with hydrazine at 365° gives 1,4-dihydroxy-2,3,6-triazanaphthalene (XXXIV).[26,27]

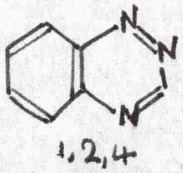


(XXXIV)

1,2,3- and 1,2,4-Triazanaphthalenes.



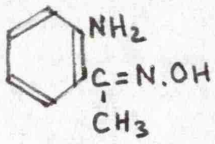
(XXXV)



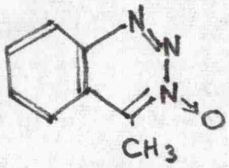
(XXXVI)

The 1,2,3- and 1,2,4-trazines have been reviewed by Wiley.[28] Derivatives of both the 1,2,3- and 1,2,4-benzotriazines (XXXV, XXXVI) are known.

The 1,2,3-triazanaphthalenes have usually been prepared by cyclisation of o-aminooximes or related compounds. Meisenheimer, Senn and Zimmermann[29] have prepared 4-methyl-1,2,3-triazanaphthalene-N-oxide (XXXVIII) by diazotisation of o-aminoacetophenone oxime (XXXVII).

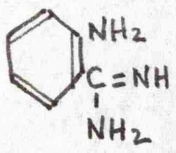


(XXXVII)



(XXXVIII)

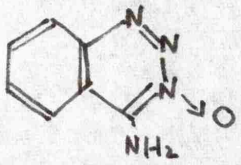
Similarly, the diazotisation of o-aminobenzamidine (XXXIX)[30] produces 4-amino-1,2,3-triazanaphthalene (XL), and the corresponding N-oxide (XLII) can be obtained from o-aminobenzamidoxime (XLI).[31] The 4-hydroxy-1,2,3-triazanaphthalene (XLIV)[32] results from the diazotisation of o-amino-acetamide (XLIII).



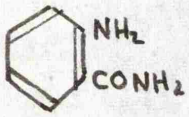
(XXXIX)

(XL)

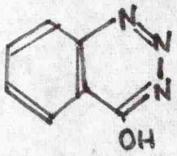
(XLI)



(XLII)



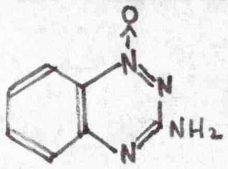
(XLIII)



(XLIV)

The 1,2,3-triazanaphthalenes are unstable and are reported to behave as diazonium salts.

The better-known 1,2,4-triazanaphthalenes, first reported by Bischler[33], have been prepared by various methods, the most common of which is the Arndt reaction.[34] The fusion of substituted o-nitroanilines with cyanamide results in the formation of the corresponding 3-amino-1,2,4-triazanaphthalene-1-oxides. o-Nitroaniline itself, on fusion with cyanamide, gives the 3-amino-compound (XLV).



(XLV)

The reaction has been applied to the preparation of a series of 1,2,4-triazanaphthalenes of potential antimalarial activity.[35]

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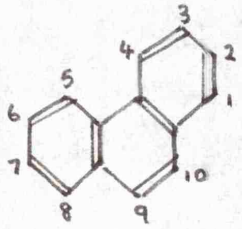
(3) TRIAZAPHENANTHRENES

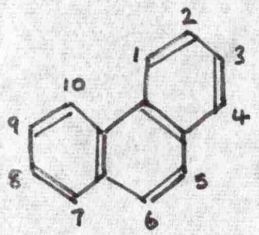
Nomenclature

Some confusion has been caused by the variety of names that have been used to describe various members of this series. ortho-Fused heterocyclic ring compounds may be named according to several methods. The I.U.P.A.C. rules recommend naming based on the relationship to a simple heterocycle, hence pyrido-cinnolines, pyridazino-quinolines and pyrido-quinozalines are all found in the literature. The alternative Stelzner system names such compounds as aza-derivatives of the corresponding homocyclic compound; in this case triazaphenanthrenes. In addition, these compounds are sometimes named as aza-derivatives of heterocycles. This applies particularly to the aza-phenanthrolines.

The numbering used in this review, as shown in (I), follows the Stelzner system which is recognised by the Chemical Society and which is commonly used in the European journals. However, the alternative numbering, as shown in (II), is also to be found, for example in the Ring Index.



(I)

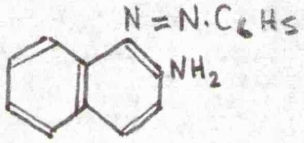


(II)

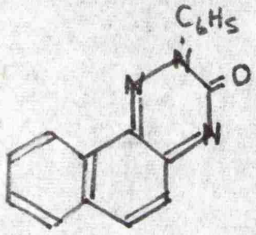
Synthesis of Triazaphenanthrenes.

Until fairly recently, very little work had been done on triazaphenanthrenes. Those compounds which were reported before 1955 were, without exception, by-products resulting from work in other fields, and no study was made of them.

The earliest authentic preparation of a triazaphenanthrene compound was by Goldschmidt and Rosell[1], who obtained 3-phenyl-2-oxo-2,3-dihydro-1,3,4-triazaphenanthrene (III) by the reaction of 1-phenylazo-2-naphthylamine (IV) with phenyl isocyanate. Compound (III) was later obtained in better yield by cyclisation with phosgene[2].

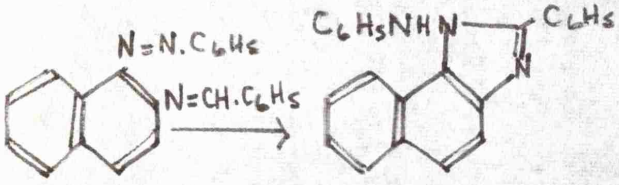


(IV)



(III)

Much of the work involving what was believed to be the 1,3,4-triazaphenanthrene system, however, has been shown to be in error[3]. In particular, Fischer[4] showed that the compounds obtained by the reaction of 1-arylazo-2-naphthylamines with aromatic aldehydes were naphthimidazoles (V) and not 2,3-dihydro-1,3,4-triazaphenanthrenes (VI), as originally formulated.



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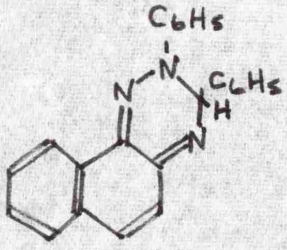
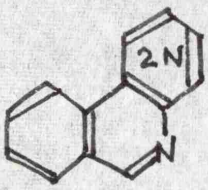


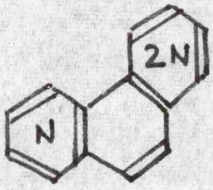
(VI)

Since the objective of the work recorded in this thesis was the synthesis of triazaphenanthrenes retaining either the phenanthridine structure (VII and VIII) or the phenanthroline structure (IX), those triazaphenanthrenes which do not fulfil the requirements of the general formulae VII, VIII, IX have been summarised briefly in Table I.

(VII)



(VIII)

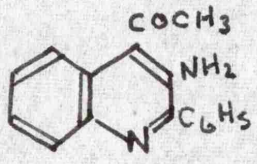


(IX)

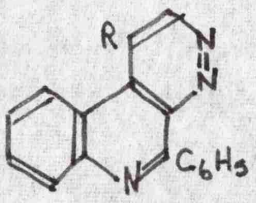
Triazaphenanthrenes having the above basic structures will be listed more fully as follows:

1,2,9-Triazaphenanthrenes.

Derivatives of this ring system were first reported by Atkinson and Mattocks[5]. 4-Hydroxy-10-phenyl-1,2,9-triazaphenanthrene (XI; R = OH) was prepared by diazotisation and ring closure of 4-acetyl-3-amino-2-phenylquinoline (X), in a strongly basic medium.



(X)



(XI)

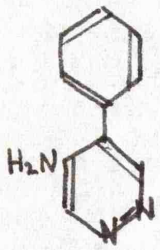
4-Chloro-10-phenyl-1,2,9-triazaphenanthrene (XI; R = Cl) was obtained

from the hydroxy-derivative, and was converted into the phenoxy-compound (XI; R = C_6H_5O). 4-Amino-10-phenyl-1,2,9-triazaphenanthrene (XI; R = NH_2) was prepared from the phenoxy-compound by heating with ammonium acetate. All attempts to prepare the parent base (XI; R = H) failed.

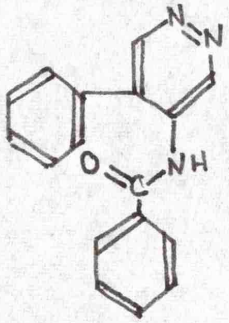
1,2,10- and 2,3,10-Triazaphenanthrenes.

Cyclodehydration of benzamido-phenylpyridazines by Atkinson and Rodway[6] has led to 9-aryl-derivatives of the hitherto unreported 1,2,10- and 2,3,10-triazaphenanthrenes.

Benzoylation of 5-amino-4-phenylpyridazine (XII) yielded the 4-benzamido-derivative (XIII), which was cyclised by heating with phosphorus pentoxide in nitrobenzene at 180° to give 9-phenyl-2,3,10-triazaphenanthrene (XIV; $R_1 = R_2 = H$). Parallel reactions gave the 9-m-nitrophenyl- and 9-p-nitrophenyl-derivatives (respectively $R_1 = H$; $R_2 = NO_2$ and $R_1 = NO_2$; $R_2 = H$). These were also reduced to the corresponding amino-derivatives.



(XII)



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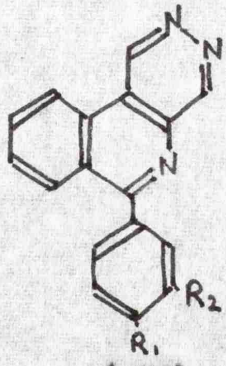
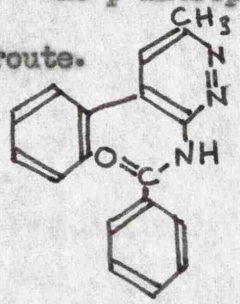


(XIV)

In a similar way, benzoylation of 3-amino-4-phenyl-6-methyl-

pyridazine (XV) and subsequent cyclodehydration of the benzamido-derivative (XVI) by heating at 220° with a mixture of aluminium chloride and sodium chloride led to 3-methyl-9-phenyl-1,2,10-triaza-phenanthrene (XVII; R = H). The p-nitrophenyl-derivative (XVII; R = NO_2) was obtained by a similar route.

(XV)



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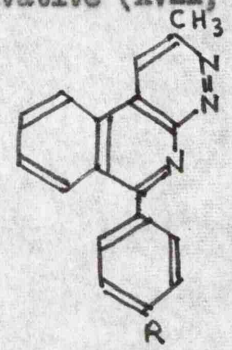
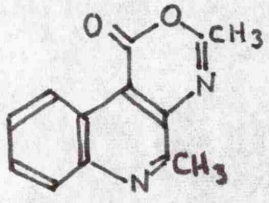


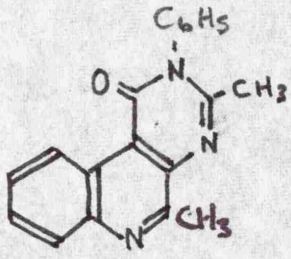
(XVII)

1,3,9-Triazaphenanthrenes.

Gulland and Robinson[7] in 1925, prepared 3,4-dihydro-2,10-dimethyl-4-oxo-3-phenyl-1,3,9-triazaphenanthrene (XX) by boiling anhydro-3-acetamido-2-methylcinchoninic acid (XIX) with aniline. No further work was carried out on this compound.



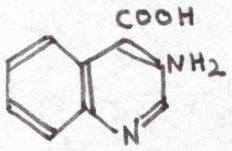
(XIX)



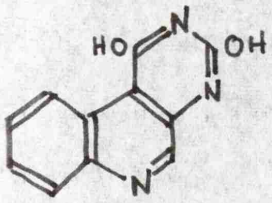
(XX)

It was not until 1943 that other 1,3,9-triazaphenanthrene-derivatives were prepared by Colonna[8]. Reaction of 3-aminocinchoninic acid (XXI) with urea, acetamide and formamide gave respectively the

three triazaphenanthrenes (XXII, XXIII and XXIV).

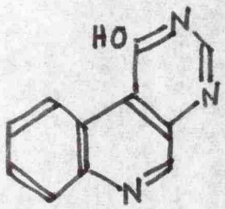


(XXI)



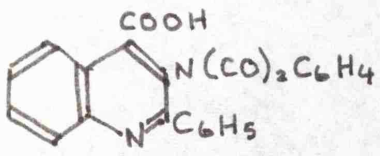
(XXII)

(XXIII)



(XXIV)

More recently, Atkinson and Mattocks[6] have prepared and investigated some of the reactions of 10-phenyl-1,3,9-triazaphenanthrene (XXVII: R = H) and its derivatives. 3-Amino-2-phenylquinoline-4-carboxylic acid (XXVI) was prepared by dephthaloylation of the phthalimido-acid (XXV), itself prepared by a Pfitzinger reaction between isatin and phenacylphthalimide. Condensation of the amino acid with formamide gave 4-hydroxy-10-phenyl-1,3,9-triazaphenanthrene (XXVII; R = OH).



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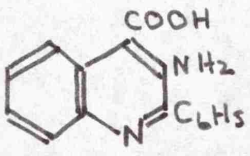
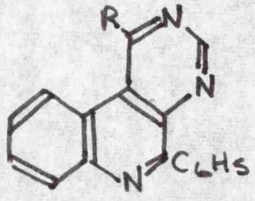


(XXVI)

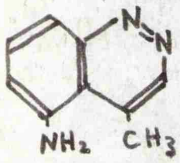


(XXVII)

4-Chloro-, 4-phenoxy- and 4-amino-derivatives were prepared from the hydroxy-compound and 10-phenyl-1,3,9-triazaphenanthrene was prepared from the 4-chloro-compound via the p-toluenesulphonhydrazide.

3,4,5-Triazaphenanthrenes.

All representatives of this ring system so far reported have been prepared by the cyclisation of derivatives of 8-aminocinnoline. McKenzie and Hamilton[9] condensed 8-amino-4-methylcinnoline (XXVIII) with ethoxymethylenemalonic ester and cyclised the product (XXIX) to obtain 7-carbethoxy-8-hydroxy-1-methyl-3,4,5-triazaphenanthrene (XXX; R = COOEt). Hydrolysis provided the 7-carboxy-8-hydroxy-derivative (XXX; R = COOH) and decarboxylation of the product gave the 8-hydroxy-compound (XXX; R = H).



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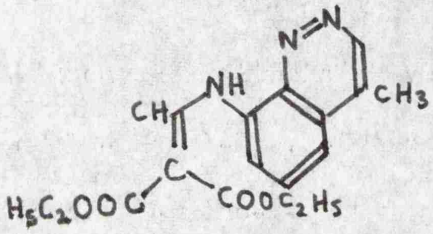

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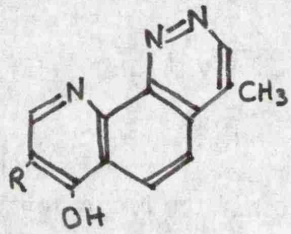
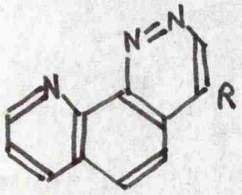
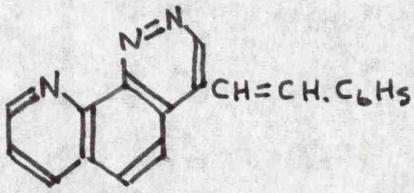


(XXX)

More recently, Case and Brennan[10], starting with the same aminocinnoline and using the Skraup reaction, have prepared 1-methyl-3,4,5-triazaphenanthrene (XXXI; R = Me). Condensation of the product with benzaldehyde gave the 1-styryl-compound (XXXII), oxidation of which gave the 1-carboxylic acid (XXXI; R = COOH). Subsequent decarboxylation gave the parent base (XXXI; R = H).



(XXXI)



(XXXII)

These compounds have attracted interest due to their structural relationship to o-phenanthroline, the well-known complexing agent and indicator. Hobday, Tomlinson and Irving[11], following the work of Case and Brennan,[10] have examined the reaction of 4-methyl- and 4,9-dimethyl-3,4,5-triazaphenanthrenes with metal ions.

TABLE I

Position of ring N atoms	Substituents	References
1,2,4	9-ethoxy-3-oxo-2-phenyl-2,3-dihydro-	3
	9-ethoxy-2-phenyl-3-phenylimino-2,3-dihydro-	3
	3-amino-	12
	1-carbethoxy-3-oxo-1,2,3,4-tetraH-9-sulpho-	13
	1-carbethoxy-3-oxo-1,2,3,4-tetrahydro-	13
	3-oxo-1,2,3,4-tetrahydro-9-sulpho-	13
	3-oxo-1,2,3,4-tetrahydro-	13
	3-imino-2,3-dihydro-1-oxide	14
1,3,4	3-phenyl-2-oxo-2,3-dihydro-	1,2
	2-oxo-1,2,3,4-tetrahydro-	15
	3,4-dicarbethoxy-2-oxo-1,2,3,4-tetrahydro-	15
	4-carbethoxy-2-oxo-1,2,3,4-tetrahydro-	15
	2-phenyl-	16
	3-(p-nitrophenyl)-2-carbethoxy-2,3-dihydro-	17
1,4,5	---	10
1,4,8	---	18
	2,3-dimethyl-	19
	2,3-diphenyl-	19
	3-carboxy-2-hydroxy-	20
1,5,9	---	10
	10-oxo-9,10-dihydro-	21
1,8,10	9-oxo-9,10-dihydro-	22
2,3,4	2-acetyl-1,2-dihydro-	3
2,4,5	---	10
2,4,8	1-hydroxy-	23
	1,3-dihydroxy-	23
	1-hydroxy-3-methyl-	23
3,9,10	---	24
	6-methyl-	24
	1-methyl-	25
	4-carboxy-1-methyl-	25
	4-hydroxy-1-methyl-	25

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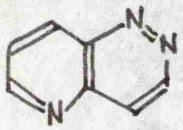
PART II

TRIAZANAPHTHALENES

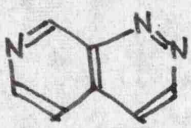
(1) INTERMEDIATES: 2-AMINO- AND 3-AMINOPYRIDINE CARBOXYLIC ACIDS.

Part II of this thesis describes attempts to prepare derivatives of the three triazanaphthalenes (I, II and III) by extending the Borsche and Widman Stoermer reactions to the cyclisation of diazotised o-aminoketones and o-aminoethylenes in the pyridine series.



1,2,5

(I)



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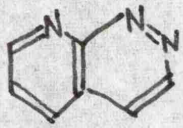
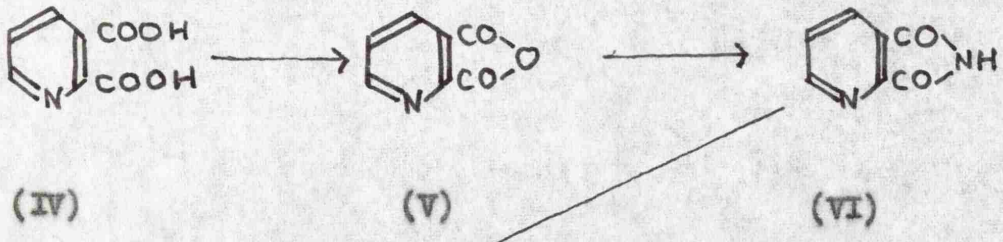


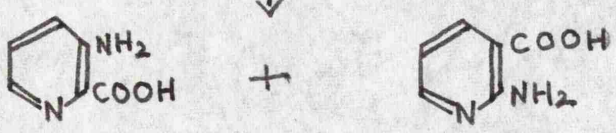
1,2,8

(III)

The most convenient starting materials for the preparation of such intermediates are the readily available o-aminopyridine carboxylic acids. These compounds are most easily obtained by synthesis from the corresponding pyridine dicarboxylic acids, and the general method used is exemplified by the preparation of 3-aminopicolinic acid (VII) from quinolinic acid (IV) shown below:



(IV) (V) (VI)



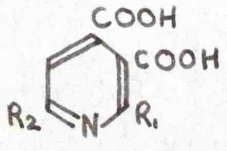
(VII) (VIII)

Quinolinic acid was prepared by the oxidation of 8-hydroxyquinoline

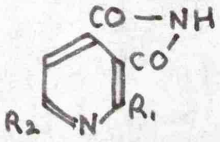
using a modification of the procedure due to Oakes, Pascoe and Rydon[1]. Quinolinimide (VI) may be obtained indirectly via the anhydride (V) or directly from quinolinic acid by reaction with acetamide in acetic anhydride - a method described by Carboni and Berti[2]. A Hofmann reaction with quinolinimide, using the method of Sucharda[3], gives a mixture of 3-aminopicolinic acid (VII), as the major product, and 2-aminonicotinic acid (VIII) in about 5-10% yield. The 3-aminopicolinic acid is difficult to isolate due to its high solubility in water. It was, however, isolated as the insoluble copper salt, from which the free amino-acid was obtained by separation of the copper as its sulphide.

Cinchomeronic acid (IX; $R_1 = R_2 = H$) is less accessible than quinolinic acid. The methods available for its preparation were reviewed and a number of these was investigated. Of those methods depending on the oxidation of isoquinoline, a recent method of Armerego and Evans[4] proved the most convenient. Unfortunately, their procedure requires a tedious extraction of the intermediate diethyl cinchomeronate with chloroform and although the authors recommend filtration through kieselguhr to remove impurities and to break the persistent emulsion, this was found to be only partially successful. Alternative procedures proved even less suitable: the oxidation of isoquinoline, using selenium dioxide in concentrated sulphuric acid[5], could not be reproduced, and the method of Lindenstruth and VanderWerf[6], using ozone oxidation, although excellent for the preparation of small

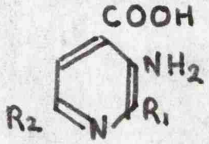
quantities, proved unsuitable when applied to larger amounts. The method finally adopted was a procedure based on the oxidation of quinine[7] with concentrated nitric acid. The relative ease of this method and the excellent yield it affords was considered ample justification for the cost of the starting material.



(IX)



(X)



(XI)

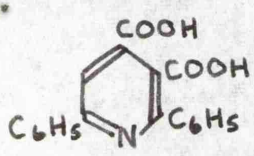
Cinchomeronic acid was converted into the imide (X; $R_1 = R_2 = H$), as described above, and a Hofmann reaction, following the method of Gabriel and Colman[8], gave 3-aminoisonicotinic acid (XI; $R_1 = R_2 = H$) in 45% yield. In this case the product was readily obtained, due to its low solubility in water.

2,6-Dimethylcinchomeronic acid (IX; $R_1 = R_2 = CH_3$) has previously been reported: ethyl acetylpyruvate[9] and ethyl β amino-crotonate[10] condense smoothly together at room temperature to give a good yield of the diethyl ester, as described by Gulland and Robinson[11]. Following the general procedure outlined earlier, 3-amino-2,6-dimethylisonicotinic acid (XI; $R_1 = R_2 = CH_3$) was obtained by a Hofmann reaction on the imide (X; $R_1 = R_2 = CH_3$).

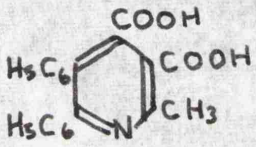
Similarly, 2-methyl-6-phenylcinchomeronic acid (IX; $R_1 = CH_3$, $R_2 = C_6H_5$), previously reported by Kao and Robinson[12], was prepared by a condensation between ethyl benzoylpyruvate and ethyl β amino-crotonate

and converted to the amino-acid (XI; $R_1 = CH_3$, $R_2 = C_6H_5$) via the corresponding imide. Mumm and Neumann[13] reported a compound which they described as the imide (X; $R_1 = CH_3$, $R_2 = C_6H_5$), prepared by a reaction between the anhydride of the dibasic acid and aqueous ammonia under pressure. These authors gave a much higher m.p. than that of the imide reported here and they submitted no analytical evidence. It seems likely, in view of the method used, that they obtained the ammonium salt.

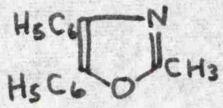
Two attempts to prepare the dicarboxylic acids (XII and XIII) failed.



(XII)



(XIII)

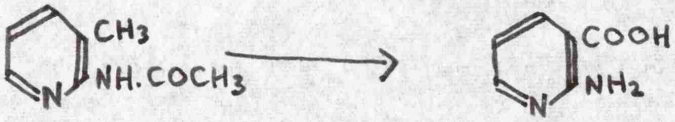


(XIV)

An attempt to prepare 2,6-diphenylcinchomeronic acid (XII) by condensation of ethyl β aminocinnamate[14] with ethyl benzoylpyruvate failed under all conditions tried. An attempt to extend a recent pyridine synthesis of Ya and Kondrateva[15] to the preparation of 2-methyl-5,6-diphenylcinchomeronic acid (XII) was also unsuccessful. The method makes use of a Diels Alder addition of maleic anhydride to substituted oxazoles. 2-Methyl-4,5-diphenyloxazole [16] (XIV) was heated with maleic anhydride under various conditions but condensation did not occur.

2-Aminonicotinic acid (VIII), already obtained as a by-product in the preparation of 3-aminopicolinic acid, was now required in

larger quantities and an alternative method was sought. The route of Robins and Hitchings[17], based on permanganate oxidation of 2-acetamido-3-methylpyridine[18], was found to give the acid in excellent overall yield.



(XV) (VIII)

EXPERIMENTAL

Quinolinic acid. — Fuming nitric acid (d. 1.5; 500 ml.) was added over 3hr. to a well-stirred suspension of 8- hydroxyquinoline (300 g.) in carbon tetrachloride (800 ml.), the temperature being maintained at 0-5° by cooling in an ice bath. The mixture was then warmed on a water bath to 40-50° and a further quantity of fuming nitric acid (750 ml.) added in 250 ml. portions over about 30 min. The temperature of the solution was raised slowly to 75-80°; this temperature was maintained, with stirring, for 1 hr. then a further quantity of nitric acid (250 ml.) was added. Heating was continued for 4hr. after which time the mixture was treated with more fuming nitric acid (500 ml.) and heated on the steam bath for a further 5hr. The whole of the above reaction was carried out in an efficient fume cupboard, since large quantities of nitrous fumes were evolved. The resulting solution was evaporated to dryness on a steam bath and the orange-coloured, crystalline residue filtered off and washed with 30% nitric acid (100 ml.), followed by water (2 x 100 ml.). The cream-coloured, crystalline product (193 g.) was filtered and dried, m.p. 185-187°. The filtrate and washings, on evaporating to about 100 ml., afforded a further quantity of quinolinic acid on cooling , (43 g.), m.p. 175-178°.

Quinolinic anhydride. — Quinolinic acid (100 g.) was heated with acetic anhydride (500 ml.) on a steam bath for 6hr. Excess acetic anhydride and acetic acid were removed from the clear solution by distilling under reduced pressure. The brown, oily residue crystallised on cooling to

afford the anhydride (85 g.), m.p. 136-138°. The anhydride was sufficiently pure to use without recrystallisation.

Quinolinimide. — A mixture of quinolinic anhydride (85 g.), acetamide (120 g.) and acetic anhydride (30 ml.) was heated under reflux in an oil bath at 125-130° for 7hr. and allowed to cool and stand overnight. The crystalline mass was filtered off, washed with 2N acetic acid (100 ml.) and water (200 ml.) and dried at 110° to afford the imide (68 g.) m.p. 238-240°.

3-Aminopicolinic acid. — To an ice-cold solution of bromine (28 ml) and sodium hydroxide (70 g.) in water (250 ml.) was added a solution of well-powdered quinolinimide (70 g.) and sodium hydroxide (140 g.) in water and ice mixture (900 g.). The resulting clear, brown solution was heated to 80° on a water bath and maintained at this temperature for 30 min. The solution was cooled, neutralised to pH 6.5 with acetic acid and allowed to stand at 0° overnight. Filtration of this solution gave 2-aminonicotinic acid as a buff-coloured, micro-crystalline solid, m.p. 298-302°.

The filtrate was treated with a solution of copper acetate (70 g.) in water (700 ml.) and the almost colourless copper salt collected. Filtration was difficult and a large Buchner funnel was used. The precipitate was collected and washed by stirring with warm water (300 ml.) The mixture was again filtered and the precipitate collected and suspended in water (250 ml.). A stream of hydrogen sulphide was passed

through the well-stirred mixture for 1hr. and the temperature maintained at 80° by heating on a water bath. The copper sulphide was filtered off and the filtrate evaporated to small bulk (c. 50 ml.), cooled and filtered to afford 3-aminopicolinic acid (32 g.) as light brown needles, m.p. 208-210°, A further amount of the product (6g.), m.p. 202-206°, was obtained by evaporation of the mother liquor.

Cinchomeric acid. -- (a) Batches of quinine (150 g.) were refluxed for about 100hr. with concentrated nitric acid (1200 ml.) and fuming nitric acid (d. 1.5; 350 ml.). The reaction was carried out in an efficient fume cupboard. The clear, yellow solution was evaporated on a steam bath and the viscous, pale yellow liquid poured into water (1000 ml.). The solution was allowed to stand at 0° overnight and then filtered to yield the acid (45 g.) as fine, colourless crystals, m.p. 264-267 (decomp.); literature values range from 249-251° (decomp.) to 266-268° . Evaporation of the filtrate, followed by oxidation of the oily residue, as described above, gave a further quantity (19 g.) of cinchomeronic acid. The product was used without further recrystallisation.

(b) To an ice-cold mixture of isoquinoline (178 g.), anhydrous copper sulphate (4.6 g.) and mercuric nitrate monohydrate (10 g.) was added cautiously sulphuric acid (d. 1.84; 400 ml.). The mixture was then heated to about 230° and nitric acid (d. 1.42; 470 ml.) added over 2¼ hr.

during which time a stream of air was drawn through the mixture and the volatile products distilled. After addition of the nitric acid was complete, the mixture was heated for a further 30 min., the air flow being continued. The mixture was warmed with urea (50 g.) at 100° for 30 min., before being refluxed for 7hr. with methanol (500 ml.) and benzene (300 ml.). After cooling, the mixture was poured on to ice and adjusted to pH 10 with ammonia. The benzene layer was separated and the aqueous layer extracted with chloroform (5 x 600 ml.), filtration through kieselguhr being necessary after each extraction to break up the emulsion. Filtration was difficult, owing to the formation of a fine, black precipitate during basification; this made replacement of the kieselguhr necessary. The combined chloroform extracts were shaken with solid sodium bicarbonate, dried ($MgSO_4$) and distilled, to afford dimethyl cinchomeronate (105 g.), b.p. 95-100°/ 1.5 mm.

The ester (100 g.) was refluxed with 4N-hydrochloric acid (250 ml.) for 3hr. and the solution evaporated to afford cinchomeronic acid (86 g.) m.p. 263-266° (decomp.).

Cinchomeronic anhydride. -- Cinchomeronic acid (100 g.) was heated with acetic anhydride (500 ml.) at 105-110° in an oil bath for 5hr. The acetic acid and excess acetic anhydride were removed under reduced pressure to yield, on cooling, a light brown, crystalline mass (92 g.) of the anhydride, m.p. 76-78°.

Cinchomeronimide. -- A mixture of the anhydride (41 g.), acetamide (50 g.)

and acetic anhydride (20 ml.) was heated in an oil bath at 125-130° for 6hr. and then allowed to cool overnight. The solid mass (35 g.) which separated was broken up, collected and washed well with dilute acetic acid (2N acid; 100 ml.), followed by water (200 ml.). The imide was dried at 110° to afford a buff-coloured solid, m.p. 232-236°. Gabriel and Colman[8] give m.p. 231-232°.

3-Amino-isonicotinic acid. -- Well-powdered cinchomeronimide (24 g.) was added to a solution of bromine (28 g.) and potassium hydroxide (50 g.) in water (400 ml.) at 0°. After half an hour's stirring at 0°, a further amount of potassium hydroxide (20 g.) in water (200 ml.) was added and the solution heated to 75-80° on a steam bath. This temperature was maintained for 30 min. and then the solution was cooled in ice and adjusted to pH 6.0 with glacial acetic acid. The buff-coloured solid (12.5 g.) which separated was collected, washed well with water (200 ml.) and dried at 110° to afford the amino-acid, m.p. 304-307°. Bachmann and Barker[19] give m.p. 319-320°.

Ethyl acetylpyruvate. -- A mixture of dry ethyl oxalate (337 ml.) and dry acetone (183 ml.) was added, with efficient stirring, to a solution of sodium (62.5 g.) in absolute alcohol (1400 ml.). The resulting precipitate was filtered on a large Buchner funnel and washed with ethanol (100 ml.); it was then treated with a mixture of water (750 ml.) and crushed ice (500 g.) and the mixture stirred. A solution of sulphuric acid (d. 1.84; 100 ml.) and ice (200 g.) was added dropwise and the

mixture extracted with benzene (3 x 300 ml.). The combined benzene extract was dried ($MgSO_4$) and the benzene removed under reduced pressure. The residue was distilled under reduced pressure, the fraction boiling between 118° and 120° at 30 mm. being collected. The yield of crude ethyl acetylpyruvate was 230 g.

Ethyl β aminocrotonate.-- A rapid stream of ammonia gas was passed through ethyl acetoacetate (100 ml.) for 5 hr., the temperature being maintained below 40° by cooling in ice. Ether (100 ml.) was added and the water which had formed was separated. The ether solution was washed with water (2 x 50 ml.), dried ($MgSO_4$) and the ether removed under reduced pressure. The yield of crude ethyl β aminocrotonate was 94 g. The product was used without further purification.

2,6-Dimethylcinchomeronic acid.-- A mixture of ethyl β aminocrotonate (69 g.), ethyl acetylpyruvate (83 g.) and ether (40 ml.) was allowed to stand overnight at room temperature and the ether was removed under reduced pressure. The condensation product was boiled under reflux with sodium hydroxide (80 g.) in water (200 ml.) for 4 hr. The solution was diluted with water (200 ml.), cooled in ice and neutralised with 12N sulphuric acid. The acid (94 g.), m.p. 270-274°, crystallised from the solution in almost quantitative yield. (Gulland and Robinson[11] give m.p. 275° for the pure acid.) The product was used without further purification.

2,6-Dimethylcinchomeronimide.-- (a) The foregoing acid (10 g.) and

urea (5 g.) were heated together, with stirring, at 225° until ammonia was no longer evolved (about 5 min.). The temperature was then raised to 230° for a short while (about 2 min.) and the mass cooled and extracted continuously with ethanol for about 1 hr. Concentration of the orange-red ethanol solution yielded the imide (6.5 g.), m.p. 224-229°. Further recrystallisation from ethanol afforded yellow needles, m.p. 230-231°. (Gulland and Robinson[11] report yellow needles m.p. 230°).

(b) The acid (20 g.), acetamide (27 g.) and acetic anhydride (100 ml.) were heated together under reflux at 130-135° for 6 hr. The mixture was cooled and filtered to yield the crude imide (15.5 g.) as a pale yellow powder. Recrystallisation from ethanol gave yellow needles, m.p. 230-231°, not depressed on admixture with the compound prepared as described under (a) above.

3-Amino-2,6-dimethylisonicotinic acid.— The finely powdered imide (20 g.) was added to a well-stirred solution prepared from bromine (18 g.), potassium hydroxide (30 g.) and a mixture of ice and water (300 g.). The mixture was allowed to stand for 2 hr., a further quantity of potassium hydroxide solution (20 g. in 150 ml. water) was added and the mixture was heated to 80-85° for 10 min. The clear solution was just acidified with 5N-hydrochloric acid and evaporated to dryness under reduced pressure. The residue was extracted with boiling ethanol (2 x 200 ml.) and the combined, filtered solution concentrated to small bulk (about 60 ml.). Concentrated hydrochloric acid (5 ml.) was added and the solution was cooled to 0°. The crystalline hydrochloride (14 g.),

m.p. 247-249° was collected and recrystallised from 2N-hydrochloric acid to afford slender, pale yellow needles, m.p. 248°.

A concentrated aqueous solution of the hydrochloride (2g. in 8 ml. water) was treated with excess solid sodium acetate . 3-Amino-2,6-dimethylisonicotinic acid separated as pale yellow prisms, m.p. 296-297°, (Gabriel and Colman[8] report m.p. 295°). For subsequent experiments the acid was used as its hydrochloride.

Ethyl benzoylpyruvate.— Acetophenone (236 g.) was added to a solution of sodium ethoxide, prepared from absolute ethanol (1050 ml.) and sodium (64.5 g.) and the mixture was cooled to 0°. Diethyl oxalate (409 g.) was then added over about 1 hr., with efficient stirring, the temperature being maintained at 0°. After the mixture had been allowed to stand for 12 hr. at room temperature, the yellow sodium salt was collected and dissolved in hot water (3500 ml.). The solution was acidified with 15N-sulphuric acid, cooled and the resulting oil extracted with ether, (3 x 300 ml.). After drying ($MgSO_4$), the ether was removed under reduced pressure. The crude ethyl benzoylpyruvate (520 g.) solidified on standing to a crystalline mass, m.p. 40-43°.

2-Methyl-6-phenylcinchomeronic acid.— A mixture of ethyl benzoylpyruvate (220 g.)and ethyl aminocrotonate (130 g.) was allowed to stand. The temperature rose to 35° and remained at above 30° for several hrs. After standing for about 24 hr., the mixture had set to a semi-crystalline mass. The condensation product was heated in an oil bath at 130° for

2 hr.; a smooth separation of water occurred. The resulting oily product was boiled under reflux with 5N-sodium hydroxide (250 ml.) for 2 hr. The oil dissolved to give a pale yellow solution which was just acidified to Congo red with concentrated hydrochloric acid. The mixture was cooled and the granular precipitate collected. A small amount of oily impurity was removed by washing with ether (2 x 20 ml.). Recrystallisation from 50% aqueous ethanol gave the acid as small, colourless needles, m.p. 217 -218°. (Mumm and Neumann[13] report m.p. 217°).

2-Methyl-6-phenylcinchomeronic anhydride.— The foregoing acid (50 g.) was heated under reflux on a steam bath for 5 hr. with acetic anhydride (300 ml.). Evaporation of the mixture to about 150 ml., under reduced pressure, followed by filtration of the cooled mixture, gave the anhydride (39 g.) as long, colourless needles, m.p. 195-196°. (Mumm and Neumann[13] report m.p. 196°).

2-Methyl-6-phenylcinchomeronimide.— (a) The foregoing anhydride (39 g.) mixed with acetamide (50 g.) and acetic anhydride (10 ml.) was heated to 125-130° in an oil bath and retained at this temperature for 6 hr. The crystalline precipitate (24 g.) which separated was collected, washed with acetic acid and with water and then recrystallised from acetone to yield the imide as small, colourless needles, m.p. 163°. (Found: C,70.6; H,4.2; N,11.8. $C_{14}H_{10}O_2N_2$ requires C,70.9; H,4.5; N,11.6%). (Mumm and Neumann[13] report an imide m.p. 249° but give no analysis).

(b) The acid (10 g.) was mixed with urea (5 g.) and heated, with stirring, at 210° for 10 min. The temperature was then raised to about 220° for a further 5 min. (until ammonia was no longer evolved) and the resulting pasty mass was allowed to cool to room temperature. Extraction with hot ethanol (4 x 50 ml.) provided, on concentration of the solution, the imide (7.1 g.) as almost colourless needles, m.p.163°. The melting point was not depressed on admixture with the compound prepared as described under (a) above.

3-Amino-2-methyl-6-phenylisonicotinic acid.— The well-powdered imide (30 g.) was added to an ice-cold solution prepared from bromine(30 g.), sodium hydroxide (29 g.) and a mixture of ice and water (300 g.). After stirring for 15 min., the temperature was raised to 70-80° for 1 hr. and the solution was then cooled and acidified to Congo red with concentrated hydrochloric acid. The solution was evaporated to dryness under reduced pressure and the pale yellow residue extracted with ethanol (3 x 150 ml.). The combined ethanol extract was filtered to remove inorganic material and treated with 5N-hydrochloric acid (10 ml.). Evaporation of the solution to about 30 ml. provided, on cooling, a yellow-brown residue (17 g.). Recrystallisation from 2N-hydrochloric acid (charcoal) gave 3-amino-2-methyl-6-phenylisonicotinic acid hydrochloride as long, pale yellow needles, m.p.241-242°. (Found: C,54.9; H,5.9; N,9.9; Cl, 12.4. $C_{13}H_{13}O_2N_2Cl.H_2O$ requires C,55.1; H,5.3; N,9.9; Cl,12.5%).

Attempts to obtain the free amino acid by neutralisation of an aqueous solution of the hydrochloride gave a dense, gelatinous precipitate

which was extremely difficult to filter. For this reason it was found more convenient to use the amino-acid as its hydrochloride in subsequent preparations of the ethyl ester.

Ethyl β aminocinnamate.— To a Grignard reagent prepared from bromobenzene (20.6 g.) and magnesium (3.4 g.) in dry ether (150 ml.), was added ethyl cyanoacetate (6 g.) in ether (50 ml.) over about 30 min. The solution was stirred under reflux for 20 hr. and, after cooling, was treated with 4N-sulphuric acid (40 ml.). The ether layer was separated and the aqueous layer extracted with a further quantity of ether (100 ml.). The combined ether extract was dried ($MgSO_4$) and the ether evaporated. The resulting orange-yellow oil (8.8 g.) was distilled under reduced pressure to yield two fractions: a biphenyl fraction (1.7 g.), b.p.$_{15}$ 138-142°, and ethyl β aminocinnamate (6.0 g.) as an almost colourless liquid, b.p.$_{15}$ 179-181°.

Attempted preparation of 2,6-diphenylcinchomeronic acid.— A mixture of ethyl benzoylpyruvate (5.5 g.) and ethyl β aminocinnamate (5.0 g.) was warmed to 35° and then allowed to stand at room temperature overnight. The condensation product, which formed as an oily, crystalline mass, was heated to 130-135° in an oil bath. Heating was continued for 6 hr. and the dark, oily mixture allowed to cool. The product was boiled under reflux for 3 hr. with concentrated hydrochloric acid (30 ml.) and, after cooling, was diluted with water (30 ml.) and made alkaline with 4N-sodium hydroxide solution. Extraction with benzene (2 x 20 ml.)

gave, after drying and evaporation, a dark brown oil (5.2 g.). Neutralisation of the alkaline solution gave no precipitate and no product could be obtained by concentration of the neutral solution.

Further attempts to obtain the acid by cyclisation of the condensation product at higher temperatures gave dark, high-boiling, resinous material which yielded no useful products on attempted hydrolysis with either concentrated hydrochloric acid or 6N-sodium hydroxide solution.

2-Methyl-4,5-diphenyloxazole.— A mixture of benzoin acetate (28 g.), ammonium acetate (38 g.) and glacial acetic acid (100 ml.) was boiled under reflux for 1 hr. and poured into water (400 ml.), The mixture was extracted with benzene (3 x 200 ml.) and the combined benzene solution was washed with sodium carbonate solution and then dried ($MgSO_4$). Removal of the benzene, followed by distillation under reduced pressure, gave 2-methyl-4,5-diphenyloxazole (23 g.) as a colourless liquid, b.p.$_{20}$ 218-220°.

Neutralisation of the aqueous layer gave 2-methyl-4,5-diphenyl-glyoxaline (1.7 g.) as colourless needles from ethyl acetate, m.p. 239°.

Attempted preparation of 2- methyl-5,6-diphenylcinchomeronic acid.— The foregoing oxazole (10 g.) and maleic anhydride (8 g.) were refluxed together in benzene (75 ml.) for 15 hr. and the solution cooled and shaken with water (100 ml.). The aqueous layer was separated and evaporated to dryness under reduced pressure to yield a colourless, crystalline residue (6.4 g.). This residue was freely soluble in water

and proved to be maleic acid, m.p. and mixed m.p. 127-129°. Further extraction of the benzene layer with 2N-sodium hydroxide solution, followed by neutralisation of the alkaline extract, gave no precipitate. The benzene layer, after being washed with water and dried ($MgSO_4$), afforded on distillation under reduced pressure, unchanged 2-methyl-4,5-diphenyloxazole (8.5 g.), b.p. (18-20 mm.) 218-220° and a small amount (0.4 g.) of resinous material from which no useful product could be obtained. Various modifications of the above procedure, using higher boiling solvents, yielded only unchanged starting materials.

2-Acetamido-3-methylpyridine.-- A mixture of 2-amino-3-methylpyridine (120 g.), dissolved in acetic anhydride (200 ml.), was boiled under reflux for 15 min. The excess acetic anhydride and acetic acid were removed and the product distilled under reduced pressure to give 2-acetamido-3-methylpyridine (116 g.) as a colourless oil, b.p.(20 mm) 179-180°. The product solidified to give material, m.p. 62-63° (Seide[18] gives m.p. 64°).

2-Aminonicotinic acid.-- Batches of 2-acetamido-3-methylpyridine were oxidised by the following method: a solution of the acetamido compound (20 g.), ~~dissolved~~ in water (2000 ml.), was heated to 70-75° and stirred efficiently. Potassium permanganate (50 g.) was added in one batch and the mixture stirred at about 75° for 5 hr. by which time all the potassium permanganate colour had disappeared. The solution was

filtered to remove manganese dioxide and the residue was washed well with hot water. The combined filtrate and washings were evaporated to dryness in a rotary evaporator and the colourless residue was dissolved in water (100 ml.). The solution was acidified by addition of concentrated hydrochloric acid and excess acid (100 ml.) was added. This solution was boiled under reflux for 15 min., cooled to room temperature and adjusted to pH 5.0 with concentrated ammonia. The solution was allowed to stand at 0° overnight and the colourless, crystalline solid (10.5 g.) which separated, was collected and had m.p. 304–308°.

The product was used without further purification.

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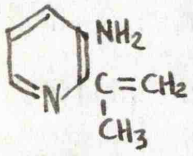
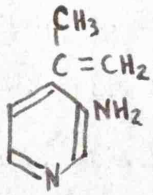
(2) INTERMEDIATES: PREPARATION OF AMINO-PROPENES IN THE PYRIDINE SERIES

A number of aminopyridyl-propenes were required for investigations into the Widman Stoermer reaction and this section describes the preparation of the four propenes (I, II, III and IV), shown below:



(I)



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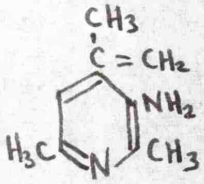
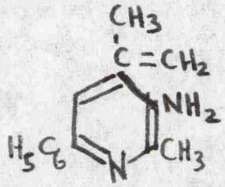
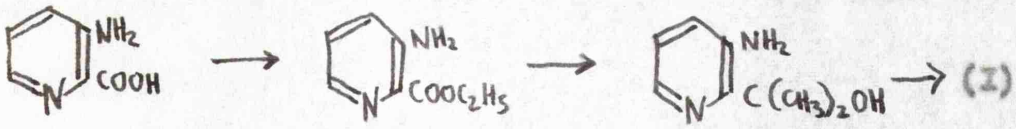


(III)



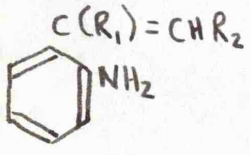
(IV)

The general route used for their preparation from the amino-acid involves a Grignard reaction between the amino-ester and methyl magnesium iodide, followed by dehydration of the resulting tertiary carbinol. The scheme is illustrated below for the preparation of 2-(3'-amino-2'-pyridyl)-propene (I) from 3-aminopicolinic acid (V):

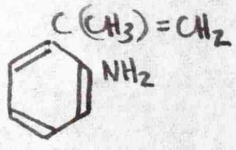


(V) (VI) (VII)

This method has been used by Stoermer and Fincke[1] and by Simpson and Stephenson[2] for the preparation of aryl substituted ethylenes (VIII) from amino-ketones, also by both Jacobs[3] and Atkinson and Simpson[4] for the preparation of 2-(o-aminophenyl)-propene (IX) from methyl anthranilate.



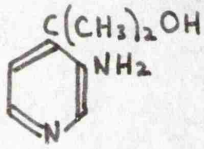
(VIII)



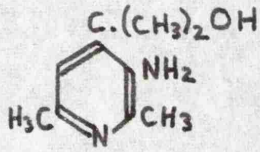
(IX)

Esterification of 3-aminopicolinic acid (V) and the other amino-acids, described in the previous section, proved difficult and attempts to esterify using azeotropic methods or the Fischer-Speier procedure failed. However, these esters could be obtained in up to 70% yield by heating the amino-acid in a mixture of equal volumes of concentrated sulphuric acid and ethanol for long periods.

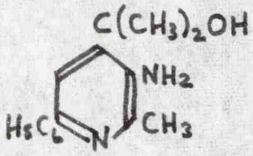
Grignard reactions between methyl magnesium iodide and the ethyl esters gave the four crystalline carbinols (VII, X, XI and XII) in fair yield.



(X)

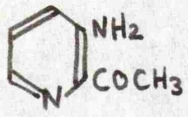


(XI)

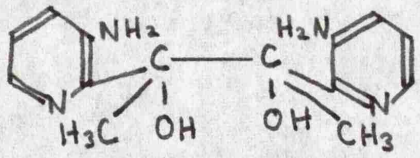


(XII)

In the case of the Grignard reaction with ethyl 3-aminopicolinate, however, a second product was formed in varying amounts, sometimes even predominating over the carbinol. This compound was easily separated from the carbinol, owing to its much lower solubility in ether. From the analysis, the compound was first thought to be the amino-ketone (XIII) but although an aromatic amino group was present (positive diazotisation and coupling with 2-naphthol), an absence of CH_3CO- was indicated by negative reactions with the usual reagents. Molecular weight determination (mean value 283), however, pointed to the molecular formula $C_{14}H_{18}N_4O_2$. This evidence and the presence of an OH-group, indicated by a strong band in the I.R. spectrum at 3420 cm^{-1}, led to the tentative suggestion of the pinacol structure (XIV).



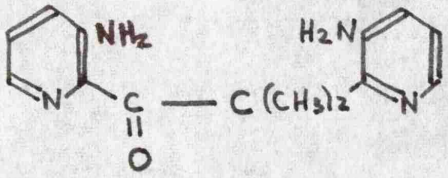
(XIII)



(XIV)

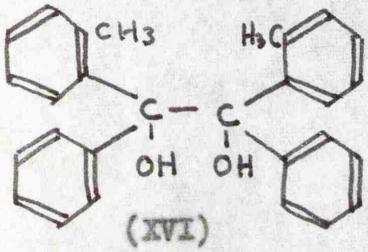
If the assigned structure were correct, reaction with glycol-splitting reagents should yield the amino-ketone (XIII). A successful oxidation of the compound was, in fact, carried out, using chromium trioxide in acetic acid as the reagent - a method adopted by Bachmann and Chu[5] for the scission of pinacols. 2-Acetyl-3-amino-pyridine was isolated from the reaction products and identified by analysis and by 2,4-dinitrophenylhydrazone formation. Attempts to oxidise the pinacol with periodic acid[6] failed, possibly because of the formation of an insoluble periodate of the base. Lead tetraacetate, however, oxidised the compound readily at room temperature and although the reaction gave mainly dark, tarry products, the same amino-ketone (XIII) was separated in low yield by chromatography on alumina.

A number of methods is available for the rearrangement of pinacols: attempted rearrangement with iodine in acetic acid[5] gave only unchanged starting starting material, but hot, concentrated hydrochloric acid gave a new compound whose analysis corresponded to that of the pinacolone (XV).

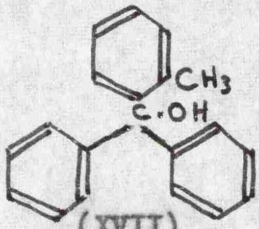


(XV)

Although pinacols are not usual products of Grignard reactions with esters, their formation has been reported. Boyd and Hatt[7] obtained both pinacols and ketones from esters in addition to the expected tertiary carbinol. For example, the reaction between phenyl magnesium bromide and ethyl o-toluate produced diphenyl di-o-tolylpinacol (XVI) as well as diphenyl o-tolylcarbinol (XVII).



(XVI)

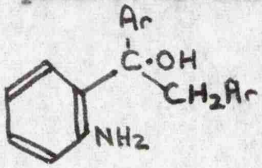


(XVII)

These authors stress, however, that pinacols are formed only in the presence of excess magnesium and propose that pinacol formation is the result of reduction of the intermediate ketone. The reduction of ketones by magnesium in the presence of Grignard reagents was well established by Gomberg and Bachmann[8]. In view of the recommendations of both Boyd and Hatt[7] and Barnett, Cook and Nixon[9] that prior filtration of the Grignard reagent prevents pinacol formation, experiments were carried out using filtered methyl magnesium iodide solution. In these reactions the formation of the by-product was either substantially reduced or, in certain cases, completely prevented.

Unlike diaryl carbinols (XVIII), which are readily dehydrated[2], the tertiary carbinols (VII, X, XI and XII) could not be dehydrated under mild conditions: experiments with both iodine-toluene[3] under reflux and with hot, dilute mineral acid were unsuccessful.

The methods eventually adopted for converting the carbinols to the required propenes (I, II, III and IV) were either reflux in 50% v/v sulphuric acid, or the action of cold, concentrated sulphuric acid. The amino-propenes were all obtained as colourless oils which could not be crystallised (compare Simpson and Stephenson[2]) and were characterised by either picrate or benzoate formation.



(XVIII)

EXPERIMENTAL

Ethyl-3-aminopicolinate.-- (a) 3-Aminopicolinic acid (5 g.) was boiled under reflux for 7 hr. with a saturated solution of hydrogen chloride in ethanol (50 ml.). The solution was cooled and treated with petroleum ether (b.p. 40-60°; 100 ml.)and the buff-coloured, crystalline solid (1.9 g.) was collected. Recrystallisation from benzene-light petroleum ether afforded the ester as colourless needles, m.p. 132° (Oakes, Pascoe and Rydon[10] report m.p. 132°).

(b) The acid (20 g.) was heated under reflux on a steam bath with ethanol (40 ml.) and sulphuric acid (d. 1.84; 20 ml.). Heating was continued for 30 hr. and the mixture was poured into ice and water (300 g.). The clear, brown solution was stirred and neutralised by addition of solid sodium carbonate. The mixture was allowed to stand for 30 min. and the crystalline precipitate (16 g.) was filtered, washed well with water and dried at 80°. Recrystallisation provided ethyl-3-aminopicolinate (13.8 g.), m.p. 132°. A further quantity (1.2 g.) of the ester was obtained by extracting the aqueous filtrate with ether (2 x 50 ml.) and evaporating the dried ether solution.

Dimethyl-(3-amino-2-pyridyl)-carbinol.-- (a) A solution of ethyl-3-aminopicolinate (12 g.) in sodium-dried benzene (250 ml.) was added, with stirring during 30 min. to a Grignard solution prepared from magnesium (5.2 g.) and methyl iodide (33 g.) in dry ether (250 ml.). This Grignard solution had previously been filtered through kieselguhr under an atmosphere of dry nitrogen. The mixture was refluxed for a

further 5 hr. and the resulting yellow complex was decomposed by pouring into an ice-water mixture (500 g.), saturated with ammonium chloride and stirred for 30 min. The organic layer was separated and extracted with 5N-hydrochloric acid (2 x 50 ml.). The combined aqueous solutions were then neutralised by the addition of 5N hydrochloric acid and extracted with ether (3 x 200 ml.). The ether solution was dried ($MgSO_4$) and evaporated, finally under reduced pressure, to yield the carbinol as a yellow oil (8.5 g.) which was extremely difficult to crystallise. However, extraction with boiling petroleum ether, (b.p.60-80°) afforded dimethyl-(3-amino-2-pyridyl)-carbinol as colourless prisms, m.p. 91-92°, after the solution had been allowed to stand for several days at 0°. (Found:C,62.6; H,7.7; N,18.2. $C_8H_{12}ON_2$ requires C,63.1; H,8.0; N,18.4%).

Treatment of the oily carbinol with benzoyl chloride in pyridine gave dimethyl-(3-benzamido-2-pyridyl)-carbinol as colourless plates, from methanol, m.p. 129-130°. (Found:C,69.7; H,6.2; N,11.4. $C_{15}H_{16}O_2N_2$ requires C,70.3; H,6.2; N,11.0%).

(b) The preparation described above was carried out without filtration of the Grignard solution. The reagent prepared from magnesium (9.0 g.) and methyl iodide (53 g.) in dry ether (400 ml.), was treated with the ester dissolved in dry benzene (500 ml.). Treatment of the oily product, with ether (25 ml.) gave two products. Evaporation of the ether filtrate gave dimethyl-(3-amino-2-pyridyl)-carbinol (A) (9 g.) as a pale yellow oil identical with the product described under (a) above. A second product

(B)

(3.4 g.), only sparingly soluble in ether, gave on recrystallisation from benzene, yellow needles, m.p. 156° (Found: C,61.6; H,5.7; N,20.9. $C_{14}H_{18}N_4O_2$ requires C,61.4; H,6.5; N,20.5%). Molecular weight determinations, using a modified Spencer-Cottrell apparatus, gave a mean value of 283 from two determinations (270, 296). The molecular weight required by $C_{14}H_{18}N_4O_2$ is 274. Infra-red spectrum (KCl disc) max. at 3420, 3170, 3050, 2980, 2930, 1945, 1885, 1815, 1667, 1615, 1574, 1515, 1504, 1463, 1415, 1372, 1288, 1233, 1180, 1150, 1108, 1085, 1043, 1002, 953, 925, 908, 875, 862, 800, 772, 705 cm^{-1}.

Attempts to form a 2,4-dinitrophenylhydrazone and an oxime failed. Diazotisation and coupling with alkaline 2-naphthol gave a positive azo-dye formation.

Reactions of the unknown Grignard reaction product, (product B).

Oxidation with chromium trioxide.— Product B (810 mg.) was dissolved in glacial acetic acid (12 ml.) and treated with chromium trioxide (250 mg.). The dark red solution was heated under reflux on a steam bath for 45 min. and after cooling to room temperature, was poured into water (50 ml.). The mixture was basified with 4N-sodium hydroxide and extracted with ether (5 x 50 ml.) to give a pale yellow solution. This solution was dried ($MgSO_4$) and evaporated to yield a pleasant-smelling oil (320 mg.) which crystallised on standing to an almost colourless solid. Extraction with 60-80° petrol ether (2 x 20 ml.) gave, after cooling, a pale yellow, crystalline solid (220 mg.). Further recrystallisation from 60-80° petrol ether gave 2-acetyl-3-aminopyridine as pale yellow plates, m.p. 63-64° (Found C,61.3; H,5.6

N,20.4 $C_7H_8N_2O$ requires C,61.7; H,5.9; N,20.6%). The 2,4-dinitrophenylhydrazone hydrochloride, prepared in ethanol/HCl, separated as long, yellow needles from acetic acid, m.p. 276-277° (Found: C,44.1; H,3.9; N,23.7; Cl,10.6. $C_{13}H_{12}N_8O_4HCl$ requires C,44.2; H,3.7; N,23.8; Cl,10.1%).

Attempted oxidation of product B with periodic acid.— A number of periodic oxidations was attempted and a typical experiment is described as follows: product B (0.0025 mole ; 685 mg.) was shaken with 2N-sulphuric acid (2 ml.), water (30 ml.) and sodium periodate (0.005 mole ; 1.07 g.). After the mixture had been shaken for a few minutes, a pale yellow solid separated which was probably the periodate of the base. The mixture was allowed to stand for 4 days and then treated with excess 2N-sodium hydroxide. The buff-coloured precipitate (600 mg.) which separated was identified, after recrystallisation, as the starting material, m.p. and mixed m.p. 156°.

Quantitative determination of the excess periodate in similar experiments showed that no oxidation was occurring.

Attempted oxidation of product B with lead tetraacetate.— Product B (680 mg.) was dissolved in glacial acetic acid (7 ml.) and treated with lead tetraacetate (1.2 g.) added in small portions. The lead tetraacetate dissolved slowly to give a dark brown solution which was allowed to stand at room temperature for 90 min. The solution was then diluted with water (50 ml.) and after neutralisation with solid sodium carbonate, was extracted with chloroform (2 x 50 ml.).

The dried ($MgSO_4$) chloroform extract was evaporated under reduced pressure to yield a brittle dark brown solid (450 mg.). This residue was chromatographed on alumina (40 x 1 cm) and elution commenced with 10:1 v/v light petroleum (b.p. 60-80°) - benzene. When the pale yellow front had reached the bottom of the column the eluant was changed to 3:2 v/v benzene-light petroleum (b.p. 68°) and fractions collected. The yellow band was eluted and evaporation of the first fractions afforded an almost colourless, oily solid (165 mg.) which provided 2-acetyl-3-aminopyridine as pale yellow plates on recrystallisation from petroleum ether (b.p. 60-80°), m.p. 63-64°. A mixed m.p. with the product obtained by chromium trioxide oxidation of B was undepressed.

Further development of the chromatogram with benzene and benzene-methanol mixtures gave only dark, tarry products which were not further examined.

Attempted rearrangement of product B.--

(a) Reaction with iodine in acetic acid.-- Product B (600 mg.) and iodine (500 mg.) were dissolved in glacial acetic acid (25 ml.) and boiled under reflux for 30 min. The solution, cooled to room temperature, was poured into a saturated aqueous solution of sulphur dioxide and the resulting mixture made alkaline by the addition of 4N-sodium hydroxide. The pale yellow, crystalline precipitate (420 mg.) which separated was collected and recrystallised from benzene. It was shown by m.p. and mixed m.p. 156° to be identical with the starting

material.

(b) Reaction with concentrated hydrochloric acid.— Product B (300 mg.) was dissolved in concentrated acid (20 ml.) and the clear solution was boiled under reflux for 1 hr. The solution was diluted to about 50 ml. with water and neutralised by the addition of solid sodium carbonate. The oily precipitate (260 mg.) which separated solidified when the mixture was allowed to stand at 0° for 30 min. The solid was then collected, washed well with water and separated from some insoluble material by dissolving in benzene (5 ml.) and filtering the mixture. The solid obtained by evaporation of the benzene solution (210 mg.) was recrystallised from 50:50 benzene-petroleum ether (60-80°) to yield long, pale yellow needles, m.p. 154°, depressed on admixture with a sample of the pure starting material (Found: C, 66.4; H, 5.7; N, 21.4. $C_{14}H_{18}N_4O$ requires C, 65.6; H, 6.3; N, 21.9%).

2-(3'-amino-2'-pyridyl)-propene.— (a) Crude dimethyl-(3-amino-2-pyridyl)-carbinol (12 g.) was dissolved slowly, with stirring, in sulphuric acid (d. 1.84 ; 100 ml.). The orange-yellow solution was allowed to stand for 4 hr., poured on to an ice-water mixture (200 g.) and neutralised by addition of 6N-sodium hydroxide. The pale yellow oil which separated was extracted with ether (2 x 200 ml.) and the ether solution dried ($MgSO_4$). Removal of the ether, finally under reduced pressure, gave the aminopropene (9.8 g.) as an almost colourless oil. A picrate, prepared in benzene, gave on recrystallisation from ethanol, clusters of small, yellow needles, m.p. 185-186° (Found: C, 45.5; H, 3.2; N, 18.8. $C_{14}H_{13}N_5O_7$ requires C, 46.3; H, 3.6; N, 19.3%).

(b) The carbinol (25 g.) was dissolved in a mixture of sulphuric acid (d. 1.84 : 30 ml.) and water (75 ml.) and the clear solution boiled under reflux for 4 hr. The cooled solution was diluted with water and neutralised with solid sodium carbonate. The oily propene (18 g.) was obtained as described in (a). Distillation under reduced pressure gave 2-(3'-amino-2'-pyridyl)-propene (13.5 g.), b.p. 135-139° (9-10 mm.).

(c) The carbinol (6.0 g.) was heated under reflux for 6 hr. in dry toluene (30 ml.) containing a crystal of iodine. A separator was used to trap out any water produced. No dehydration occurred and the carbinol was recovered unchanged.

Ethyl-3-aminoisonicotinate.— A mixture of 3-aminoisonicotinic acid (80 g.), ethanol (160 ml.) and concentrated sulphuric acid (80 ml.) was heated on a steam bath for 20 hr. and then poured into water (600 ml.). The solution was made alkaline with saturated aqueous sodium carbonate solution and the light brown, oily ester which separated was extracted with ether (3 x 400 ml.). After the ether solution had been dried ($MgSO_4$) and evaporated, the crude, brown oil (77 g.) which resulted was extracted with petroleum ether (b.p. 60-80°; 4 x 100 ml.). The ester crystallised from the petroleum ether as a pale yellow solid. Further recrystallisation from petroleum ether gave ethyl-3-aminoisonicotinate (67 g.) as yellow needles, m.p. 65-65.5° (Found: C, 57.2; H, 6.1; N, 16.8. $C_8H_{10}O_2N_2$ requires C, 57.7; H, 6.1; N, 17.3%).

Dimethyl-(3-amino-4-pyridyl)-methanol.-- To a Grignard reagent, prepared from magnesium (38.4 g.) and methyl iodide (227 g.) in dry ether (1200 ml.), was added over 30 min. a solution of ethyl-3-amino-isonicotinate (66.4 g.) in benzene (1000 ml.). The mixture was refluxed for 4 hr. in an atmosphere of nitrogen, cooled and poured into ice-water (500 g.). The cold mixture was acidified with concentrated hydrochloric acid (200 ml.) and the aqueous layer separated. The organic layer was extracted with 4N-hydrochloric acid (about 100 ml.) and the combined acid solutions neutralised to pH 7.0 with 4N-sodium hydroxide. The resulting mixture was continuously extracted with ether (1000 ml.) for 10 hr. During the extraction a colourless, crystalline product separated from the ether solution. This product (40.5 g.) was collected and had m.p. 155-158°. A further amount of the product (1.2 g.) was obtained on concentrating the mother liquor to about 20 ml. Recrystallisation of the combined solids from benzene gave dimethyl-(3-amino-4-pyridyl)-methanol (37 g.) as large, colourless plates, m.p. 160-161° (Found: C,62.3; H,7.8; N,18.6. $C_8H_{12}N_2O$ requires C,63.1; H,8.0; N,18.4%).

2-(3'-Amino-4'-pyridyl)-propene.-- The foregoing carbinol (42 g.) was dehydrated by method (b), used for the preparation of 2-(3'-amino-2'-pyridyl)-propene. Evaporation of the ether extract gave the propene as a viscous oil (31.8 g.). Attempts to crystallise the oil either by cooling or by extraction with hot ligroin failed. A picrate,

prepared in benzene, crystallised from methanol as small, yellow needles, m.p. 132-133° (Found: C,45.4; H,3.8; N,18.8; $C_{14}H_{18}N_8O_7$ requires C,46.3; H,3.6; N,19.3%).

Ethyl-3-amino-2,6-dimethylisonicotinate.— A mixture of 3-amino-2,6-dimethylisonicotinic acid hydrochloride (15 g.), ethanol (30 ml.) and concentrated sulphuric acid (15 ml.) was heated under reflux on a steam bath for 15 hr., cooled and neutralised with saturated sodium carbonate solution. The yellow oil which was liberated slowly solidified and was filtered and washed well with water to yield the crude ester (9.2 g.), m.p. 41-43°. Recrystallisation from petroleum ether (b.p. 60-80°) gave long, pale yellow needles, m.p. 47-48° (Found: C,62.5; H,7.3; N,14.0. $C_{10}H_{14}N_2O_2$ requires C,61.8; H,7.3; N,14.4%).

Dimethyl-(3-amino-2,6-dimethyl-4-pyridyl)-methanol.— This compound was obtained by the same method as that used for the preparation of dimethyl-(3-amino-4-pyridyl)-methanol. A Grignard reagent, prepared from magnesium (9.6 g.) and methyl iodide (56.8 g.) in dry ether (350 ml.), was reacted with the foregoing ester (19.4 g.) in benzene (300 ml.). The product, obtained as described above, gave on recrystallisation from 1:1 benzene-petroleum ether (b.p. 60-80°), dimethyl-(3-amino-2,6-dimethyl-4-pyridyl)-methanol as colourless prisms, m.p. 113° (Found: C,66.6; H,9.2; N,16.0. $C_{10}H_{16}N_2O$ requires C,66.6; H,8.95; N,15.6%).

2-(3'-Amino-2',6'-dimethyl-4'-pyridyl-)propene.— The foregoing carbinol (2 g.), dissolved in 50% v/v sulphuric acid (30 ml.), was boiled under reflux for 30 min., diluted with water (20 ml.) and cooled. The pale yellow oil, liberated on neutralisation with saturated sodium carbonate solution, was extracted with ether (2 x 25 ml.). Evaporation of the dried ($MgSO_4$) ether solution, finally under reduced pressure, gave the propene as an almost colourless oil (1.6 g.). Benzoylation, using benzoyl chloride in pyridine, gave 2-(3'-benzamido-2',6'-dimethyl-4'-pyridyl)-propene, m.p. 154-155° (Found: C,76.7; H,7.0; N,10.3. $C_{17}H_{18}N_2O$ requires C,76.7; H,6.8; N,10.5%).

Ethyl-3-amino-2-methyl-6-phenylisonicotinate.— This compound was obtained by the same method as that used for the preparation of ethyl-3-amino-2,6-dimethylisonicotinate. The foregoing amino-acid hydrochloride (50 g.) was reacted with ethanol (100 ml.) and concentrated sulphuric acid (50 ml.) and the product, obtained as before, was recrystallised from petroleum ether (b.p. 60-80°) to afford the ester as pale yellow needles, m.p. 90-91° (Found: C,70.1; H,6.5; N,11.0. $C_{15}H_{16}N_2O_2$ requires C,70.3; H,6.3; N,10.9%).

Dimethyl-(3-amino-2-methyl-6-phenyl-4-pyridyl)-methanol.— This compound was prepared by the Grignard reaction described for a number of foregoing carbinols. The ester (5.2 g.) was reacted with a Grignard reagent prepared from magnesium (1.9 g.) and methyl iodide (11.5 g)

in ether (100 ml.) and benzene (100 ml.). The product (2.6 g.) was obtained in the usual manner and recrystallisation from 1:1 benzene-petroleum ether (b.p. 60-80°) gave colourless plates (2.2 g.), m.p.107° (Found: C,74.3; H,7.4; N,11.6. $C_{18}H_{18}N_2O$ requires C,74.4; H,7.5; N,11.6%).

2-(3'-Amino-2'-methyl-6'-phenyl-4'-pyridyl)-propene.— The foregoing carbinol (10 g.), dissolved in 50% v/v sulphuric acid (60 ml.), was boiled under reflux, diluted with water (60 ml.) and cooled. The propene (8.5 g.) was obtained as a pale yellow oil, after neutralisation and extraction with ether. The oil was readily soluble in hot ligroin, from which it separated easily but without crystallisation, even on standing for some days at 0°. Treatment of the oily product with benzoyl chloride in pyridine readily gave the N.N-dibenzoyl compound as small, colourless needles from ethanol, m.p. 224-225° (Found: C,79.9; H,5.9; N,6.9% $C_{29}H_{24}N_2O_2$ requires C,80.5; H,5.6; N,6.5%).

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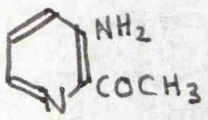
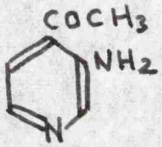
(3) INTERMEDIATES: PREPARATION OF AMINO-KETONES IN THE PYRIDINE SERIES.

This section describes the preparation of the three amino-ketones (I, II and III) which were required for investigations into the Borsche reaction with the intention of preparing 4-hydroxytriazanaphthalenes. Up to the time of writing no amino-ketones in the pyridine series have been recorded in the literature and of those shown below, the acetyl-~~compounds~~ derivatives of 3-aminopyridine proved especially difficult to prepare.



(I)



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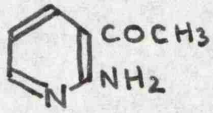
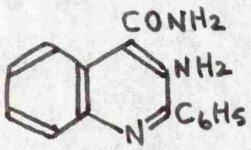


(III)

Of the general methods available for the preparation of methyl ketones from carboxylic acids, it was decided to follow a route to 2-acetyl-3-aminopyridine (I) via a Grignard reaction between the corresponding amide and methyl magnesium iodide. This method has been used successfully by Atkinson and Mattocks[1] for the preparation of 4-acetyl-3-amino-2-phenylquinoline (IV) from the corresponding amide (V).



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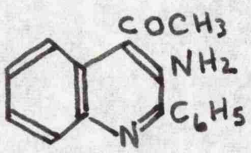
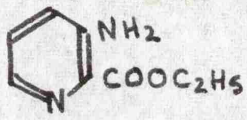


(IV)

3-Aminopicolinamide (VII) was prepared from the ester (VI)

by reaction with aqueous ammonia. The method has been reported by Oakes, Pascoe and Rydon[2] but is unsuitable for the preparation of large quantities of the amide. A number of experiments established the best conditions of the reaction and provided sufficient amide for preliminary experiments with Grignard reagents.



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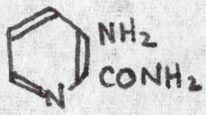
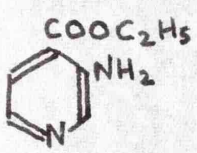
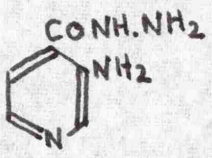


(VII)

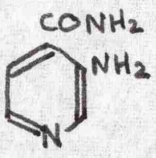
Similar attempts to prepare 3-aminoisonicotinamide (X) from the corresponding ester by reaction with ammonia failed, and alternative methods were sought. The obvious route via the acid chloride is made difficult by the tendency of amino-groups to react with both phosphorus pentachloride and thionyl chloride. An alternative route based on the acid hydrazide (IX) was successfully used. Ethyl-3-aminoisonicotinate (VIII) is readily converted to the corresponding hydrazide (IX) which was split by Raney nickel to give the amide (X) - a method due to Ainsworth[3].



(VIII)



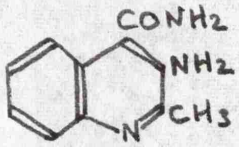
(IX)



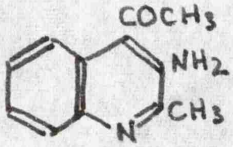
(X)

All attempts to convert these amino-amides into the corresponding acetyl-compounds by reaction with methyl magnesium iodide were

unsuccessful. The experimental conditions were varied: high boiling solvents, such as anisole and tetrahydrofuran were tried, and reactions in a large excess of reagent were attempted but in each case only unchanged amide was obtained. It is worth noting that attempts to convert a related amide (XI) to the ketone (XII) by Archibald[4] also failed.

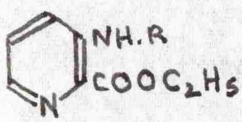


(XI)



(XII)

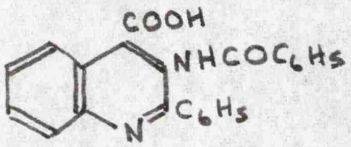
An alternative route to the amino-ketone (I), using Claisen condensations between substituted esters (XIII) and ethyl acetate, was now attempted. It is essential to protect the amino-group before attempting such reactions to prevent a spontaneous cyclisation between the amino-group and the keto-ester group formed during condensation. An attempted reaction between ethyl acetate and the 3-benzamido-compound (XIII; R = C_6H_5CO-), following a procedure used by Winstein,[5] gave a high-melting product from which the required benzamido-ketone (XIV) could not be obtained by the usual methods for decarboxylation. The product was not further examined and a condensation was attempted between the 3-p-toluenesulphonamido-ester (XIII; R = p-$CH_3C_6H_4SO_2$-). and ethyl acetate. In this case, attempts to bring about reaction failed and the ester was recovered unchanged.



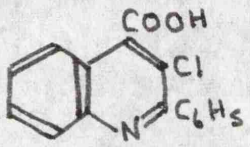
(XIII)

(XIV)

A widely used method for the conversion of carboxylic acids to the corresponding methyl ketones makes use of the reaction between the acid chloride and diethyl malonate[6]. Unfortunately, during the attempted preparation of acid chlorides, using either phosphorus pentachloride or thionyl chloride, the amino-group of an amino-acid frequently enters into the reaction, (cf. Anschutz and Boedeker[7]). Protection by acetylation or benzoylation is often of little use. For example, Atkinson and Mattocks[1] have shown that attempts to prepare the acid chloride of the acid (XV) by reaction with thionyl chloride resulted in the formation of the chloro-compound (XVI).

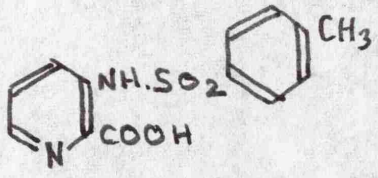


(XV)



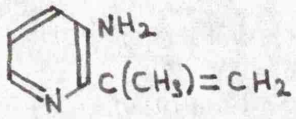
(XVI)

An alternative method of protection would use the 3-phthalimido-derivative but this was rejected, since the protecting group is particularly difficult to hydrolyse. It was decided to follow the common procedure of protection by reaction with p-toluenesulphonyl chloride. Reaction of the 3-p-toluenesulphonamido-acid (XVII) with thionyl chloride readily gave the acid chloride under mild conditions but the product proved to be very unstable and all attempts to condense it with diethyl malonate failed.

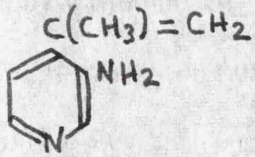


(XVII)

At this stage the two amino-propenes (XVIII and XIX), described in the last section, became available in fair overall yield, and the synthesis of the two ketones (I and II) by ozonolysis of these propenes was considered. Cook and Whitmore[8] describe the preparation of a number of ketones by the splitting of ozonides, and Kaslow and Dale Stayner[9] have used the method for the preparation of pyridine- and quinoline-carboxylic acids from the corresponding styryl-derivatives.

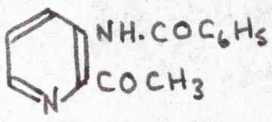


(XVIII)

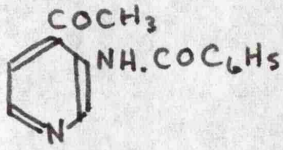


(XIX)

Preliminary experiments showed that ozonolysis of the amino-propenes resulted in extensive oxidation of the amino-group with the formation of dark, tarry products. For this reason both the amino-propenes were converted to the corresponding benzamido-propenes by reaction of benzoyl chloride in pyridine. Ozonolysis of the benzamido-propenes by treatment with 5% ozonised oxygen in acetic acid solution, followed by splitting of the ozonides with 30% hydrogen peroxide (method due to Kaslow and Dale Stayner[9]), gave the benzamido-ketones (XX and XXI) in good yield.



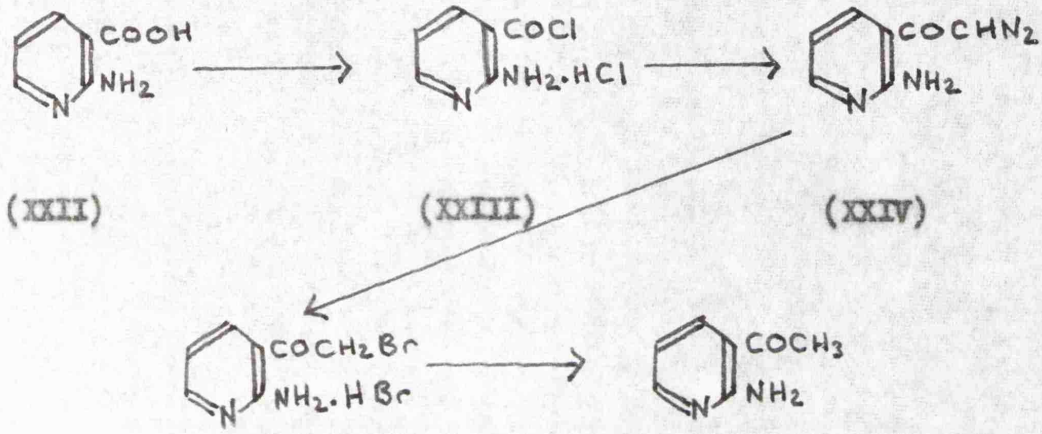
(XX)



(XXI)

Subsequent hydrolysis of the benzamido-ketones with concentrated hydrochloric acid gave the required amino-ketones (I and II).

The amino-ketone (III) proved less difficult to obtain. Miescher and Kagi[10] had already reported the preparation of 2-amino-3-diazoacetylpyridine (XXIV) and its convertion to the bromo-ketone (XXV), and their work has been repeated to give a good overall yield of the bromo-ketone.



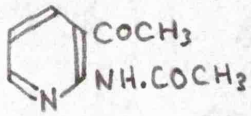
(XXII) (XXIII) (XXIV)

(XXV) (III)

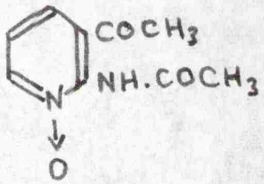
Treatment of 2-aminonicotinic acid (XXII) with phosphorus pentachloride in acetyl chloride readily gave the acid chloride hydrochloride (XXIII) which on treatment with diazomethane in dichloromethane gave the diazoketone (XXIV), using a method due to Lutz[11]. Reaction of the diazoketone with hydrobromic acid gave the bromo-ketone (XXV) and this, on reduction with stannous chloride, afforded the required amino-ketone (III).

For experiments in the Borsche reaction it was decided to convert this amino-ketone into its N-oxide (XXVIII). N-Oxides of both amino-

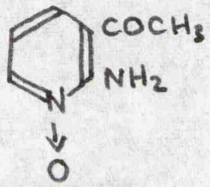
pyridines and acetylpyridines are well known: 3-acetylpyridine-N-oxide has been prepared by Saburo and Kanno[12] and 2-aminopyridine-N-oxide has been described by Katritsky[13] and by Adams and Miyano[14]. In view of the recommendation of Katritsky[13] that the amino-group should be protected during N-oxidation, it was decided to prepare the acetamido-derivative (XXVI) before reaction with 30% hydrogen peroxide. Although it was anticipated that a final stage involving hydrolysis of the intermediate acetamido-ketone-N-oxide would be necessary, isolation of the product of N-oxidation showed that the amino-ketone -N-oxide (XXVIII) itself had been obtained.



(XXVI)



(XXVII)



(XXVIII)

EXPERIMENTAL

3-Aminopicolinamide.-- (a) Ethyl-3-aminopicolinate (500 mg.) was shaken with concentrated ammonia (d. 0.88 ; 20 ml.) for 36 hr., the mixture was diluted with water (30 ml.) and extracted with chloroform (3 x 20 ml.). After removal of the chloroform from the dried ($MgSO_4$) combined extract, the residue (380 mg.) was recrystallised from benzene to give the amide, m.p. 182-185° (Oakes, Pascoe and Rydon[2] give 184°). (b) The ester (500 mg.) was dissolved in ethanol (10 ml.) and concentrated ammonia (10 ml.), and a stream of ammonia was passed through the solution at about 30° for 6 hr. The solution was evaporated to dryness and the residue extracted with hot benzene (3 x 20 ml.) to afford, on further recrystallisation, the unchanged ester, m.p. and mixed m.p. with a pure sample 130-131°.

Attempted Grignard reactions between 3-aminopicolinamide and methyl magnesium iodide.-- (a) Reaction in ether-benzene.-- 3-Amino-picolinamide (1.5 g.), suspended in benzene (150 ml.), was added over 15 min. to a Grignard reagent prepared from magnesium (1.2 g.) and methyl iodide (7.2 g.) in ether (150 ml.) and the mixture was boiled under reflux in an atmosphere of nitrogen for 15 hr. The reaction mixture was poured on to ice-water (100 g.) and the aqueous layer separated. The organic layer was further extracted with 5N-hydrochloric acid (2 x 50 ml.). The combined aqueous extract was neutralised with solid sodium bicarbonate and the mixture extracted with ether (4 x 100 ml.). Evaporation of the dried ($MgSO_4$) ether

solution gave an almost colourless residue (1.2 g.), identified after recrystallisation as the unchanged amide, m.p. 179-181° (a mixed m.p. with the pure starting material was undepressed).

(b) Reaction in anisole.— The amide (1.5 g.), suspended in dry anisole (75 ml.), was added over 15 min. to a Grignard reagent, prepared from magnesium (1.5 g.) and methyl iodide (8.6 g.) in ether (50 ml.). The ether was distilled from the mixture until the reaction temperature rose to 150°. Reflux was continued for 24 hr., the cooled mixture poured on to ice-water, treated with concentrated hydrochloric acid (20 ml.) and stirred for 1 hr. The aqueous layer was separated, basified and extracted with ether, to yield the unchanged amide on recrystallisation.

(c) Attempted reaction with an excess of Grignard reagent in tetrahydrofuran.— A suspension of the powdered amide (1.5 g.; 0.01 mole) in dry tetrahydrofuran (150 ml.) was added to a Grignard reagent prepared from magnesium (2.4 g. ; 0.1 mole) and methyl iodide (14.2 g. ; 0.1 mole) in dry ether (100 ml.). The ether was removed from the reaction mixture by distillation and reflux continued for 36 hr. after which time the mixture was poured on to ice-water. After acidification and ether extraction, the only compound isolated was the unchanged amide (1.2 g.).

Ethyl-3-benzamidopicolinate.— A solution of ethyl-3-aminopicolinate (2 g.) in pyridine (10 ml.) was treated with benzoyl chloride (1.8 ml.)

and the mixture heated on a steam bath for 15 min. The solution was poured into water and the buff precipitate (2.1 g.) collected and recrystallised from the 50% aqueous ethanol to yield the benzamido-ester as colourless plates, m.p. 71-72° (Found: C,66.3; H,5.3; N,10.7. $C_{14}H_{14}N_2O_3$ requires C,66.6; H,5.2; N,10.4%).

Ethyl-3-(p-toluenesulphonamido)-picolinate.— The ester (1.0 g.) was suspended in 10% sodium carbonate solution (50 ml.) and p-toluene-sulphonyl chloride (1.3 g.) was added to the suspension at 75° and the mixture was stirred for 1hr. The reaction mixture was poured into 2N-sulphuric acid (30 ml.) and the cream-white precipitate was collected and recrystallised from methanol to yield the p-toluene-sulphonamido-ester, m.p. 182-183° (Found: C,51.9; H,4.1; N,9.1. $C_{15}H_{16}N_2O_4S$ requires C,52.3; H,4.4; N,8.75%).

Attempted Claisen condensations with ethyl acetate.— (a) Sodium (0.75 g.) was dissolved in ethanol (2.0 ml.) and dry toluene (10 ml.) and a suspension of ethyl-3-benzamidopicolinate (2.5 g.) in toluene (15 ml.) and ethyl acetate (3 ml.) was added, and the mixture boiled gently under reflux for 6 hr. The dark brown solution was treated with water (50 ml.) and the mixture made just acid with 2N-hydrochloric acid. The pale yellow precipitate (1.9 g.) was collected and treated with 20% v/v sulphuric acid under reflux for 2 hr. The clear solution was cooled and neutralised with sodium bicarbonate, yielding a yellow solid (1.6 g.) on filtration. Recrystallisation was difficult but a

product (1.2 g.), m.p. 309-312° (with darkening) was obtained by crystallisation from a large volume of ethanol. Attempts to diazotise and couple this product with alkaline 2-naphthol were negative and the product was not further investigated.

(b) A mixture of ethyl-3-(p-toluenesulphonamido)-picolinate (2.0 g.), sodium ethoxide (prepared from sodium (0.75 g.) and ethanol (1 ml.)), ethyl acetate (2 ml.) and benzene (5 ml.) was boiled under reflux for 48 hr. The mixture was poured on to ice-water and extracted with 6N-hydrochloric acid (20 ml.). The product, obtained by basification of the aqueous extract, was identical with the starting material, m.p. and mixed m.p. 181-182°.

3-(p-Toluenesulphonamido)-picolinic acid.— 3-Aminopicolinic acid (7.0 g.), dissolved in 20% sodium carbonate solution (80 ml.), was heated to 60° and treated with p-toluenesulphonyl chloride (12.0 g.) added in four amounts over 20 min. The mixture was stirred during the addition and after 30 min. the solution was cooled and poured into excess 4N-hydrochloric acid (100 ml.). The cream-white precipitate was collected, washed well with water and recrystallised from ethanol to give the acid (11 g.), m.p. 185-186° (Found: C,52.9; H,3.9; N,10.4. $C_{13}H_{12}N_2O_4S$ requires C,53.3; H,4.1; N,9.9%).

Attempts to react 3-(p-toluenesulphonamido)-picolinic acid chloride with malonic ester.— 3-(p-toluenesulphonamido)-picolinic acid (1.5 g.) was heated under reflux with thionyl chloride (2 ml.) for 30 min. The

excess of reagent was removed by distillation under reduced pressure and traces of thionyl chloride were removed by further distillation with benzene (15 ml.). The crude acid chloride (1.6 g.) was obtained as a granular, yellow-brown solid which darkened and decomposed readily when kept or when heated. Treatment of the acid chloride (200 mg.) with aniline (200 mg.) in ether (100 ml.) gave the anilide, m.p. 212° (Found: C,61.5; H,4.2; N,10.8. $C_{12}H_{17}N_3O_3S$ requires C,60.8; H,4.2; N,10.8%).

A suspension of the acid chloride (1 g.) in benzene (20 ml.) was added to a hot, stirred suspension of sodiomalonic ester, prepared from diethyl malonate (1.0 ml.) and powdered sodium (0.2 g.) in benzene (10 ml.); the mixture was stirred for 18 hr. at room temperature and then boiled under reflux for 6 hr. The mixture (containing much dark brown, insoluble material) was stirred at 60° for 15 min. with 4N-hydrochloric acid (30 ml.). The aqueous layer was separated, neutralised with sodium carbonate and extracted with benzene (3 x 20 ml.). Evaporation of the dark red benzene solution gave a red, oily solid (220 mg.). Attempts to convert this condensation product to the ketone by reflux in 30% v/v sulphuric acid (20 ml.) produced only tarry material (150 mg.) on ether extraction, from which no useful crystalline material could be obtained either by solvent extraction or chromatography on alumina.

2-(3'-Benzamido-2'-pyridyl)-propene.— 2-(3'-amino-2'-pyridyl)-propene (4 g.), dissolved in pyridine (20 ml.), was treated dropwise with

benzoyl chloride (4.5 ml.) over 15 min. The mixture was heated on a steam bath under reflux for 30 min. and poured into water (100 ml.). The pyridine was removed by partial evaporation of the solution under reduced pressure and the oily benzamido-propene (7.7 g.) obtained by ether extraction. The product was difficult to crystallise but several extractions from petroleum ether (b.p. 60-80°) followed by storage at 0° for some days gave 2-(3'-benzamido-2'-pyridyl)-propene as large, colourless polyhedra, m.p. 85-86° (Found: C,75.7; H,5.95; N,11.5. $C_{15}H_{14}N_2O$ requires C,75.6; H,5.95; N,11.8%).

2-Acetyl-3-benzamidopyridine.— The foregoing oily benzamido-propene (7.0 g.) was dissolved in glacial acetic acid (60 ml.) and treated with 5% ozonised oxygen at about 7 litres/hr. for 6 hr. at about 20°. During the reaction the solution changed from pale yellow to colourless. Hydrogen peroxide (3% ; 20 ml.) was added and the solution was heated on a steam bath for 15 min.; the solution was then cooled to 0° and treated with 4N-sodium hydroxide until precipitation was complete. The oily precipitate (5.6 g.) was collected, washed well with water and recrystallised several times from 50% aqueous ethanol to yield 2-acetyl-3-benzamidopyridine (4.5 g.), as long, colourless needles, m.p. 90° (Found: C,70.1; H,4.8; N,11.7. $C_{14}H_{12}N_2O_2$ requires C,70.0; H,5.0; N,11.7%).

2-Acetyl-3-aminopyridine.— (a) 2-(3'-amino-2'-pyridyl)-propene (1.0 g.), dissolved in acetic acid, was treated with ozonised oxygen

for 3 hr. During this time the solution slowly darkened to an orange-brown. Treatment with hydrogen peroxide (3% ; 10 ml.) at 70° for 1 hr., followed by basification and extraction with ether (4 x 50 ml.) gave, on evaporation of the dried ether solution, a dark brown, tarry product. Chromatography on alumina provided no useful product.

(b) 2-Acetyl-3-benzamidopyridine (5 g.) in concentrated hydrochloric acid (40 ml.) was boiled under reflux for 2 hr. During the reaction benzoic acid collected in the condenser. The solution was cooled, filtered to remove benzoic acid and neutralised with 4N-ammonium hydroxide. The oily emulsion was extracted with ether (3 x 100 ml.) to afford, on evaporation of the dried ($MgSO_4$) ether solution, a pale yellow oil (2.2 g.). Extraction of the oil with hot petroleum ether (b.p. 60-80°) gave the amino-ketone (1.7 g.), m.p. 55-60°. Further recrystallisation from petroleum ether gave 2-acetyl-3-aminopyridine as pale yellow plates, m.p. 63-64°. A mixed m.p. with a pure sample of 2-acetyl-3-aminopyridine, prepared by oxidation of the supposed pinacol described in Section (2), was undepressed.

3-Aminoisonicotinic acid hydrazide.— Ethyl-3-aminoisonicotinate (6.4 g.) and hydrazine hydrate (99-100% ; 4.0 ml.) were heated together on a steam bath for 1 hr. and the crystalline product (4.8 g.) which separated, was collected and recrystallised from the minimum amount of ethanol to give the hydrazide, m.p. 184-186° (Oakes, Pascoe and Rydon[2] give m.p. 186-187°).

3-Aminoisonicotinamide.— (a) Ammonia gas was passed through a solution of ethyl-3-aminoisonicotinate (500 mg.) in alcohol (15 ml.) for 4 hr. and the solution was allowed to stand over-night. The solvent was removed to yield the unchanged ester, m.p. 54-60°. Recrystallisation gave the pure ester (mixed m.p. undepressed).

(b) 3-Aminoisonicotinic acid hydrazide (100 mg.), suspended in water (2 ml.) and concentrated ammonia (d. 0.88 ; 0.5 ml.), was added to an ice-cold solution of sodium metaperiodate (150 mg.) in N-ammonium hydroxide (4 ml.) and the mixture was shaken for 40 min. The solution was treated with barium acetate (250 mg. in 2 ml. water) and filtered. The filtrate was adjusted to pH 7.0 and extracted with chloroform (2 x 25 ml.). Evaporation of the dried chloroform extract gave only a small amount (15 mg.) of a non-crystallisable oil.

(c) 3-Aminoisonicotinic acid hydrazide (1.5 g.) in 95% v/v aqueous ethanol (100 ml.), was treated with Raney nickel (12 g.) in ethanol. The mixture was refluxed for 3 hr. and filtered while hot. The blue, fluorescent filtrate was evaporated and the solid residue (1.2 g.) recrystallised from water to yield the amide as colourless needles, m.p. 159-160° (Found: C,52.7; H,5.3; N,30.6. $C_6H_7N_3O$ requires C,52.5; H,5.1; N,30.6%).

Attempted Grignard reaction between 3-aminoisonicotinamide and methyl magnesium iodide. Reaction in anisole.— The method used was identical with that attempted with 3-aminopicolinamide. The amide

(1.5 g.) in anisole (75 ml.) was boiled under reflux with a Grignard reagent prepared from magnesium (1.5 g.) and methyl iodide (8.6 g.). Addition of water and extraction with ether gave only unchanged 3-amino-isonicotinamide, m.p. and mixed m.p. with pure starting material 158-160°.

2-(3'-Benzamido-4'-pyridyl)-propene.— 2-(3'-amino-4'-pyridyl)-propene (10 g.) in pyridine (30 ml.) was treated with benzoyl chloride (10 ml.) and the product was obtained as described for the 2-pyridyl compound. The oily benzamido-propene (14.5 g.) proved very difficult to crystallise but extraction with light petroleum ether (b.p. 40-60°) gave, on long standing, a crystalline solid, m.p. 104° (Found: C,75.4; H,5.6; $C_{15}H_{14}N_2O$ requires C,75.6; H,5.95%).

4-Acetyl-3-benzamidopyridine.— The foregoing oily benzamido-propene (24 g.) in glacial acetic acid (200 ml.) was treated with ozonised oxygen for 12 hr. and the product was isolated as described above for the 2-acetyl compound. Recrystallisation from 50% aqueous alcohol gave 4-acetyl-3-benzamidopyridine (16 g.), m.p. 121-122° (Found: C,69.2; H,4.9; N,11.4. $C_{14}H_{12}N_2O_2$ requires C,69.9; H,5.0; N,11.6%).

4-Acetyl-3-aminopyridine.— The foregoing benzamido-ketone was hydrolysed as described for the 2-acetyl compound. The ketone (2 g.) was boiled under reflux for 2 hr. in concentrated hydrochloric acid (25 ml.). Ether extraction gave a yellow oil (1.1 g.) which crystallised on standing and which, on recrystallisation from petroleum ether (b.p. 80-100°)

gave 4-acetyl-3-aminopyridine (0.8 g.) as pale yellow plates, m.p.87° (Found: C,62.2; H,6.1; N,20.5. $C_7H_8N_2O$ requires C,61.7; H,5.9; N,20.6%).

A 2,4-dinitrophenylhydrazone hydrochloride, prepared in alcohol separated from acetic acid as red needles, m.p. 287-288° (Found: C,44.5; H,3.9; N,23.6; Cl,9.8. $C_{13}H_{12}N_8O_4.HCl$ requires C,44.2; H,3.7; N,23.8; Cl,10.1%).

2-Aminonicotinic acid chloride hydrochloride.— 2-Aminonicotinic acid (12.5 g.) was added in about 1 g. quantities to a stirred suspension of well-powdered phosphorus pentachloride (25 g.) in acetyl chloride (25 ml.). A vigorous reaction occurred and cooling was necessary to maintain the temperature at 20-25°. Towards the end of the addition a yellow solid separated and the mixture was allowed to stand for a further 30 min. after addition was complete. The solid product (11.5 g.) was collected and washed well with dichloromethane to afford the acid chloride hydrochloride, m.p. 185-190° (with decomposition), (Miescher and Kagi[10] give m.p. 188-190°).

2-Amino-3-diazoacetylpyridine.— A solution of diazomethane in dichloromethane was prepared as follows: moist nitrosomethylurea (92 g.) was added in small portions to a well-stirred mixture of dichloromethane (1400 ml.) and 50% w/v potassium hydroxide (200 g.). When addition was complete, the mixture was treated with ice-water (400 ml.) and the pale yellow diazomethane solution syphoned off and dried (NaOH pellets). The solution was then cooled to 0° and

treated with the foregoing acid chloride (28 g.), added in small quantities over about 30 min. The mixture was allowed to stand over night, filtered to remove a little insoluble material and evaporated under reduced pressure. The orange-brown residue (16 g.), which was very soluble in dichloromethane, was treated with methanol (15 ml.) and filtered to yield the 2-amino-3-diazoacetylpyridine (13.5 g.) as a bright yellow, microcrystalline solid, m.p. 147-151° (with decomp.) (Miescher and Kagi[10] give m.p. 163°). The compound was used without further purification.

2-Amino-3-bromoacetylpyridine hydrobromide.— The foregoing diazoketone (12.0 g.) was added in small quantities over 15 min. to stirred hydrobromic acid, prepared from hydrobromic acid (d. 1.5 ; 30 ml.) and water (30 ml.). Vigorous evolution of nitrogen occurred and towards the end of the addition a bulky precipitate separated. The mixture was finally heated on a water bath, cooled and filtered after about 5 min., to afford the crude bromoacetyl-hydrobromide (4.8 g.), m.p. 215-217°. A small amount of the hydrobromide was dissolved in water (0.1 g. in 10 ml.) at 35° and treated with solid sodium acetate. The yellow precipate (350 mg.) of the bromoketone was filtered off and after drying, had m.p. 105-107° (Miescher and Kagi[10] give m.p. 113°).

2-Amino-3-acetylpyridine. — The foregoing bromoacetyl hydrobromide (15 g.) was suspended in 4N-hydrochloric acid (190 ml.) and treated with stannous chloride dihydrate (27 g.). The mixture was heated on a steam bath under reflux for 3 hr., cooled and made strongly

alkaline with sodium hydroxide (15 g.) in water (250 ml.). Extraction with ether (4 x 200 ml.), followed by concentration of the combined, dried (Na_2SO_4) ether extracts to about 15 ml., gave the ketone (6.2 g.) as colourless needles, m.p. 139° (Found: C,62.0; H,5.9; N,20.5. $C_7H_8N_2O$ requires C,61.7; H,5.9; N,20.6%).

A 2,4-dinitrophenylhydrazone hydrochloride, prepared in ethanol/HCl, separated as orange-red needles , m.p. 290-291°, from acetic acid. (Found: C,44.1; H,3.9; N,25.7; Cl,10.6. $C_{13}H_{12}N_6O_4.HCl$ requires C,44.2; H,3.7; N,23.8; Cl,10.1%).

2-Acetamido-3-acetylpyridine.— The amino-ketone (2 g.) was boiled under reflux with acetic anhydride (3 ml.) for 30 min., cooled, and the water and acetic acid removed under reduced pressure, after the reaction mixture had been treated with water (10 ml.). The residue, on recrystallisation from 1:1 benzene-petroleum ether (b.p. 60-80°), gave the acetamido-ketone (2.0 g.) as colourless plates, m.p. 114° (Found: C,59.8; H,5.4; N,16.2. $C_9H_{10}N_2O_2$ requires C,60.6; H,5.7; N,15.7%).

3-Acetyl-2-aminopyridine-N-oxide.— The foregoing acetamido-ketone (890 mg.; 0.005 mole), dissolved in glacial acetic acid (5 ml.) was treated with hydrogen peroxide (30% ; 1.4 g.) and the mixture was heated under reflux at 65-70° (bath) for 8 hr. At temperatures above 70° the yield of N-oxide decreased substantially. The orange-yellow solution was treated with water (10 ml.) and evaporated under reduced pressure to give an orange oil which partially crystallised on cooling.

The oil was dissolved in water (30 ml.), treated with sodium carbonate (1 g.) and the solution was continuously extracted with chloroform (50 ml.) to afford a yellow chloroform solution which was dried and evaporated to give a pale yellow, crystalline solid (510 mg.), m.p. 155-160°. Several recrystallisations from benzene gave the N-oxide (370 mg.) as almost colourless platelets, m.p. 184-185° (Found: C,55.7; H,5.2; N,18.2. $C_7H_8N_2O_2$ requires C,55.2; H,5.3; N,18.4%).

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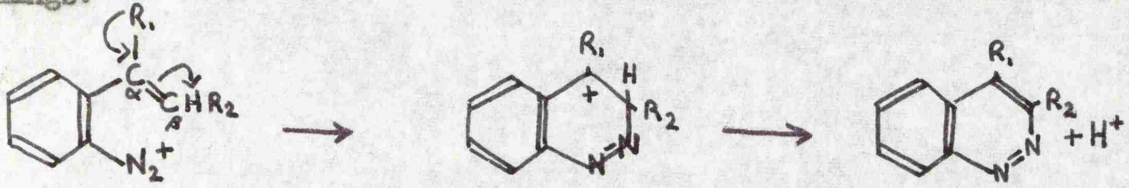
(4) THE WIDMAN-STOERMER REACTION: The reaction between o-amino-pyridyl-propenes and nitrous acid.

The effect of substituents R_1 and R_2 on the cyclisation of diazotised o-aminophenylethylenes (I) has been widely studied by Stoermer and Fincke[1] and by Simpson and Schofield and their co-workers[2,3,4,5] and the general ionic mechanism given below is in accord with their findings:



(I) (II) (III)

The attack by the diazonium cation at C_β requires a polarisation of the ethylenic linkage, as indicated in (I), and the essential requirement for this to occur is that R_1 must be an electron-donating group. Thus, it is found that the reaction proceeds successfully when R_1 is methyl or aryl but fails completely when R_1 is hydrogen or carboxyl. If R_2 has sufficient electron-withdrawing power at C_β, then according to this mechanism, the reaction should be retarded and, in fact, this is so: when R_2 is phenyl or a heterocyclic nucleus, such as 2-pyridyl, the reaction fails. However, when R_1 is aryl and particularly p-methoxyphenyl, cinnoline formation is rendered rapid and the yield is usually excellent, even when R_2 is electron-withdrawing, since the supply of electrons is sufficiently great to override any opposing effect at C_β.

Reference to Table I, which summarises the effect of different

substituents R_1 and R_2, well illustrates the effect of heterocyclic nuclei on the reaction.

Table I: the effect of substituents on the Widman-Stoermer reaction.

R_1	R_2	% Yield	Ref.
H	H	No cinnoline formed.	3
CH_3	H	89 46	6 7
C_6H_5	H	Almost quantitative.	1
2-Pyridyl	H	16	4
3-Pyridyl	H	46	5
4-Pyridyl	H	20	5
2-Quinolyl	H	No cinnoline formed.	8
2-Pyridyl	CH_3	43	5
3-Pyridyl	CH_3	77	5
2-Pyridyl	C_6H_5	Picrate only. Low yield.	4
2-Quinolyl	C_6H_5	Tarry products only.	4
H	C_6H_5	No cinnoline formed.	3
C_6H_5	C_6H_5	Almost quantitative.	3
C_6H_5	2-Pyridyl	34	5
H	2-Pyridyl	No cinnoline formed.	8
H	2-Quinolyl	No cinnoline formed.	8
p-Methoxyphenyl	2-Pyridyl	84	5
p-Methoxyphenyl	2-Quinolyl	48	5

The effect of heterocyclic nuclei on the closely related v. Richter synthesis is illustrated by a number of examples given in Table II.

Table II

R_1	R_2	% Yield	Ref.
H	H	35	9
C_6H_5	H	59	10
2-Pyridyl	H	Phenolic material only.	10
2-Pyridyl	Cl	Phenolic material only.	10

Cyclisation in the Widman-Stoermer and v. Richter reactions is always in competition with phenol formation and with the Pschorr reaction in cases where R_1 is aryl. In general, it has been found more favourable to carry out cyclisation at low temperatures and in weakly acid media. The yields quoted in Table I are optimum yields for cinnoline formation and it has been found that attempts to cyclise diazotised o-aminoethylenes, particularly those in which R_1 and R_2 are basic groups, in a strong acid solution, result in low yields. Nunn and Schofield[8] showed, for example, that whereas 4-(3'-pyridyl)-cinnoline could be obtained in 43% yield by cyclisation of the diazotised amine (I; R = 3-pyridyl; R_2 = H) at low acid concentration, only tar formation occurred in 2N-hydrochloric acid. These authors have also noted the value of working in sulphuric rather than hydrochloric acid.

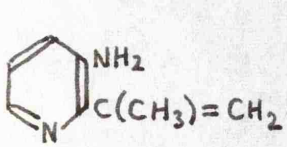
This dependency of cinnoline yield on pH. can be readily explained.

A pyridyl or quinolyl group at either C_α or C_β becomes increasingly electron-withdrawing in acid solution, due to protonation, and unless the supply of electrons at C_β can be increased by the presence of an electron-donating group such as p-methoxyphenyl at C_α, cinnoline formation will be hindered.

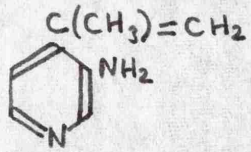
The value of working in weakly acid media seems to apply generally when R_1 is not strongly electron-releasing. Jacobs[6] has reported an excellent yield of 4-methylcinnoline by cyclisation of diazotised 2-(o-aminophenyl)-propene under these conditions.

Another important observation to be made from the results in Table I is the effect of the position of attachment of the heterocyclic nucleus on the yield of cinnoline. It can be seen that 2- and 4-pyridyl have a more powerful retarding effect on the reaction than the 3-pyridyl group. This is an expected result, since protonation makes itself felt more at the 2- and 4- positions. A ~~tautomeric~~ transition of charge to the 3- position is not possible.

The experimental work described in this section is concerned with the diazotisation of the four o-aminopyridylpropenes (IV, V, VI and VII) which has not been described previously.



(IV)



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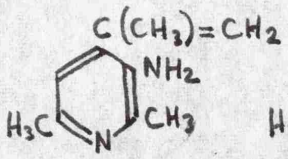

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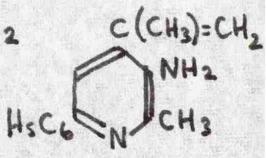


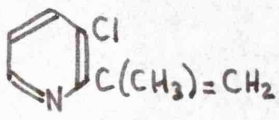
(VII)

It would have been useful to have examined the reaction with the

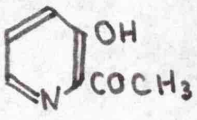
propenyl-group in the 3-position but diazotisation of 2- and 4-amino-groups in pyridine is effected only under special conditions.

A number of experiments was carried out with 2-(3'-amino-2'-pyridyl)-propene (IV) with very limited success. Attempted cyclisation in concentrated hydrochloric acid at 60° provided a non-crystallisable, neutral oil on extraction with ether. The compound contained chlorine and analysis of a picrate prepared from the oil showed that it was probably the chloro-compound (VIII) formed by replacement of the diazonium group by chlorine.

Attempted cyclisation in N-hydrochloric acid by long standing at room temperature was accompanied by much loss of nitrogen and extraction of the basified solution with ether provided none of the required triazanaphthalene. The phenolic fraction, obtained by ether extraction of the neutral reaction mixture, afforded two products on vacuum sublimation: a small amount of a compound which sublimed readily and whose analysis indicated the hydroxy-ketone (IX) and a product whose analysis indicated a hydrate of the hydroxy-propene (X).* The former was presumably obtained from the propene (IV) during the reaction by oxidation with excess nitrous acid. These products were not further examined.



(VIII)



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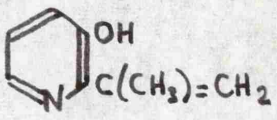
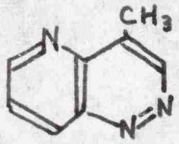


(X)

* or the hydroxy-carbinol formed by hydration of the double bond

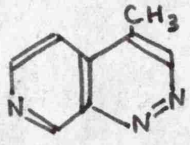
Diazotisation in dilute sulphuric acid, followed by dilution to low acidity and storage in the dark for several days, was accompanied by the formation of much dark red, insoluble material which was probably the product of diazo coupling. Continuous extraction of the mixture with ether gave a small amount of dark red oil from which no product could be obtained by crystallisation. Treatment with picric acid in benzene, however, gave the picrate of 4-methyl-1,2,5-triazanaphthalene (XI) in very poor yield.



(XI)

A further experiment in which cyclisation was attempted in sodium acetate solution resulted in the formation of much dark red azo-dye. This product could be extracted with chloroform but afforded no triazanaphthalene by chromatography on alumina.

The diazotisation of 2-(3'-amino-4'-pyridyl)-propene was then examined and 4-methyl-1,2,7-triazanaphthalene (XII) was successfully isolated, though never in better than 25% yield.



(XII)

A number of experiments was carried out to determine the best conditions for cyclisation and the results are summarised in Table III. The product, isolated by continuous ether extraction, was usually contaminated with much dark red impurity and recrystallisation was difficult. Purification was most easily effected by chromatography on alumina.

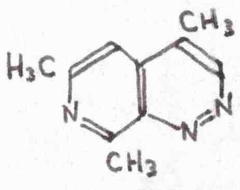
Table III Cyclisation of diazotised 2-(3'-amino-4'-pyridyl)-propene.

Reaction conditions	Wt. of product from 1 g. of amino-propene
(a) Conc. hydrochloric acid at 60°.	Tarry material only.
(b) 2N-sulphuric acid at room temp. for 5 days.	Base isolated as picrate (65 mg.) only.
(c) 0.1N-sulphuric acid at room temp. for 5 days.	60 mg.
(d) Very dilute sulphuric acid (less than 0.001N) at room temp. for 10 days.	230 mg.
(e) Sodium acetate solution at room temp. for 5 days.	65 mg. Much dark red material.
(f) 0.1N-Sodium hydroxide at room temp. for 5 days.	160 mg.

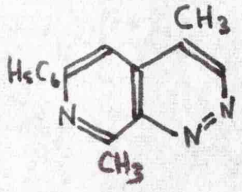
In the case of both the 2-pyridyl- and 4-pyridyl-propenes attempts to cyclise in strong acid solution failed or gave very low yields of the triazanaphthalene, presumably because of the powerful retarding effect on the reaction of the protonated ring nitrogen atom. Attempts to improve the yields by reaction at room temperature in very dilute acid or alkaline media were only partially successful and in the case of the 2-pyridyl-propene, the free base was never isolated. The best yields were obtained when method (d) - essentially that used by Jacobs[6] - was adopted, but a number of preparations failed to give a yield of 4-methyl-1,2,7-triazanaphthalene better than 25%. Although attempts to cyclise in sodium acetate (e) and in alkaline solution (f) gave the triazanaphthalene, yields were not improved.

The fact that the formation of triazanaphthalene is almost completely inhibited in the case of the 2-pyridyl-propene may be explained by the more powerful influence of the nuclear nitrogen atom when in the 2- position, and this is confirmed to some extent by the observations of Nunn and Schofield[5], already noted in Table I.

Similar difficulties were encountered in the attempted cyclisation of the two propenes (VI and VII). The diazotisation of the amino-propene (VI) gave the required 4,6,8-trimethyl-1,2,7-triazanaphthalene (XIII), although the best yield obtained was only 15%, using the method of Jacobs[6]. Cyclisation in alkaline solution also gave the base but in an even lower yield. In both cases it was again necessary to separate the product from much impurity by chromatography on alumina. All attempts to isolate 4,8-dimethyl-6-phenyl-1,2,7-triazanaphthalene (XIV) from the diazotised amino-propene (VII) failed. The crude, tarry material obtained by attempted cyclisation in very dilute sulphuric acid, however, gave a small amount of the picrate on treatment with picric acid in benzene. The amount of picrate obtained did not permit attempts to isolate the free base.



(XIII)



(XIV)

EXPERIMENTAL

Reaction of 2-(3'-amino-2'-pyridyl)-propene with nitrous acid.

(a) Reaction in concentrated hydrochloric acid: the amino-propene (1 g.) was dissolved in concentrated hydrochloric acid (10 ml.), cooled to 0° and treated at 0-5° with solid sodium nitrite (420 mg.). The yellow-orange solution gave a positive coupling reaction with alkaline 2-naphthol. After having stood for 10 min., the solution was warmed slowly to 60-65° on a water bath and retained at this temperature for about 1 hr. (until coupling had ceased). During the reaction much effervescence - probably nitrogen - occurred. The solution was cooled, diluted with water (20 ml.) and made alkaline with 4N-sodium hydroxide solution. The brown solution was continuously extracted with ether (200 ml.) for 4 hr. and the dried ($MgSO_4$) ether solution evaporated to give a pale yellow oil (100 mg.) which did not crystallise on standing overnight at 0°. The oil could not be crystallised by cooling a hot petroleum ether extract, but a picrate was prepared in ethanol, which separated from benzene as bright yellow needles, m.p. 145°. The substance was probably 2-(3'-chloro-2'-pyridyl)-propene picrate (Found: C,43.4; H,3.1; N,14.6; Cl,8.6. $C_{14}H_{11}N_4O_7Cl$ requires C,43.9; H,3.0; N,14.6; Cl,9.3%).

(b) Reaction in N-hydrochloric acid: the amino-propene (1 g.) was dissolved in N-hydrochloric acid (20 ml.) and diazotised with solid sodium nitrite, as described in (a) above. The solution was stored for 3 days in the dark, during which time slow gas evolution

occurred and the mixture darkened to a deep red-brown. Basification and continuous extraction with ether (500 ml.) for 15 hr. gave, on evaporation, a small amount (60 mg.) of dark red residue, m.p. 265-275°, which was not further investigated. The alkaline solution was just neutralised with 2N-hydrochloric acid and extracted with ether (4 x 100 ml.) Evaporation of the dried ether extract gave a light brown oil (650 mg.) which partially crystallised on cooling. Vacuum sublimation of this phenolic fraction gave a colourless sublimate (110 mg.), which crystallised from a small amount of petroleum ether (b.p. 40-60°) to give colourless plates, m.p. 55°. The substance was probably 2-acetyl-3-hydroxypyridine (Found: C,60.4; H,5.4; N,10.1. $C_7H_7NO_2$ requires C,61.3; H,5.1; N,10.2%). The non-volatile residue left after vacuum sublimation crystallised readily from petroleum ether (b.p. 60-80°) to afford colourless, deliquescent needles of 2-(3'-hydroxy-2'-pyridyl)-propene, m.p. 52° (Found: C,62.7; H,7.2; N,9.1. $C_8H_9NO.H_2O$ requires C,63.2; H,7.1; N,8.7%).

(c) Reaction in very dilute sulphuric acid: the amino-propene (1 g.), dissolved in 4N-sulphuric acid (5 ml.), was diazotised with a solution of sodium nitrite (450 mg.) in water (10 ml.) at 0-5°. The solution was poured onto an ice-water mixture (300 g.) and allowed to stand in the dark at room temperature for 10 days. The dark red solution was basified with 4N-sodium hydroxide and continuously extracted with ether (300 ml.) for 5 hr. The yellow-orange ether solution was evaporated, finally under reduced pressure, to give a deep red,

pleasant-smelling oil (55 mg.). The oil did not solidify on standing for several days at 0°. Treatment with picric acid in hot ethanol gave a green, oily precipitate which soon solidified on standing. Recrystallisation of the solid from methanol gave 4-methyl-1,2,5-triazanaphthalene picrate (35 mg.) as clusters of green-yellow needles, m.p. 228° (Found: C,44.0; H,2.9; N,22.4. $C_{14}H_{10}N_6O_7$ requires C,44.9; H,2.7; N,22.5%). The small quantities of picrate obtained did not permit isolation of the free base.

(d) Reaction in sodium acetate solution: the amino-propene (1 g.) was diazotised in 4N-sulphuric acid solution (6 ml.), as described in (c) above, and the solution was poured slowly into an ice-cold, saturated sodium acetate solution (25 ml.) at 0-5°, with stirring. The solution was allowed to warm to room temperature and was then kept in the dark for 3 days. During this time a red-brown solid was precipitated and much gas evolution was noticed. The solid product (400 mg.) was collected and had m.p. 265-280°. This product, dissolved in ethyl acetate, was chromatographed on alumina (40 x 2.5 cm) and elution commenced with benzene. When the orange-red front had nearly reached the bottom of the column, the eluant was changed to 10% v/v ethyl acetate-benzene and fractions were collected. Evaporation of the first fractions gave a deep red solid (65 mg.), m.p. 245-250°, which was probably an azo-dye and was not further examined. No other recognisable products were obtained by further development of the chromatogram.

Continuous extraction of the filtrate with benzene gave a small

amount of dark oil on evaporation, but treatment with picric acid afforded no crystalline product.

Reaction of 2-(3'-amino-4'-pyridyl)-propene with nitrous acid.

(a) Reaction in concentrated hydrochloric acid: the amino-propene (1 g.), dissolved in concentrated hydrochloric acid (15 ml.), was cooled to 0° and treated with solid sodium nitrite (450 mg.) at 0-5°. The clear, pale yellow solution was warmed to 60-65° on a water bath. A vigorous effervescence (probably nitrogen) occurred and after about 30 min. the solution no longer coupled with alkaline 2-naphthol. The solution was then diluted with water (20 ml.) and basified with 2N-sodium hydroxide. The dark mixture was extracted continuously with benzene (200 ml.) to give, on evaporation, a small amount of tarry material (90 mg.) which provided no crystalline product on extraction with petroleum ether. The basified solution was just neutralised to give an oily emulsion. The phenolic fraction (650 mg.) was obtained by extraction with ether (2 x 100 ml.) as a brown oil. Attempts to obtain a crystalline product were unsuccessful.

(b) Reaction in 2N-sulphuric acid: the amino-propene (1 g.), dissolved in 2N-sulphuric acid (20 ml.), was diazotised at 0-5° with solid sodium nitrite (450 mg.) and the solution was allowed to stand in the dark for 5 days at room temperature. During this time nitrogen was slowly lost and the coupling power had disappeared after 5 days. Basification of the solution and continuous extraction with ether for 4 hr. gave a small amount (80 mg.) of a yellow-brown oil.

Extraction for a further 8 hr. gave no additional product. Treatment of the oil with picric acid in benzene gave 4-methyl-1,2,7-triaza-naphthalene picrate (65 mg.) which crystallised from methanol as small, green needles, m.p. 255° (Found: C,44.0; H,2.9; N,22.4. $C_{14}H_{10}N_6O_7$ requires C,44.9; H,2.7; N,22.5%).

(c) Reaction in 0.1N-sulphuric acid: the amino-propene (1 g.) was diazotised as described in (b) above. The solution was poured into ice-water mixture (95 g.) and allowed to stand for 5 days. During this time the mixture darkened and a red-brown solid separated. The mixture was basified and continuously extracted with ether (500 ml.) to afford, on evaporation of the dried ether extract, a pinkish red, crystalline mass (160 mg.). The product was chromatographed on alumina (30 x 2 cm). Elution was commenced with 2:3 v/v benzene-light petroleum ether and changed to pure benzene when the first pale yellow band had nearly reached the bottom of the column. 50 ml. fractions were collected and the pale yellow band was eluted after 15 fractions had been collected. Evaporation of fractions 1-5 gave an almost colourless, crystalline residue (18 mg.), m.p. 115-120°; fractions 5-10 gave a crystalline residue (45 mg.), m.p. 120-124°; fractions 10-15 gave a light brown, crystalline residue (20 mg.), m.p. 118-122°. Subsequent fractions gave only small amounts of coloured products which were not further examined. Further recrystallisation of the material from fractions 1-15, using petroleum ether (b.p. 40-60°), gave 4-methyl-1,2,7-triazanaphthalene as small, almost colourless leaflets, m.p. 125°(Found: C, 66.2; H,4.85; N,28.9. $C_8H_7N_3$ requires

C,66.2; H,4.85; N,28.95%). Infra red spectra (nujol mull), max 1612, 1574, 1518, 1487, 1423, 1390, 1295, 1258, 1198, 1150, 1125, 1065, 1023, 992, 946, 900, 890, 842, cm^{-1}.

(d) Reaction in very dilute sulphuric acid: the amino-propene (1 g.), dissolved in N-sulphuric acid (5 ml.), was diazotised, as described in (b) above. The solution was allowed to stand for 10 min. and then poured into ice-water (500 ml.). It was then stored in the dark for 10 days at room temperature, during which time much brown-red precipitate formed. Basification and continuous extraction with benzene (200 ml.) gave on evaporation a red, crystalline mass (380 mg.). Chromatography on alumina, as described in (c) above, gave on further crystallisation from petroleum ether, 4-methyl-1,2,7-triazanaphthalene, m.p. and mixed m.p. with foregoing product 124-125°, (230 mg.; 21%).

This method was subsequently used for preparing 4-methyl-1,2,7-triazanaphthalene and yields were usually about 20%. In a typical experiment the amino-propene (15 g.) gave the crude triazanaphthalene (4.8 g.) which on purification by chromatography, gave the base (3.2 g.; 18%), m.p. 123-125°.

(e) Reaction in sodium acetate solution: the amino-propene (1 g.) was diazotised as described in the foregoing experiment and the solution added dropwise to an ice-cold, saturated sodium acetate solution (50 ml.). The dark solution was allowed to stand for 5 days at room temperature, treated with 2N-sodium hydroxide solution (20 ml.) and continuously extracted with chloroform (100 ml.) for 6 hr.

The orange-red chloroform solution was dried and evaporated to about 10 ml. The dark red solid (85 mg.), m.p. 305-315°, was collected and the filtrate evaporated to dryness under reduced pressure. The red, crystalline residue (170 mg.) was chromatographed on alumina, as described in (c) above, to afford 4-methyl-1,2,7-triazanaphthalene (65 mg.), m.p. 123-124°, identical with the foregoing product.

(f) Reaction in sodium hydroxide solution: the amino-propene (1 g.), diazotised in 4N-hydrochloric acid (8 ml.) with 5% sodium nitrite solution (13 ml.) at 0-5°, was added dropwise over 20 min. to a stirred, ice-cold 4N-sodium hydroxide solution (25 ml.). The brown-black, oily solution was allowed to stand in the dark for 5 days at room temperature. It was then continuously extracted with ether for 8 hr., after which time the yellow ether solution was dried and evaporated to afford a dark, oily solid (350 mg.). Extraction for a further 20 hr. provided only a small amount (40 mg.) of dark, red-brown solid. The crude product afforded 4-methyl-1,2,7-triazanaphthalene (160 mg.), m.p. 124-125°, by the usual chromatographic method.

Reaction of 2-(3'-amino-2',6'-dimethyl-4'-pyridyl)-propene with nitrous acid.

(a) Reaction in very dilute sulphuric acid: a solution of the oily propene (5 g.) in sulphuric acid (d. 1.84; 3 ml.) and water (25 ml.) was diazotised at 0° with solid sodium nitrite (2.1 g.) in water (10 ml.). The clear, pale yellow solution was poured slowly into ice-water mixture (500 g.) and then allowed to stand in the dark at room

temperature for 5 days. The resulting dark brown solution was basified with 4N-sodium hydroxide and continuously extracted with benzene (600 ml.) Removal of the benzene under reduced pressure gave a brown, oily solid (1.4 g.) which was chromatographed on alumina (60 x 2.5 cm). The solid was applied to the column in warm benzene (5 ml.) and elution commenced with light petroleum ether (b.p. 60-80°). When the first pale yellow band had nearly reached the bottom of the column the eluant was changed to 1:1 v/v benzene-light petroleum ether and 50 ml. fractions were collected. After 30 fractions had been collected, the pale yellow band was completely eluted. Evaporation of fractions 1-5 gave a yellow, oily solid (40 mg.), m.p. 118-130°; fractions 5-10 gave a light brown, crystalline solid (150 mg.), m.p. 135-138°; fractions 10-20 gave an almost colourless solid (480 mg.), m.p. 137-140°; fractions 20-25 gave similar material (170 mg.), m.p. 135-140°; fractions 25-30 gave only a small amount (20 mg.) of red-brown solid, m.p. 128-135°. Subsequent fractions gave only small amounts of coloured products which were not further examined. The combined material from fractions 1-25 was recrystallised from petroleum ether to give 4,6,8-trimethyl-1,2,7-triazanaphthalene (700 mg.; 15%) as almost colourless leaflets, m.p. 142-143° (Found: C,69.7; H,6.7; N,23.7. $C_{10}H_{11}N_3$ requires C,69.3; H,6.4; N,24.3%). A picrate separated from ethanol as clusters of yellow-green needles , m.p. 181-182° (Found: C,48.1; H,3.6; N,20.4. $C_{16}H_{14}N_6O_7$ requires C,47.8; H,3.5; N,20.9%). Infra red spectrum of 4,6,8-trimethyl-1,2,7-triazanaphthalene (KBr disc), max 1608, 1580, 1528, 1497, 1446, 1390, 1345, 1310, 1265, 1225, 1163, 1132, 1043, 1020 984, 957, 940, 890, 867, 802, 728 cm^{-1}.

(b) Reaction in sodium hydroxide solution: the amino-propene (5 g.) was diazotised as described in (a) above, and the solution was added dropwise, with stirring, to ice-cold 2N-sodium hydroxide (200 ml.). The solution darkened rapidly. It was allowed to stand in the dark for 5 days. Continuous extraction with ether provided, on evaporation, a dark brown, oily product (1.1 g.) from which 4,6,8-trimethyl-1,2,7-triazanaphthalene (580 mg.), m.p. 141-142°, was obtained by chromatography on alumina.

Reaction of 2-(3'-amino-2'-methyl-6'-phenyl-4'-pyridyl)-propene with nitrous acid.

Reaction in very dilute sulphuric acid: the amino-propene (5.0 g.), dissolved in sulphuric acid (d. 1.84; 3 ml.) and water (25 ml.), was diazotised with sodium nitrite (1.4 g.) in water (10 ml.) and allowed to stand at 0° for 10 min. The solution was diluted to 500 ml. with ice-water mixture and allowed to stand at room temperature for 5 days. Alkali insoluble products were obtained by basification and continuous extraction with benzene (300 ml.) for 8 hr. Evaporation of the benzene solution provided a red, tarry material (350 mg.) which on treatment with picric acid in benzene gave 4,8-dimethyl-6-phenyl-1,2,7-triazanaphthalene picrate as dark green needles (from methanol), m.p. 217-218°. (Found: C,55.4; H,3.1; N,17.9. $C_{22}H_{17}N_6O_7$ requires C,55.3; H,3.6; N,17.6%).

In other experiments attempts were made to obtain the free base by chromatographic separation of the crude product, but without success.

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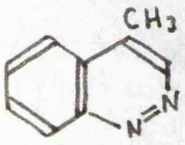
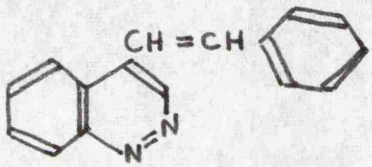
(5) DERIVATIVES OF 1,2,7-TRIAZANAPHTHALENE.

The activity of alkyl groups when attached α or γ to a nitrogen atom (as in 2-picoline) is well known. The reactivity of the methyl group in 4-methylcinnoline (I) was established by Jacobs[1] and by Atkinson and Simpson[2] who showed that the 4-methyl group readily condensed with aromatic aldehydes. Condensation of the base (I) with benzaldehyde[1] in the presence of zinc chloride gave the 4-styryl-derivative (II). Condensation of the ethiodide of the base with p-dimethylaminobenzaldehyde[2,3] gave the cyanine dye, 4-p-dimethylamino-styryl-1-ethylcinnolinium iodide (III),



(I)



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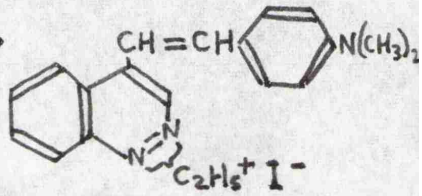
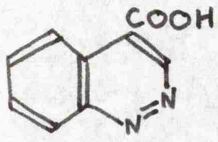


(III)

More recently, the condensation of 4-methylcinnolines has been the subject of a paper by Castle and Cox[4]. The reaction with benzaldehyde can be used as the first stage in a route to various derivatives of cinnoline and related heterocycles. Jacobs and co-workers[1] converted the styryl derivative (II) to the parent base (V) by oxidation to the carboxylic acid (IV) and subsequent decarboxylation. Case and Brennan[5] have used an analagous route to obtain the parent base (VI; R = H) from 1-methyl-3,4,5-triaza-phenanthrene (VI; R = CH_3).



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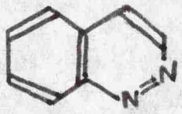

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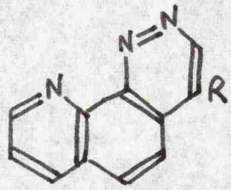
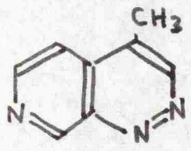


(VI)

The poor overall yields of 4-methyl-1,2,7-triazanaphthalene (VII) did not permit a full investigation of its properties but a number of derivatives has been obtained and the activity of the 4-methyl group has been established.

Reaction of the 4-methyl derivative with benzaldehyde in the presence of zinc chloride, following the method of Ainley and King[6] for 4-styrylquinoline, gave 4-styryl-1,2,7-triazanaphthalene (VIII). An alternative method, recommended by Castle and Cox[4], used hydrochloric acid as the condensing agent and was also successful. In each case, however, the yield was poor (about 25%).

The 4-styryl compound was oxidised to the carboxylic acid (IX) using aqueous potassium permanganate at low temperatures. The same acid was also obtained by direct oxidation of the 4-methyl compound with potassium permanganate.



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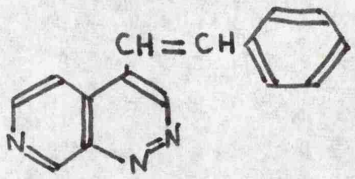

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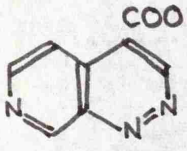
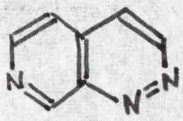


(IX)



(X)

Only limited amounts of the acid became available and an attempt to prepare the parent base (X) by decarboxylation in benzophenone, using the method of Schofield and Simpson[7], failed to provide a crystalline product. A picrate was obtained, however, with the correct analysis for the picrate of 1,2,7-triazanaphthalene (X).

EXPERIMENTAL

4-Methyl-1,2,7-triazanaphthalene methiodide.— The base (100 mg.) was refluxed with methyl iodide (50 mg.) in methanol (5 ml.) for 3 hr. and evaporated to dryness. Recrystallisation of the residue from methanol gave the methiodide (110 mg.) as dark red needles, m.p. 163-164° (Found: C,38.1; H,3.3; N,15.0; I,43.9. $C_9H_{10}N_3I$ requires C,37.6; H,3.5; N,14.6; I,44.3%).

4-Styryl-1,2,7-triazanaphthalene.— (a) The base (500 mg.) was refluxed for 3 hr. with benzaldehyde (2 g.) and anhydrous zinc chloride (150 mg.). The mixture was cooled and treated with ether (25 ml.) and 4N-hydrochloric acid (10 ml.). The organic layer was removed and the acid extract treated with concentrated hydrochloric acid (5 ml.) to give the 4-styryl-derivative as a yellow, crystalline hydrochloride (310 mg.). The hydrochloride was dissolved in water (15 ml.) and basified with 4N-ammonium hydroxide. The yellow-brown, oily solid which separated was collected, washed well with water and recrystallised from methanol (charcoal) to give 4-styryl-1,2,7-triazanaphthalene (230 mg.) as yellow plates, m.p. 95-96° (Found: C,76.7; H,4.5; N,18.8. $C_{13}H_{11}N_3$ requires C,77.2; H,4.8; N,18.0%). (b) Concentrated hydrochloric acid (1.0 ml.) was added to a solution of the base (250 mg.) in acetone (10 ml.) and the solution stirred and cooled to 0°. The precipitated hydrochloride was collected and dried, then suspended in benzaldehyde (1 ml.) and the mixture was

heated at 150-160° (oil bath) while dry hydrogen chloride was passed through the suspension at a steady rate. The mixture darkened almost immediately. After 90 min. it was cooled and stirred with ether (15 ml.) and water (10 ml.). The aqueous layer was separated and basified with saturated sodium carbonate solution. The mixture was then continuously extracted with ether (50 ml.). Removal of the solvent from the washed and dried ($MgSO_4$) ether extract provided a brown, oily product (90 mg.) from which 4-styryl-1,2,7-triazanaphthalene was obtained by recrystallisation from methanol, m.p. and mixed m.p. with the product prepared by method (a) 95-96°.

1,2,7-Triazanaphthalene-4-carboxylic acid. (a) The crude styryl derivative (250 mg.) was suspended in water (25 ml.) and treated with potassium permanganate (500 mg.) added in small quantities, at room temperature. The mixture was stirred and the temperature raised to 40° and maintained at 35-40° for 15 min. After cooling, the mixture was filtered and the manganese dioxide washed with 2N-sodium hydroxide to remove any product. The combined filtrate and washings were evaporated to about 5 ml. and neutralised with 6N-hydrochloric acid. The fine precipitate which separated was collected and purified by reprecipitation from alkaline (Na_2CO_3) solution to afford the acid as a buff, microcrystalline solid, m.p. 202-203° (Found: C,54.5; H,2.4; N,25.0. $C_8H_5N_3O_2$ requires C,54.9; H,2.8; N,24.0%).

(b) A solution of 4-methyl-1,2,7-triazanaphthalene (100 mg.) in

water (15 ml.) was treated at 35° with saturated potassium permanganate (10 ml.) added dropwise during 30 min. with mechanical stirring. After a further 15 min. alcohol (1 ml.) was added and the mixture filtered. Chloroform extraction (3 x 10 ml.) gave on evaporation in vacuo, a small amount of crystalline material (20 mg.), identified as the unchanged base (m.p. and mixed m.p. 125°). The alkaline solution was concentrated under reduced pressure to about 5 ml. and acidified with 2N-sulphuric acid. A buff-coloured precipitate (35 mg.) separated and was collected and shown to be identical with the acid prepared by the oxidation of the 4-styryl derivative (m.p. and mixed m.p. 201-203°).

1,2,7-Triazanaphthalene.-- 1,2,7-triazanaphthalene-4-carboxylic acid (100 mg.) was heated with benzophenone (1 g.) under nitrogen for 30 min. at 155-165° (oil bath). The reaction mixture was cooled, dissolved in ether (20 ml.) and extracted with 3N-hydrochloric acid (3 x 10 ml.). The acid extracts were combined, washed with ether (20 ml.) and neutralised with saturated sodium carbonate solution. Extraction with ether (5 x 50 ml.) provided, on evaporation of the dried ($MgSO_4$) ether solution, a dark brown oil (45 mg.). A picrate was obtained from the crude material by treatment with picric acid in benzene. Recrystallisation from ethanol gave 1,2,7-triazanaphthalene picrate as yellow-green needles, m.p. 205-206° (Found: C,43.2; H,2.2; N,23.6. $C_{12}H_8N_6O_7$ requires C,43.4; H,2.2; N,25.3%).

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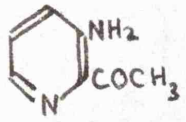
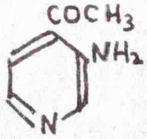
(6) THE BORSCHE REACTION: The reaction between pyridine amino-ketones and nitrous acid.

This section describes attempts made to extend the Borsche reaction to the preparation of 4-hydroxytriazanaphthalenes by the cyclisation of o-amino-ketones (I), (II) and (III).



(I)



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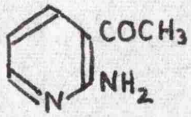
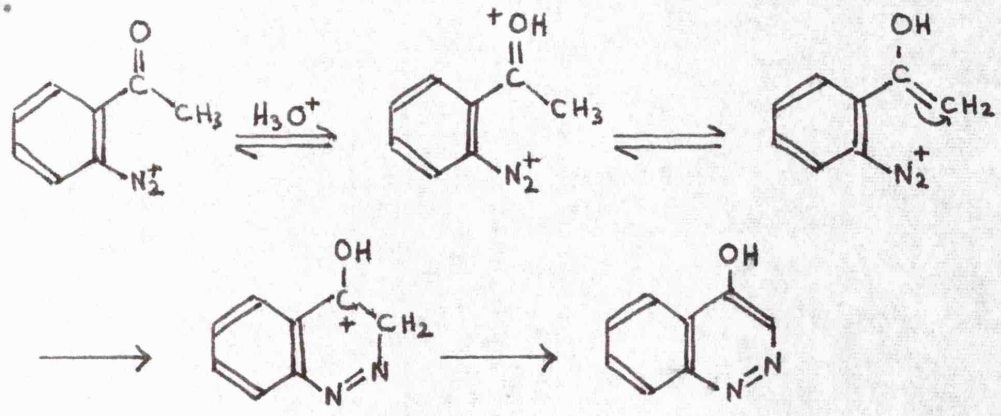
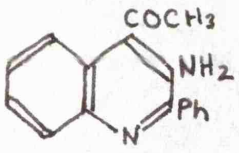


(III)

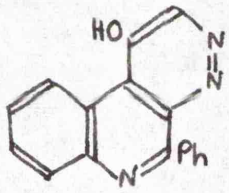
Previous work[1,2] on the reaction has shown that electron-withdrawing substituents at C_3 and C_5 in the 2-aminoacetophenone increase both the rate of cyclisation and the yield of cinnoline, presumably by increasing the electrophilic nature of the diazonium cation. The advantage of working in concentrated acid media, particularly concentrated hydrochloric acid has been stressed. These observations are in agreement with a mechanism for the reaction proposed by Leonard and Boyd[8] which has an acid-catalysed enolisation as its first stage.



However, it seemed likely that cyclisation of the diazotised amino-ketones (I) and (II) would be difficult, since the nuclear nitrogen atom might have a pronounced inhibiting effect on the enolisation of the methyl ketone. Moreover, it would not be an advantage to work in powerfully acidic media, as protonation of the ring nitrogen atom would even further increase the electron-withdrawing effect at the α and γ positions of the pyridine ring. This is partly confirmed by the work of Atkinson and Mattocks[4]: diazotisation of the amino-ketone (IV) in concentrated hydrochloric acid and attempted cyclisation gave a very low yield of the hydroxy-triazaphenanthrene (V), the major product being the chloro-compound (VI).



(IV)



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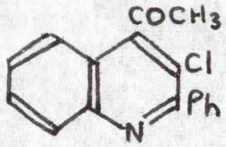
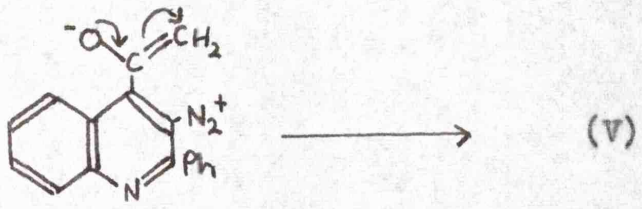


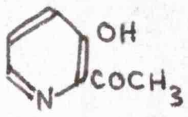
(VI)

However, in a strongly alkaline medium at room temperature the required product (V) was obtained in over 80% yield. It appears that in this case the mechanism of ring closure is more correctly represented as an intramolecular coupling of the diazonium cation with the enolate anion (VII), the latter stabilised in an alkaline environment.

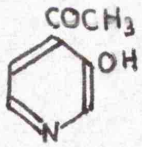


(VII) (V)

It was decided, therefore, to examine the reactions of the ketones (I) and (II) in both concentrated acid and in alkali, but experiments carried out under a variety of conditions failed to produce the required hydroxy-triazanaphthalene. Attempted cyclisation in concentrated hydrochloric acid gave only phenolic products (VIII) and (IX), isolated and identified by 2,4-dinitrophenylhydrazone formation. The hydroxy-ketone (VIII) had previously been obtained as a decomposition product during the attempted cyclisation of the diazotised amino-propene (X), (see page 98).



(VIII)



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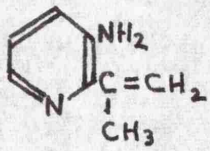
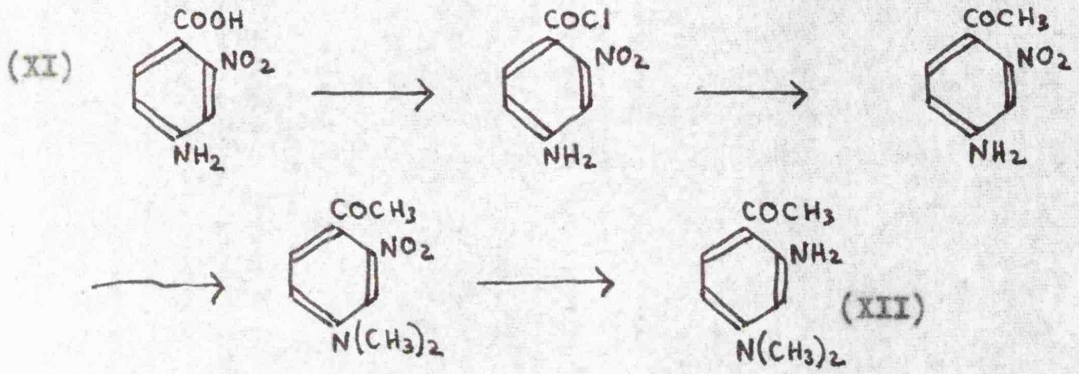


(X)

The alternative procedure of treating the diazonium salt solution with alkali failed completely. The products isolated were not identified but in view of their dark red colour and high melting point, it seems likely that they were azo-compounds formed by intermolecular coupling of the diazonium compound in alkaline solution. In the case of the reaction carried out by Atkinson and Mattocks[4] side reactions would have been unlikely, owing to the absence of free o- and p-positions in the heterocyclic ring.

The retarding effect on the Borsche reaction of powerful electron-withdrawing substituents is further borne out by the preparation and attempted cyclisation of 2-amino-4-dimethylamino-acetophenone in acid solution (XII). The starting material, 4-amino-2-nitrobenzoic acid (XI) was prepared by the method of Blanksma and Hoegen[1] and converted to the ketone (XII) by the route outlined below:

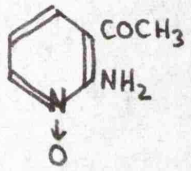


Attempted cyclisation of the diazotised amino-ketone in acid solution failed to give any of the required hydroxy-cinnoline and the only product isolated was 4-dimethylamino-2-hydroxyacetophenone. A reaction in alkaline solution produced only dark coloured material from which no useful product could be obtained.

The difficulty of diazotising amino-groups α and γ to a ring nitrogen atom is well known and the reaction usually goes only under forcing conditions. This makes the application of both the Borsche and Widman-Stoermer reactions to the preparation of 1,2,6- and 1,2,8-triazanaphthalenes particularly difficult. However, a number of methods are available for the diazotisation of 'heterocyclic' amino-groups[6,7,8,9] and it was decided to apply several of these to the

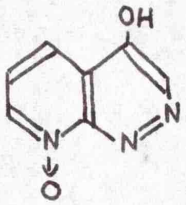
amino-ketone (III). Treatment with amyl nitrite in a number of solvents and application of the method of Murray and Langham[9] failed to effect diazotisation.

It has been established that the N-oxidation of 4-aminopyridine renders the amino-group capable of diazotisation under normal conditions.[10] The solution undergoes coupling and Sandmeyer reactions have led to various 4-substituted pyridine-N-oxides. In view of these observations, it seemed worthwhile to prepare and examine the reaction of the N-oxide (XIII)



(XIII)

Reaction of the compound with sodium nitrite in both concentrated hydrochloric acid and sulphuric-acetic acid at 0° gave a solution which coupled readily with alkaline 2-naphthol. Cyclisation of the diazotised amino-ketone was attempted under various conditions. A successful cyclisation was achieved by allowing the solution to stand for several days at room temperature. Extraction with chloroform provided 4-hydroxy-1,2,8-triazanaphthalene-N[8]-oxide in 25% yield (XIV).



(XIV)

Unfortunately, the low overall yield of the N-oxide (XIII) did not permit any further experiments.

EXPERIMENTAL

Reaction between 2-acetyl-3-aminopyridine and nitrous acid.

(a) Reaction in concentrated hydrochloric acid.— The amino-ketone (250 mg.) was dissolved in concentrated hydrochloric acid (10 ml.) and treated with solid sodium nitrite (100 mg.) at 0-5°. The clear solution was allowed to stand for 30 min. at about 5° and was then warmed slowly to about 60°. A vigorous effervescence occurred and the solution darkened to orange-yellow. The temperature was maintained at 60-65° for 2 hr. and the solution was then evaporated under reduced pressure to small bulk. The residue was carefully neutralised with 2N-ammonium hydroxide. No precipitate formed but continuous extraction of the neutral solution gave, on evaporation of the dried ether extract, a light yellow oil (180 mg.) from which 2-acetyl-3-hydroxypyridine (110 mg.) was obtained by vacuum sublimation. The product which had m.p. 50-53° was further purified by recrystallisation from light petroleum ether (b.p. 40-60°) to give colourless plates, m.p. 55°. The hydroxy-ketone was shown to be identical with the product obtained during the diazotisation of 2-(3'-amino-2'-pyridyl)-propene (see page 103), a mixed m.p. being undepressed.

Further attempts to effect cyclisation by long standing in strong acid solution at room temperature were unsuccessful.

(b) Reaction in sodium hydroxide solution.— The amino-ketone (250 mg.) in 4N-hydrochloric acid (8 ml.) was treated at 0° with solid sodium nitrite (90 mg.). The yellow solution was treated

dropwise with 5N-sodium hydroxide solution (12 ml.), the temperature being maintained below 0° for the whole of the addition. During the addition much frothing occurred with the separation of a bulky red-brown precipitate. The alkaline mixture was allowed to attain room temperature, left to stand for 1 hr. and filtered. The dark red solid (140 mg.) which was obtained had m.p. 200-250°. This material proved difficult to purify but separated from 1:1 aqueous acetic acid as a red amorphous solid (70 mg.), m.p. 310-320°. This product was not further investigated. Neutralisation of the alkaline filtrate gave only a small amount (40 mg.) of dark brown, oily precipitate from which no useful product could be obtained.

Reaction between 4-acetyl-3-aminopyridine and nitrous acid.

(a) Reaction in sulphuric-acetic acid mixture.-- The amino-ketone (250 mg.), dissolved in glacial acetic acid (3 ml.) and sulphuric acid (d. 1.84; 1 ml.), was treated with sodium nitrite (100 mg.) at 0°. The pale yellow solution was allowed to stand for 1 hr. at 0-5° and was then slowly warmed to 60° on a water bath when a vigorous effervescence occurred. After 15 min. a small quantity of the solution no longer coupled with alkaline 2-naphthol. The solution was heated for a further 30 min. and was then poured into water (10 ml.). Neutralisation of the solution with 4N-sodium hydroxide afforded an oily emulsion which was continuously extracted with chloroform (50 ml.). The dried chloroform solution gave, on evaporation, a pale yellow oil (170 mg.). Attempts to isolate a crystalline product

failed but treatment of the crude oil with 2,4-dinitrophenylhydrazine in alcohol-concentrated hydrochloric acid gave the 2,4-dinitrophenylhydrazone of 4-acetyl-3-hydroxypyridine as yellow needles from acetic acid, m.p. 248-249° (Found: C,49.5; H,3.8; N,21.6. $C_{13}H_{11}N_5O_5$ requires C,49.2; H,3.5; N,22.1%).

Attempts to cyclise the diazotised amino-ketone in both concentrated hydrochloric acid and formic acid failed to produce any of the required hydroxy-triazanaphthalene.

(b) Reaction in sodium hydroxide solution.— The amino-ketone (250 mg.) was dissolved in concentrated hydrochloric acid (2 ml) and water (8 ml), and the clear solution treated at 0° with solid sodium nitrite (100 mg.). The solution, which coupled readily with alkaline 2-naphthol, was allowed to stand for 5 min. and was then treated with excess of 5N-sodium hydroxide (about 10 ml) below 0°. The mixture rapidly darkened, with much frothing and the dark solid (130 mg.) was collected after 1 hr. at room temperature. Attempted recrystallisation of this material did not afford any well-defined compound but solid material which separated from 50% acetic acid had m.p. 360°.

Neutralisation of the alkaline filtrate with 4N-hydrochloric acid gave more brown intractable material (40 mg.) of high m.p.

4-Amino-2-nitroacetophenone.— 4-Amino-2-nitrobenzoic acid[5] (45 g) was heated under reflux with thionyl chloride (125 ml) for 15 min., the excess of thionyl chloride and the crude acid chloride was

was removed,

dissolved in dioxan (100 ml) and added to a solution of magnesium (5.4 g) in a mixture of diethyl malonate (35.5 g.), ethanol (20 ml.), and ether (25 ml.). The mixture was refluxed for 30 min. and shaken with sulphuric acid (250 ml ; 10% v/v) until all solid material had dissolved. The organic layer was removed, the mixture extracted with ether (2 x 100 ml.), and the combined extracts were washed with water, dried, and evaporated. The crude product was dissolved in a mixture of acetic acid (75 ml.), concentrated sulphuric acid (10 ml.), and water (50 ml.), and refluxed for 3 hr. The cooled mixture was basified with ammonia and the precipitate was collected, dried, and recrystallised from benzene. Recrystallisation from water gave 4-amino-2-nitroacetophenone as yellow needles (12 g., 26.7%), m.p. 133-134° (Found: C,52.9; H,4.45; N,14.6. $C_8H_8N_2O_3$ requires C,53.3; H,4.8; N,15.55%).

Treatment with 2,4-dinitrophenylhydrazine in alcohol gave the 2,4-dinitrophenylhydrazone as red leaflets from acetic acid, m.p. 257° (Found: C,47.4; H,3.8; $C_{14}H_{12}N_8O_6$ requires C,46.7; H,3.4%).

4-Dimethylamino-2-nitroacetophenone.— 4-Amino-2-nitroacetophenone (1.8 g.) was stirred under reflux with a solution of sodium carbonate (anhydrous; 14 g.) in water (35 ml.) and treated dropwise during 1 hr. with dimethyl sulphate (15 g.). The mixture was heated under reflux for a further 30 min. and then cooled. The yellow solid (1.5 g.) which separated was crystallised from ethanol to give the ketone (1.3 g., 70%) as pale yellow needles, m.p. 155-156° (Found: C,57.6; H,6.1; N,13.7. $C_{10}H_{12}N_2O_3$ requires C,57.7; H,5.8; N,13.5%).

2-Amino-4-dimethylaminoacetophenone.— To a solution of the foregoing nitro-compound (2.5 g.) in concentrated hydrochloric acid (25 ml.) was added, in small amounts, stannous chloride dihydrate (10 g.). The mixture was heated under reflux for 5 min., cooled and made strongly alkaline with 4N-sodium hydroxide. The crude product (1.5 g.), obtained by extraction with ether (3 x 100 ml.), was recrystallised from isopropyl alcohol to give the amino-ketone as colourless needles, m.p. 114-115° (Found: C,66.9; H,8.0; N,15.9. $C_{10}H_{14}N_2O$ requires C,67.4; H,7.9; N,15.7%).

Reaction between 2-amino-4-dimethylaminoacetophenone and nitrous acid.

(a) Reaction in sulphuric-acetic acid solution.— A solution of the amine (0.8 g.) in glacial acetic acid (5 ml.) and 10N-sulphuric acid (5 ml.) was cooled to 0° and treated with solid sodium nitrite (200 mg.) in small portions. This solution (1 ml.) coupled with 2-naphthol in alkaline solution to give the azo-compound which formed red crystals, m.p. 276-277° (from ethanol). The remainder of the solution was allowed to attain room temperature slowly (evolution of nitrogen was noted) and set aside for several days. It was heated to 75° for 15 min., cooled, diluted with water (25 ml.) and the solid (0.5 g.) was collected, washed with water and dried. Recrystallisation from ethanol gave 4-dimethylamino-2-hydroxyacetophenone as needles, m.p. 122° (Peckmann and Schall[11] give m.p. 120°) (Found: C,67.0; H,7.6; N,7.9. Calc. for $C_{10}H_{13}NO_2$: C,67.0; H,7.3; N,7.8%).

Further attempts to cyclise the diazonium salt in other acid

media at both room temperature and at 70° gave the same hydroxy-ketone.

(b) Reaction in sodium hydroxide solution.— To a solution of the amine (400 mg.) in 5N-sulphuric acid (5 ml.) was added solid sodium nitrite (100 mg.), the temperature being kept below 5°. After 5 min. the solution was treated at 0-5° with excess of 5N-sodium hydroxide (6 ml.). The mixture rapidly darkened and the brown solid (200 mg.) which separated was collected, but no useful material could be obtained from this product.

The alkaline filtrate was neutralised with 2N-sulphuric acid but yielded only 4-dimethylamino-2-hydroxyacetophenone, m.p. and mixed m.p. 122°.

Reaction between 3-acetyl-2-aminopyridine-N-oxide and nitrous acid.

(a) Reaction in concentrated hydrochloric acid.— The amino-ketone (250 mg.) was dissolved in concentrated hydrochloric acid (5 ml.) and treated at 0° with solid sodium nitrite (100 mg.). The solution, which coupled readily with alkaline 2-naphthol, was allowed to stand at room temperature for 5 days. At the end of this time coupling properties had ceased. Excess hydrochloric acid was removed under reduced pressure and the sticky residue was dissolved in water (5 ml.), adjusted to pH8.0 with 2N-ammonium hydroxide and continuously extracted with chloroform for 6 hr. The dried chloroform solution was evaporated to yield a yellow-brown, oily solid (110 mg.). Several recrystallisations gave 4-hydroxy-1,2,8-triazanaphthalene-N^{8}-oxide (45 mg.) as small, almost colourless plates, m.p. 238° (Found: C,51.2; H,3.25; N,25.4. $C_7H_5N_3O_2$ requires C,51.5; H,3.1; N,25.8%).

(b) Reaction in sodium hydroxide solution.— The amino-ketone (200 mg.), dissolved in 4N-sulphuric acid (5 ml.), was treated with sodium nitrite (80 mg.) in water (3 ml.) at 0°. The solution was allowed to stand at 0° for 10 min. and was then treated dropwise at this temperature with 4N-sodium hydroxide until the solution was strongly alkaline. The solution, which developed a deep red colour, was allowed to stand for 1 hr. at room temperature and was then carefully neutralised with 2N-sulphuric acid. Continuous extraction with chloroform for 6 hr. gave, on evaporation of the chloroform solution, a brittle, red solid (60 mg.), m.p. 280-300° (azo-dye). Column chromatography on alumina gave on elution with benzene-ethyl acetate only coloured material.

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10. Ochiai, Teshigawa, Oda and Naito, Chem. Abs., 45, 8527 g,h. J. Pharm. Soc. Japan, 1944, 6(5/6A),1-2; 1945, 5/6A,1-2.

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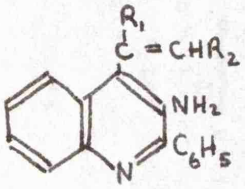
PART III

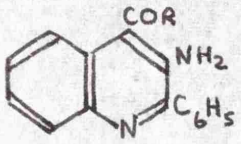
TRIAZAPHENANTHRENES

(1) INTERMEDIATES: (A) DERIVATIVES OF 3-AMINOQUINOLINE.

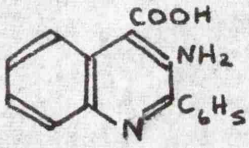
For investigations into the Borsche and Widman-Stoermer reactions various amino-ethylenes (I) and amino-ketones (II) in the quinoline series were required. The key intermediate used for the synthesis of these compounds was 3-amino-2-phenylquinoline-4-carboxylic acid (III).



(I)

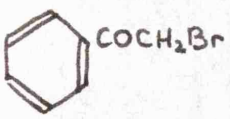


(II)



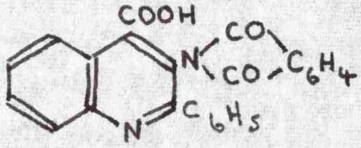
(III)

Phenacyl bromide (IV), prepared from acetophenone by the method of Petrow, Stack and Wragg[1], was condensed with potassium phthalimide using Gabriel's[2] modification of the method of Goedeckmeyer[3] to give phenacylphthalimide (V). The condensation of phenacylphthalimide with isatin - an application of the Pfitzinger reaction - gave an excellent overall yield (80%) of 3-phthalimido-2-phenylquinoline-4-carboxylic acid (VI).



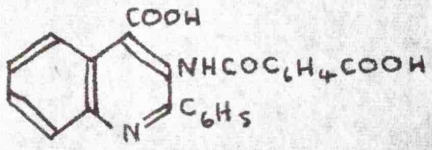
(IV)

(V)

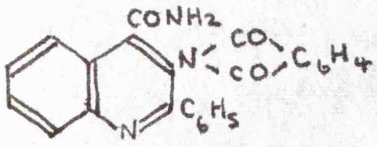


(VI)

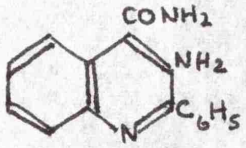
This product was first reported by Berlingozzi and Marzella[4] who incorrectly formulated it as the 3-phthalamic acid (VII). The correct structure (VI) was assigned by Atkinson and Mattocks[5]:

(VII) 

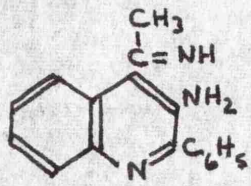
Following the procedure of Atkinson and Mattocks[5], the phthalimido acid was converted to the acid chloride by heating under reflux with thionyl chloride. The excess thionyl chloride was removed and the residue dissolved in benzene and treated with ammonia to provide 3-phthalimido-2-phenylquinoline-4-carboxyamide (VIII). Dephthaloylation with hydrazine in pyridine gave the required 3-amino-2-phenylquinoline-4-carboxyamide (IX). Treatment of this amide with the appropriate Grignard reagent was carried out essentially as described by the above authors and the intermediate ketimine (X) was hydrolysed by heating under reflux with hydrochloric acid to provide the required ketones (II).



(VIII)



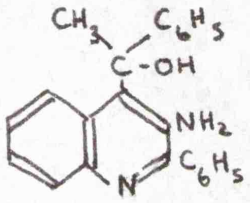
(IX)



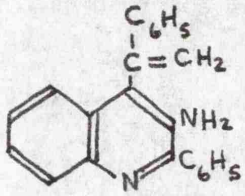
(X)

Thus, the amide reacted with methyl magnesium iodide to give 4-acetyl-3-amino-2-phenylquinoline (II : R = CH_3), and with ethyl magnesium iodide to give ethyl-4-(3'-amino-2'-phenylquinolyl)-ketone (II : R = C_2H_5).

These two ketones were used to provide substituted ethylenes (I) by further Grignard reactions and subsequent dehydration of the resulting tertiary carbinols. A Grignard reaction between 4-acetyl-3-amino-2-phenylquinoline and phenyl magnesium bromide gave methyl-phenyl-(3-amino-2-phenyl-4-quinolyl)-methanol (XI) in 75% yield. Dehydration of the product occurred smoothly in about 50% v/v sulphuric acid to give 1-phenyl-1-(3'-amino-2'-phenyl-4'-quinolyl)-ethylene (XII). Yields of the ethylene fell to about 5% in cold concentrated sulphuric acid, probably due to extensive sulphonation.

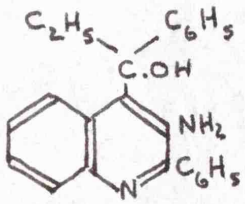


(XI)

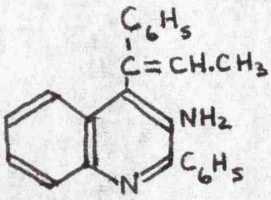


(XII)

Identical reactions with ethyl-4-(3'-amino-2'-phenylquinolyl)-ketone gave 2-methyl-1-phenyl-1-(3'-amino-2'-phenyl-4'-quinolyl)-ethylene, (XIV). by dehydration of the intermediate carbinol (XIII).



(XIII)



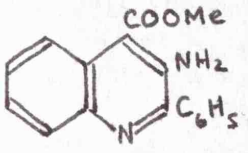
(XIV)

Experiments by Mattocks[6] on the dephthaloylation of the phthalimido acid (VI) did not support the claims previously made in

the literature by Berlingozzi and Marzella[4]: acid hydrolysis gave poor yields. The amino-acid (III), however, was obtained in good yields by reaction with hydrazine in acetic acid.

Attempts to esterify the amino-acid with ethanol-sulphuric acid, by the Fischer-Speier procedure or by phosphorus pentachloride-benzene-ethanol have all proved unsuccessful but methyl-3-amino-2-phenyl-quinoline-4-carboxylate (XV) was obtained in reasonable yield by treatment of the acid with a large excess of diazomethane in ether.

The ester was converted to dimethyl-(3-amino-2-phenyl-4-quinolyl)-methanol (XVI) by a Grignard reaction with methyl magnesium iodide and subsequent dehydration was effected most conveniently in cold, concentrated sulphuric acid to give 2-(3'-amino-2'-phenyl-4'-quinolyl)-propene (XVII). Other methods attempted for dehydration of the carbinol proved unsuccessful.



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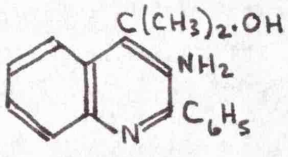
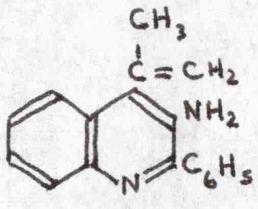


(XVI)

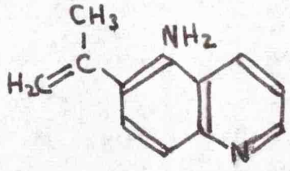


(XVII)

In all three cases the substituted ethylenes obtained were difficult to crystallise and with 2-methyl-1-phenyl-1-(3'-amino-2'-phenyl-4'-quinolyl)-ethylene (XIV) all attempts failed. The compound was characterised by preparation and analysis of the picrate.

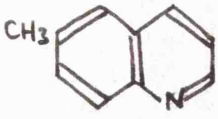
(B) DERIVATIVES OF 5-AMINOQUINOLINE.

The synthetic route to 2-(5'-amino-6'-quinolyl)-propene (I) is described in this section.



(I)

The starting material for the synthesis, 6-methylquinoline (II) was readily obtained by a Skraup reaction on p-toluidine, and when nitrated according to the directions of Long and Schofield[7], gave an excellent yield of 5-nitro-6-methylquinoline (III). The oxidation of this compound to the corresponding carboxylic acid (IV) proved rather difficult and although alkaline permanganate has been used successfully to oxidise a number of nitropicolines,[8] the reagent failed completely in this case. Chromic acid oxidation, which has been used for the oxidation of several methylquinolines,[9,10,11] was successful, however, and when carefully controlled, gave 5-nitroquinoline-6-carboxylic acid (IV) in about 50% yield.



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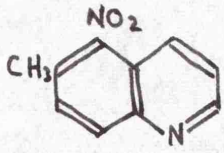

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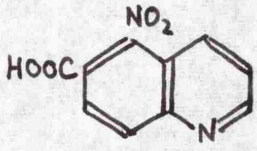
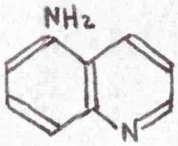


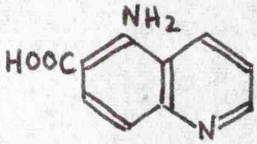
(IV)

The amino acid (VI) has previously been reported by Bogert[12] who used an unusual reaction between 5-nitro-6-methylquinoline (III) and ethanolic potassium hydroxide. Attempts to repeat the work were not successful and a direct reduction of the nitro-acid was tried. The

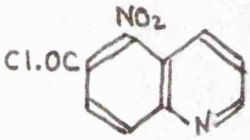
reduction was unfortunately accompanied by decarboxylation and 5-aminoquinoline (V) was the only product isolated. In view of these difficulties, it was decided to prepare and reduce the nitro-ester (VIII). Esterification of the nitro-acid was achieved only by long reflux in a mixture of equal amounts of ethyl alcohol and concentrated sulphuric acid. Alternatively, the ester was obtained by a reaction between the nitro-acid chloride (VII) and ethanol. The nitro-ester was reduced smoothly, using a stannous chloride-acetic acid reagent reported by Albert[18], to give ethyl 5-aminoquinoline-6-carboxylate (IX).



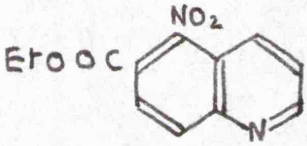
(V)



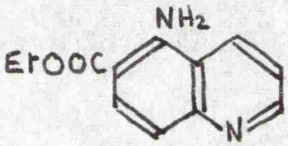
(VI)



(VII)

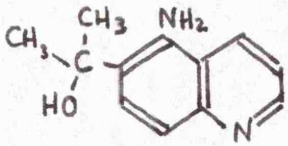


(VIII)



(IX)

A Grignard reaction between the amino-ester (IX) and methyl magnesium iodide gave the tertiary carbinol (X) in fair yield, and this on dehydration in 12N-sulphuric acid, gave the required crystalline amino-propene (I).



(X) ⟶ (I)

EXPERIMENTAL

ω-Bromoacetophenone.— Batches of acetophenone (200 g.) mixed with acetic acid (100 ml.) were brominated during 30 min. with bromine (86 ml.) dissolved in acetic acid (200 ml.) in a bright light. The liquor was poured on to ice (1500 g.) with stirring, allowed to stand, and the product (190 g.) filtered off and recrystallised from ethanol yielding colourless leaflets, m.p. 48 - 50°.

Potassium phthalimide.— Phthalimide (80 g.) was heated under reflux with absolute alcohol (1600 ml.) for 15 min. and the resulting solution decanted into a large beaker containing a solution of potassium hydroxide (30.5 g.) in water (30 ml.) and ethanol (90 ml.). The mixture was cooled, with stirring, and the yellow crystals of potassium phthalimide (80 g.) filtered off. A further batch of phthalimide (80 g.) was dissolved in the alcoholic filtrate and the procedure repeated. The two crops of crystals (175 g.) were washed with acetone (200 ml.) and dried at 80°.

Phenacyl phthalimide. — To a solution of ω-bromo-acetophenone (120 g.) in warm ethanol was added potassium phthalimide (120 g.) and the mixture boiled under reflux for 3 hr. with mechanical stirring. After cooling in ice, water was added (300 ml.), the mixture filtered, and the residue (96 g.), m.p. 161-163°, washed first with alcohol (200 ml.) and then with water (200 ml.),. The white crystalline phenacyl phthalimide was sufficiently pure for further use without recrystallisation.

2 - phenyl - 3 - phthalimidoquinoline-4-carboxylic acid.--- Phenacyl phthalimide (80 g.), dissolved in a hot solution of potassium hydroxide (61 g.) in water (60 ml.), was added with stirring to a hot solution of isatin (44 g.) and potassium hydroxide (18 g.) in water (20 ml.) A further quantity of aqueous potassium hydroxide (38 g. in 75 ml.) was added to the mixture which was then allowed to stand at room temperature for 6 days. The solution was then almost neutralised with hydrochloric acid (ca. 50 ml.), after which most of the ethanol was removed by distillation under reduced pressure, water being added to maintain the original volume. Acidification with dilute hydrochloric acid (150 ml. concentrated acid and 850 ml. of water) precipitated a granular, yellow solid which was collected and partially purified by digestion with hot 1% hydrochloric acid (2litres) to provide 2-phenyl-3-phthalimidoquinoline-4-carboxylic acid as a pale yellow powder, m.p. 268-270° (decomp.) (98 g.). Atkinson and Mattocks give m.p. 278° (decomp.).

2-Phenyl-3-phthalimidoquinoline-4-carboxyamide. --2-Phenyl-3-phthalimidoquinoline-4-carboxylic acid (200 g.) and thionyl chloride (600 ml.) were heated under reflux for 15 min. Excess of thionyl chloride was removed by distillation under reduced pressure, then benzene was added and distilled off to remove the last traces of thionyl chloride. The residual solid in benzene (4 litres) was cooled to 0° and dry ammonia gas was passed into the solution for 30 min. The resulting white solid was filtered off, washed with water, then ethanol, and dried to provide the crude amide (182 g.), m.p. 326-329°.

Recrystallisation from acetic acid provided 2-phenyl-3-phthalimido-quinoline-4-carboxyamide as colourless needles, m.p. 343-344°. Atkinson and Mattocks give m.p. 343°.

3-Amino-2-phenylquinoline-4-carboxyamide. -- The foregoing crude phthalimido-amide (200 g.) was suspended in pyridine (700 ml.) and treated carefully with hydrazine hydrate (350 ml.; 98%). After heating the mixture under reflux for 2hr., it was poured into water (7 litres) and the white precipitate was collected, washed with water and dried. The amido-amide (110 g.) had m.p. 266-267°, unchanged on recrystallisation from methanol. Atkinson and Mattocks give m.p. 265°.

4-Acetyl-3-amino-2-phenylquinoline. -- 3-amino-2-phenylquinoline-4-carboxyamide (35 g.) was added with stirring during 15 min. to a Grignard reagent prepared from magnesium (18 g.) and methyl iodide (54 ml.) in ether (230 ml.) and benzene (600 ml.). The mixture was refluxed for 4 hr., cooled and poured into ice (800 g.). It was then treated with concentrated hydrochloric acid (300 ml.) and stirred for 30 min. The organic layer was extracted with 5N. hydrochloric acid (2 x 200 ml.) and the combined acid solutions were basified with ammonium hydroxide (d. 0.880). The mixture was then extracted with benzene and the washed and dried ($MgSO_4$) benzene solution evaporated. The sticky solid obtained was triturated with ether to yield the ketimide (26 g.) as a light brown solid, m.p. 130-132°). Atkinson and Mattocks give 130-133°.

The ketimide (20 g.) was hydrolised to the amino ketone by heating under reflux with water (100 ml.) and concentrated hydrochloric

acid (50 ml.) for 1 hr. The reaction mixture was cooled, basified with 4N sodium hydroxide and extracted with ether (3 x 200 ml.). The ether solution was dried ($MgSO_4$) and evaporated to yield a yellow oil which crystallised from n-hexane to give 4-acetyl-2-phenylquinoline as pale yellow needles (18.2 g.), m.p.93-94°. Atkinson and Mattocks give m.p. 93-94°.

Methyl phenyl (3'-amino-2'-phenyl-4'-quinolyl) methanol. -- 4-Acetyl-3-amino-2-phenylquinoline (10 g.) in dry ether (300 ml.) was added during 1hr. at 0°, with stirring, to a Grignard reagent prepared from magnesium (3.6 g.) and dry redistilled bromobenzene (16.1 ml.) in dry ether (400 ml.). After heating under reflux for 5hr. and leaving overnight at room temperature, the mixture was stirred with ice (300 g.) and concentrated hydrochloric acid (150 ml.). The organic layer was extracted with 5N-hydrochloric acid (2 x 100 ml.) and the combined acid solutions basified with 4N sodium hydroxide solution. The mixture was extracted with ether (3 x 250 ml.) and the washed and dried ($MgSO_4$) ether solution concentrated to yield a colourless solid (9.2 g.). Recrystallisation from ether provided methyl phenyl (3'-amino-2'-phenyl-4'-quinolyl) methanol as colourless prisms, m.p. 172-173°. (Found: C,81.1; H,5.9; N,8.2. $C_{23}H_{20}N_2O$ requires C,81.2; H,6.1; N8.0 %)

1-Phenyl-1-(3'-amino-2'-phenyl-4'-quinolyl) ethylene. -- The foregoing carbinol (8 g.) was dissolved in concentrated sulphuric acid (40 ml.) and water (35 ml.). The solution was heated under reflux for 1hr., cooled and poured on to ice (100 g.). The mixture was basified with

5N sodium hydroxide solution and the oily product extracted with ether (4 x 150 ml.). The ether solution was dried ($MgSO_4$) and evaporated finally under reduced pressure to yield a light brown oil (7 g.) which did not crystallise after standing for several days. The oil was extracted with boiling n-hexane and the solution was allowed to stand at 0°. The colourless oily product crystallised after 2-3 days as colourless needles. Recrystallisation from n-hexane provided 1-phenyl-1-(3'-amino-2'-phenyl-4'-quinolyl) ethylene (5.8 g.) m.p.101-102° (Found: C,86.2; H,5.5; N,8.8. $C_{23}H_{18}N_2$ requires C,85.7; H,5.6; N,8.7%).

Ethyl 4-(3'-amino-2'-phenylquinolyl) ketone. — 3-amino-2-phenylquinoline-4-carboxyamide (20 g.) was added with stirring during 15 min. to a Grignard reagent prepared from magnesium (10.3 g.) and ethyl iodide (34 ml.) in ether (150 ml.) and benzene (400 ml.). The mixture was heated under reflux for 4 hr., cooled and stirred with ice (500 g.) and concentrated hydrochloric acid (200 ml.) for 15 min. The organic layer was extracted with 5N-hydrochloric acid (200 ml.) and the combined acid solutions basified with ammonia solution (d. 0.880) and extracted with benzene (3 x 250 ml.). Evaporation of the washed and dried ($MgSO_4$) extract yielded a sticky solid (16.8 g.) which on recrystallisation from benzene-light petroleum, yielded the ketimide as colourless crystals m.p. 191° (Found C,78.4; H,5.5; N,16.1. $C_{18}H_{17}N_3$ requires C,78.5; H,6.2; N15.3%).

The ketone was obtained by refluxing the ketimide (10 g.) with water (50 ml.) and concentrated hydrochloric acid (25 ml.) for 1 hr.

The reaction mixture was basified with 4N sodium hydroxide and extracted with ether (3 x 100 ml.) and the residue from evaporation of the dry extract was recrystallised from n-hexane to yield the ketone (8.5 g.) as pale yellow needles, m.p. 78°. (Found: C,78.0; H,6.0;N,10.6. $C_{18}H_{16}N_2O$ requires C,78.3; H,5.7; N,10.2%).

Ethyl phenyl (3'-amino-2'-phenylquinolyl) carbinol. — To a Grignard solution prepared from magnesium (3.6 g.) and bromobenzene (17 ml.) in dry ether (200 ml.) was added a solution of ethyl-4-(3'-amino-2'-phenylquinolyl) ketone (9.0 g.) in ether (200 ml.). The mixture was refluxed in an atmosphere of dry nitrogen for 3hr., allowed to stand overnight and poured into a mixture of ice and water (300 g.); concentrated hydrochloric acid (50 ml.) was added and the mixture stirred for 15 min. The acid layer was separated and the organic layer extracted with a further quantity of 5N-hydrochloric acid (2 x 50 ml.). The combined acid extracts were basified with 5N sodium hydroxide and extracted with ether (5 x 100 ml.). The dried ether extract was evaporated to small bulk (25 ml.) to yield colourless needles (8.5 g.) of the carbinol, m.p. 153°. (Found: C,80.6; H,6.7; N,7.6. $C_{24}H_{22}N_2O$ requires C,81.3; H,6.3; N,7.9 %).

2-Methyl-1-phenyl-1-(3'-amino-2'-phenyl-4'-quinolyl) ethylene. — The foregoing carbinol (8.0 g.) was dissolved in concentrated sulphuric acid (25 ml.) and water (30 ml.) and boiled under reflux for 1hr. The cooled solution was poured into water (200 ml.), basified with

5N-sodium hydroxide and the liberated oil extracted with ether (3 x 200 ml.). The combined ether extract was evaporated after drying ($MgSO_4$) to yield 2-ethyl-1-phenyl-1-(3'-amino-2'-phenyl-4'-quinolyl) ethylene (6.4 g.) as a pale yellow oil. All attempts to crystallise the oil, by storing for several weeks at 0° and by extracting with light petroleum ether, failed. Treatment of the oily ethylene (250 mg.) with picric acid (250 mg.) in ethanol solution (5 ml.) gave 2-ethyl-1-phenyl-1-(3'amino-2'-phenyl-4'-quinolyl) ethylene picrate as pale yellow needles (from ethanol), m.p. 196-197°. (Found: C,63.9; H,4.3; N,11.7. $C_{30}H_{23}N_5O_7$ requires C,63.7; H,4.1; N,12.4 %).

Methyl 3-amino-2-phenylquinoline-4-carboxylate. — 3-amino-2-phenylquinoline-4-carboxylic acid (44.5 g.) was suspended in ether, with mechanical stirring and treated at room temperature with diazomethane in ether (250 ml.) prepared from N-nitroso-N-methylurea (60 g.). Stirring was continued for 1hr. and insoluble material filtered. The filtrate was treated with sufficient acetic acid to destroy unreacted diazomethane, then washed with water and dried. Removal of the ether and crystallisation of the residual red oil from light petroleum (b.p. 80-100°) provided long, pale yellow needles of methyl 3-amino-2-phenylquinoline-4-carboxylate (23.0 g.), m.p. 101-102°. (Found: C,72.8; H,5.1; N,10.2. $C_{17}H_{14}N_2O_2$ requires C,73.4; H,5.1; N,10.1 %).

Dimethyl (3'-amino-2'-phenyl-4'-quinolyl) carbinol. —
Methyl 3-amino-2-phenylquinoline-4-carboxylate (20 g.) in dry ether (600 ml.) was added to a Grignard reagent prepared from magnesium (10.4 g.) and methyl iodide (26.8 g.) in dry ether (800 ml.). The addition was carried out during 1hr. under an atmosphere of nitrogen. The mixture was refluxed for 5hr. and left overnight at room temperature. Saturated ice-cold ammonium chloride solution (200 ml.) was added slowly with stirring the ether layer was separated and the aqueous layer was made almost neutral with hydrochloric acid and extracted with ether (3 x 200 ml.) The combined ether extracts were washed with water (2 x 300 ml.), dried and concentrated to crystallisation, the crystals being collected from the cold concentrate (6.55 g.), m.p. 178-181°. Mother liquors yielded a further 8.45 g. Recrystallisation from ether of the combined material provided dimethyl (3'-amino-2'-phenyl-4'-quinolyl) carbinol as large, colourless, shining prisms (10.4 g.), m.p. 188-190°. (Found: C,77.3; H,6.4; N,9.9. $C_{18}H_{18}N_2O$ requires C,77.7; H,6.5; N,10.1 %).

2-(3'-amino-2'-phenyl-4'-quinolyl) propene. — The carbinol (5.35 g.) was dissolved in concentrated sulphuric acid (50 ml.) with initial cooling to keep the mixture at room temperature. After the solution had been allowed to stand for 3hr., it was poured on to crushed ice (500 g.), made alkaline with 6N sodium hydroxide solution and extracted with ether (3 x 200 ml.). The combined ether extracts were washed with water, dried and evaporated to provide a green solid (4.7 g.), m.p. 87-88°. Recrystallisation from n-hexane provided 2-(3'-amino-2'-phenyl-4'-quinolyl)

propene as large, colourless needles, m.p. 88°. (Found: C,82.5; H,6.2; N,10.9. $C_{18}H_{16}N_2$ requires C,83.0; H,6.2; N,10.8%).

6-Methylquinoline.— A mixture of p-toluidine (42.5 g.), ferrous sulphate (14.4 g.), boric acid (26 g.), o-nitrophenol (32.8 g.) and glycerol (150 g.) was treated with sulphuric acid (d. 1.84 ; 72 ml.) and the mixture heated carefully until reaction began. The source of heat was removed and the reaction allowed to continue under self-reflux for 20 min. After the initial reaction had subsided the mixture was heated under reflux for a further 7 hr., treated with water (800 ml.) and sodium nitrite (10 g.) and boiled for 15 min. The solution was made alkaline with 6N. sodium hydroxide solution and the mixture steam distilled until about 6 l. of distillate had been collected. Extraction of the distillate with ether (3 x 200 ml.), followed by removal of the ether from the dried (Na_2SO_4) solution gave 6-methylquinoline as an almost colourless oil, (51 g.). The product was used without further purification.

6-Methyl-5-nitroquinoline.— A solution of 6-methylquinoline (50 g.) in sulphuric acid (d. 1.84 ; 130 ml.) was cooled to 0° and treated during 90 min. with a mixture of nitric acid (d. 1.42 ; 32 ml.) and sulphuric acid (d. 1.84 ; 50 ml.) at 0 - 5°. After addition was complete the solution was allowed to stand for 10 min. and then poured on to ice (500 g.). The solution was further diluted with water (500 ml.) and then neutralised by the addition of solid sodium bicarbonate. The

yellow, granular precipitate (41 g.) was collected and after drying at 70°, was recrystallised from acetone to yield the nitro-compound as pale yellow needles, m.p. 116° (Long and Schofield give 116 - 117°).

5-Nitroquinoline-6-carboxylic acid.— 6-methyl-5-nitroquinoline (30 g.) was dissolved in sulphuric acid (d. 1.84 ; 120 ml.) and water (100 ml.) and was treated dropwise at 90-95° with a solution of sodium dichromate (60 g.) in water (50 ml.) and sulphuric acid (22 ml.). The addition took about 1 hr. and was carried out with efficient stirring and careful control of temperature. The resulting dark green solution was allowed to stand at about 90° for a further 30 min. and then cooled to below room temperature. Partial neutralisation with 5N-sodium hydroxide gave the acid (21 g.) as a colourless solid after filtration. Recrystallisation from ethanol provided colourless micro-crystals, m.p. 296 - 297°, of the pure 5-nitroquinoline-6-carboxylic acid (Found: C,55.4; H,3.0; N,12.6. $C_{10}H_6N_2O_4$ requires C,55.1; H,2.75; N,12.8%).

5-Nitroquinoline-6-carboxylic acid chloride hydrochloride.— The above acid (8.0 g.) was added in small amounts (about 0.5 g.) to a mixture of well-powdered phosphorus pentachloride (10.0 g.) and acetyl chloride (10.0 ml.), the temperature being maintained at about 20°. The yellow solid (8.4 g.) which separated was collected, washed well with several 10 ml. quantities of dichloromethane and dried at room temperature to yield the acid chloride hydrochloride. The product, which had m.p. 250

was used without purification.

Ethyl-5-nitroquinoline-6-carboxylate.— (a) 5-Nitroquinoline-6-carboxylic acid (10.0 g.) was dissolved in a mixture of ethanol (20 ml.) and sulphuric acid (d. 1.84 ; 10 ml.) and the solution heated under reflux on a steam bath for 10 hr. The resulting solution was poured into water (200 ml.) and made alkaline with solid sodium carbonate. The light brown solid (8.8 g.) which separated was collected, washed well with water and recrystallised from 20% aqueous alcohol to afford the ester as pale yellow needles, m.p. 116° (Found C,58.4; H,4.25; N,11.3. $C_{12}H_{10}N_2O_4$ requires C,58.5; H,4.05; N,11.3%).

(b) 5-Nitroquinoline-6-carboxylic acid chloride hydrochloride (500 mg.) was treated with ethanol (5 ml.), warmed to 50° and allowed to stand at this temperature for about 15 min. The excess alcohol was removed under reduced pressure and the resulting oily product recrystallised from aqueous alcohol (charcoal) to yield the ester as pale yellow needles (380 mg.), m.p. 116°. The m.p. was not depressed on admixture with a sample prepared by method (a).

Ethyl-5-aminoquinoline-6-carboxylate.— The above nitro-ester (1 g.) was reduced by a stannous chloride reagent, prepared in bulk by passing dry HCl gas through a stirred suspension of stannous chloride (112 g.) in a mixture of acetic anhydride (100 ml.) and acetic acid (400 ml.) until a clear solution was obtained.

The nitro-ester was added in small quantities to the reagent (30 ml.) with stirring. After about 10 min. a cream complex separated

which was collected and stirred with 4N-sodium hydroxide (50 ml.). Extraction of the mixture with ether (4 x 100 ml.) provided, on evaporation of the dried ($MgSO_4$) ether extract, a pale yellow solid (650 mg.), m.p. 78-84°. Recrystallisation from petroleum ether (b.p. 60-80°) and separation from a small amount (50 mg.) of brown, insoluble residue, gave ethyl 5-aminoquinoline-6-carboxylate as colourless blades, m.p. 112° (Found: C,66.4; H,5.5; N,12.9. $C_{12}H_{12}N_2O_2$ requires C,66.6; H,5.6; N,12.9%).

Reduction of 5-nitroquinoline-6-carboxylic acid.-- A stirred mixture of the nitro-acid (2.2 g.), stannous chloride dihydrate (6.7 g.) and glacial acetic acid (15 ml.) was treated dropwise at 80° with concentrated hydrochloric acid (10 ml.) and allowed to stand at 70-80° for 5 hr. The mixture was cooled, diluted to about 300 ml. with water, and treated with hydrogen sulphide until precipitation of the sulphide was complete. The clear, orange solution, obtained on filtration, was evaporated to about 50 ml. and made alkaline with 2N-sodium hydroxide. The flocculent, grey-white precipitate was collected and recrystallised from water (charcoal) to afford 5-aminoquinoline (950 mg.), m.p. and mixed m.p. with a pure, known sample 101°.

Dimethyl-(5'-amino-6'-quinolyl)-methanol.-- Ethyl 5-aminoquinoline-6-carboxylate (8.5 g.), dissolved in dry ether (300 ml.), was added to a Grignard reagent prepared from magnesium (5.2 g.) and methyl iodide

(13.4 g.) in dry ether (400 ml.). The addition was carried out during 30 min. in an atmosphere of dry nitrogen. The mixture was refluxed for 6 hr. and then allowed to stand overnight at room temperature. The mixture was poured slowly, with stirring, into ice-cold 5N-hydrochloric acid (80 ml.) and the aqueous layer separated. The acid solution was neutralised with 4N-sodium hydroxide and was then extracted with benzene (3 x 200 ml.) to yield, on evaporation of the dried benzene solution, the crude carbinol (6.2 g.) as an almost colourless solid. Recrystallisation from petroleum ether, (b.p. 60-80°) gave dimethyl-(5-amino-6-quinolyl)-methanol as long, colourless needles m.p. 154° (Found: C,71.6; H,6.7; N,13.7. $C_{12}H_{14}N_2O$ requires C,71.2; H,7.0; N,13.9%).

2-(5'-Amino-6'-quinolyl)-propene.— The foregoing carbinol (5 g.) was dissolved in 12N-sulphuric acid (100 ml.) and the solution boiled under reflux for 4 hr. The resulting clear solution was poured on to crushed ice (100 g.) and neutralised with solid sodium carbonate. Extraction with ether provided, on evaporation of the dried ether extract, the amino-propene as a pale yellow oil (3.8 g.) which soon solidified on cooling at 0°. Extraction of the oil and recrystallisation using 50/50 benzene-petroleum ether (b.p. 60-80°), gave 2-(5'-amino-6'-quinolyl)-propene as small, colourless needles, m.p. 111° (Found: C,77.8; H,6.5; N,15.0. $C_{12}H_{12}N_2$ requires C,78.2; H,6.6; N,15.2%).

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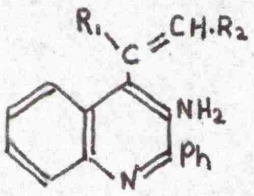
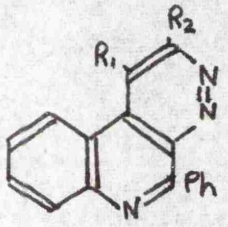
(2) THE WIDMAN-STOERMER REACTION: The reaction between o-amino-quinolylethylenes and nitrous acid.

The effect of heterocyclic nuclei on the Widman-Stoermer reaction has already been discussed in Part II of this thesis (page 94) and the retarding effect of the pyridine ring has been illustrated by studies in the reaction of various aminopyridyl-propenes with nitrous acid. The experimental work described in this section is an extension of these studies to a number of amino-ethylenes in the quinoline series (I), (II), (III), (IV), with the intention of preparing the alkyl and aryl-1,2,9-triazaphenanthrenes (V) and the methyl derivative of the hitherto unreported 3,4,8-triazaphenanthrene (VI).

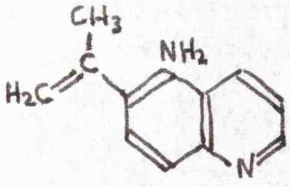
	R_1	R_2
(I)	Me	H
(II)	Ph	H
(III)	Ph	Me

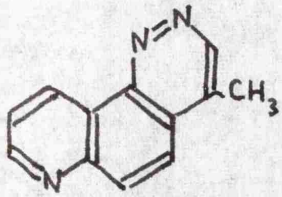




(V)

(IV)





(VI)

The results of these experiments are summarised in the table below:

Compound	% Yield of cyclised product		
	a	b	c
(I)	Picrate only, in low yield.	No product.	No product.
(II)	---	45	90
(III)	---	18	48
(IV)	60	17	27

a) Method of Jacobs[1] in very dilute acid.

b) Concentrated hydrochloric acid at 50-60°.

c) Sulphuric-acetic acid.

The results obtained are in general agreement with previous investigations of the Widman-Stoermer reaction. In the case of the propene (I), 4-methyl-1,2,9-triazaphenanthrene (V; R_1 = Me, R_2 = H) was isolated in only very low yield as its picrate, probably due to the powerful inhibiting effect of the hetero atom. The susceptibility of the reaction to acid concentration is illustrated by the failure to isolate any product in reactions b and c except the phenol formed by decomposition of the diazonium salt.

Moderate yields of 1-methyl-3,4,8-triazaphenanthrene (VI) were obtained on diazotisation of the propene (IV), however, particularly under the conditions used by Jacobs. These results were predictable since the cyclisation in this case is occurring between substituents in the benzene half of the quinoline molecule where the ring nitrogen atom is exerting little influence.

The fact that aryl groups in competition with heterocyclic nuclei often lead to good yields of cyclised products[2] is illustrated by the fair to excellent yields obtained in the case of the two 1,2,9-triazaphenanthrenes (V; R_1 = Ph, R_2 = H and R_1 = Ph, R_2 = Me) even in a strongly acidic environment. The cyclisation of the amino-ethylene (II) in acetic-sulphuric acid at room temperature produced an almost quantitative yield of 4,10-diphenyl-1,2,9-triazaphenanthrene. The much lower yields of 3-methyl-4,10-diphenyl-1,2,9-triazaphenanthrene obtained by cyclisation of the diazotised amino-ethylene (III) are difficult to explain, however, since the methyl group at the Cβ carbon atom of the ethylene group might be expected to facilitate the reaction by electron release.

EXPERIMENTAL

Reaction of 2-(3'-amino-2'-phenyl-4'-quinolyl)-propene with nitrous acid.--(a) The amino-propene (2 g.) in water (10 ml.) and sulphuric acid (d. 1.84; 1 ml.) was cooled to below 0° and treated dropwise, with stirring, with a solution of sodium nitrite (500 mg.) in water (2 ml.). After the solution had been maintained at about 0-5° for 1 hr., it was poured into water (75 ml.) and stored in the dark, at room temperature, for 7 days. During this time, the solution slowly darkened and a brown precipitate formed. Continuous extraction with chloroform (250 ml.) gave, after drying ($MgSO_4$), and evaporation of the chloroform under reduced pressure, a dark, oily product (250 mg.) which solidified on standing. Neither extraction with ligroin nor chromatography on alumina afforded any useful product. However, treatment of the residue with picric acid in methanol solution yielded a small amount of 4-methyl-10-phenyl-1,2,9-triazaphenanthrene picrate (45 mg.), m.p. 235°, as yellow-green needles, after several recrystallisations from methanol. (Found: C,57.0; H,3.3; N,17.0. $C_{24}H_{18}O_7N_6$ requires C,57.6; H,3.2; N,16.8%).

(b) The amino-propene (500 mg.) in water (2 ml.) and sulphuric acid (d. 1.84; 0.2 ml.) was cooled below 0° and diazotised by dropwise addition of a solution of sodium nitrite (180 mg.) in water (2 ml.). The solution was kept at 0° for 1 hr. and then diluted to 10 ml. with water and allowed to stand for 2 days at room temperature. The dark brown, amorphous solid (210 mg.) which separated was filtered. It could not be crystallised and did not melt below 320°, although it decomposed and softened at about 110°. Extraction with both benzene and with dilute sodium hydroxide

afforded no useful product.

(c) The amino-propene (500 mg.) was dissolved in 4N hydrochloric acid (6 ml.) and the solution cooled to 0°. Sodium nitrite (150 mg.) in water (2 ml.) was added dropwise and the clear, yellow solution allowed to stand at about 0° for 10 min. The solution was then warmed to 50-60° when a vigorous effervescence occurred (probably nitrogen evolution). The coupling reaction became negative after about 5 min. and heating was continued for a further 10 min. The orange-yellow solution was basified with 2N sodium hydroxide solution and continuously extracted with chloroform (100 ml.). Evaporation of the chloroform gave only a small amount (20 mg.) of oily residue from which no useful product could be obtained. The aqueous solution was neutralised by addition of dilute hydrochloric acid. The oily precipitate (220 mg.) rapidly solidified and was collected. Recrystallisation from 50:50 benzene-petroleum ether (60-80°) afforded 2-(3'-hydroxy-2'-phenyl-4'-quinolyl)-propene as small, colourless blades, m.p.109-110° (Found: C,82.2; H,5.9; N,5.2. $C_{18}H_{15}ON$ requires C,82.7; H,5.8; N,5.4%).

4,10-Diphenyl-1,2,9-triazaphenanthrene.— (a) A solution of the amine (8 g.) in glacial acetic acid (15 ml.) and sulphuric acid (d. 1.84; 2 ml.) was treated dropwise at about 0° over 30 min. with sodium nitrite (1.8 g.) in water (10 ml.). The resulting dark red solution was allowed to stand at room temperature for 2 hr. and then poured into water (150 ml.). The buff-yellow solid (7.5 g.) which precipitated from methanol to yield 4,10-diphenyl-1,2,9-triazaphenanthrene as pale yellow needles

(7.3 g.), m.p. 185-186° (Found: C,82.0; H,4.45; N,13.1. $C_{22}H_{15}N_3$ requires C,82.9; H,4.5; N,12.6%). Infra-red sprectrum (Nujol mull); max. at 1585, 1565, 1551, 1517, 1507, 1406, 1316, 1306, 1238, 1208, 1172, 1166, 1148, 1138, 1112, 1069, 1022, 990, 972, 947, 914, 855, 837, 828, 767, 760, 741, 731, 725, 708, 700, and 692 cm^{-1}.

(b) The amine (500 mg.), dissolved in concentrated hydrochloric acid (3 ml.) and water (1 ml.), was diazotised at 0° with solid sodium nitrite (120 mg.) and the solution was allowed to stand for 5 min. The mixture was treated with a further quantity of concentrated hydrochloric acid (5 ml.) and heated at 50-60° for 30 min. The solution was concentrated under reduced pressure and then treated with water (30 ml.) to yield, on filtration, 4,10-diphenyl-1,2,9-triazaphenanthrene (230 mg.) as yellow needles from methanol, m.p. and mixed m.p. 185-186°.

3-Methyl-4,10-diphenyl-1,2,9-triazaphenanthrene.— (a) 2-Methyl-1-phenyl-1-(3'-amino-2'-phenyl-4'-quinolyl)-ethylene (2 g.) was dissolved in glacial acetic acid (8 ml.) and sulphuric acid (d. 1.84; 1.0 ml.) at below 0° and treated dropwise at 0-5° with sodium nitrite (450 mg.) in water (5 ml.). The solution was allowed to stand at room temperature for 30 min. and was then poured into water (50 ml.). The mixture was made alkaline with 4N-sodium hydroxide and the yellow-green precipitate was collected, washed well with water and recrystallised from ethanol to afford 3-methyl-4,10-diphenyl-1,2,9-triazaphenanthrene (920 mg.) as pale yellow needles, m.p. 192°.

(Found: C,82.4; H,5.0; N,12.2. $C_{24}H_{17}N_3$ requires C,83.0; H,4.9; N,12.1%). Neutralisation of the alkaline filtrate with 2N-hydrochloric acid gave a green precipitate (350 mg.) which was collected and recrystallised from methanol (charcoal) to yield 2-methyl-1-phenyl-1-(3'-hydroxy-2'-phenyl-4'-quinolyl)-ethylene as colourless needles, m.p. 131-132° (Found: C,84.7; H,5.7; N,5.2. $C_{24}H_{19}NO$ requires C,85.4; H,5.7; N,4.2%).

(b) The amino-propene (500 mg.), dissolved in concentrated hydrochloric acid (10 ml.), was diazotised with solid sodium nitrite (120 mg.) and the solution was then warmed to about 60° on a water bath. The solution darkened, with some effervescence, and coupling properties ceased after about 15 min. The solution was allowed to stand for a further 15 min. and was then made alkaline with 4N-ammonium hydroxide. The sticky, dark yellow precipitate (170 mg.) which separated, was collected and afforded 3-methyl-4,10-diphenyl-1,2,9-triazaphenanthrene (90 mg.) as yellow needles, m.p. 191-192°, after several recrystallisations from ethanol. A mixed m.p. with the product obtained by method (a) above was undepressed.

1-Methyl-3,4,8-triazaphenanthrene.— (a) 2-(5'-Amino-6'-quinolyl)-propene (1.0 g.), dissolved in 5N-sulphuric acid (5 ml.), was treated at 0-5° with sodium nitrite solution (5%; 10.0 ml.). The resulting pale yellow solution was diluted with ice-water mixture (600 g.) and the mixture allowed to stand in the dark, at room temperature for 5 days. The solution was made alkaline with 2N-sodium hydroxide

and continuously extracted with ether for 24 hr. to give, on evaporation of the dried ether solution, an almost colourless solid (770 mg.). Recrystallisation from petroleum ether (b.p. 60-80°) gave 1-methyl-3,4,8-triazaphenanthrene (620 mg.) as colourless plates, m.p. 184° (Found: C,73.5; H,5.0; N,21.3. $C_{12}H_9N_3$ requires C,73.9; H,4.6; N,21.5%). Infra-red spectrum (KBr disc): max. at 1618, 1578, 1522, 1482, 1385, 1357, 1300, 1214, 1103, 1065, 1030, 1015, 920, 842, 795, and 690 $cm.^{-1}$

(b) The amino-propene (250 mg.), dissolved in glacial acetic acid (8 ml.) and sulphuric acid (d. 1.84; 1.0 ml.), was diazotised with solid sodium nitrite (100 mg.) at 0-5°. The solution was diluted with water (5 ml.), allowed to stand for 15 min. at 0-5°, and then heated slowly to about 60°. After the solution had been maintained at this temperature for 1 hr., water (20 ml.) was added and sufficient solid sodium carbonate to render the solution alkaline. The mixture was continuously extracted with ether (100 ml.) for 24 hr. and the ether solution provided, on evaporation, a light brown, oily solid (130 mg.) from which 1-methyl-3,4,8-triazaphenanthrene (70 mg.) was obtained by recrystallisation from petroleum ether, as colourless plates, m.p. 184°. A mixed m.p. with the product obtained by method (a) above was undepressed.

(c) The amino-propene (250 mg.), dissolved in concentrated hydrochloric acid (5 ml.), was diazotised with solid sodium nitrite (100 mg.) at 0-5° and allowed to stand for 15 min. A further amount of concentrated

hydrochloric acid (10 ml.) was added and the clear solution heated at 55-60° for 1 hr. After this time, the solution no longer coupled with alkaline 2-naphthol. Excess hydrochloric acid was removed by evaporation to about 5 ml. under reduced pressure. The solution was then diluted with water (20 ml.), made alkaline with 2N-sodium hydroxide and extracted continuously with benzene (100 ml.) for 24 hr. Removal of the benzene from the dried ($MgSO_4$) solution gave a brown oil (100 mg.) which solidified on standing and from which 1-methyl-3,4,8-triazaphenanthrene (45 mg.) was obtained as almost colourless plates, m.p. 184°, by several recrystallisations from petroleum ether (b.p. 60-80°).

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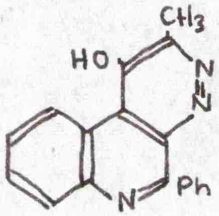
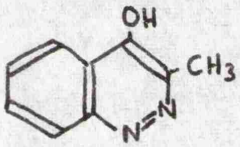
(5) DERIVATIVES OF 3-METHYL-10-PHENYL-1,2,9-TRIAZAPHENANTHRENE.

The starting material for this series of compounds, namely the amino-ketone (I) has been converted to 4-hydroxy-3-methyl-10-phenyl-1,2,9-triazaphenanthrene (II) by diazotisation and cyclisation, using a modified Borsche reaction. That the reaction is applicable to o-amino ethyl-ketones has been shown by Kenoford, Schofield and Simpson[1] who obtained 4-hydroxy-3-methylcinnoline (III) by the cyclisation of diazotised o-aminopropiophenone.

(I)



(II)

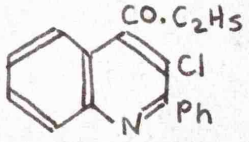


(III)

Atkinson and Mattocks[2] found that the diazotisation and attempted cyclisation of 4-acetyl-3-amino-2-phenylquinoline failed under normal acid conditions but was successful in an alkaline environment (see page 120).

In the present case, ethyl-4-(3'-amino-2'-phenylquinolyl)-ketone (I) was diazotised, and attempted cyclisation in acid solution afforded low yields of the required hydroxy-triazaphenanthrene (II). Treatment with excess hydrochloric acid gave as the major product the 3-chloro-compound (IV). Several examples of the replacement of a diazonium group by chlorine in hydrochloric acid have been reported. A comparable example is that due to Schatzmann[3] who diazotised a 2-aminothiazole in hydrochloric acid and obtained the 2-chloro derivative. Attempts

to remedy this reaction by cyclisation in sulphuric acid were unsuccessful, leading only to replacement of the amino group by hydroxyl (V).



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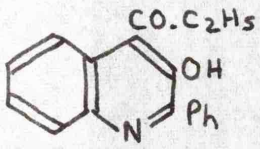


(V)

Using the procedure of Atkinson and Mattocks[2], the diazotised solution was strongly basified, the temperature being kept below 0°. The basic solution, on being allowed to warm up slowly, gave an excellent yield of the required hydroxy-triazaphenanthrene (II). This is a further illustration of the probable generalised nature of the modified Borsche reaction.

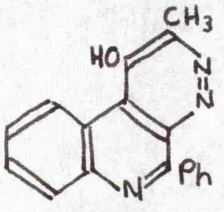
The hydroxy-compound (II) was readily converted to the chloro-compound (VI) by heating it with a mixture of phosphoryl chloride and phosphorus pentachloride. Attempts to prepare the amine (VIII) by treatment of the chloro-compound (VI) with ammonia gas and phenol at 180° gave the 4-phenoxy-compound (VII). Replacement of the ammonia by potassium hydroxide, according to the method of Keneford and Simpson[4] gave the phenoxy-compound in similar yield.

The amine (VIII) was prepared from the phenoxy-compound (VII) by fusion with ammonium acetate (cf. Keneford, Schofield and Simpson[1]);

when the latter reagent was replaced by acetamide and a stream of ammonia was passed through the hot mixture, an improved yield of the amine was obtained. A monomethiodide (IX) was prepared by heating the amine with methyl iodide in methanol.

Treatment of the hydroxy-compound (II) with dimethyl sulphate and alkali yielded the N-methyl derivative (X) distinct from the O-methyl isomer (XI), prepared from the chloro-compound (VI) and sodium methoxide.

Attempts to prepare the base, 3-methyl-10-phenyl-1,2,9-triaza-phenanthrene (XII), from the 4-chloro derivative by the use of p-toluenesulphonhydrazide (method due to Albert and Royer[5]) failed to produce an intermediate compound. Direct reduction of the 4-hydroxy derivative using lithium aluminium hydride produced small amounts of the base, isolated as its picrate. Yields were too low to permit isolation of the free base. This method was used successfully by Badger[8] for the reduction of benzacridone and phenanthridone.



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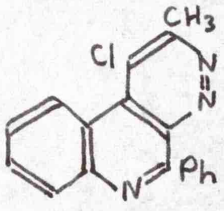

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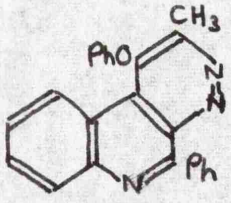

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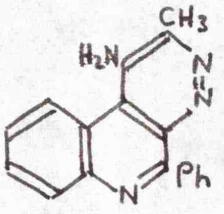

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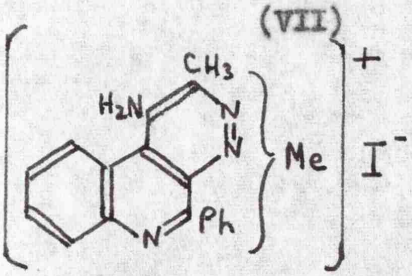

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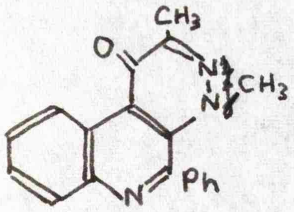

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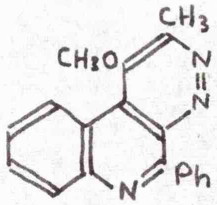


(XI)

(XII)

EXPERIMENTAL

Action of nitrous acid on ethyl 4-(3'-amino-2'-phenylquinolyl)-ketone.—(a) A hot solution of the amino-ketone (1 g.) in concentrated hydrochloric acid (2.5 ml.) and water (10 ml.) was cooled to -5° and the finely divided suspension was treated below 0° with a solution of sodium nitrite (300 mg.) in water (5 ml.) during 5 min. The solution was then treated with 6N sodium hydroxide solution (10 ml.), with stirring, and the mixture allowed to warm to room temperature during 2 hr. A small amount of dark brown precipitate was filtered off and the orange-yellow solution neutralised with 5N hydrochloric acid. The precipitate of 4-hydroxy-3-methyl-10-phenyl-1,2,9-triazaphenanthrene (900 mg.) was collected. Recrystallisation from ethanol yielded colourless leaflets, m.p. 202° (Found: C,75.2; H,4.6; N,14.6. $C_{18}H_{13}N_3O$ requires C,76.0; H,5.0; N,14.7%).

(b) The ketone (500 mg.) was dissolved in concentrated hydrochloric acid (5 ml.) and treated at 0° with a solution of sodium nitrite (150 mg.) in water (1 ml.) during 5 min. After a few minutes, concentrated hydrochloric acid (10 ml.) was added and the mixture was heated at 60° for 2 hr. Excess hydrochloric acid was then removed under reduced pressure and the residue neutralised with a concentrated solution of sodium acetate. The oily solid (400 mg.) was collected and after drying, was digested with n-hexane to yield an insoluble fraction (30 mg., m.p. 195-197°), identical with the hydroxy-compound, m.p. 202°, and a soluble fraction, m.p. 83-84°, identified as ethyl-4-(3'-chloro-2'-phenyl-quinolyl)-ketone. (Found: C,72.6; H,4.6; N,4.5; Cl, 11.6. $C_{18}H_{14}NOCl$ requires C,73.1; H,4.8; N,4.7; Cl,12.0%).

(c) The ketone (250 mg.) was dissolved in dilute (10%) sulphuric acid (5 ml.) and was diazotised at 0° with a solution of sodium nitrite (80 mg.) in water (1 ml.) during 5 min. The solution was allowed to stand at 0° for a further 5 min. and then at 70° for 1 hr. (a gas, probably nitrogen, was evolved). The mixture was neutralised with ammonia solution, the oily precipitate extracted with chloroform (2 x 25 ml.) and the dried ($MgSO_4$) extract evaporated, yielding a sticky, yellow solid (160 mg.). Several recrystallisations from petroleum-ether b.p. 80-100°) gave almost colourless needles of ethyl-4-(3'-hydroxy-2'-phenylquinolyl)-ketone, m.p. 89-90°. (Found: C,77.5; H,5.1; N,5.3. $C_{18}H_{15}O_2N$ requires C,78.0; H,5.5; N,5.0%). The compound was readily soluble in dilute alkalis.

4-chloro-3-methyl-10-phenyl-1,2,9-triazaphenanthrene.— The 4-hydroxy compound (600 mg.), phosphorus pentachloride (1 g.) and phosphoryl chloride (4.5 ml.) were heated together under reflux for 2 hr. The excess phosphoryl chloride was distilled off under reduced pressure and the residue was shaken with benzene (25 ml.), ice (20 g.) and 2N-sodium hydroxide (15 ml.) for 20 min. The benzene layer was collected and the aqueous layer extracted with a further quantity of benzene (2 x 20 ml.). The combined benzene extracts were dried ($MgSO_4$) and evaporated to yield a buff solid (550 mg.) m.p. 180-183°. The pure chloro compound, m.p. 186° crystallised as colourless blades from ethyl acetate. (Found: C,71.0; H,4.3; N,12.6; Cl,12.1. $C_{18}H_{12}N_3Cl$ requires C,70.7; H,4.0; N,13.7; Cl,11.6%).

4-Phenoxy-3-methyl-10-phenyl-1,2,9-triazaphenanthrene.— (a) A stream of

dry ammonia was passed through a solution of the chloro-compound (200 mg.) in phenol (1.5 g.) at 180°. The stirred solution was then heated on a steam bath with sodium hydroxide solution (2 g. in 15 ml.) for 15 min., cooled and the product collected and washed with 3N-sodium hydroxide solution and then with water. The product (220 mg., m.p. 152-156°) crystallised from methyl acetate to give colourless needles of the phenoxy-compound, m.p. 159-160°. (Found: C,79.3; H,4.8; N,11.3. $C_{24}H_{17}ON_3$ requires C,79.3; H,4.7; N,11.6%).

(b) The chloro-compound (300 mg.) was heated on a steam bath for 2 hr. with potassium hydroxide (100 mg.) in phenol (1.5 g.). The mixture was cooled and digested with warm 2N-sodium hydroxide solution (25 ml.). The precipitated phenoxy-compound (300 mg.) was collected and crystallised from methyl acetate, m.p. and mixed m.p. 159-160°.

4-amino-3-methyl-10-phenyl-1,2,9-triazaphenanthrene.— (a) The phenoxy-compound (200 mg.) was heated in an open tube with ammonium acetate (2g.) at 180-200° in an oil bath for 3 hr., the ammonium acetate being renewed when necessary. The cold mixture was digested with dilute sodium hydroxide solution and the well-washed, crude product (110 mg.), m.p. 235-240° was recrystallised from nitromethane to provide light brown needles of the amine, m.p. 245-246° (Found: C,72.6; H,5.0; N,17.6. $C_{18}H_{14}N_4.H_2O$ requires C,71.1; H,5.3; N,18.4%).

(b) A stream of dry ammonia was passed for 30 min. through a solution of the phenoxy-compound (100 mg.) in acetamide (1 g.) at 175° ± 5°. The mixture was cooled and diluted with water, and the precipitated product

m.p. 225-230°, was collected and washed well with water. This material could be separated into two fractions: the amino-compound (65 mg., m.p. 245-246°), soluble in warm dilute hydrochloric acid, and the insoluble, unchanged phenoxy-compound (20 mg., m.p. 157-158°).

4-Amino-3-methyl-10-phenyl-1,2,9-triazaphenanthrene methiodide.— The amine (100 mg.) was heated under reflux with methyl iodide (1 ml.) and methanol (1ml.) for 3 hr., then cooled and the yellow, crystalline precipitate (80 mg.) recrystallised from methanol to give orange-yellow needles (60 mg.) of the methiodide, m.p. 263° (decomp.). (Found: C,53.8; H,3.7; N,13.0; I,29.2. $C_{19}H_{17}N_4I$ requires C,53.3; H,3.9; N,13.1; I,29.7%).

4-Acetamido-3-methyl-10-phenyl-1,2,9-triazaphenanthrene.— The amine (50 mg.) was heated under reflux with acetic anhydride (0.5 ml.) for 15 min. The cold solution was shaken with water (2 ml.) and ethanol (1 ml.) and the product (35 mg.) was collected. Recrystallisation from acetic acid provided the acetyl-derivative as colourless plates, m.p. 267-268°. (Found: C,73.0; H,4.5; N,17.4. $C_{20}H_{15}ON_4$ requires C,73.4; H,4.6; N,17.1%).

4-Methoxy-3-methyl-10-phenyl-1,2,9-triazaphenanthrene.— The 4-chloro-compound was treated with methanolic sodium methoxide, prepared from sodium (100 mg.) and methanol (15 ml.) and the mixture heated under reflux for 2 hr. The solution was concentrated to half-volume, then cooled and the resulting silky precipitate (100 mg.)collected and recrystallised from ethyl alcohol to provide colourless needles of the methoxy-compound, m.p. 201-202° (Found: C,76.2; H,5.1; N,14.4. $C_{19}H_{15}ON_3$

requires C,75.7; H,5.0; N,14.0%).

N-Methyl-4-oxo-3-methyl-10-phenyl-1,2,9-triazaphenanthrene.— A cold solution of the hydroxy-compound (100 mg.) in 3N sodium hydroxide (2 ml.) was treated with dimethyl sulphate (0.1 ml.) and the suspension heated at ca.50° for 5min. The product (90 mg.) which rapidly solidified, was collected and recrystallised from ethyl alcohol to provide the methyl-derivative as colourless leaflets, m.p. 243-244° (Found: C,75.6; H,5.0; N,13.9. $C_{19}H_{15}ON_3$ requires C,75.7;H,5.0; N,14.0%).

Attempted preparation of 3-methyl-10-phenyl-1,2,9-triazaphenanthrene.— (a) The 4-hydroxy-compound (250 mg.), suspended in dry tetrahydrofuran (5 ml.), was treated cautiously with lithium aluminium hydride (130 mg.). The mixture was refluxed for 5 hr., allowed to stand overnight and then treated with benzene (15 ml.) and a little water. The mixture was filtered and the dark brown benzene solution concentrated to about 5 ml. Excess of red mercuric oxide (50 mg.) was added and the mixture boiled under reflux for 1 hr., filtered and evaporated to yield a dark, oily residue (60 mg.). Treatment of the oil with picric acid in hot methanol solution gave 3-methyl-10-phenyl-1,2,9-triazaphenanthrene picrate (40 mg.) as yellow-green needles, m.p. 207-208°. (Found: C,58.0; H,3.5; N,16.3. $C_{24}H_{16}O_7N_6$ requires C,57.6; H,3.2; N,16.8%).

(b) The 4-hydroxy-compound (200 mg.) in dry tetrahydrofuran (10 ml.) was treated as described above with lithium aluminium hydride (80 mg.) and the mixture boiled under reflux for 4 hr. Wet ether (10 ml.) was added and the mixture filtered. The residue was washed with a further

quantity of ether (10 ml.) and the combined ether extracts evaporated to yield a light brown oil (65 mg.) . Treatment with picric acid in methanol gave, on cooling, only a small amount (10 mg.) of the above picrate, m.p. and mixed m.p. 207-208°.

(c) The 4-chloro-compound (100 mg.) and p-toluenesulphonhydrazide (150 mg.) were dissolved in chloroform (5 ml.) and heated together under reflux for 3 hr. The colour of the solution rapidly darkened to a deep red-brown and on cooling only a small amount of a high-melting, dark brown solid separated. No recognisable product could be obtained from the chloroform solution by evaporation and extraction with warm, dilute sodium hydroxide solution.

REFERENCES

1. Keneford, Schofield and Simpson, J., 1948, 358.

2. Atkinson and Mattocks, J., 1957, 3722.

3. Schatzmann, Ann., 1891, 261, 6.

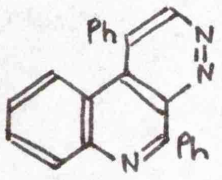
4. Keneford and Simpson, J., 1947, 920.

5. Albert and Royer, J., 1949, 1148.

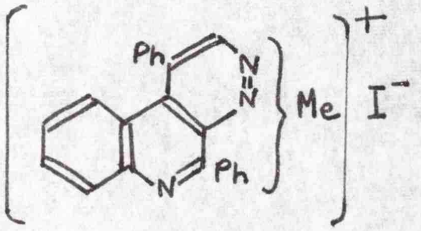
6. Badger, Stedler and Thomson, J., 1951, 3207.

(4) REACTIONS OF 4,10-DIPHENYL-1,2,9-TRIAZAPHENANTHRENE.

This section describes a number of experiments with the above triazaphenanthrene (I) which were undertaken for the purpose of comparison with the 4-arylcinnolines, to which it is closely related. Treatment of the base with methyl iodide in nitromethane gave the methiodide (II). Quaternary salt formation occurs fairly readily in alcoholic solution with a number of 4-arylcinnolines [1], but attempts to prepare the methiodide (II) in methanol were unsuccessful.



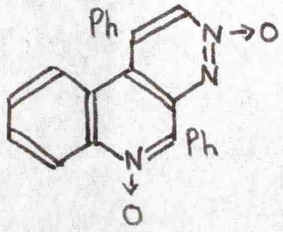
(I)



(II)

In experiments to examine the possibility of retention of the azo-group (-N = N-) reactivity in substituted cinnolines, Atkinson and Simpson[2] established N-oxide formation as a characteristic property of 4-arylcinnolines. In contrast to the di-N-oxides of quinoxaline, the N-oxides of 4-arylcinnolines showed no peroxidic properties (cf. McIlwain[3]). Under the conditions used by Atkinson and Simpson[2] oxidation of 4,10-diphenyl-1,2,9-triazaphenanthrene (I) afforded a di-N-oxide, (III). However, at lower temperatures it was possible to isolate the mono-N-oxide (IV). The structures drawn for the two N-oxides are only tentative, since the site of N-oxidation in these compounds has not been determined. From a consideration of the charge

densities of the nitrogen atoms of azanaphthalenes and azaphenanthrenes calculated by Longuet-Higgins and Coulson[4], it seems that N_9 and either N_1 or N_3 are likely sites of N-oxidation. Recent studies by Ames and Kucharska[5] have shown that the basic centre in cinnoline is N_2 and not N_1 as suggested earlier and structure (III) is proposed for the di-N-oxide.



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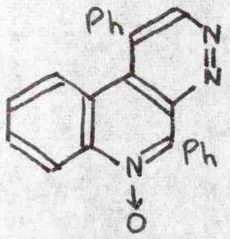
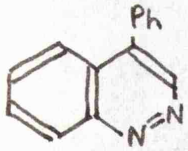


(IV)

Oxidation of 4-phenylcinnoline (V) by Stoermer and Fincke[1] with aqueous potassium permanganate gave the pyridazine dicarboxylic acid (VI) from which they obtained the pyridazine by degradation.



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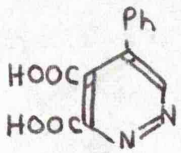

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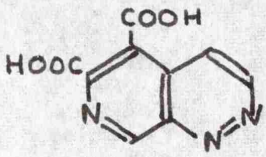


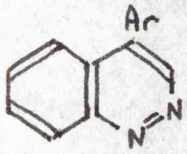
(VII)

Attempted oxidation of the triazaphenanthrene under the same conditions, however, gave none of the required triazanaphthalene dicarboxylic acid (VII). The benzene ring when fused to pyridazine is apparently more susceptible to oxidation than when fused to a pyridine ring.

The most interesting property of 4-arylcinnolines (VIII) is their behaviour on reduction. Atkinson and Simpson[2] examined the

behaviour of these compounds on reduction with sodium in ethanol and found that under these conditions the cinnoline was reduced to the 3-arylindole ((X) with loss of ammonia. These observations were in keeping with those of Neber, Knoller, Herbst and Trissler[6] who found that reduction with various media yielded 3-phenylindole from 4-phenylcinnoline and oxindole from 4-hydroxycinnoline.

Atkinson and Simpson suggested that the reaction might proceed by cyclisation of the unstable intermediate diamine (IX).



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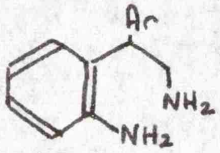

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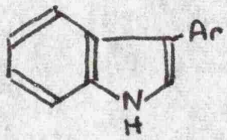
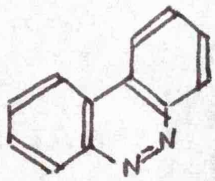


(X)

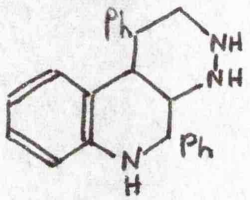
The diamines do not apparently survive the conditions of the reaction, but they have been isolated as reduction products of some benzocinnolines of type (XI) by King and King[7].



(XI)

4,10-Diphenyl-1,2,9-triazaphenanthrene proved less susceptible to reduction than the arylcinnolines examined by Atkinson and Simpson[2]. Thus, reaction with sodium in ethanol occurred without loss of ammonia.

The identity of the product has not been fully established but its analysis corresponds to either the octahydrotriazaphenanthrene (XII) or the diamine (XIII). The latter is unlikely, however, since the absence of an aromatic group has been shown by attempted diazotisation and coupling.



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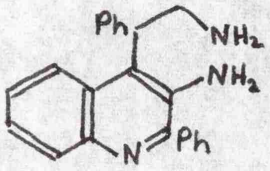
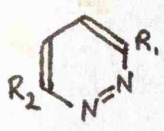
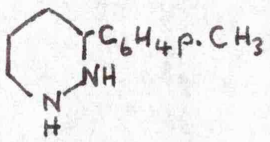


(XIII)

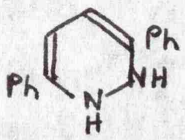
Reference to the behaviour of a number of pyridazines on reduction with sodium in ethanol is useful. Pyridazine (XIV : $R_1 = R_2 = H$) itself gives diaminobutane in low yield (Marquis[8]). Substituted pyridazines, however, are more difficult to reduce, particularly when aryl-groups are present. Katzellenbogen[9] has shown that the reduction of 3-p-tolylpyridazine (XIV : R_1 = p-tolyl, $R_2 = H$) gives mainly the hexahydro-derivative (XV), whereas Paal and Dencks[10], working with 3,6-diphenylpyridazine (XIV : $R_1 = R_2$ = phenyl), obtained only the dihydro-derivative (XVI) under the same conditions.



(XIV)



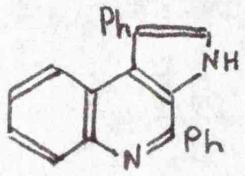
(XV)



(XVI)

These results are in keeping with the observation of Atkinson and Simpson[2], who showed that 3,4-diarylcinnolines can not be reduced to indoles.

Acid reduction of the triazaphenanthrene (I), using zinc amalgam in acetic acid gave a new reduction product whose analysis corresponds to 1,5-diphenylpyrrolo-(2,3-c)-quinoline (XVII) obtained by loss of nitrogen as ammonia from the pyridazine ring. This reaction is analagous to the reduction of 4-phenylcinnoline to 3-phenylindole under the same conditions (cf. Stoermer and Fincke[1]).



(XVII)

EXPERIMENTAL

4,10-Diphenyl-1,2,9-triazaphenanthrene methiodide.— (a) 4,10-diphenyl-1,2,9-triazaphenanthrene (100 mg.) in methyl alcohol (5 ml.) was boiled under reflux with methyl iodide (1 ml.) for 3 hr. The solution was allowed to cool and the precipitate (85 mg.) was collected to yield, on crystallisation from methyl alcohol, pale yellow needles, m.p. 180-182°. A mixed m.p. with the starting material was undepressed.
(b) The base (100 mg.), dissolved in nitromethane (5 ml.), was boiled under reflux with methyl iodide (1 ml.) for 1 hr. The dark red solution was concentrated under reduced pressure to about 1 ml. and cooled to room temperature. The mixture was filtered to yield 4,10-diphenyl-1,2,9-triazaphenanthrene methiodide (100 mg.), m.p. 242-251°. Recrystallisation from methanol gave yellow-orange needles (turning crimson on drying at 120°), m.p. 259°. (Found: C, 60.5; H, 3.9; N, 8.8; I, 25.8. $C_{24}H_{18}N_3I$ requires C, 60.6; H, 3.8; N, 8.9; I, 26.7%).

4,10-Diphenyl-1,2,9-triazaphenanthrene di-N-oxide.— 4,10-diphenyl-1,2,9-triazaphenanthrene (200 mg.) in glacial acetic acid (3 ml.) was treated with hydrogen peroxide (30%; 1.2 ml.) and heated at 90-95° for 1 hr. The clear, yellow solution was allowed to stand overnight and the yellow crystals (190 mg.) which separated were collected and recrystallised from 50% aqueous acetic acid to yield long, bright yellow needles, m.p. 293°, of the di-N-oxide (Found: C, 75.2; H, 3.9; N, 11.5. $C_{23}H_{15}O_2N_3$ requires C, 75.6; H, 4.1; N, 11.5%). Infra-red spectrum

(Nujol mull); max. at 1954, 1937, 1889, 1840, 1784, 1756, 1600, 1587, 1579, 1568, 1516, 1412, 1320, 1287, 1273, 1250, 1239, 1235, 1205, 1182, 1169, 1155, 1146, 1132, 1070, 1039, 1025, 1008, 993, 976, 967, 930, 914, 886, 872, 852, 836, 808, 788, 781, 773, 744, 726, 701, 697, 692, 679 and 658 cm.$^{-1}$

4,10-Diphenyl-1,2,9-triazaphenanthrene N-oxide.— 4,10-diphenyl-1,2,9-triazaphenanthrene (400 mg.), dissolved in glacial acetic acid (10 ml.), was treated with hydrogen peroxide (30%; 2 ml.) and allowed to stand for 24 hr. at 25-30°. The solution was poured into water (10 ml.) and filtered to yield a pale yellow solid (350 mg.). Extraction of this solid with hot methanol (3 x 5 ml.) gave, on evaporation, pale yellow needles (200 mg.) of the starting material, m.p. and mixed m.p. 185-186°. Recrystallisation of the residue from 50% aqueous acetic acid gave 4,10-diphenyl-1,2,9-triazaphenanthrene N-oxide as small, yellow needles, m.p. 202°. (Found: C,76.0; H,5.0; N,14.7. $C_{18}H_{12}ON_3$ requires C,75.2; H,4.6; N,14.6%).

Attempted reaction of N-oxides with potassium iodide.— (a) The di-N-oxide (5 mg.) in 50% aqueous acetic acid (1 ml.) was treated with 10% aqueous potassium iodide (0.5 ml.) and the solution retained at 100° for 30 min. Addition of starch solution gave no blue colouration .
(b) The foregoing experiment was repeated using the mono-N-oxide (5 mg.); no iodine was liberated after heating forl hr. at 100°.

Reduction of 4,10-diphenyl-1,2,9-triazaphenanthrene.— (a) 4,10-diphenyl-1,2,9-triazaphenanthrene (900 mg.) in alcohol (25 ml.) was refluxed and treated with sodium (2.5 g.; ca. 20 pieces) during 30 min., added through a trap to avoid the loss of evolved gases which were led via the reflux condenser into two flasks containing 0.1 N sulphuric acid. After the sodium had dissolved, the system was swept out with a slow stream of nitrogen for 30 min. and the excess hydrochloric acid determined by titration with 0.1 N sodium hydroxide. Two runs were carried out and a mean value of 4% (results agreed within 4%) was obtained for the percentage of ammonia evolved.

The solution was poured into water (200 ml.) and the buff-coloured precipitate was collected, dried and extracted with hot methanol to leave a residue (150 mg.) of unchanged starting material, m.p. and mixed m.p. 185-186°, after recrystallisation. The methanol solution was evaporated under reduced pressure to afford an oily solid (500 mg.). Extraction of the solid with several quantities of petroleum ether (3 x 10 ml.; b.p. 60-80°) gave a solid which on further recrystallisation from petroleum ether afforded the reduction product as colourless blades, m.p. 81-82°. (Found: C,80.4; H,6.6; N,12.0. $C_{22}H_{21}N_3$ requires C,81.4; H,6.2; N,12.4%).

A negative result was obtained on attempted diazotisation and coupling of the above reduction product with alkaline 2-naphthol.

(b) 4,10-diphenyl-1,2,9-triazaphenanthrene (500 mg.) was dissolved in

33% aqueous acetic acid (3 ml.) and refluxed for 2 hr. with zinc amalgam (1 g.). The mixture was cooled, treated with water (20 ml.) and after being rendered alkaline with 4N sodium hydroxide, was extracted with ether (3 x 50 ml.). The combined ether extract was dried ($MgSO_4$) and the ether evaporated to leave a pale yellow oil (320 mg.) which crystallised to an oily solid on standing at 0°. Recrystallisation from 50% benzene-petroleum ether (b.p. 60-80°) gave the reduction product, 1,5-diphenyl-pyrrolo-(2,3-c)-quinoline, as small, colourless plates, m.p. 75-76°. (Found: C,85.2; H,5.3; N,8.9. $C_{23}H_{16}N_2$ requires C,86.2; H,5.0; N,8.8%).

Attempted oxidation of 4,10-diphenyl-1,2,9-triazaphenanthrene.— The base (1.0 g.) was boiled under reflux with aqueous sodium hydroxide (600 mg. NaOH in 50 ml. of water) and treated with potassium permanganate (7.0 g.) added in 1 g. portions over 1 hr. The mixture was refluxed for 24 hr. and excess potassium permanganate was removed by the addition of alcohol (2 ml.). The mixture was cooled and filtered. The black manganese dioxide residue was dried and extracted with hot ethanol (3 x 50 ml.) to yield unchanged starting material (850 mg.), m.p. and mixed m.p. 185-186°.

Evaporation of the alkaline filtrate, followed by neutralisation with 2N-sulphuric acid yielded, on filtration, a small amount (30 mg.) of a brown solid from which no useful product could be obtained.

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Triazaphenanthrenes. Part VI.* Further Observations on the Widman–Stoermer and Borsche Reactions

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Triazaphenanthrenes. Part VI.* Further Observations on the Widman–Stoermer and Borsche Reactions

By C. M. Atkinson and B. N. Biddle

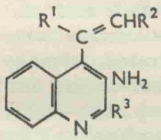
The named reactions have been applied to the synthesis of new 1,2,9-triazaphenanthrenes and 1,2,7- and 1,2,5-triazanaphthalenes. A modified Borsche cyclisation appears to be generally applicable to aminoquinolines but attempts to extend this to simpler aromatic systems have failed.

THE Widman–Stoermer reaction has been used [1] to provide an excellent yield of 4-methylcinnoline by cyclisation in dilute alkaline solution of diazotised *o*-isopropenylaniline. One essential for the success of this reaction is an electron-donating group on the α-carbon atom of the olefinic side-chain, and an α-aryl group has a beneficial effect.[2] The presence of heterocyclic nuclei at the α- or the β-position has been shown to have an inhibiting effect on cinnoline formation, owing to their powerful electron-withdrawing effects, particularly in strong-acid media.[3,4]

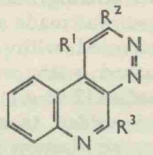
The presence of aryl groups, however, in competition with heterocyclic nuclei, often led to high yields of the cinnoline [3] but when heterocyclic nuclei were present the yield of cinnoline was particularly susceptible to pH because of protonation of the hetero-atom.

This work has now been extended by a study of the cyclisation of a number of amino-ethylenes in the quinoline and pyridine series, and a preliminary study has been made of the resulting new heterocycles.

The ethylenes (I)—(IV) were best prepared by dehydration with boiling sulphuric acid (50%, v/v) of



	R^1	R^2	R^3
(I)	Me	H	Ph
(II)	Ph	H	Ph
(III)	Ph	Me	Ph
(IV)	Me	H	Me



(V)

carbinols obtained by standard Grignard procedures with esters and ketones. Dehydration using iodine in toluene failed, and yields were low when concentrated sulphuric acid was used.

Diazotisation of the amines (I)—(IV) gave yields of triazaphenanthrenes (V) which varied with the substituents, being good for (II), poor for (III), and nil for (I) and (IV). These results are in general agreement with previous investigations of the Widman–Stoermer reaction [2-4] but it is difficult to explain the low yield from (III).

Attempted reduction of 4,10-diphenyl-1,2,9-triazaphenanthrene (V; $R^1 = R^3 = Ph$, $R^2 = H$) to the corresponding pyrroloquinoline (cf. ref. 4) with sodium and ethanol was unsuccessful. Ammonia was not evolved, and the major product appears to be the 1,2,3,4,9,10-hexahydro-derivative. This agrees with the formation of hexahydropyridazines from simple pyridazines,[5] although reduction of 3,6-diphenylpyridazine yields the dihydro-derivative,[6] and pyridazine itself undergoes ring-opening to give a small amount of diamine.[7] Reduction of (V; $R^1 = R^3 = Ph$, $R^2 = H$) with zinc amalgam in 33% acetic acid gave the desired pyrroloquinoline (cf. the reduction of 4-phenylcinnoline to 3-phenylindole [8]). 4,10-Diphenyl-1,2,9-triazaphenanthrene was stable towards prolonged treatment with hot permanganate but readily gave a di-*N*-oxide with hydrogen peroxide–acetic acid; milder conditions gave a mono-*N*-oxide. Neither of the *N*-oxides showed peroxide properties (cf. quinoxaline *N*-oxides [9]).

In the pyridine series the amino-propenes (VI)—(IX) were prepared by dehydration of the appropriate carbinols. During the preparation of 2-(3-amino-2-pyridyl)-propan-2-ol a second product was obtained, often as the major product. This is most probably the pinacol, having regard to the isolation of 2-acetyl-3-aminopyridine after treatment with chromic oxide in acetic acid, and conversion into a pinacolone with hot concentrated hydrochloric acid, but not with iodine in acetic acid.[10] However, the pinacol was stable to sodium periodate, and treatment with lead tetra-acetate gave no identifiable product. Pinacol formation during the reaction between an ester and a Grignard reagent was observed by Boyd and Hatt,[11] and the reduction of ketones to pinacols by magnesium in the presence of a Grignard reagent is well known.[12] Pinacol formation was finally prevented by filtration of the Grignard reagent through kieselguhr.

In all cases diazotisation and cyclisation of the aminopropenes gave 4-methyl derivatives of the respective new triazanaphthalenes (X) [from (VI), (VII), and (VIII)] and (XI) [from (IX)].

Unfortunately yields were very poor, and in two cases, (VIII) and (IX), the corresponding triazanaphthalenes were isolated only as picrates. Examination of various

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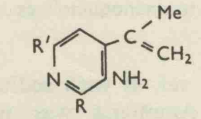
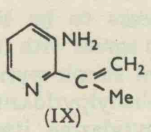
methods for cyclisation showed that success followed only when the method of Jacobs *et al.*[1] was used.

Attempted diazotisation and cyclisation of (IX) in concentrated hydrochloric acid failed, but 3-chloro-2-isopropenylpyridine (picrate) and 2-acetyl-3-hydroxypyridine were isolated, the latter probably formed by

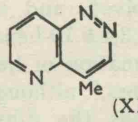


(VI) R = R′ = H
(VII) R = R′ = Me
(VIII) R = Me, R′ = Ph



(IX)

(X)



(XI)

oxidation of the propene with excess of nitrous acid. A third compound, represented as a hydrate of 3-hydroxy-2-isopropenylpyridine, was also isolated. Attempted cyclisation in alkaline solution gave a dark red, high-melting compound which was not identified. These low yields of the desired products seem to indicate that the electron-releasing power of a methyl group at the α-position is insufficient to overcome the effect of the nitrogen atom at the ring α- or γ-positions, in spite of the fact that cyclisation was carried out in the absence of strong acids.

The low yields of the methyl triazanaphthalenes did not permit full examination of their properties. In the case of 4-methyl-1,2,7-triazanaphthalene, where yields of up to 20% were obtained, the reactivity of the 4-methyl group was established by condensation of the base with benzaldehyde in the presence of zinc chloride, to give 4-styryl-1,2,7-triazanaphthalene. Oxidation of this styryl derivative gave 1,2,7-triazanaphthalene-4-carboxylic acid, but the yield was too low to permit attempted decarboxylation to the parent base.

The Borsche reaction, cyclisation of a diazotised *o*-aminoaryl ketone to form a 4-hydroxycinnoline, is normally best carried out in strong acid.[13] However, cyclisation of diazotised 4-acetyl-3-amino-2-phenylquinoline required [14] an alkaline medium for good results. It was suggested that, in strong acid, salt formation at the ring nitrogen atom inhibited enolisation of the carbonyl group, but that in alkali the diazonium cation coupled with the enolate anion.

In order to test this hypothesis in a simpler system, the ring-closures of diazotised 2-amino-4-dimethylaminoacetophenone, 4-acetyl-3-aminopyridine, and 2-acetyl-3-aminopyridine have been investigated under a variety of conditions. Unfortunately, in all cases a product arising from cyclisation could not be isolated; in acid solution, nitrogen was lost and phenolic compounds formed, while in alkali the only isolable products could not be purified and were probably formed by intermolecular coupling. Of the required starting materials, 2-amino-4-dimethylaminoacetophenone was prepared from 4-amino-2-nitrobenzoic acid through 4-amino-2-nitroacetophenone. Synthesis of the aminopyridyl ketones was extremely difficult and was eventually achieved by ozonolysis of the corresponding benzamidopyridylpropene and subsequent hydrolysis.

Although these results are disappointing, further evidence of the generalised nature of the modified Borsche reaction (in alkali) has been obtained. Cyclisation of 3-amino-2-phenyl-4-propionylquinoline in concentrated hydrochloric acid, rather than in alkali, gave much lower yields of 4-hydroxy-3-methyl-10-phenyl-1,2,9-triazaphenanthrene, and 3-chloro-2-phenyl-4-propionylquinoline was isolated.

This 4-hydroxy-triazaphenanthrene was readily converted into the amino-derivative through the 4-chloro- and 4-phenoxy-compounds, and quaternisation of the amine gave only one methiodide. Methylation of the hydroxy-triazaphenanthrene gave an *N*-methyl derivative, different from the *O*-methyl compound as prepared from the chloro-triazaphenanthrene and sodium methoxide.

EXPERIMENTAL

2-(3-Amino-2-methyl-4-quinolyl)propan-2-ol.— Methyl 3-amino-2-methylquinoline-4-carboxylate [15] (6·0 g.) in dry ether (50 ml.) was added at 0° under nitrogen during 1 hr. to a stirred Grignard reagent prepared from magnesium (4·33 g.) and methyl iodide (11·2 ml.) in dry ether (300 ml.). The mixture was heated under reflux for 6 hr. and set aside overnight, ammonium chloride (60 g.) in ice–water added with stirring, and the organic layer separated. The aqueous layer was made almost neutral with hydrochloric acid, and extracted with ether, and the combined extracts were washed with water, dried, and concentrated. Orange needles (2·85 g.), m. p. 182—186°, separated on cooling and were added to a second crop (1·0 g.), m. p. 180—185°; recrystallisation from ether provided the *carbinol* (3·1 g., 52%), m. p. 191—194° (Found: C, 72·3; H, 7·1; N, 12·8. $C_{13}H_{16}N_2$ requires C, 72·2; H, 7·5; N, 13·0%).

2-(3-Amino-2-methyl-4-quinolyl)propene.— 2-(3-Amino-2-methyl-4-quinolyl)propan-2-ol (1·0 g.) was dissolved in concentrated sulphuric acid (20 ml.) with initial cooling to keep the mixture at room temperature. After 3 hr. the solution was poured on to crushed ice (100 g.) made alkaline with 6N-sodium hydroxide, and extracted thrice with ether; the combined extracts were washed with water, dried, and evaporated, to yield a yellow-orange solid (0·86 g.), m. p. 80—82°. Recrystallisation thrice from n-hexane furnished needles of the *product* (0·56 g., 61·1%), m. p. 85° (Found: C, 78·8; H, 7·2; N, 14·4. $C_{13}H_{14}N_2$ requires C, 78·8; H, 7·1; N, 14·1%).

Methyl 3-Amino-2-phenylquinoline-4-carboxylate.— A stirred suspension of 3-amino-2-phenylquinoline-4-carboxylic acid [16] (44·5 g.) in ether was treated at room temperature with diazomethane prepared from *N*-nitroso-*N*-methylurea (60 g.) in ether (250 ml.). The reaction mixture was worked up as usual, and crystallisation of the residual red oil from light petroleum (b. p. 80—100°) provided long pale yellow

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[16] C. M. Atkinson and A. R. Mattocks, *J. Chem. Soc.*, 1957, 3718.

needles of the *product* (23·0 g., 49·1%), m. p. 101—102° (Found: C, 72·8; H, 5·1; N, 10·2. $C_{17}H_{14}N_2O_2$ requires C, 73·4; H, 5·1; N, 10·1%).

2-(3-*Amino*-2-*phenyl*-4-*quinolyl*)*propan*-2-*ol*.—Prepared as described above for the 2-methyl analogue, from 3-amino-2-phenylquinoline-4-carboxylate (20 g.), the pure *carbinol* separated from ether as prisms (10·4 g., 52%), m. p. 188—190° (Found: C, 77·3; H, 6·4; N, 9·9. $C_{18}H_{18}N_2O$ requires C, 77·7; H, 6·5; N, 10·1%).

2-(3-*Amino*-2-*phenyl*-4-*quinolyl*)*propene*.—The carbinol (5·35 g.) was dehydrated as described above with concentrated sulphuric acid (50 ml.). Recrystallisation of the product (4·7 g., 93·9%), m. p. 87—88° from n-hexane provided 2-(3-*amino*-2-*phenyl*-4-*quinolyl*)*propene* as needles, m. p. 88° (Found: C, 82·5; H, 6·2; N, 10·9. $C_{18}H_{16}N_2$ requires C, 83·0; H, 6·2; N, 10·8%).

1-(3-*Amino*-2-*phenyl*-4-*quinolyl*)-1-*phenylethanol*.—4-Acetyl-3-amino-2-phenylquinoline [14] (10 g.) in dry ether (300 ml.) was added during 1 hr. at 0° with stirring to a Grignard reagent prepared from magnesium (3·6 g.) and dry redistilled bromobenzene (16·2 ml.) in dry ether (400 ml.). The mixture was heated under reflux, then worked up as usual, to yield prisms (9·2 g., 71·1%), m. p. 165—169°. Recrystallisation from ether provided the *carbinol*, m. p. 172—173° (Found: C, 81·1; H, 5·9; N, 8·2. $C_{23}H_{20}N_2O$ requires C, 81·2; H, 6·1; N, 8·0%).

1-(3-*Amino*-2-*phenyl*-4-*quinolyl*)-1-*phenylethylene*.—A solution of the foregoing carbinol (8 g.) in concentrated sulphuric acid (40 ml.) and water (35 ml.) was heated under reflux for 1 hr., cooled, and poured on to ice (100 g.). After working up as usual, the resulting brown oil (7 g.) was extracted with boiling n-hexane, and the solution set aside at 0° for 2—3 days to provide crude colourless needles. Recrystallisation from n-hexane gave the pure *olefin* (5·8 g., 76·6%), m. p. 101—102° (Found: C, 86·2; H, 5·5; N, 8·8. $C_{23}H_{18}N_2$ requires C, 85·7; H, 5·6; N, 8·7%).

3-*Amino*-2-*phenyl*-4-*propionylquinoline*.—3-Amino-2-phenylquinoline-4-carboxyamide [11] (20 g.) was added with stirring during 15 min. to a Grignard reagent prepared from magnesium (10·3 g.) and ethyl iodide (34 ml.) in ether (150 ml.) and benzene (400 ml.). The mixture was heated under reflux for 4 hr., cooled, and stirred with ice (500 g.) and concentrated hydrochloric acid (200 g.) for 15 min. Extraction in the usual way yielded a sticky solid (16·8 g.) which on recrystallisation from benzene–light petroleum gave the *ketimide* as colourless crystals, m. p. 191° (Found: C, 78·4; H, 5·5; N, 16·1. $C_{18}H_{17}N_3$ requires C, 78·5; H, 6·2; N, 15·3%). This (10 g.) was heated under reflux with water (50 ml.) and concentrated hydrochloric acid (25 ml.) for 1 hr. The reaction mixture was basified (sodium hydroxide), extracted thrice with ether, and the residue from evaporation of the dried extract was recrystallised from n-hexane, to yield the *ketone* (8·5 g., 40·5%) as pale yellow needles, m. p. 78° (Found: C, 78·0; H, 6·0; N, 10·6. $C_{18}H_{16}N_2O$ requires C, 78·3; H, 5·7; N, 10·2%).

1-(3-*Amino*-2-*phenylquinolyl*)-1-*phenylpropan*-1-*ol*.—To a Grignard solution prepared from magnesium (3·6 g.) and bromobenzene (17 ml.) in dry ether (200 ml.) was added a solution of 3-amino-2-phenyl-4-propionylquinoline (9·0 g.) in ether (200 ml.). The mixture was refluxed in an atmosphere of dry nitrogen for 3 hr. then worked up in the usual manner, to yield needles (8·5 g., 73·1%) of the *carbinol*, m. p. 153° (from ether) (Found: C, 80·6; H, 6·7; N, 7·6. $C_{24}H_{23}N_2O$ requires C, 81·3; H, 6·3; N, 7·9%).

1-(3-*Amino*-2-*phenyl*-4-*quinolyl*)-1-*phenylpropene*.—The foregoing carbinol (8·0 g.) was dehydrated in boiling concentrated sulphuric acid (25 ml.) and water (30 ml.) as usual, to yield the olefin (6·4 g.) as a pale yellow uncrystallisable oil; *picrate*, needles (from ethanol), m. p. 196—197° (Found: C, 63·9; H, 4·3; N, 11·7. $C_{30}H_{22}N_8O_7$ requires C, 63·7; H, 4·1; N, 12·4%).

4,10-*Diphenyl*-1,2,9-*triazaphenanthrene*.—1-(3-Amino-2-phenyl-4-quinolyl)-1-phenylethylene (8 g.) in glacial acetic acid (15 ml.) and concentrated sulphuric acid (2 ml.) was treated dropwise during ½ hr. with sodium nitrite (1·8 g.) in water (10 ml.). The resulting dark red solution was allowed to stand at room temperature for 2 hr. and poured into water (150 ml.). The solid (7·5 g.) which precipitated was washed with water and recrystallised from methanol, to yield the *triazaphenanthrene* as pale yellow needles (6·4 g., 77·1%), m. p. 185—186° (Found: C, 82·0; H, 4·5; N, 13·1. $C_{23}H_{15}N_3$ requires C, 82·9; H, 4·5; N, 12·6%); *methiodide*, prepared under reflux in nitromethane, crystallised as orange-yellow needles, m. p. 259° (Found: C, 60·5; H, 3·9; I, 25·8; N, 8·8. $C_{24}H_{18}IN_3$ requires C, 60·6; H, 3·8; I, 26·7; N, 8·9%).

N-*Oxides of* 4,10-*Diphenyl*-1,2,9-*triazaphenanthrene*.—(*a*) The base (400 mg.) in glacial acetic acid (10 ml.) was treated with 30% hydrogen peroxide (2 ml.) and set aside for 24 hr. The mixture was poured into water and the solid was collected and dried at 80°; extraction with methanol (2 × 20 ml.) gave pale yellow needles of the starting material (150 mg.), m. p. 185—186°. Recrystallisation of the residue from 50% aqueous acetic acid gave the required N-*oxide* as yellow needles, m. p. 198—199° (Found: C, 79·7; H, 4·6; N, 12·4. $C_{23}H_{15}N_3O$ requires C, 79·1; H, 4·3; N, 12·0%).

(*b*) The base (200 mg.) in glacial acetic acid (3 ml.) was heated at 90—95° for 1 hr. with 30% hydrogen peroxide (1·2 ml.). The crystalline solid (190 mg.) which separated on cooling was recrystallised from 50% aqueous acetic acid, to yield the *di*-N-*oxide* as pale yellow needles, m. p. 293° (Found: C, 75·2; H, 3·9; N, 11·5. $C_{23}H_{16}N_3O_2$ requires C, 75·6; H, 4·1; N, 11·5%).

Reduction of 4,10-*Diphenyl*-1,2,9-*triazaphenanthrene*.—(*a*) The base (900 mg.) in ethanol (25 ml.) was heated under reflux and treated with sodium (2·5 g.; *ca.* 20 pieces) during ½ hr. The solution was poured into water (200 ml.), and the buff coloured precipitate (700 mg.) was collected, dried, and extracted with cold methanol (10 ml.) to remove starting material (150 mg.), m.p. and mixed m. p. 185—186°. The methanol solution was evaporated to an oily solid which, on recrystallisation from light petroleum (b. p. 60—80°), gave colourless needles of 1,2,3,4,9,10-*hexahydro*-4,10-*diphenyl*-1,2,9-*triazaphenanthrene*, m. p. 81—82° (Found: C, 80·4; H, 6·6; N, 12·0. $C_{23}H_{21}N_3$ requires C, 81·4; H, 6·2; N, 12·4%).

(*b*) The base (500 mg.) was dissolved in 33% aqueous acetic acid (3 ml.) and heated under reflux for 2 hr. with zinc amalgam (1 g.), cooled, treated with water (20 ml.), made alkaline with 4N-sodium hydroxide, extracted thrice with ether, and the extract concentrated to a pale yellow oil (320 mg.) which crystallised to an oily solid on standing. Recrystallisation from 50% benzene–light petroleum (b. p. 60—80°) gave plates of 1,4-*diphenylpyrrolo*[2,3-c]-*quinoline*, m. p. 75—76° (Found: C, 85·2; H, 5·3; N, 8·9. $C_{23}H_{16}N_2$ requires C, 86·2; H, 5·0; N, 8·8%).

3-*Methyl*-4-*phenyl*-1,2,9-*triazaphenanthrene*.—1-(3-Amino-2-phenyl-4-quinolyl)-1-phenylpropene (1 g.) was dissolved in glacial acetic acid (4 ml.) and concentrated sulphuric acid (1·0 ml.), cooled, and treated dropwise at

0° with sodium nitrite (200 mg.) in water (2 ml.). The solution was allowed to stand until no coupling reaction was evident, and poured into water (20 ml.). The precipitate (850 mg.) was collected, washed with water, and treated with 2N-sodium hydroxide (20 ml.). The insoluble material (70 mg.) was filtered off, washed with water, and recrystallised from ethanol, to give yellow needles of the *triazaphenanthrene*, m. p. 192° (Found: C, 82·4; H, 5·0; N, 12·2. $C_{24}H_{17}N_3$ requires C, 83·0; H, 4·9; N, 12·1%). Neutralisation of the alkaline filtrate with 2N-hydrochloric acid gave a precipitate (600 mg.) which was collected, washed well with water, and recrystallised from methanol (charcoal), to yield needles of 1-(3-*hydroxy*-2-*phenyl*-4-*quinolyl*)-1-*phenylpropene*, m. p. 131—132° (Found: C, 84·7; H, 5·3; N, 5·2. $C_{24}H_{19}NO$ requires C, 85·4; H, 5·7; N, 4·2%).

Ethyl 3-*Aminoisonicotinate*.—A mixture of 3-aminoisonicotinic acid [17] (80 g.), ethanol (160 ml.), and concentrated sulphuric acid (80 ml.) was heated under reflux on a steam-bath for 30 hr., and the resulting solution poured into water (1 l.). Ether extraction of the basified (Na_2CO_3) mixture, and recrystallisation of the residue from light petroleum (b. p. 60—80°), yielded pale yellow needles (67 g., 69%) of the *ester*, m. p. 65° (Found: C, 57·2; H, 6·1; N, 16·8. $C_8H_{10}N_2O_2$ requires C, 57·7; H, 6·1; N, 17·3%).

2-(3-*Amino*-4-*pyridyl*)*propan*-2-*ol*.—A solution of the foregoing ester (66 g.) in dry benzene (1 l.) was added, with stirring during ½ hr., to a Grignard solution prepared from magnesium (38 g.) and methyl iodide (80 g.) in dry ether (1200 ml.). The mixture was heated under reflux for 4 hr., cooled, and worked up as usual. Continuous extraction with ether for 10 hr., and concentration of the ether solution to 100 ml., gave the *carbinol* (40·5 g., 61·4%) as long needles, m. p. 160—161° (from benzene) (Found: C, 62·3; H, 7·8; N, 18·6. $C_8H_{12}N_2O$ requires C, 63·1; H, 8·0; N, 18·4%).

2-(3-*Amino*-4-*pyridyl*)*propene*.—The carbinol (42 g.) was dissolved, with cooling, in concentrated sulphuric acid (300 ml.) and set aside at room temperature for 6 hr. The reaction mixture was worked up as usual, to give a pale yellow oil (32 g.). Attempts to crystallise this propene from light petroleum (b. p. 60—80°) failed but the *benzoyl derivative* (benzoyl chloride in pyridine) crystallised with difficulty from light petroleum (b. p. 60—80°) as prisms, m. p. 104° (Found: C, 75·4; H, 5·6. $C_{18}H_{14}N_2O$ requires C, 75·6; H, 5·9%); *picrate* small needles, m. p. 133° (Found: C, 45·4; H, 3·8; N, 18·8. $C_{14}H_{13}N_5O$ requires C, 46·3; H, 3·6; N, 19·3%).

Ethyl 3-*Amino*-2,6-*dimethylisonicotinate*.—A solution of 3-amino-2,6-dimethylisonicotinic acid hydrochloride [18] (15 g.) in ethanol (30 ml.) and concentrated sulphuric acid (15 ml.) was heated under reflux on a steam-bath for 15 hr. and worked up as usual. The ester (10·5 g., 61·4%) crystallised from light petroleum (b. p. 60—80°) as needles, m. p. 47—48° (Found: C, 62·5; H, 7·3; N, 14·0. $C_{10}H_{14}N_2O_2$ requires C, 61·8; H, 7·3; N, 14·4%).

2-(3-*Amino*-2,6-*dimethylpyridyl*)*propan*-2-*ol*.—This was prepared as usual from the foregoing ester (19 g.), magnesium (9·5 g.), methyl iodide (57 g.), and ether (350 ml.); the carbinol formed prisms (11 g., 57·3%), m. p. 113° [from 50% benzene–light petroleum (b. p. 60—80°)] (Found: C, 66·6; H, 9·2; N, 16·0. $C_{10}H_{16}N_2O$ requires C, 66·6; H, 8·95; N, 15·6%).

4-(3-*Amino*-2,6-*dimethylpyridyl*)*propene*.—Dehydration of the carbinol with boiling 50% v/v sulphuric acid formed a yellow oil which could not be made to crystallise; the *benzoyl derivative* (prepared in pyridine with benzoyl chloride) crystallised as small prisms, m. p. 155° (Found: C, 76·7; H, 7·0; N, 10·3. $C_{17}H_{18}N_2O$ requires C, 76·7; H, 6·8; N, 10·5%).

2-*Methyl*-6-*phenylcinchomeronimide*.—2-Methyl-6-phenylcinchomeronic acid [18] (50 g.) was heated on a steam-bath for 5 hr. with acetic anhydride (300 ml.), and the mixture concentrated to about 150 ml. under reduced pressure. The anhydride (39 g.), needles, m. p. 195—196° (lit.,[19] 196°) was mixed with acetamide (50 g.) and acetic anhydride (10 ml.), and heated to 125—130° (oil bath) under reflux, and retained at this temperature for 6 hr. The *imide* (24 g., 51·8%), which was washed with acetic acid and then water, formed needles, m. p. 163° (from acetone) (Found: C, 70·6; H, 4·2; N, 11·8. $C_{14}H_{10}N_2O_2$ requires C, 70·9; H, 4·5; N, 11·6%).

3-*Amino*-2-*methyl*-6-*phenylisonicotinic Acid*.—The well powdered imide (10 g.) was added at 0° to a stirred solution of bromine (7·4 g.) in sodium hydroxide (9·5 g. in 100 ml. of water). After 15 min. the mixture was heated at 70—80° for 1 hr., cooled, and acidified to Congo Red with concentrated hydrochloric acid. The solution was evaporated to dryness under reduced pressure and the residue extracted with ethanol (3 × 150 ml.). The combined extracts were treated with 5N-hydrochloric acid (10 ml.), and the solution was evaporated to about 30 ml. and cooled. The solid (17 g.) was collected and recrystallised from 2N-hydrochloric acid (charcoal), to provide pale yellow needles, m. p. 241—242°, of 3-*amino*-2-*methyl*-6-*phenylisonicotinic acid hydrochloride* (Found: C, 54·9; H, 5·9; Cl, 12·4; N, 9·9. $C_{13}H_{13}ClN_2O_2,H_2O$ requires C, 55·1; H, 5·3; Cl, 12·5; N, 9·9%). Attempts to obtain the free acid by neutralisation of aqueous solutions of the hydrochloride gave only gelatinous material.

Ethyl 3-*Amino*-2-*methyl*-6-*phenylisonicotinate*.—Prepared as usual from the amino-acid hydrochloride (50 g.), the *ester* (33 g., 63·2%) crystallised from light petroleum (b. p. 60—80°) as pale yellow needles, m. p. 90—91° (Found: C, 70·1; H, 6·5; N, 11·0. $C_{15}H_{18}N_2O_2$ requires C, 70·3; H, 6·3; N, 10·9%).

2-(3-*Amino*-2-*methyl*-6-*phenyl*-4-*pyridyl*)*propan*-2-*ol*.—Prepared as usual from the above ester (5·2 g.), magnesium (1·9 g.), and methyl iodide (11·5 g.) in ether (100 ml.) and benzene (100 ml.), the *carbinol* formed plates (2·6 g., 52·9%), m. p. 107° [from 50% benzene–light petroleum (b. p. 60—80°)] (Found: C, 74·3; H, 7·4; N, 11·6. $C_{15}H_{18}N_2O$ requires C, 74·4; H, 7·5; N, 11·6%).

2-(3-*Amino*-2-*methyl*-6-*phenyl*-4-*pyridyl*)*propene*.—Dehydration of the above carbinol (10 g.) by heating under reflux for 1 hr. with 18N-sulphuric acid (60 ml.), and isolation as usual, provided the propene (8·5 g.) as an uncrystallisable yellow oil; the *dibenzoyl deriative* (from benzoyl chloride in pyridine) formed small needles, m. p. 224—225° (from ethanol) (Found: C, 79·9; H, 5·9; N, 6·9. $C_{29}H_{24}N_2O_2$ requires C, 80·5; H, 5·6; N, 6·5%).

4-*Methyl*-1,2,7-*triazanaphthalene*.—(*a*) A solution of 2-(3-amino-4-pyridyl)propene (15 g.) in sulphuric acid (*d* 1·84; 8·5 ml.) and water (80 ml.) was treated with sodium nitrite (7·5 g.) in water (25 ml.), added during 15 min. at 0°. The solution was then poured into ice–water (300 g.) and set aside for 3 days in the dark at room temperature.

[17] S. Gabriel and J. Colman, *Ber.*, 1902, **35**, 2831.
[18] Y.-S. Kao and R. Robinson, *J. Chem. Soc.*, 1955, 2865.
[19] O. Mumm and R. Neumann, *Ber.*, 1926, **59**, 1616.

After 2 days (the solution no longer coupled with alkaline 2-naphthol) the solution was made alkaline with 4N-sodium hydroxide and continuously extracted with benzene (600 ml.) for 6 hr. The benzene solution was evaporated under reduced pressure, to yield a red oily product (4·4 g.) which solidified on standing. Chromatography on alumina 1 : 1 (v/v) benzene–light petroleum (b. p. 60—80°) gave *4-methyl-1,2,7-triazanaphthalene* (2·8 g., 17·3%) as leaflets, m. p. 125° [from light petroleum (b. p. 60—80°)] (Found: C, 68·2; H, 4·8; N, 29·8. $C_8H_7N_3$ requires C, 68·2; H, 4·9; N, 28·9%); *picrate*, m. p. 255°, needles (from benzene) (Found: C, 44·0; H, 3·0; N, 22·4. $C_{14}H_{10}N_6O$ requires C, 44·9; H, 2·7; N, 22·5%); *methiodide*, red needles, m. p. 163—164° (Found: C, 38·1; H, 3·3; I, 43·9; N, 15·0. $C_9H_{10}IN_2$ requires C, 37·6; H, 3·5; I, 44·3; N, 14·6%).

(*b*) The propene (6·5 g.) in concentrated hydrochloric acid (32 ml.) and water (70 ml.) was diazotised with sodium nitrite (80 ml. of 5% solution) at 0°, set aside at 0° for 15 min., and treated at 0° with 4N-sodium hydroxide (120 ml.). After 24 hr. at room temperature the solution was continuously extracted with ether for 8 hr., to yield an oil (2·1 g.) from which 4-methyl-1,2,7-triazanaphthalene (0·8 g., 11·3%), m. p. 125°, was obtained by chromatography on alumina.

4-Styryl-1,2,7-triazanapthalene.—The base (500 mg.) was heated under reflux for 3 hr. with benzaldehyde (2 g.) and anhydrous zinc chloride (150 mg.). The mixture was cooled and treated with ether (25 ml.) and 2N-hydrochloric acid (10 ml.); the hydrochloride, in water (25 ml.), was basified with 2N-sodium hydroxide, and the dark solid filtered off, washed thoroughly with water, and recrystallised from methanol (charcoal), to provide the *product* (230 mg., 29%) as yellow plates, m. p. 95—96° (Found: C, 76·7; H, 4·5; N, 18·8. $C_{15}H_{11}N_3$ requires C, 77·2; H, 4·8; N, 18·0%).

1,2,7-Triazanaphthalene-4-carboxylic Acid.—The styryl derivative (250 mg.) was suspended in water and stirred at room temperature with potassium permanganate (500 mg.) added in small portions during about 15 min. The mixture was then heated at 35—40° for 15 min., cooled, filtered, and the precipitate washed with 2N-sodium hydroxide (10 ml.). The combined filtrates were evaporated to *ca.* 5 ml., neutralised with 4N-hydrochloric acid, and the solid (90 mg.) was collected and purified by precipitation from solution in sodium carbonate solution after decolorisation with charcoal. The *product* (60 mg., 31·7%) was obtained as buff coloured micro-crystals, m. p. 202—203° (Found: C, 54·5; H, 2·4; N, 23·0. $C_8H_5N_3O_2$ requires C, 54·9; H, 2·8; N, 24·0%).

4,6,8-Trimethyl-1,2,7-triazanaphthalene.—A solution of 2-(3-amino-2,6-dimethyl-4-pyridyl)propene (4·8 g.) in sulphuric acid (*d* 1·84; 3 ml.) and water (25 ml.) was diazotised at 0° with sodium nitrite (2·1 g.) in water (10 ml.). The solution was poured into ice and water (350 g.) and set aside in the dark at room temperature for 3 days. The solution was basified with 4N-sodium hydroxide and continuously extracted with benzene (600 ml.). Removal of the benzene under reduced pressure gave tarry material (1·4 g.) from which the *product* (750 mg., 14·6%), leaflets, m. p. 142—143° [from light petroleum (b. p. 40—60°)], was obtained by chromatography on alumina in 1 : 1 (v/v) benzene–light petroleum (b. p. 60—80°) (Found: C, 69·7; H, 6·7; N, 23·7. $C_{10}H_{11}N_3$ requires C, 69·3; H, 6·4; N, 24·3%). The *picrate* separated from ethanol as clusters of green needles, m. p. 181—182° (Found: C, 48·1; H, 3·6; N, 20·4. $C_{16}H_{14}N_6O_7$ requires C, 47·8; H, 3·5; N, 20·9%).

4,8-Dimethyl-6-phenyl-1,2,7-triazanaphthalene.—A solution of 2-(3-amino-2-methyl-6-phenyl-4-pyridyl)propene (4·5 g.) in sulphuric acid (*d* 1·84; 3 ml.) and water (25 ml.) was treated at 0° with sodium nitrite (1·4 g.) in water (10 ml.) and set aside at 0° for 10 min. The solution was diluted to about 400 ml. with ice–water and left at room temperature for 5 days. Alkali-insoluble products were obtained as in previous experiments by basification and continuous extraction with benzene. The resulting tar (350 mg.) was treated with ether (10 ml.), and the dark insoluble solid (120 mg.; m. p. 360°) removed. The ether-soluble fraction was dissolved in benzene (5 ml.) and treated with picric acid, to yield greenish yellow needles of the picrate, m. p. 217—218° (Found: C, 55·4; H, 3·1; N, 17·9. $C_{22}H_{17}N_6O_7$ requires C, 55·3; H, 3·6; N, 17·6%).

Ethyl 3-Aminopicolinate.—The method used was essentially that of Oakes, Pascoe, and Rydon,[20] but heating under reflux for 36 hr. was necessary for a good yield of the ester.

2-(3-Amino-2-pyridyl)propan-2-ol.—(*a*) A solution of ethyl 3-aminopicolinate (12 g.) in dry benzene (250 ml.) was added, with stirring during ½ hr., to a Grignard solution prepared from magnesium (5·2 g.) and methyl iodide (33 g.) in dry ether (250 ml.) and previously filtered through kieselguhr in an atmosphere of dry nitrogen. After heating under reflux for 4 hr. the mixture was worked up as usual and yielded an oily carbinol (8·5 g.). Benzoylation with benzoyl chloride in pyridine gave the *product* as plates, m. p. 129—130° (Found: C, 69·7; H, 6·2; N, 11·4. $C_{15}H_{16}N_2O_2$ requires C, 70·3; H, 6·2; N, 11·0%).

(*b*) The above reaction between the ester (20·5 g.) was repeated but without filtration of the Grignard solution, prepared from magnesium (9·0 g.) and methyl iodide (53 g.) in ether (400 ml.). Treatment of the reaction mixture as described above gave an oily product which, on treatment with ether (50 ml.), gave the carbinol (10 g.) and the *pinacol* (3·4 g.) which crystallised from benzene as yellow needles, m. p. 156° (Found: C, 61·6; H, 5·7; N, 20·9. $C_{14}H_{18}N_4O_2$ requires C, 61·4; H, 6·5; N, 20·5%). The pinacol (300 mg.), in concentrated hydrochloric acid (10 ml.), was heated under reflux for 1 hr., poured into water (10 ml.), and neutralised with sodium carbonate. The pale yellow oily product (230 mg.) was dissolved in benzene (5 ml.), filtered from a small amount of inorganic material, and the product (180 mg.) recrystallised from 1 : 1 benzene–light petroleum (b. p. 60—80°), to yield the *pinacolone* as needes, m. p. 154° (Found: C, 66·4; H, 5·7; N, 21·4. $C_{14}H_{16}N_4O$ requires C, 65·6; H, 6·3; N, 21·9%).

2-Acetyl-3-aminopyridine.—The pinacol (800 mg.) was dissolved in glacial acetic acid (12 ml.), treated with chromium trioxide (250 mg.), and heated on a steam-bath for 45 min. The solution was poured into water (50 ml.), neutralised with sodium carbonate, extracted thrice with ether, and the dried ($MgSO_4$) extract was evaporated to dryness. The oil (220 mg.) solidified after several hours at 0°, and crystallised from light petroleum (b. p. 40—60°) as yellow *plates*, m. p. 63—64° (Found: C, 61·3; H, 5·6; N, 20·4. $C_7H_8N_2O$ requires C, 61·7; H, 5·9; N, 20·6%). The *2,4-dinitrophenylhydrazone hydrochloride* formed needles, m. p. 276—277° (from glacial acetic acid) (Found: C, 44·1; H, 3·9; Cl, 10·6; N, 25·7. $C_{13}H_{13}ClN_6O_4$ requires C, 44·2; H, 3·7; Cl, 10·1; N, 23·8%).

[20] V. Oakes, R. Pascoe, and H. N. Rydon, *J. Chem. Soc.*, 1956, 1045.

2-(3-*Benzamido*-2-*pyridyl*)*propene*.—The oily carbinol (12·0 g.) was dissolved in 18N-sulphuric acid (100 ml.), heated under reflux for 45 min., and the mixture worked up as usual. Treatment of the oily propene with benzoyl chloride in pyridine gave the *product* as polyhedra, m. p. 85—86° [from light petroleum (b. p. 60—80°)] (Found: C, 75·7; H, 6·0; N, 11·45. $C_{15}H_{14}N_2O$ requires C, 75·6; H, 5·95; N, 11·75%); *picrate*, needles (from ethanol), m. p. 185—186° (Found: C, 45·3; H, 3·3; N, 18·8. $C_{14}H_{13}N_5O_7$ requires C, 46·3; H, 3·6; N, 19·3%). Attempted dehydration of the carbinol using iodine in boiling toluene failed.

4-*Methyl*-1,2,5-*triazanaphthalene*.—(*a*) The crude propene (6 g.) was dissolved in concentrated hydrochloric acid (25 ml.) and water (50 ml.), cooled to below 0°, and treated with solid sodium nitrite (2·5 g.). The clear solution was set aside for a further 10 min. at 0°, then warmed to 50—60°, when the solution darkened, much effervescence occurred, and the coupling reaction was negative after 10 min. The solution was basified with 4N-sodium hydroxide, extracted continuously with ether for 6 hr., and the uncrystallisable oil (600 mg.) converted into 2-(3-*chloro*-2-*pyridyl*)-*propene picrate* (350 mg.), a microcrystalline solid, m. p. 145° (from ethanol) (Found: C, 42·4; H, 3·45; Cl, 8·6; N, 14·7. $C_{14}H_{11}N_4O_7,H_2O$ requires C, 41·9; H, 3·3; Cl, 8·9; N, 14·0%). Neutralisation of the mother-liquor gave an oily emulsion from which was extracted with ether (3 × 50 ml.) a pale yellow oil (3·5 g.). Vacuum-sublimation yielded 2-*acetyl*-3-*hydroxypyridine* (200 mg.) as long needles, m. p. 55—56° (Found: C, 60·4; H, 5·5; N, 10·1. $C_7H_7NO_2$ requires C, 61·3; H, 5·1; N, 10·2%). The residual oil solidified, and recrystallisation from light petroleum (b. p. 40—60°) gave needles, m. p. 52—53° of 2-(3-*hydroxy*-2-*pyridyl*)*propene* (Found: C, 63·2; H, 7·2; N, 8·9. C_8H_9NO,H_2O requires C, 62·8; H, 7·2; N, 9·2%).

(*b*) The propene (2 g.) was diazotised in hydrochloric acid (10 ml.; conc.) and water (40 ml.) with sodium nitrite (26 ml. of 5% solution). After 10 min. at 0° the solution was poured into water (300 ml.) and set aside for 5 days in the dark. The solution was basified with 4N-sodium hydroxide and continuously extracted with benzene, to yield, on evaporation, an oil (120 mg.) which could not be recrystallised from n-hexane, but gave 4-*methyl*-1,2,5-*triazanaphthalene picrate* (170 mg.), m. p. 228°, needles (from benzene) (Found: C, 44·1; H, 2·9; N, 22·4. $C_{14}H_{10}N_6O_7$ requires C, 44·9; H, 2·7; N, 22·5%).

4-*Amino*-2-*nitroacetophenone*.— 4-Amino-2-nitrobenzoic acid [21] (45 g.) was heated under reflux with thionyl chloride (125 ml.) for 15 min., the excess of thionyl chloride was removed, and the crude acid chloride was dissolved in dioxan (100 ml.) and added to a solution of magnesium (5·4 g.) in a mixture of diethyl malonate (35·5 g.), ethanol (20 ml.), and ether (25 ml.). The mixture was refluxed for 30 min., and shaken with sulphuric acid (250 ml.; 10% v/v) until all solid material had dissolved. The organic layer was removed, the mixture extracted with ether (2 × 100 ml.), and the combined extracts were washed with water, dried, and evaporated. The crude product was dissolved in a mixture of acetic acid (75 ml.), concentrated sulphuric acid (10 ml.), and water (50 ml.), and refluxed for 3 hr. The cooled mixture was basified with ammonia and the precipitate was collected, dried, and recrystallised from benzene. Recrystallisation from water gave 4-*amino*-2-*nitroacetophenone* as yellow needles (12 g., 26·7%), m. p. 133—134° (Found: C, 52·9; H, 4·45; N, 14·6. $C_8H_8N_2O_3$ requires C, 53·3; H, 4·8; N, 15·55%); 2,4-*dinitrophenylhydrazone*, red leaflets, m. p. 237° (from acetic acid) (Found: C, 47·4; H, 3·8. $C_{14}H_{14}N_4O_2$ requires C, 46·7; H, 3·4).

4-*Dimethylamino*-2-*nitroacetophenone*.— 4-Amino-2-nitroacetophenone (1·8 g.) was stirred under reflux with a solution of sodium carbonate (anhydrous; 14 g.) in water (35 ml.) and treated dropwise during 1 hr. with dimethyl sulphate (15 g.). After heating under reflux for a further ½ hr. the mixture was cooled. The solid (1·5 g., 72·4%) was recrystallised from ethanol, to give the *ketone* as pale yellow needles, m. p. 155—156° (Found: C, 57·6; H, 6·1; N, 13·7. $C_{10}H_{12}N_2O_2$ requires C, 57·7; H, 5·8; N, 13·5%).

2-*Amino*-4-*dimethylaminoacetophenone*.—To a solution of the nitro-compound (2·5 g.) in concentrated hydrochloric acid (25 ml.) was added, portionwise, stannous chloride dihydrate (10 g.). The mixture was heated under reflux for 5 min., cooled, and made alkaline with 4N-sodium hydroxide. The crude product (1·5 g.) obtained by extraction with ether, was recrystallised from isopropyl alcohol to give needles, m. p. 114—115°, of the *product* (Found: C, 66·9; H, 8·0; N, 15·9. $C_{10}H_{14}N_2O$ requires C, 67·4; H, 7·9; N, 15·7%).

Reaction of 2-*Amino*-4-*dimethylaminoacetophenone with Nitrous Acid*.—(*a*) A solution of the amine (0·8 g.) in glacial acetic acid (5 ml.) and 10N-sulphuric acid (5 ml.) was cooled to 0° and treated with sodium nitrite (0·2 g.) in small portions. This solution (1 ml.) coupled with 2-naphthol in alkaline solution to give the azo-compound which formed red crystals, m. p. 276—277° (from ethanol). The remainder of the solution was allowed to attain room temperature slowly (evolution of nitrogen was noted) and set aside for several days. It was heated to 75° for 15 min., cooled, diluted with water (25 ml.), and the solid (0·5 g.) was collected, washed, and dried. Recrystallisation from ethanol gave 4-dimethylamino-2-hydroxyacetophenone as needles, m. p. 121·5—122·5° (lit.,[22] 120°) (Found: C, 67·0; H, 7·60; N, 7·9. Calc. for $C_{10}H_{13}NO_2$: C, 67·0; H, 7·3; N, 7·8%). Further attempts to cyclise the diazonium salt in other acid media at both room temperature and at 70° gave the same hydroxy-ketone.

(*b*) To a solution of the amine (0·4 g.) in 5N-sulphuric acid (5 ml.) was added solid sodium nitrite (0·1 g.) the temperature being kept below 5°. After 5 min. the solution was treated with excess of 5N-sodium hydroxide (*ca.* 6 ml.). The mixture rapidly darkened and the solid (200 mg.) was collected, but no useful material could be obtained from this product.

The alkaline filtrate was neutralised with 2N-sulphuric acid but yielded only 4-dimethylamino-2-hydroxyacetophenone.

4-*Acetyl*-3-*aminopyridine*.— 2-(3-Benzamido-4-pyridyl) propene (5 g.) in acetic acid (100 ml.) was treated with ozonized oxygen (containing 5—6% ozone) at about 7 l. per hr. for 6 hr. at 15—20°. Hydrogen peroxide (100 vol.; 10 ml.) was added, and the solution heated on a steam-bath for 1 hr. After pouring into ice–water (100 g.), the mixture was partially neutralised with 4N-sodium hydroxide (50 ml.), and the colourless crystalline product (3·4 g.) was collected, washed with water, and dried at 60°. Recrystallisation from 50% aqueous ethanol gave 4-*acetyl*-3-*benzamidopyridine* as needles, m. p. 121—122° (Found: C, 69·3; H, 4·9; N, 11·4. $C_{14}H_{12}N_2O_2$ requires C, 70·0; H, 5·0; N,

[21] J. J. Blanksma and D. Hoegen, *Rec. Trav. chim.*, 1946, **65**, 333.

[22] H. V. Peckmann and M. Schall, *Ber.*, 1899, **32**, 3690.

11·7%). This (2 g.) was heated with concentrated hydrochloric acid (25 ml.) under reflux for 2 hr., to provide *4-acetyl-3-aminopyridine* (0·9 g.) as yellow plates, m. p. 87° [from light petroleum (b. p. 80—100°)] (Found: C, 62·2; H, 6·15; N, 20·45. $C_7H_8N_2O$ requires C, 61·7; H, 5·9; N, 20·6%); *2,4-dinitrophenylhydrazone hydrochloride*, pale yellow needles, m. p. 287—288° (decomp.) (from acetic acid) (Found: C, 44·5; H, 3·9; Cl, 9·8; N, 26·2. $C_{13}H_{13}ClN_8O_4$ requires C, 44·2; H, 3·7; Cl, 10·1; N, 23·8%).

2-Acetyl-3-aminopyridine.—Prepared as for the 4-acetyl derivative using 2-(3-benzamido-4-pyridyl)propene (5 g.), the crude product (4·1 g.) was recrystallised from 50% aqueous alcohol, to give needles of the *ketone* (3·7 g.), m. p. 89—90° (Found: C, 70·1; H, 4·8; N, 11·7. $C_{14}H_{22}N_2O_2$ requires C, 70·0; H, 5·0; N, 11·7%). Hydrolysis of the benzamido-compound (3 g.) as before gave the *amino-ketone* as yellow plates, m. p. 63—64° [from light petroleum (b. p. 40—60°)]. The acetyl compound was identical (mixed m. p.) with the product obtained by chromium trioxide oxidation of the pinacol (described above) from a Grignard reaction between ethyl 3-aminopicolinate and methylmagnesium iodide.

Action of Nitrous Acid on 4-Acetyl-3-aminopyridine.—(*a*) A solution of the ketone (250 mg.) in acetic acid (3 ml.) and concentrated sulphuric acid (1 ml.) was treated with solid sodium nitrite (100 mg.) at 0°, set aside for 5 min., and then slowly heated to 50—60° on a water-bath. After the vigorous effervescence subsided the solution was cooled, poured into water (10 ml.), and neutralised with 4N-sodium hydroxide. Extraction of the yellow solution with chloroform (2 × 50 ml.) and evaporation of the dried chloroform extract gave 4-acetyl-3-hydroxypyridine as an uncrystallisable oil (190 mg.); *2,4-dinitrophenylhydrazone*, needles, m. p. 248—249° (from acetic acid) (Found: C, 49·5; H, 3·8; N, 21·6. $C_{13}H_{11}N_5O_5$ requires C, 49·2; H, 3·5; N, 22·1%).

(*b*) The ketone (250 mg.) was dissolved in concentrated hydrochloric acid (2 ml.) and water (8 ml.), and the clear solution treated at 0° with solid sodium nitrite (100 mg.). The solution was allowed to stand for 5 min. and was then treated with excess of 5N-sodium hydroxide (about 10 ml.) below 0°. The mixture rapidly darkened, with much frothing, and the dark solid (130 mg.) was collected after 1 hr. at room temperature. Attempted recrystallisation of this material did not afford any well defined compound but solid which separated from 50% acetic acid had m. p. 360°.

Neutralisation of the alkaline filtrate with 4N-hydrochloric acid gave more brown intractable material (40 mg.) of high m. p.

Action of Nitrous Acid on 2-Acetyl-3-aminopyridine.—(*a*) A solution of the amino-ketone (250 mg.) in concentrated hydrochloric acid (4 ml.) was treated at 0° with sodium nitrite (100 mg.). More concentrated hydrochloric acid (6 ml.) was added and the solution was heated to 60° on a water-bath for about 1 hr. (effervescence and coupling ceased after 10 min.). The solution was concentrated to about 2 ml. under reduced pressure, make alkaline with ammonia, and the oil was extracted with ether, to provide material (40 mg.) which contained chlorine and was probably 2-acetyl-3-chloropyridine. The aqueous solution was neutralised with 2N-hydrochloric acid, and extracted with ether, to provide a yellow oil (130 mg.) which solidified on standing. Vacuum-sublimation provided 2-acetyl-3-hydroxypyridine, m. p. 55—56°, identical with material obtained (above) during the diazotisation of 2-(3-amino-2-pyridyl)propene; *2,4-dinitrophenylhydrazone*, orange-yellow needles, m. p. 261—262° (from acetic acid) (Found: C, 49·5; H, 3·6; N, 21·5. $C_{13}H_{11}N_5O_6$ requires C, 49·2; H, 3·5; N, 22·1%).

(*b*) The amino-ketone (100 mg.) was diazotised in concentrated hydrochloric acid (1 ml.) and water (5 ml.) with solid sodium nitrite (40 mg.) below 0°, and after 5 min. 2N-sodium hydroxide (10 ml.) was added. The solution darkened rapidly, gas was evolved, and a dark brown precipitate (55 mg.), m. p. 300°, separated; this would not crystallise. Neutralisation of the alkaline filtrate with 2N-hydrochloric acid yielded a red-brown solid (20 mg.), m. p. 320—340°.

4-Hydroxy-3-methyl-10-phenyl-1,2,9-triazaphenanthrene.—(*a*) A hot solution of 3-amino-2-phenyl-4-propionylquinoline (1·0 g.) in concentrated hydrochloric acid (2·5 ml.) and water (10 ml.) was cooled to −5°, and the finely divided suspension treated below 0° with sodium nitrite (250 mg.) in water (5 ml.) during 5 min. The solution was then treated with 6N-sodium hydroxide (10 ml.) and allowed to warm to room temperature during 2 hr. A small amount of precipitate was filtered off and the orange-yellow solution was neutralised with 5N-hydrochloric acid. The precipitate (900 mg.) was collected, dried, and recrystallised from ethanol, to give leaflets, m. p. 202°, of the *product* (Found: C, 75·2; H, 4·6; N, 14·6. $C_{18}H_{13}N_3O$ requires C, 76·0; H, 5·0; N, 14·7%).

(*b*) The amino-ketone (500 mg.) was dissolved in concentrated hydrochloric acid (1·5 ml.) and treated at 0° with sodium nitrite (150 mg.) in water (1 ml.). After a few minutes, concentrated hydrochloric acid (10 ml.) was added and the mixture heated at 60° for 2 hr. (nitrogen evolved). Excess of hydrochloric acid was removed under reduced pressure and the residue neutralised with a concentrated solution of sodium acetate. The oily solid (400 mg.) was collected, dried, and digested with n-hexane, to yield an insoluble fraction [80 mg.; m. p. and mixed m. p. with the product from (*a*) 195—197°] and a soluble fraction, m. p. 83—84°, identified as *ethyl-3-chloro-2-phenyl-4-quinolyl ketone* (Found: C, 72·6; H, 4·6; Cl, 11·6; N, 4·5. $C_{18}H_{14}ClNO$ requires C, 73·1; H, 4·8; Cl, 12·0; N, 4·7%).

4-Chloro-3-methyl-10-phenyl-1,2,9-triazaphenanthrene.—The hydroxy-compound (600 mg.), phosphorus pentachloride (900 mg.), and phosphoryl chloride (4·5 ml.) were heated together under reflux for 2 hr. The excess of phosphoryl chloride was distilled under reduced pressure and the residue was shaken with benzene (25 ml.), ice (20 g.), and 3N-sodium hydroxide (10 ml.). The benzene layer was collected, the aqueous layer extracted twice with further benzene, and the combined benzene extracts were dried ($MgSO_4$) and evaporated, to yield a solid (550 mg.), m. p. 180—183°. The *chloro-compound*, m. p. 186°, crystallised from ethyl acetate as blades (Found: C, 71·0; H, 4·3; Cl, 12·1; N, 12·6. $C_{18}H_{12}ClN_3$ requires C, 70·7; H, 4·0; Cl, 11·6; N, 13·7%).

3-Methyl-4-phenoxy-10-phenyl-1,2,9-triazaphenanthrene.—The chloro-compound (300 mg.) was heated on a steam-bath for 2 hr. with potassium hydroxide (100 mg.) in phenol (1·5 g.). The product was cooled, digested with warm 2N-sodium hydroxide (25 ml.), and the solid (300 mg.) recrystallised from methyl acetate, from which the pure phenoxy-compound separated as needles, m. p. 159—160° (Found: C, 79·3; H, 4·8; N, 11·3. $C_{24}H_{17}N_3O$ requires C, 79·3; H, 4·7; N, 11·6%).

4-Amino-3-methyl-10-phenyl-1,2,9-triazaphenanthrene.—(*a*) The phenoxy-compound (200 mg.) was heated in an open tube with ammonium acetate (2 g.) at 180—200°

in an oil-bath for 3 hr., the ammonium acetate being renewed when necessary. The cold mixture was digested with 2N-sodium hydroxide, and the well washed crude product (110 mg.) was recrystallised from nitromethane, to provide pale brown needles of the *amine*, m. p. 245—246° (Found: C, 72·6; H, 5·0; N, 17·6. $C_{18}H_{14}N_4,H_2O$ requires C, 71·1; H, 5·3; N, 18·4%); *methiodide*, needles (from methanol), m. p. 263° (decomp.) (Found: C, 52·9; H, 3·75; I, 29·2; N, 12·8. $C_{19}H_{17}IN_4$ requires C, 53·2; H, 4·0; I, 29·7; N, 13·1%).

(*b*) A stream of dry ammonia was passed for ½ hr. through a solution of the phenoxy-compound (100 mg.) in acetamide (1 g.) at 175° ± 5°. The mixture was cooled, diluted with water, and the precipitate (65 mg.), m. p. 225—230°, washed and dried. Recrystallisation from nitromethane gave the amine, m. p. 245—246°.

4-*Methoxy*-3-*methyl*-10-*phenyl*-1,2,9-*triazaphenanthrene*.—The chloro-compound (100 mg.) was heated under reflux for 2 hr. with methanolic sodium methoxide prepared from sodium (0·25 g.) and methanol (15 ml.). The *methoxy-compound* formed needles, m. p. 201—202° (from ethyl alcohol) (Found: C, 76·2; H, 5·1; N, 14·4. $C_{19}H_{15}N_3O$ requires C, 75·7; H, 5·0; N, 14·0%).

N-*Methyl*-3-*methyl*-4-*oxo*-10-*phenyl*-1,2,9-*triazaphenanthrene*.—A cold solution of the hydroxy-compound (100 mg.) in 3N-sodium hydroxide (2 ml.) was treated with dimethyl sulphate and the suspension was heated at *ca.* 50° for 5 min. The *derivative*, m. p. 243—244°, crystallised from ethyl alcohol as leaflets (Found: C, 75·6; H, 5·0; N, 13·9. $C_{19}H_{15}N_3O$ requires C, 75·7; H, 5·0; N, 14·0%).

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