STUDIES IN THE CARBAZOLE
AND PYRIDOBENZIMINAZOLE SERIES

by

Ernest B. McCall, B.Sc.

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PREFACE

The original aim of this research was the investigation of the possibility of preparing derivatives of tetrahydrocarbazole by condensation of 2-chlorocyclohexanone and substituted anilines. It was also hoped that the method might be extended to the synthesis of derivatives of tetrahydrocarboline by employing substituted 2-aminopyridines. The somewhat unexpected results obtained from a study of this second condensation reaction, necessitated the division of the thesis into two quite distinct parts. Each part contains an introductory section reviewing previous work in the field; a discussion of the results obtained in the present investigation; and an experimental section in which all relevant details of experimental procedure are described.

It should be noted that the work described in Part II was commenced whilst investigations in Part I were still being carried out, and consequently the scope of the tetrahydrocarbazole synthesis has not been as fully investigated as had been originally intended.

The author would like to take this opportunity of expressing his gratitude to Dr. Neil Campbell for guidance and encouragement so freely given during this research. Thanks are also due to the Department of Scientific and Industrial Research for a Grant, during the tenure of which this work was carried out.
PART I

STUDIES IN THE CARBAZOLE SERIES
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INTRODUCTION

Occurrence and Isolation

In 1872, Graebe and Glaser (1) discovered in the anthracene fraction of coal tar a hitherto unknown heterocyclic compound of molecular formula \( \text{C}_{12} \text{H}_9 \text{N} \) to which they gave the name carbazole, and in the same year, Graebe (2) effected its synthesis by pyrolysis of aniline and suggested that it might possess an "imidodiphenyl" structure. The correctness of Graebe's suggestion has since been demonstrated by numerous syntheses, and carbazole is still occasionally referred to in the literature as diphenylene-imine or dibenzo-pyrrole.

This anthracene fraction of coal tar boiling between 290° and 350° is the main commercial source of carbazole, and several methods are employed for the removal of the heterocyclic constituent from the other hydrocarbons present (3). The solid obtained on cooling the anthracene fraction contains approximately 20% of carbazole admixed with 30% anthracene and 50% phenanthrene and other components, and by a suitable choice of solvent, pyridine for example, it is possible to extract the carbazole from the mixture. Another method makes use of the acidic character of the hydrogen of the imino group, the non volatile potassium carbazole formed with
potassium hydroxide being freed from anthracene and phenanthrene by distillation. Carbazole can readily be regenerated from its potassium derivative by treatment of the latter with water.

Although the derivatives of carbazole are as yet incompletely investigated, several have found use in commerce chiefly as dyestuff intermediates: carbazole hydroxy sulphonic- and carboxylic acids may be used as secondary components in the manufacture of azo-dyes; the tetrazo compound derived from $3:6$-diaminocarbazole can be coupled to form several direct cotton dyes; and by treatment of the carbazole indophenol obtained from carbazole and nitrosophenol, with sodium polysulphide the very important "Hydron-Blue" dyestuff can be obtained. Carbazole also finds use as a stabilizer in certain explosive compositions, and its N-vinyl derivative readily yields a transparent, thermoplastic polymer of high softening point which has found several uses in industry under the trade name of Luvican.

The patent literature of the past fifty years covers many processes for the manufacture of carbazole and its derivatives, and if the suggested value of these compounds as potential intermediates in the preparation of further dyestuffs and chemotherapeutic agents materialises, carbazole may well find application in many other commercial processes.
3.

Syntheses

Several of the earlier methods devised for the synthesis of carbazole are now only of academic interest because of their very limited applicability or low yields: Graebe (2) prepared carbazole by pyrolysis of aniline and also of diphenylamine; Blank (4) passed o-aminodiphenyl over red hot lime in a combustion tube and obtained carbazole; and Tauber (5) produced carbazole in good yield by heating 2:2'-diaminodiphenyl with 25% sulphuric acid at 200°.

The two most important syntheses of carbazole and its derivatives, however, are those devised by Graebe and Ullman and Borsche.

The method of Graebe and Ullman (6) is of wide application and is based on the ease with which 1-phenyl-1:2:3-benzotriazole (II) loses nitrogen on heating to give a quantitative yield of carbazole (III).

The 1-phenyl-1:2:3-benzotriazole is obtained by treatment of o-aminodiphenylamine (I) with nitrous acid. Various systems of numbering the carbon and nitrogen atoms of carbazole are to be found in the literature, but the one given above which will be used throughout
this thesis is that adopted by most British and American journals. Ullman\(^{(7)}\) also synthesised a number of the methyl- chloro- and aminosubstituted carbazoles by this method, but other workers have found that certain substituent groups either inhibit the cyclization or give greatly diminished yields at this stage. Bremer \(^{(8)}\) who was investigating the cyclization of \(^4\prime\)-methyl-(IV,\(R=\text{CH}_3\)), \(^4\prime\)-amino-(IV,\(R=\text{NH}_2\)), \(^4\prime\)-bromo-(IV,\(R=\text{Br}\)) and \(^4\prime\)-methoxy-5-amino-1:2:3-benzotriazole (IV,\(R=\text{OCH}_3\))

\[
\begin{align*}
\text{IV} & \quad \text{V} \\
\quad & \\
\end{align*}
\]

 discovered that the first gave a good yield of 3-amino-6-methylcarbazole (V,\(R=\text{CH}_3\)); the second gave only a trace of 3:6-diaminocarbazole; and the other two decomposed during cyclization and gave no carbazole derivatives. Preston, Tucker and Cameron \(^{(9)}\) have shown that the Graebe-Ullmann method can be used for the preparation of nitro- (trace), acetyl- (22\%) and cyanocarbazoles (34\%), but the yields given in parentheses indicate that these substituents also decrease the ease with which the benzotriazole can be cyclized. The limitations of the Graebe-Ullmann method have also been noted by Campbell and MacLean \(^{(10)}\) in their attempt to find a general method for the synthesis of 1-substituted derivatives of carbazole. By heating 7-bromo-1-phenylbenzo-
triazole-5-carboxylic acid (VI) with quicklime they hoped to obtain 1-bromocarbazole, but as a result of simultaneous decarboxylation and debromination carbazole itself was formed.

\[
\text{COOH} \quad \begin{array}{c}
\text{Br} \\
\text{N} \quad \text{N} \quad \text{N} \\
\text{\_\_\_\_}
\end{array} \quad \rightarrow \quad \begin{array}{c}
\text{N} \quad \text{N} \\
\text{\_\_\_\_}
\end{array}
\]

**VI**

The Borsche synthesis is of more general application than the Graebe-Ullman method, but the initial products are \(1:2:3:4\)-tetrahydrocarbazoles and therefore the value of the method depends on the satisfactory dehydrogenation of these tetrahydro compounds. Borsche (11) by extending the well known Fischer indole synthesis to cyclic ketones like cyclohexanone showed that cyclohexanone phenylhydrazone (VII)

\[
\text{NH} \quad \begin{array}{c}
\text{\_\_\_\_}
\end{array} \quad \begin{array}{c}
\text{NH} \\
\text{\_\_\_\_}
\end{array} \quad \begin{array}{c}
\text{\_\_\_\_}
\end{array}
\]

**VII**

and its methyl, chloro, bromo and nitro substituted derivatives readily lost ammonia in warm sulphuric acid to give the corresponding substituted derivatives of \(1:2:3:4\)-tetrahydrocarbazole (VIII). The very thorough investigations of Plant (12, 13, 14) and Barclay and Campbell (15) have demonstrated
clearly the full scope of this method, and these workers have also shown that the use of a meta substituted phenylhydrazine (IX) like m-bromo-(14), m-chloro-(13) or m-nitrophenylhydrazine (15) frequently leads to the formation of a mixture of the two theoretically possible 5- and 7- substituted tetrahydrocarbazoles (Xa and Xb)

\[
\begin{align*}
\text{IX} & \quad \rightarrow \quad \text{Xa} + \text{Xb}
\end{align*}
\]

Barclay and Campbell in their search for a suitable dehydrogenating agent for these substituted tetrahydrocarbazoles discovered that chloranil (tetrachlorophenzoquinone) effected conversion to the corresponding carbazoles in good yield without affecting the substituent groups, the method being vastly superior to earlier methods employing lead oxide (11), palladous chloride (16) and mercuric acetate and sulphur (17).

An interesting modification of the Borsche synthesis has recently been introduced by Rogers and Corson (18) in which the condensation of the cyclohexanone and phenylhydrazine and cyclization of the resultant phenylhydrazone are carried out in one stage in glacial acetic acid or alcoholic hydrogen chloride. In this way tetrahydrocarbazole and several of its methyl derivatives have been obtained in 70% - 90% yield.
A further modification of the Borsche method leading to the formation of 1-keto-1:2:3:4-tetrahydrocarbazole has been studied by Coffey (19). He showed that cyclohexanone and amyl formate react in the presence of sodium to give oxymethylene cyclohexanone (XI), and this on treatment with benzene diazonium chloride gives the monophenylhydrazone of 1:2-cyclohexanedione (XII). This phenylhydrazone loses ammonia on boiling with a mixture of glacial acetic and concentrated hydrochloric acid simultaneously cyclizing to 1-ketotetrahydrocarbazole (XIII). Mears, Oakeshott and Plant (20) have prepared the 6- and 8-methyl-; the 5-, 6- and 7-bromo-; and the 6-nitro derivatives of 1-ketotetrahydrocarbazole in a similar manner using the appropriate diazonium chloride, and they have effected the reduction of 1-ketotetrahydrocarbazole to tetrahydrocarbazole by heating with phosphorous and hydriodic acid. Anderson (21) has prepared a number of the methyl and dimethyl derivatives of 1-ketotetrahydrocarbazole in this way, and has shown that the reduction of the ketone group in these compounds can be effected in good yield by the application of Clemmensen's method with zinc amalgam and hydrochloric acid.
In addition to providing a method of preparing several otherwise inaccessible derivatives of carbazole, these synthetic methods furnish proof of the structure of carbazole derivatives formed by direct substitution.
Properties of Carbazole and its behaviour on substitution

Carbazole is an extremely stable substance: it can be distilled over zinc dust without decomposition (1); it dissolves only sparingly in cold concentrated sulphuric acid and is precipitated unchanged on dilution of the acid; and it is unaffected by treatment with concentrated hydrochloric acid at temperatures as high as 300° (22). In spite of this exceptional stability, however, carbazole can readily be detected by the bluish-green colour, observed when a trace dissolved in sulphuric acid is treated with one drop of nitric acid, and by the well defined crystalline addition compounds it forms with picric acid and trinitrobenzene. Substituted carbazoles are similarly identified.

The preparation of derivatives of carbazole by direct substitution can best be reviewed by considering the N-substituted and C-substituted derivatives separately.

N-Substituted carbazoles

The N-substituted derivatives may be obtained in some cases by treatment of carbazole with the appropriate reagent, but the most suitable starting substances are the N-potassium carbazole formed with potassium hydroxide, and the carbazole-N-magnesium iodide obtained with Grignard reagents. Potassium carbazole reacts with alkyl, aryl or acyl halides to yield the corresponding N-alkyl, aryl or acyl
derivative, but the method cannot be applied to compounds such as nitro- or halogeno- carbazoles since the preparation of the potassium derivative entails fusion with potassium hydroxide. Stevens and Tucker (23) have surmounted this difficulty by effecting the condensation of carbazole and the appropriate alkylating or acylating agent in alcohol or acetone in the presence of sodium or potassium hydroxide. The N-acyl derivatives can also be prepared from the carbazole magnesium iodide, but the method is more tedious.

Potassium carbazole on treatment with carbon dioxide yields potassium carbazole-N-carboxylate, and this on acid hydrolysis or further carbon dioxide treatment (24) gives carbazole-1-carboxylic acid.

**C-Substituted carbazoles**

A limited number of substituted carbazoles may be prepared by direct nitration, halogenation, sulphonation and etc., but the drawback to this method is that unless the correct conditions are employed, mixtures containing mono-, di- and trisubstituted isomers may result.

The 3- and 6-positions, and to a lesser extent the 1- and 8-positions are the reactive centres of the carbazole system, and successive substitution takes place at these positions in the order given, bromination for example giving 3-bromo-, 3 : 6-dibromo-1 : 3 : 6-tribromo- or 1 : 3 : 6 : 8-tetramethylcarbazo- depending on the amount of
bromine used. Nitration gives in the first instance 75% of 3-nitro- and 4% of 1-nitrocarbazole (25), but exhaustive nitration leads to attack at all four reactive positions giving 1 : 3 : 6 : 8-tetranitrocarbazole. In the Friedel-Crafts reaction carbazole behaves somewhat similarly, giving with aluminium chloride and acetyl or benzoyl chloride the 3 : 6-diacyl- (26) or the 3 : 6-dibenzoylcarbazole (27). N-Acylcarbazoles on the other hand give 2 : 9-derivatives which can readily be converted to 2-acylcarbazoles (28) by hydrolysis. Plant and Williams (28) have shown that these 2- and 3-acetylcarbazoles give the corresponding carboxylic acids on fusion with potassium hydroxide.

In addition to these direct methods of obtaining substituted carbazoles, many of the standard methods of replacing groups may be employed: cyanocarbazoles can be prepared by reduction of nitrocarbazoles followed by diazotisation of the aminocarbazoles and treatment with cuprous cyanide; the important hydroxycarbazole sulphonic acids can be obtained by stepwise replacement of the sulphonyl groups in polysulphonic acids by the action of alkali; and the difficulty accessible 1-nitrocarbazole can be prepared by the nitration of carbazole-3 : 6-dicarboxylic acid followed by decarboxylation of the resultant 1-nitro compound (9).

The preparation of 2- and 4-substituted derivatives of carbazole by direct substitution is
not possible, and to obtain them recourse must be made to the synthetic methods already discussed.

Reduction of carbazole with sodium and alcohol (29) gives 1 : 2 : 3 : 4-tetrahydrocarbazole and with a stronger agent like phosphorous and hydriodic acid (30) the 1 : 2 : 3 : 4 : 10 : 11-hexahydrocarbazole is produced. The two extra hydrogen atoms in the hexahydro compound have entered the 10- and 11-positions, and this remarkable reactivity of the 10 : 11 double bond is probably the outstanding property of tetrahydrocarbazole. Under certain conditions, N-substituted tetrahydrocarbazoles instead of being nitrated with nitric acid, add on the acid at the 10 : 11 bond of the reduced ring. Perkin and Plant (17) have shown, for example, that N-benzoyltetrahydrocarbazole (XIV) gives mainly 10-hydroxy-9-benzoyl-11-nitrohexahydrocarbazole (XV) which is degraded with alkali to δ-(o-benzoylaminobenzoyl) valeric acid (XVI) according to the scheme suggested below. Linnell and Perkin (31) found

![Chemical Structures](image-url)
that N-phenyltetrahydrocarbazole reacts with nitric acid in a similar fashion, and the degradation of the product with alkali appears to take place by an identical mechanism. Although structure XVa was not isolated by either of these sets of workers this is not unexpected, since the amide grouping will readily hydrolyse in the presence of alkali. Compounds of a similar nature appear to have been formed in a neutral medium during the recrystallisation of certain of the dimethyltetrahydrocarbazoles prepared in this research (cf. p. 26)
Mechanism of the Reaction between $\alpha$-Halogenated Ketones and Arylamines

Before attempting a discussion of the results obtained during the course of this research, it will be necessary to give an outline of the existing theories on the mechanism of the condensation between $\alpha$-halogenated ketones and arylamines, and in particular of the cyclization of phenacylanilines. Although the condensation of 2-chlorocyclohexanone and arylamines has only been outlined in a patent, it seems highly probable that it will take place by a similar mechanism.

The first reaction of this type to be examined was the condensation of aniline and phenacyl bromide by which

\[
\text{XVII}
\]

Mohlau (32) prepared phenacylaniline (XVII).

Mohlau's observation (33) that the phenacylaniline reacted further with aniline was later confirmed by Fischer and Schmitt (34), who

\[
\text{XVIII}
\]

showed that the resulting compound was 2-phenylindole (XVIII), the structure of which had already been
established by synthesis and degradation. At first it was believed that the expected 3-phenylindole had isomerised to 2-phenylindole under the conditions employed in the cyclization, since Fischer and Schmitt (35) had demonstrated that this isomerisation takes place when the 3-isomer is heated with zinc chloride. Ince (36), however, by heating 3-phenylindole with aniline hydrochloride at temperatures as high as 230° observed no rearrangement, and it was concluded that the suggested isomerisation was extremely doubtful under the conditions employed.

It was left to Bischler (37) to provide the solution to this apparent anomaly, and to formulate a mechanism for the reaction between aniline and phenacyl bromide. According to Bischler the reaction takes place in three stages:

(i) Direct replacement of the halogen by the arylamino group giving phenacylaniline (XVII).

(ii) Reaction of a second mole of aniline with the phenacylaniline to form the aniline-anil (XIX).

(iii) Cyclization of the aniline-anil by loss of one molecule of aniline to give structure XX, which immediately rearranges to 2-phenylindole. It is important to note that it is the second mole of aniline participating in the reaction which remains
intact in the indole structure.

In support of his theory Bischler showed that with excess p-toluidine, phenacylaniline gave 2-phenyl-5-methylindole (XXI), whilst

\[
\text{XXI} \quad \text{XXII}
\]

phenacyl-p-toluidine (XXII) with excess aniline gave 2-phenylindole.

More recent results obtained from a study of the cyclization of several phenacylamines with various aromatic amine salts and zinc chloride, however, have demonstrated the inadequacy of the Bischler theory, and have brought objections from two sets of investigations.

Verkade and Janetzky (38) repeated some of the earlier work and whilst they agree that phenacylaniline gives 2-phenylindole when fused with zinc chloride and heated with aniline hydrochloride, they found that it was unchanged on boiling with aniline, if the reactants were first freed from all traces of acid. They also discovered that phenacyl-N-methylaniline (XXIII) when heated with an equal weight of N-methylaniline hydrochloride gave a high

\[
\text{XXIII} \xrightarrow{\text{Co-C}_{6}\text{H}_{5}} \text{XXIV} + \text{XXV}
\]
yield of 3-phenyl-1-methylindole, along with a much smaller amount of the 2-phenyl compound (XXV), and that molecular amounts of phenacylaniline and o-toluidine in the presence of hydrochloric acid gave 2-phenylindole along with a smaller amount of 2-phenyl-7-methylindole, whereas Bischler employing excess o-toluidine had only noted the formation of the latter.

From a fairly extensive study of the cyclization of phenacylanilines of type XXVI where R and R' are aryl and alkyl groups respectively, Verkade and Janetzky (38, 39) have concluded that this may take place by one of two methods:

(i) Indolisation by "true ring closure" to give compounds of type XXVII.

(ii) Indolisation by "rearrangement" giving indoles of type XXVIII. Included in this class are several phenacylanilines which do not really fit in with either scheme giving indoles by what is termed a "seeming cyclization".

Although Verkade and Janetzky have presented a theory which fits their experimental observations, they make no attempt to explain the mechanism of their postulated "rearrangement" or "true ring closure".

Crowther, Mann and Purdie (40) agree with Verkade and Janetzky that the cyclization of phenacylanilines is an acid catalysed reaction, and
claim that much of the early work in this field was invalidated by the use of impure phenacylamines. They have shown that phenacylaniline and aniline when pure react

\[
\begin{align*}
C_6H_5-NH-CH=CH_2 & \rightarrow C_6H_5-NH-CH=CH_2 \\
OH & \rightarrow + H_2N-C_6H_5 \\
C_6H_5-NH-CH=CH_2 & \rightarrow C_6H_5-NH-CH=CH_2 \\
\end{align*}
\]

XXIX
to give a triamine, XXIX, and that phenacylaniline with boiling o-toluidine undergoes a slow interchange according

\[
\begin{align*}
C_6H_5-NH-CH=CH_2 & \rightarrow C_6H_5-NH-CH=CH_2 \\
OH & \rightarrow + o-CH_3.C_6H_4.NH_2 \\
C_6H_5-NH-CH=CH_2 & \rightarrow C_6H_5-NH-CH=CH_2 \\
\end{align*}
\]

XXIX

to the equation above, the rate depending on the active mass of the constituents present. If the mixture is free from amine salts, triamines of type XXIX will be formed, but when such salts are present cyclization of the phenacylanilines will occur. In the presence of large quantities of o-toluidine, the reaction will be displaced towards the right and 2-phenyl-7-methylindole will be the main product of cyclization, but if the mixture contains only a trace of o-toluidine 2-phenylindole will be the main component of the cyclization product.

A much more important fact has been discovered by Mann and Brown ([41], however, in their investigations on the cyclization of phenacylanilines of the type \(C_6H_5-NH-CH.CO.R'\).
Verkade and Janetzky had already studied indole formation from compounds of this type, but whilst they examined compounds in which \( R' \) was an alkyl group and \( R \) an aryl group, Mann and Brown selected two similar groups.

They prepared the two isomeric

\[
\begin{align*}
\text{XXX} & : \quad \begin{array}{c}
\text{C}_6\text{H}_5\text{NH} \cdot \text{CH} \cdot \text{C}_6\text{H}_5 \cdot \text{CO} \cdot \text{C}_6\text{H}_5 \\
\end{array} \\
\text{XXXI} & : \quad \begin{array}{c}
\text{C}_6\text{H}_5\text{NH} \cdot \text{CH} \cdot \text{C}_6\text{H}_5 \cdot \text{CO} \cdot \text{C}_6\text{H}_5 \\
\end{array}
\end{align*}
\]

1-phenyl-\( p \)-methylphenacylaniline (XXX) and 1-\( p \)-tolylyphenacylaniline (XXXI) and from a study of their ring closure under varying conditions observed that both always cyclized to 2-phenyl-\( 3 \)-\( p \)-tolylindole. More important, however, was the observation that in the presence of acids at moderate temperatures XXXI isomerised to XXX without ring closing, structure XXX apparently being the more stable isomer. If this rearrangement prior to cyclization is a general phenomenon, then the majority of the cyclizations can readily be explained, the formation of 2-phenylindole from phenacylaniline for example resulting

\[
\text{C}_6\text{H}_5\text{NH} \cdot \text{CH}_2 \cdot \text{CO} \cdot \text{C}_6\text{H}_5 \rightarrow \text{C}_6\text{H}_5\text{NH} \cdot \text{CH} \cdot \text{C}_6\text{H}_5 \cdot \text{CHO} 
\]

from the above isomerisation preceding the cyclization.

Mann and Brown have presented a very elaborate mechanism to explain this conversion at the phenacylaniline stage, but until rearrangements of this type have received a more thorough examination, it must be
regarded as purely speculative. Although these two sets of investigators apparently reject the Bischler hypothesis of diamine formation, Julian and his collaborators (42) in America have actually succeeded in isolating an aniline-anil (XXXIII) of the Bischler type in the conversion of

```
\[
\begin{align*}
\text{XXXII} & \quad \text{XXXIII} \\
C_6H_5\text{CH-NH}C_6H_5 & \rightarrow C_6H_5\text{-C-NH}C_6H_5 \\
C_6H_5\text{-CO} & \quad C_6H_5\text{-C-NH}C_6H_5
\end{align*}
\]
```

desylaniline (XXXII) into 2 : 3-diphenylindole (XXXIV) with aniline and hydrochloric acid. They do point out, however, that Bischler's contention that it is the first arylamine molecule to react with the halogenated ketone which is eliminated in the cyclization is weak, since in the ene-diol structure XXXIII the two arylamine groups are identical, and the designation of the "first" to any aniline molecule entering the reaction loses its significance. Julian holds the view that the Bischler mechanism if suitably modified will explain the formation of many indoles from phenacylamines, but asserts that the interaction of an α-bromoketone and an arylamine is a complicated system that may involve simultaneously seven different reactions.
PUPJPQSE AhD GhhEBAh PLAIi OF KhSBAhCh This series of investigations was prompted by the discovery that a process for the manufacture of tetrahydrocarbazole and its methyl derivatives developed and patented (43) in Germany in 1923 had apparently received little or no attention from the many investigators of the carbazole field. By condensing aniline (XXXV) and its C- and N-substituted monomethyl derivatives with

\[
\text{XXXV} + \text{XXXVI} \rightarrow \text{XXXVII}
\]

\[
R = H \text{ or } \text{CH}_3
\]

2-chlorocyclohexanone (XXXVI), Ott, the discoverer of the process prepared tetrahydrocarbazole, 3-methyl-tetrahydrocarbazole, 6-methyltetrahydrocarbazole and N-methyl-tetrahydrocarbazole. The condensation reaction involving loss of water and hydrochloric acid proceeded smoothly at 150° in the presence of excess amine, potassium carbonate or potassium acetate as the acid binding agent.

The purpose of this research was to investigate the scope of this method by attempting the preparation of other substituted tetrahydrocarbazoles. As in the Borsche synthesis, this chlorocyclohexanone method should theoretically lead to the formation of a mixture of 5- and 7-substituted tetrahydrocarbazoles
when a meta substituted aniline is employed. By condensation of methyl substituted 2-chlorocyclohexanones, it should be possible to prepare monomethyltetrahydrocarbazoles containing the methyl substituent in the reduced ring.

It was also hoped to prepare the intermediate aminoketones, and to discover if their cyclization was governed by the rules pertaining to the ring closure of phenacylanilines discussed in the previous section.
DISCUSSION OF RESULTS

Preparation of Methyl- and Dimethyltetrahydrocarbazoles

1 : 2 : 3 : 4-Tetrahydrocarbazole and its 6-methyl- (XXXVII) and 8-methyl- derivatives (XXXVIII)

![XXXVII](image1)

![XXXVIII](image2)

were prepared in 60% yield by condensation of 2-bromo-cyclohexanone and the appropriate arylamine at 150°C in the presence of excess amine. The German patent describes their preparation in quantitative yield by condensation of 2-chlorocyclohexanone and the appropriate arylamine, but it is difficult to understand how the yields can be quantitative whatever the halogenoketone employed, since Kötz and Grethe (44) have shown that both 2-chlorocyclohexanone and 2-bromocyclohexanone give Δ₂-cyclohexanone (XXXIX) when warmed with aniline in ether. It is possible, however, that the more reactive 2-bromocyclohexanone suffers more intramolecular dehydrohalogenation leaving a smaller amount available for the intermolecular reaction with the aniline which forms the tetrahydrocarbazole.
Tetrahydrocarbazole has been prepared in 90% yield by the modification of the Borsche method introduced by Rogers and Corson (18), and the methyltetrahydrocarbazoles have been prepared by the Borsche method in unspecified yields, but both suffer from the disadvantage that the arylamine must first be converted to the corresponding phenylhydrazine and in the case of the methyl compounds, these may undergo decomposition on standing in air.

At this stage it was discovered that 2-bromocyclohexanone was too unstable to permit of its being prepared in large quantities and stored for future use. The compound was a pale yellow oil when freshly distilled, but it rapidly darkened in colour and within a week it had been converted to a dark brown resin which gave off copious fumes of hydrobromic acid on exposure to the air. Because of this instability of the bromo-isomer, 2-chlorocyclohexanone was used for the subsequent condensations. The chloroketone can be stored in the refrigerator for long periods without suffering any apparent decomposition.

When p-2-xylidine and m-4-xylidine were boiled under reflux with 2-chlorocyclohexanone in alcohol, 5: 8-dimethyl-(XL) and 6: 8-dimethyltetrahydrocarbazole (XLI)
respectively were readily formed, the yield in each case approaching 40%. No method is recorded in the literature for the preparation of dimethyltetrahydrocarbazoles in which both methyl groups are in the aromatic ring, presumably because of the known instability of 2:4- (45) and 2:5-dimethylphenyldrazine (46). These compounds lose ammonia readily in the atmosphere, and therefore their condensation with cyclohexanone in the first stage of the Borsche synthesis would no doubt be troublesome. Anderson (21), has prepared the 5:8- and 6:8-dimethyltetrahydrocarbazoles by the modification of the Borsche method discussed in the introduction, and he has effected their dehydrogenation to the corresponding dimethyl carbazoles with chloranil, but his work is as yet unpublished.

An interesting fact has come to light regarding the stability of 5:8- and 6:8-dimethyltetrahydrocarbazole. When a saturated boiling solution of these compounds in light-petroleum is cooled quickly, the bulk of the tetrahydrocarbazole readily crystallises, but if a dilute solution is employed, or if the mother liquor from the rapid crystallisation is allowed to stand for ten to fifteen minutes a different compound is frequently obtained. These compounds will not redissolve when the light-petroleum is again heated to the boiling point; they melt with decomposition at a temperature above the melting point of the tetrahydrocarbazole, this temperature varying with the rate of heating; they are only sparingly soluble
in benzene and toluene, but dissolve fairly readily in alcohol to give solutions possessing a bright green fluorescence in ultra-violet light; and their solutions in alcohol or benzene will not form a picrate, whereas the initial tetrahydrocarbazoles readily form chocolate coloured picrates in either alcohol or benzene. Analysis results have indicated that they possess a molecular formula C_{14}H_{17}O_2N_i, i.e. a structure formed by the addition of two oxygen atoms per molecule to the original tetrahydrocarbazole, and until further evidence is obtained it is tentatively suggested that

![Structures XLII and XLIII](https://example.com/structures.png)

these oxidation products obtained from 5:8- and 6:8-dimethyltetrahydrocarbazole are represented by structures XLII and XLIII respectively.

XLII and XLIII require C, 72.68; H, 7.41; N, 6.06

Found for XLII C, 72.66; H, 7.46; N, 6.10

Found for XLIII C, 73.70; H, 7.71; N, 5.90.

It is worth noting that in the case of compound XLIII, the specimen analysed was that obtained from the light-petroleum mother liquor and might conceivably have been contaminated with 6:8-dimethyltetrahydrocarbazole, whereas the sample of XLII was recrystallised from alcohol prior to being analysed.

Structures XLII and XLIII are consistent with the
properties of these compounds already mentioned, but several additional reactions were carried out in an attempt to detect the ketone and amide groups. Compounds XLII and XLIII each gave a gelatinous, red-brown solid with dinitrophenylhydrazine but these products had a very indefinite melting point and because of their very low solubility could not be recrystallised satisfactorily. Compound XLII dissolved readily in boiling alcoholic potash and after fifteen minutes the solution gave a potassium salt, but attempts to isolate the free acid were unsuccessful possibly because of its amphoteric nature.

Despite the failure of these experiments to give conclusive proof of the presence of the ketone and amide groups, they do indicate that such groups are present, and in view of the known reactivity (p.12) of the 10 : 11 double bond in tetrahydrocarbazole, it seems probable that oxidation would readily occur at this point. The formation of oxygen containing compounds during the recrystallisation of dimethyltetrahydrocarbazoles has also been observed by Anderson (21) in the course of his investigations on the extension of Coffey's method of synthesis.

By condensation of diazotised o-4-xylidine and oxymethylene cyclohexanone, and cyclization of the resultant dimethylphenylhydrazone of 1 : 2-cyclohexanedione, Anderson obtained a mixture of
of 5:6- (XLIV) and 6:7-dimethyl-1-keto-tetrahydrocarbazole (XLV) which he separated by fractional crystallisation. Reduction of the ketone groups followed by dehydrogenation gave the 2:3- and 3:4-dimethylcarbazoles, which were orientated by a synthesis of the latter from

5-bromo-o-4-xyldine by Coffey's method via 5:6-dimethyl-8-bromo-1-ketotetrahydrocarbazole (XLVI). In this case the ortho bromine substituent allows only one mode of ring closure, and by reduction and dehydrogenation Anderson obtained 1-bromo-3:4-dimethylcarbazole (XLVII) from which authentic 3:4-dimethylcarbazole was easily prepared.

When o-4-xyldine and 2-chlorocyclohexanone were condensed, however, only a 13% yield of the 6:7-dimethyltetrahydrocarbazole was obtained.

Unfortunately the crude product was purified by crystallisation instead of by the vacuum distillation method employed in the two previous cases, and during this crystallisation at least 50% of the product underwent a change presumably analogous to that already discussed. The 6:7-dimethyltetrahydrocarbazole method over a 10° range but it is doubtful if it contained any of the theoretically possible 5:6- isomer for the following reasons:
(i) It gave a picrate which had a sharp melting point before being recrystallised.

(ii) It was dehydrogenated to 2 : 3-dimethylcarbazole and although this was only obtained in 42% yield the product had a sharp melting point.

(iii) The 6 : 7-dimethyltetrahydrocarbazole prepared by Anderson also melted over a 10° range, and this had been obtained by reduction of a pure 6 : 7-dimethyl-1-ketotetrahydrocarbazole obtained by a separation of compounds XLIV and XLV.

It is interesting to note that Verkade and Janetzky (47) only obtained one trimethylindole by condensation of m-toluidine and methyl-α-bromoethyl ketone, as the formation of both 2 : 3 : 4- and 2 : 3 : 6-trimethylindole is theoretically possible in this reaction.
Preparation of Chloro- and attempted preparation of Bromotetrahydrocarbazoles

Condensation of ortho and p-chloroaniline with 2-chlorocyclohexanone was effected by heating with excess amine at the boiling point, and at 150\(^\circ\) respectively, and in this way

![Chemical Structures](image)

8-chlorotetrahydrocarbazole (XLVIII) and 6-chlorotetrahydrocarbazole (XLIX) were obtained. The yields were low, but again comparison with those obtained by application of the Borsche method was impossible because of the unspecified yields given in the literature.

Although Borsche (11) and Campbell and Barclay (15) have obtained 8-chlorotetrahydrocarbazole as a solid melting at 55\(^\circ\), the product obtained by this 2-chlorocyclohexanone method could not be crystallised. The pale yellow syrup, however, readily formed a picrate, and was dehydrogenated to 1-chlorocarbazole in 20\% yield by treatment with chloranil. When a portion of the syrup not employed in the dehydrogenation was dissolved in xylene and allowed to stand in this solvent for several days, a colourless crystalline compound, m.p. 134\(^\circ\) (d), gradually separated from the solution. In addition to possessing a melting point quite different from that
Addendum: The oxidation of tetrahydrocarbazoles during recrystallisation has recently been noted by workers at Liverpool (Nature, Aug. 27th 1949, p.362), but they assign a peroxide structure to the resultant compounds.
of 8-chlorotetrahydrocarbazole, this compound was almost insoluble in light-petroleum and benzene and would not form a picrate. It was only sparingly soluble in alcohol and acetone, and the resultant solutions possessed a bright-green fluorescence similar to that given by the oxygen containing dimethyltetrahydrocarbazole degradation products. The analysis of this compound

\[ \text{L} \quad \text{LI} \]

has indicated that it is probably formed in a similar manner by the addition of oxygen at the 10.11 double bond.

Structure L requires C, 60.63; H, 5.09; N, 5.90; Cl, 14.91. Found for compound m.p. 134° (d) - C, 61.31; H, 5.27; N, 6.02; Cl, 14.78.

At first it was suspected that this compound of m.p. 134° (d) was an intermediate, possibly 2(o-chlorophenylamino)-cyclohexanone (LI), formed along with the 8-chlorotetrahydrocarbazole in the condensation of 2-chlorocyclohexanone and o-chloroaniline, but this was shown to be incorrect by preparing compound LI, and by the fact that the compound of m.p. 134° was also obtained when cyclohexanone o-chlorophenyl-hydrazone was cyclized by Borsche's method. This latter result proves that the compound must be formed from 8-chlorotetrahydrocarbazole, since it is highly
improbable that the same intermediate could be formed by two such different condensations. A first attempt to prepare 8-chlorotetrahydrocarbazole by

![Diagram](image)

ring closure of cyclohexanone-o-chlorophenylhydrazone (LII) with sulphuric acid gave only the compound of m.p. $134^\circ$ (d), but repetition gave the required 8-chlorotetrahydrocarbazole, m.p. $56^\circ - 57^\circ$ which was dehydrogenated to 1-chlorocarbazole in 35% yield with chloranil. Further cyclizations of cyclohexanone-o-chlorophenylhydrazone gave mixtures of 8-chlorotetrahydrocarbazole and the compound of m.p. $134^\circ$.

It is interesting to note that Barnes, Pausacker and Schubert (48) have obtained a mixture of 8-chlorotetrahydrocarbazole and a small amount of 12-hydroxy-1:2:3:4-tetrahydroisocarbazole (LIII) by the sulphuric acid cyclization of cyclohexanone-o-chlorophenylhydrazone, but they make no mention of the isolation of a compound of m.p. $134^\circ$. This is perhaps explained by the fact that chromatographic methods were employed in the attempts to obtain 8-chlorotetrahydrocarbazole discussed above, and the consequent prolonged exposure of its benzene solution to the air has favoured the aerial oxidation of the 10:11 bond.
Although Plant and Moggridge (13) obtained a mixture of 5-chloro- (LIV) and 7-chlorotetrahydrocarbazole (LV) by ring closure of cyclohexanone m-chlorophenylhydrazone, the condensation of m-chloroaniline and 2-chlorocyclohexanone gave as far as could be ascertained only the 7-chloro isomer. The mother liquor from the recrystallisation of the crude condensation product was evaporated and the residue was distilled in vacuo, but the distillate which solidified in the side arm proved to be 7-chlorotetrahydrocarbazole. Any 5-chlorotetrahydrocarbazole formed in the condensation should have distilled before the 7-isomer, since the former is a syrup and the latter a solid, m.p. 181°. This is in agreement with the observations of Bischler (37), who found that the cyclization of phenacyl-m-chloroaniline hydrochloride gave only one of the two theoretically possible disubstituted indoles. He was unable to decide, however, whether this product was 2-phenyl-4-chloro- or 2-phenyl-6-chloroindole.

The condensations of 2-chlorocyclohexanone and o- and p-bromoaniline have been unsuccessful. With the latter, condensation at 150° gave a dark coloured, charred, ether insoluble mass, and when the former
was condensed with 2-chlorocyclohexanone in alcohol, the condensation product decomposed to a black resin when it was distilled in vacuo. An attempted condensation of 2-chlorocyclohexanone and 2:4-dichloroaniline gave a similar result.

It is worth noting that although the yields of chloro- and dimethyltetrahydrocarbazoles prepared by this 2-chlorocyclohexanone method are only 30%, the amine hydrochloride formed as a by-product is always obtained in almost quantitative yield. This indicates that most of the 2-chlorocyclohexanone is undergoing an intramolecular loss of hydrochloric acid, and less than half of the acid is removed by the intermolecular dehydrohalogenation necessary for tetrahydrocarbazole formation.
Preparation and attempted cyclization of halogen substituted 2-Phenylaminocyclohexanones

It seems probable that the first stage in this reaction between arylamines and 2-chlorocyclohexanone will be a condensation of the reactive halogen with the amino group, and that the tetrahydrocarbazole will be formed by cyclodehydration of this intermediate aminoketone. Intermediate aminoketones of this type were readily prepared by heating the reactants in boiling alcohol in the presence of sodium carbonate. In this way 2-(o-chlorophenylamino)-

![Chemical Structures]

LVII cyclohexanone (LVI), 2-(p-chlorophenylamino)-cyclohexanone (LVII) and the corresponding bromo compounds were obtained. Julian and his collaborators (42) prepared indole intermediates of a similar type by condensing α-bromo ketones and aniline in alcohol in the presence of sodium carbonate at room temperatures, but with 2-chlorocyclohexanone carbon dioxide evolution could not be detected at this temperature, and even at the boiling point of the alcohol the rate of condensation was slow. The yields of the substituted 2-phenylaminocyclohexanones were generally below 50% indicating that the amount of 2-chlorocyclohexanone available for interaction with the aniline
is again reduced as a result of $\Delta_2$-cyclohexenone formation.

These intermediate aminoketones were prepared for the purpose of examining the conditions required for their cyclization to tetrahydrocarbazoles.

Attempted cyclizations of 2-(p-chlorophenylamino)-cyclohexanone with glacial acetic acid saturated with hydrobromic acid and with acetic anhydride were unsuccessful, but when the aminoketone was heated with p-chloroaniline hydrochloride, 6-chlorotetrahydrocarbazole was obtained in 22% yield. The isomeric 2-(o-chlorophenylamino)-cyclohexanone was also recovered unchanged when its solution in acetic acid was saturated with hydrobromic acid.

When 2-(p-bromophenylamino)-cyclohexanone was heated with p-bromoaniline hydrochloride much charring occurred, and the final product was very similar to that obtained in the direct condensation at $150^\circ$ without the carbonate. The charring was eliminated by heating the reactants in an atmosphere of nitrogen, but 6-bromotetrahydrocarbazole could not be detected in the product. When molecular amounts of the aminoketone and p-bromoaniline were heated together, no reaction occurred below $150^\circ$, but as soon as this temperature was reached the mixture began to boil briskly and eventually gave a brittle, black resin similar to that described above. Attempts to ring close 2-(p-bromophenylamino)-cyclohexanone with concentrated sulphuric acid and 90% formic acid were
equally unsuccessful. When the aminoketone and aniline hydrochloride were heated at 150°, tetrahydrocarbazole was obtained as the cyclization product. This can be explained either by the occurrence of an interchange of p-bromophenylamino- and phenylamino groups of the type discovered by Crowther, Mann and Purdie (40) to give

LVIII

which cyclizes in the presence of the amine hydrochlorides, or by the formation of a diamine (LIX) of the Bischler type which ring closes by loss of p-bromoaniline.

It was perhaps unfortunate that 2-(p-bromophenylamino)-cyclohexanone was selected for the main part of these cyclization studies, since it now appears very doubtful if its conversion to 6-bromotetrahydrocarbazole is possible under any circumstances. The decomposition which occurs when it is heated with p-bromoaniline and its hydrochloride does not appear to be the result of interaction with these compounds, since the aminoketone itself decomposes to a dark coloured resin when it is heated above its m.p. The presence of these compounds, however, appears to lower the temperature at which this decomposition takes place. It is perhaps significant that 2-(o-bromophenylamino)-cyclohexanone and 2-(2': 4'-dichlorophenylamino)-
cyclohexanone, the other aminoketones which failed to cyclize to the corresponding tetrahydrocarbazoles when heated with the appropriate aniline hydrochlorides also decompose when they are heated above their melting points. This fact probably explains the decomposition during distillation of the syrup obtained by condensation of o-bromoaniline and 2 : 4-dichloroaniline with 2-chlorocyclohexanone. As 8-bromo- and 6 : 8-dichlorotetrahydrocarbazole should distil satisfactorily, it seems probable that the reaction has not proceeded beyond the intermediate aminoketone stage, even although the condensation was carried out in the absence of sodium carbonate.

It is interesting to note that Verkade and Janetzky (47) obtained a dark coloured

resin when they attempted to ring close 2-(4'-bromo-phenyl) -aminobutanone (LX) to 2 : 3-dimethyl-5-bromoindole (LXI), since this aminoketone also contains a bromo substituent para to the amino group.

Although the results obtained from a study of the cyclization of these intermediate aminoketones have been disappointing, several definite conclusions can be drawn. The cyclization of substituted 2-phenylaminocyclohexanones does not follow the same mechanism as the ring closure of the pyridylamino-
cyclohexanones discussed in Part II, since the latter lose water in the presence of acids whereas the former can only be cyclized under acidic conditions if an amine is also present. It seems highly probable that the presence of aniline hydrohalides is essential for the cyclization of these 2-phenylaminocyclohexanones, and that the mechanism of cyclization is very closely related to that of the phenacylanilines already discussed. Although Ott (43) prepared tetrahydrocarbazole by condensation of aniline and 2-chlorocyclohexanone in the presence of sodium carbonate, and Hughes and Lions (49) prepared 6:7-dimethoxy-tetrahydrocarbazole (LXIII) by

\[ \text{LXII} \rightarrow \text{LXIII} \]

condensing 4-aminoveratrole (LXII) and 2-chlorocyclohexanone in the presence of sodium acetate, it is possible that small amounts of the aniline hydrochlorides were continually being formed despite the presence of the sodium salts. When o-chloroaniline and 2-chlorocyclohexanone were condensed at the boiling point of the former over sodium acetate, 2-((o-chlorophenylamino)-cyclohexanone and not 8-chlorotetrahydrocarbazole was formed. This confirms that the cyclization of these substituted 2-phenylaminocyclohexanones is catalysed by the hydrochloride of the appropriate amine, but the facility with which
the intermediate aminoketones is ring closed appears to depend on the substituent, decreasing in the order methyl -> chloro -> bromo. It is well known that halogen substituents as a result of their electron attracting nature deactivate an aromatic ring and consequently retard further substitution, and therefore it is to be expected that the chloro derivatives will be more difficult to cyclize than the corresponding methyl substituted compounds. The slight difference in the inductive effects of chloro- and bromo substituents, however, is insufficient to explain the complete failure to cyclize the 2-(p-bromophenylamino)-cyclohexanone and obviously some other factor must influence the ring closure of bromo compounds of this type.

To ensure that 2-(p-bromophenylamino)-cyclohexanone did possess the expected aminoketone structure, its reaction with dinitrophenylhydrazine was compared with that of an intermediate which could be cyclized to the corresponding tetrahydrocarbazole. It was discovered that 2-(p-bromophenylamino)- and 2-(o-chlorophenylamino)-cyclohexanone (LXIV) both gave the same product with 2 : 4-dinitrophenylhydrazine,
the p-bromophenylamino- and o-chlorophenylamino groups of the dinitrophenylhydrazone (LXV) undergoing replacement by the 2 : 4-dinitrophenylhydrazino group in the boiling acidified alcohol to give structure (LXVI). The true dinitrophenylhydrzones (LXV) could not be isolated in the pure state, but when the aminoketones and 2 : 4-dinitrophenylhydrazine were condensed in cold acidified alcohol, products of indefinite m.p. still containing halogen were obtained. It seems likely that these consist of mixtures of compounds LXV and LXVI. When the alcohol solution was boiled for a short time, however, the replacement reaction was carried to completion and the final product in each case was structure LXVI. The structure of this compound was proved by its synthesis from 2-chlorocyclohexanone 2 : 4-dinitrophenylhydrazone (LXVII) and 2 : 4-dinitrophenylhydrazine. When these two compounds were boiled in glacial acetic acid or when 2-chlorocyclohexanone-2 : 4-dinitrophenylhydrazone itself was heated in aqueous acetic acid, compound LXVI identical to that obtained from the aminoketones was formed. In aqueous acetic acid the
2 : 4-dinitrophenylhydrazone must suffer partial hydrolysis and the liberated 2 : 4-dinitrophenylhydrazone reacts with excess dinitrophenylhydrazone to give LXVI. No reaction of this type was apparent in glacial acetic acid.

While the reactions of 2-(o-chlorophenylamino)- and 2-(p-bromophenylamino)-cyclohexanone with 2 : 4-dinitrophenylhydrazone prove that these compounds have similar structures and both possess the ketone group, they also show that the substituted phenylamino radical is readily replaced by the 2 : 4-dinitrophenylhydrazino group under acid conditions. This replacement is very similar to that described by Crowther, Mann and Purdie (40) where an interchange of phenylamino groups readily occurs in phenacylanilines (cf. p.18). The reaction between 2-chlorocyclohexanone and 2 : 4-dinitrophenylhydrazone on the other hand gives a "di-dinitrophenylhydrazone" derivative analogous to the diamines formed according to Bischler in the reaction between α-halogenated ketones and arylamines. To discover if this reaction with dinitrophenylhydrazone was general for α-halogenated ketones, 3-chloroacetophenone dinitrophenylhydrazone (LXVIII) was boiled with 2 : 4-dinitrophenylhydrazone in glacial acetic acid. After twenty-six

\[
\begin{align*}
\text{LXVIII} & \quad \text{LXIX} \\
\end{align*}
\]
hours, however, the 2 : 4-dinitrophenylhydrazone was recovered unchanged, but when the dinitrophenylhydrazone itself was boiled in aqueous acetic acid for seventy hours, the partial hydrolysis and subsequent condensation reaction again took place and the "di-dinitrophenylhydrazine" derivative LXIX was formed. In addition to this scarlet coloured "di-dinitrophenylhydrazine" compound, a dark brown compound was also formed.

Analysis results indicate that this is probably

\[ \text{LXX} \]

formed as a result of the hydrolysis of LXIX in the aqueous acetic acid:

Compound LXX, \( C_{14} H_{12} O_5 N_4 \) requires \( N, 17.7 \)

Found \( N, 17.6 \).

The reactions between \( \alpha \)-halogenated ketones and unsubstituted phenylhydrazine have attracted the attention of several investigators and van Alphen (50) has recently reviewed the somewhat varied results obtained. Freer (51) obtained

\[ \text{CH}_2 - \text{NH.NH.} \text{C}_6 \text{H}_5 \]
\[ \text{CH} \text{ = N.NH.} \text{C}_6 \text{H}_5 \]

\[ \text{LXXI} \]

\[ \text{CH}_2 \cdot \text{NH.NH.} \text{C}_6 \text{H}_5 \]
\[ \text{CH}_3 \cdot \text{C = N.NH.} \text{C}_6 \text{H}_5 \]

\[ \text{LXXII} \]

compound LXXI from phenylhydrazine and chloroacetaldehyde, and Bodforss (52) prepared LXXII in a similar way from chloroacetone. Although these compounds are similar to the products obtained by condensation of
2-chlorocyclohexanone and 4-chloroacetophenone with 2 : 4-dinitrophenylhydrazine, van Alphen has shown that the compound obtained by Hess (55) on condensing w-chloroacetophenone and unsubstituted phenylhydrazine is 1 : 3-diphenyl-(1 : 2-diazacyclobutene-2) (LXXIII). This structure is formed when only one phenylhydrazine molecule is involved in the condensation, but the analysis of compound LXIX shows that when the 2 : 4-dinitro derivative of phenylhydrazine is condensed with w-chloroacetophenone two molecules of the former participate in the condensation.
Preparation of Tetrahydrocarbazole-carboxylic acids

Methyl tetrahydrocarbazole-8-carboxylate (LXXIV) and methyl tetrahydrocarbazole-6-carboxylate (LXXV)

\[
\text{LXXIV} \quad \text{LXXV}
\]

were prepared in 35% and 30% yield respectively by condensation of 2-chlorocyclohexanone with methyl anthranilate and methyl p-aminobenzoate at 150\(^\circ\)C. In each case a brown, ether insoluble resin was formed simultaneously with the ester, but this was not further investigated. The methyl esters were readily hydrolysed to the free acids in quantitative yield in boiling alcoholic sodium hydroxide.

Tetrahydrocarbazole 6- and 8-carboxylic acids have been prepared by Plant and Collar (12) from cyclohexanone and the o- and p-hydrazinobenzoic acids, but this method suffers from the disadvantage that the aminobenzoic acids must first be converted to the corresponding hydrazino compounds, whereas in this new method the amino-acid esters can be used directly.

Tetrahydrocarbazole-8-carboxylic acid was obtained directly in 35% yield by employing anthranilic acid in the 2-chlorocyclohexanone condensation, but the condensations with the other free amino-acids were not so successful. When m- and p-aminobenzoic acid and 2-chlorocyclohexanone
were condensed at 170° - 180° a very vigorous reaction took place, and ether-insoluble, black tars were formed from which no carboxytetrahydrocarbazole could be isolated. In boiling alcohol, 2-chlorocyclohexanone and m-aminobenzoic gave a large amount of a dark crimson, ether-insoluble resin, but the ether extract gave a 2.5% yield of tetrahydrocarbazole-7-carboxylic acid (LXXVI) on evaporation. There

![LXXVI](attachment://LXXVI.png) ![LXXVII](attachment://LXXVII.png)

was no indication of the presence of the theoretically possible 5-carboxytetrahydrocarbazole (LXXVII), but in view of the very low yield of the 7-acid, a small amount of the 5-isomer might easily have escaped detection. Verkade and Lieste (54) obtained a mixture containing approximately equal amounts of

![LXXVIII](attachment://LXXVIII.png) ![LXXIX](attachment://LXXIX.png)

methyl 2:5-dimethylindole-4-carboxylate (LXXVIII) and methyl 2:5-dimethylindole-6-carboxylate (LXXIX) by condensation of methyl-α-bromoethyl ketone and methyl m-aminobenzoate.

In all the condensations between 2-chlorocyclo-
hexanone and meta substituted anilines investigated, only the 7-substituted tetrahydrocarbazole has been detected in the condensation product. This result is not unexpected, however, since the formation of 5-substituted derivatives might be hindered by a steric effect which prevents a cyclization involving the ortho hydrogen atom between the amino group and the meta substituent.
Condensation of 2-Chloro-5-methylcyclohexanone and Aniline

For a study of the condensation of aniline and a substituted 2-chlorocyclohexanone, 2-chloro-5-methylcyclohexanone was selected. Godchot and Bedos (55) have shown that inactive m-methylcyclohexanone gives a mixture of cis- and trans-2-chloro-5-methylcyclohexanone on chlorination, and although this work was repeated, and the two isomers were separated, this was not essential. In the cyclodehydration stage of the condensation reaction between this compound and an aromatic amine, geometric isomerism will disappear as soon as the tetrahydrocarbazole structure is formed.

Aniline and cis- (LXXXa) or trans-2-chloro-5-methylcyclohexanone (LXXXb) might be expected to form 3-methyltetrahydrocarbazole (LXXXI; lit. m.p. 108° - 111°), but when the condensation was carried out, a compound softening at 73° and melting between 78° and 81° was isolated. The analysis indicated that this compound possessed the expected \( C_{15} H_{15} N \) empirical formula, and therefore the indefinite melting point can only be explained if we assume that a mixture of methyltetrahydrocarbazoles has been
formed. This conclusion was supported by the easy formation of a characteristic maroon coloured picrate which also melted over a larger than usual range. When the supposed mixture of methyltetrahydrocarbazoles was dehydrogenated with chloranil a carbazole derivative, m.p. 219° - 229° was obtained in 27% yield, and purification by recrystallisation and chromatography gave instead of

![LXXXII](image) ![LXXXIII](image)

the expected 3-methylcarbazole (LXXXII), a slightly impure specimen of 2-methylcarbazole (LXXXIII). This dehydrogenation shows that the main component of the original tetrahydrocarbazole mixture was the 2-methyl derivative, the formation of which is analogous to the formation of 2-phenylindole in the cyclization of phenacylaniline.

If we assume that the first stage of the condensation between aniline and 2-chloro-5-methylcyclohexanone results in

![LXXXIV](image) ![LXXXV](image)

the formation of 2-phenylamino-5-methylcyclohexanone
(LXXXIV), it is possible that prior to cyclization this intermediate isomerises to the 4-methyl isomer (LXXXV), in the same way as 1-phenyl-p-methylphenacylaniline (XXX) rearranges to 1-p-tolylphenacylaniline (XXXI; cf. p.19). The somewhat complex ionic mechanism which Brown and Mann (41) have suggested for the isomerisation of these phenacylanilines is equally well applicable to the conversion of LXXXIV to LXXXV. Until more detailed results have been obtained, however, it would be mere speculation to postulate an isomerisation of LXXXIV to LXXXV, because the intermediate aminoketones have not been prepared in this case, whereas Brown and Mann have actually observed such a rearrangement of the phenacylanilines already mentioned. It is interesting to note that the 2-phenylamino-4- and 5-methylcyclohexanones could probably be obtained quite readily by condensing aniline with 2-chloro-4-methyl and 2-chloro-5-methylcyclohexanone in the presence of sodium carbonate.

The formation of 2-methyltetrahydrocarbazole in the condensation of aniline and 2-chloro-5-methylcyclohexanone can also be explained by the Bischler mechanism, if

\[ LXXXVI \quad LXXXVII \]

the hypothetical diamine (LXXXVI) is assumed to ring
close by loss of the phenylamino group as aniline. There is some doubt as to the structure of these diamines, however, and if in this case the isomeric ene-diol-like structure LXXXVII is formed, the elimination of either phenylamino group is equally probable, and one might expect the two reactions to proceed simultaneously giving a mixture of 2- and 3-methyltetrahydrocarbazole. That this might actually have occurred is indicated by the very low and indefinite melting point of the product obtained compared with the melting points of the 2- and 3-methyl derivatives quoted in the literature. Since the crude dehydrogenation product melted at a temperature above the melting point of 3-methylcarbazole, however, it must have contained a larger percentage of the 2-isomer, and it follows that the 2-methyl compound must also have been predominant in the original tetrahydrocarbazole mixture.

Until the isomerisation of aminoketones discovered by Brown and Mann has been shown to be a general reaction of intermediates of this type, the original Bischler diamine hypothesis must be regarded as equally satisfactory in explaining the formation of these anomalous compounds.
EXPERIMENTAL

INTRODUCTION

The melting points (macro) of all compounds were determined on the apparatus described in Campbell's "Qualitative Organic Chemistry" (p. 5) and in all cases are uncorrected. Where doubt arose, the sharpness of melting was checked on a micro-melting point apparatus (Microchim. Acta., 1937, 2, 317). Yields are expressed as percentages of the maximum theoretical amounts obtainable.

All ether and benzene solutions were dried over anhydrous sodium sulphate unless otherwise stated. Picrates were prepared by mixing boiling benzene solutions of the carbazole and picric acid, the picrate separating on cooling.

The analyses were carried out by Drs. Weiler and Strauss of Oxford.
Condensation of 2-Bromo- and 2-Chlorocyclohexanone with Aniline and its Methyl Derivatives

Preparation of 2-Bromocyclohexanone

Cyclohexanone (60 g.) was brominated in the presence of calcium carbonate by the method of Plant (J. 1930, 1597).

Yield 40 g. (37%) b.p. 95° - 115°/22 mm.

Preparation of Tetrahydrocarbazole, 6-Methyltetrahydrocarbazole and 8-Methyltetrahydrocarbazole

2-Bromocyclohexanone (5 g.) was condensed with aniline (10 g.) and o- and p-toluidine (12.5 g.) to give tetrahydrocarbazole (m.p. 114° - 116°); 8-methyltetrahydrocarbazole (m.p. 95° - 96°); and 6-methyltetrahydrocarbazole (m.p. 140° - 142°) in 65%, 55% and 60% yield respectively. The procedure employed was exactly similar to that described by Ott in the German Patent (374, 098; 1923) for the corresponding condensations with 2-chlorocyclohexanone: the bromoketone was dropped slowly on to the amine at 150° - 160° and the resultant mixture was cooled and poured into dilute hydrochloric acid, when the crude tetrahydrocarbazole was precipitated.

Preparation of 2-Chlorocyclohexanone

2-Chlorocyclohexanone was obtained as a colourless, low melting solid, b.p. 84° - 86°/12 mm., (104°/31 mm.) in 25% yield by chlorination of cyclohexanone in the presence of calcium carbonate,
(Kotz and Grete; J. Prakt. Chemie, 1909, 80, 487); in 35% yield by chlorination of cyclohexanol in the presence of calcium carbonate (Meyer; Helv. Chem. Acta, 1933, 1291); and in 55% yield by chlorination of an emulsion of cyclohexanone and water (Org. Synthesis Vol. 25, p. 22).

**Preparation of 6: 8-Dimethyltetrahydrocarbazole**

![Chemical structure of 6: 8-Dimethyltetrahydrocarbazole]

2-Chlorocyclohexanone (5 g.) and m-4-xylidine (10 g.) in alcohol (20 ml.) were boiled under reflux for 16 hours. Evaporation of the alcohol and addition of ether precipitated m-4-xylidine hydrochloride; yield 6 g., m.p. 235° - 236° (lit. 235° - 236°). The filtrate was washed in turn with dilute hydrochloric acid, water and sodium bicarbonate solution, and the dried ether solution was evaporated and distilled in vacuo to give 6: 8-dimethyltetrahydrocarbazole as a yellow syrup which rapidly crystallised.

**Yield** 2.8 g. (37%)  
**b.p.** 235° - 240°/25 mm.  
**m.p.** 100° - 106°

Crystallisation from light-petroleum (40° - 60°) gave colourless prisms, m.p. 101° - 105°.

**Analysis**

C_{14}H_{17}N requires C, 84.53; H, 8.60; N, 7.03.  
Found C, 84.92; H, 8.67; N, 6.96.
Picrate:  chocolate needles from benzene, m.p. 160° - 162°.

\[
C_{20}H_{20}O_7N_4 \text{ requires } N,13.1
\]

Found N,12.6

The recrystallisation of the 6 : 8-dimethyl-tetrahydrocarbazole from light-petroleum was found to be accompanied by decomposition. On cooling the saturated solution, only 50% of the tetrahydrocarbazole separated immediately, and the mother liquor on standing for 30 minutes gradually assumed a red coloration and simultaneously deposited a colourless product of m.p. 116° (d) (m.p. varies with rate of heating) which would not redissolve on boiling. This compound was only sparingly soluble in light-petroleum and benzene, but readily dissolved in alcohol to give strongly green fluorescent solutions. With picric acid the red coloration associated with carbazole picrate formation was not produced, and no picrate was obtained from the solution on cooling.

**Analysis**

Found C,73.70; H,7.71; N,5.90;

\[M = 242.\]

**Preparation of 5 : 8 Dimethyltetrahydrocarbazole**

2-Chlorocyclohexanone (5 g.) and p-2-xylidine (10 g.) were condensed as in the previous experiment and the crude 5 : 8-dimethyltetrahydrocarbazole was distilled in vacuo.

**Yield 2.8 g. (37%)**  b.p. 215° - 220°/20 mm.

m.p. 81° - 83°.
Recrystallisation from light-petroleum ($60^\circ - 80^\circ$) gave colourless, needle shaped prisms, m.p. $83^\circ - 86^\circ$.

**Analysis**

$C_{14}H_{17}N$ requires $C, 84.35; H, 8.60; N, 7.03$

Found $C, 84.31; H, 8.43; N, 7.35$

**Picrate:** chocolate needles from benzene, m.p. $138^\circ - 141^\circ$.

$C_{20}H_{20}O_7N_4$ requires $N, 13.1$

Found $N, 13.1$

The recrystallisation from light-petroleum again resulted in the formation of a higher melting compound which would not redissolve in the petroleum on heating.

Boiling with benzene to remove any dimethyltetrahydrocarbazole present gave a colourless solid, m.p. $133^\circ$ (d) (depends on rate of heating).

**Analysis**

Found $C, 72.20; H, 7.29; N, 6.05$

Recrystallisation from alcohol gave small pale yellow cubic shaped crystals, m.p. $140^\circ$ (d.), the alcoholic solution possessing a strong green fluorescence in ultra-violet light.

**Repeat analysis**

Found $C, 72.66; H, 7.46; N, 6.10$

$C_{14}H_{17}NO_2$ requires $C, 72.68; H, 7.31; N, 6.06$

**Preparation of 6 : 7 (5 : 6) Dimethyltetrahydrocarbazole**

\[
\begin{align*}
\text{CH}_3 & \quad \text{+} \quad \text{Cl} \quad \rightarrow \quad \text{CH}_3 \\
\text{NH}_2 & \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \\
\text{C} & \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{C} \\
\text{H}_3 & \quad \text{H}_3 \quad \text{H}_3 \quad \text{H}_3 \quad \text{H}_3
\end{align*}
\]
2-Chlorocyclohexanone (5 g.) and o-4-xylikidine (10 g.) were condensed as in the case of the m-4-isomer. Evaporation of the ether solution gave a brown solid (5.3 g.), so distillation in vacuo was not attempted. Recrystallisation from light-petroleum ($80^\circ - 100^\circ$) gave elongated prisms of the tetrahydrocarbazole.

Yield 1 g. (14%) m.p. 109$^\circ$ - 129$^\circ$.

A repeat recrystallisation from light-petroleum decreased the range of melting to 120$^\circ$ - 129$^\circ$, but the product still softened at 109$^\circ$.

Analysis

$$C_{14}H_{17}N \text{ requires } C,84.33; \text{ H,8.60; N,7.03}$$

$$\text{Found } C,84.09; \text{ H,8.61; N,7.00.}$$

(During the crystallisation of the crude product from light-petroleum, most of the dimethyltetrahydrocarbazole was converted to a compound, m.p. 127$^\circ$ (d.) similar in properties to the two obtained previously).

Picrate: chocolate needles from benzene, m.p. 166$^\circ$ - 168$^\circ$.

$$C_{20}H_{20}O_7N_4 \text{ requires } N,13.1$$

$$\text{Found } N,13.0.$$  

Dehydrogenation of the above dimethyltetrahydrocarbazole (0.6 g.) with chloranil (1.48 g.) in boiling sulphur-free xylene (15 ml.) for 24 hours by the method of Barclay and Campbell (J. 1945, 530), and purification of the resultant dimethylcarbazole (0.25 g.) by passage of its benzene solution through a short alumina column (3" x ½"), gave colourless plates,
m.p. 251° - 253°; yield 0.23 g. (42%)

Analysis

\[ \text{C}_{14} \text{H}_{15} \text{N} \text{ requires } C, 86.16; \text{ H}, 6.67 \]

Found C, 86.20; H, 6.86.

Picrate: scarlet needles from benzene, m.p. 167° - 169°.

\[ \text{C}_{20} \text{H}_{16} \text{O}_{7} \text{ N}_{4} \text{ requires N, 13.1} \]

Found N, 12.6; 12.4.

Colour test: This dimethylcarbazole did not give the characteristic blue-green colour when treated with concentrated sulphuric acid and one drop of concentrated nitric acid.
Condensation of 2-Chlorocyclohexanone and Halogen Substituted Anilines

Preparation of 6-Chlorotetrahydrocarbazole

\[
\text{Cl}_2\text{C}_{\text{H}_2}\text{NH}_2 + \text{O} \rightarrow \text{Cl}_2\text{C}_{\text{H}_2}\text{NH} - \text{Cl} \\
\]

2-Chlorocyclohexanone (4 g.) was added dropwise to p-chloroaniline (8 g.) at 150° - 160°. As the reaction proceeded the mixture began to boil gently, and p-chloroaniline hydrochloride gradually separated from the brown liquid. The semi-solid mass was extracted with ether and filtered free of the hydrochloride (4.2 g.; 85%), and the filtrate was washed with hydrochloric acid, water and sodium bicarbonate. Recrystallisation from methyl alcohol of the brown solid obtained from the ethereal solution on evaporation, gave small colourless prisms of 6-chlorotetrahydrocarbazole.

Yield 1.3 g. (20%) m.p. 141° - 143°
(lit. 143° - 144°)

Mixed m.p. with authentic specimen - no depression.

Preparation of 8-Chlorotetrahydrocarbazole

2-Chlorocyclohexanone (5 g.) and o-chloroaniline (15 g.) were condensed at the boiling point of the amine, and the resultant mixture was treated as above. The ether solution gave a yellow syrup on evaporation, and attempts to crystallise this syrup were unsuccessful. Distillation in vacuo gave a colourless
syrup which could not be crystallised from light-petroleum,

Yield 2.2 g. (27%) b.p. 180° - 200°/12 mm.

Picrate: brick-red needles from benzene, m.p. 138° - 140°.

\[ \text{C}_{18} \text{H}_{15} \text{O}_{7} \text{NCl} \] requires N, 12.9

\[ \text{Found N, 12.3.} \]

The above syrup (1 g.) which appears to consist chiefly of 8-chlorotetrahydrocarbazole was dehydrogenated by boiling with chloranil (2.4 g.) in sulphur free xylene (25 ml.) for 24 hours. After removal of tetrachlorohydroquinone (98% recovery), the xylene solution gave a pale purple solid, m.p. 95° - 100°. Recrystallisation from aqueous methyl alcohol gave almost colourless prisms of 1-chlorocarbazole

Yield 0.2 g. (20%) m.p. 117° - 115°

(lit. 125°, 109° - 110°)

Analysis

Calc. for C_{12} H_{8} N Cl Cl, 17.6

\[ \text{Found Cl, 17.4} \]

Picrate: dark orange needles from benzene, m.p. 138° - 141°.

Colour test: With concentrated sulphuric acid and one drop of concentrated nitric acid, a trace of the 1-chlorocarbazole gave an intense blue-green colour.

The 8-chlorotetrahydrocarbazole syrup which was not employed in this dehydrogenation was dissolved in xylene (25 ml.) and allowed to stand for several days. At the end of this period a considerable amount of solid material had separated from the solution in
the form of small colourless prisms, m.p. 134° (d.).

**Analysis**

Found Cl, 15.36.

Like the products produced by recrystallisation of the dimethyltetrahydrocarbazoles this compound was negligibly soluble in light-petroleum, benzene and toluene, but dissolved in hot alcohol and acetone to give solutions showing a strong blue-green fluorescence in ultra-violet light. Small colourless prisms, m.p. 134° (d.) separated from the alcohol solution on cooling.

**Repeat analysis**

Found C, 61.14; H, 5.39; N, 6.52; Cl, 16.21.

As the previous analysis had given a chlorine percentage of 15.36, a further analysis was carried out on a freshly prepared sample. 2-Chlorocyclohexanone (5 g.) and o-chloroaniline (15 g.) were condensed as previously, and the yellow syrup obtained on distillation (2.0 g., 26%; b.p. 180° - 200°/14 mm.) was dissolved in xylene as before. The solution deposited 1 g. of the compound m.p. 134° - 135° (d) on standing for several days.

Found C, 61.31; H, 5.27; N, 6.02; Cl, 14.78

C₁₂ H₁₂ O₂ N Cl requires C, 60.63; H, 5.09; N, 5.90; Cl, 14.91.

**Preparation of 7-Chlorotetrahydrocarbazole**

2-Chlorocyclohexanone (5 g.) and m-chloroaniline (10 g.) were condensed at the b.p. of the latter as in the previous experiment. The product was treated as before and the ether extract evaporated to give
the crude tetrahydrocarbazole. Recrystallisation from alcohol gave a mass of colourless plates of 7-chlorotetrahydrocarbazole.

Yield 1.9 g. m.p. 175° - 179°
(lit. 161°).

A second recrystallisation from alcohol raised the m.p. to 179° - 180°, and a mixed m.p. with authentic 7-chlorotetrahydrocarbazole showed no depression.

Picrate: maroon needles from benzene, m.p. 128° - 130°.

C₁₈ H₁₅ O₇ N₄ Cl requires N, 12.9
Found N, 12.5.

The mother liquor from the original crystallisation was evaporated and cooled when a further 0.1 g. of 7-chlorotetrahydrocarbazole was obtained, and the residue was distilled in vacuo. A small amount of a yellow oil (b.p. 250° - 260°/49 mm.) which solidified in the receiver distilled over, but the bulk of the residue darkened rapidly in colour and further distillation was accompanied by decomposition. The distillate readily crystallised from alcohol in colourless plates; yield 0.1 g.; m.p. 177° - 179°, no depression with compound obtained above.

Total yield of 7-chlorotetrahydrocarbazole 2.1 g.
(27%).

Attempted Preparation of 6-Bromotetrahydrocarbazole
2-Chlorocyclohexanone (4 g.) was added dropwise to p-bromoaniline (10.4 g.) at 150° - 160°, as in previous condensations of this type. In this case, however, a very vigorous reaction took place during the addition, and the mixture was finally converted to a brittle black, charred mass which was ground to a black powder and extracted with ether. The ether extract contained only a very small amount of a black viscous syrup which failed to yield any 6-bromotetrahydrocarbazole on trituration with methyl alcohol and which would not crystallise from this solvent.

Attempted preparation of 8-Bromotetrahydrocarbazole

A solution of 2-chlorocyclohexanone (5 g.) and o-bromoaniline (15 g.) in alcohol (20 ml.) was boiled under reflux for 16 hours, evaporated and filtered free of the precipitated o-bromoaniline hydrochloride. The salt was well triturated with ether to remove any condensation product present, and the combined ether washings and alcohol filtrate obtained above were washed with dilute hydrochloric acid, water and saturated sodium bicarbonate solution. The dried extract gave a yellow syrup on evaporation, but this would not form a picrate in benzene solution and failed to distil in vacuo, decomposing to a viscous black tar before the boiling point was reached.

Attempted Preparation of 6 : 8-Dichlorotetrahydrocarbazole
2-Chlorocyclohexanone (5 g.) and 2 : 4 dichloroaniline (12.2 g.) were condensed in boiling alcohol (20 ml.) for 16 hours and the product was isolated in the usual manner. The resultant yellow syrup failed to give a picrate and decomposed during distillation as in the previous experiment.

Preparation of \(\text{S-Chlorotetrahydrocarbazole by cyclization of cyclohexanone-o-chlorophenylhydrazone}\)

\[
\text{Cl} \quad \text{NH} \quad \text{N} \quad \text{H}_2\text{SO}_4 \rightarrow \quad \text{Cl} \quad \text{NH} \quad \text{N} \quad \text{Cl}
\]

o-Chloroaniline was diazotised and reduced by the method of Bulow (Ber., 1918, 51, 404), and the resultant o-chlorophenylhydrazone (5 g.) condensed with cyclohexanone (3.4 g.) by heating the mixture until a clear solution was obtained. The somewhat "sticky" cyclohexanone o-chlorophenylhydrazone was at once treated with sulphuric acid (50 ml., 1 : 9 vol.) and the mixture was warmed gently for ten minutes. The o-chlorophenylhydrazone melted to an orange oil during this treatment but appeared quite insoluble in the acid mixture. Isolation of the solidified oil gave the unchanged phenylhydrazone, so the solid was again treated with sulphuric acid (50 ml.) and the mixture was boiled for ten minutes. The resultant crude brown solid was purified by dissolving in benzene, drying and passing the solution through a short alumina column (10" x 1"). The orange coloured
eluate was collected in 50 ml. portions but each on evaporation gave a colourless compound m.p. 129° (d), and no 8-chlorotetrahydrocarbazole. This compound separated from methyl alcohol as colourless prisms, m.p. 134° (d). (No depression with compound obtained by condensation of 2-chlorocyclohexanone and o-chloroaniline.)

A repeat condensation of the o-chlorophenylhydrazine (6 g.) and cyclohexanone (4.1 g.) was carried out as before, and in this case the product was boiled for 15 minutes with the sulphuric acid. The dark brown solid was purified by chromatographing its benzene solution on an alumina column (12" x 1"), and the eluate was collected and evaporated to give an orange syrup which slowly crystallised, m.p. 52° - 55°. Recrystallisation from light-petroleum (60° - 80°) gave colourless prisms of 8-chlorotetrahydrocarbazole.

Yield 1.4 g. (13%) m.p. 56° - 57° (lit. 55° - 56°)

Analysis
Calc. for C_{12}H_{12}NCl C, 70.04; H, 5.88; N, 6.81; Cl, 16.1.
Found C, 69.84; H, 6.00; N, 7.10; Cl, 17.2.

The 8-chlorotetrahydrocarbazole (0.6 g.) and chloranil (1.44 g.) were boiled under reflux in sulphur free xylene (10 ml.) for 24 hours. The tetrachloroquinone (1.28 g., 89%) was removed in the usual way by cooling and extracting with potassium hydroxide (4%), and the crude 1-chlorocarbazole was obtained from the washed xylene solution after drying and
evaporating; yield 0.2 g. (35%), m.p. 109° - 110° (lit. 110°), no depression with 1 chlorocarbazole obtained previously.
Condensation of 2-Chlorocyclohexanone and Halogen Substituted Anilines in the Presence of Alkali

Preparation of 2-p-Chlorophenylaminocyclohexanone

Anhydrous sodium carbonate (3 g.) was added to a solution of 2-chlorocyclohexanone (5 g.) and p-chloroaniline (6 g.) in alcohol (20 ml.) and the mixture was boiled under reflux for five hours, filtered free of the solid sodium carbonate and sodium chloride and reduced in volume. The intermediate aminoketone crystallised from the alcohol as a mass of colourless prisms on cooling.

Yield 3.7 g. (44%) m.p. 131° - 134°

Recrystallisation from alcohol gave small colourless prisms, m.p. 132° - 133° which could be distilled at atmospheric pressure without decomposition.

Analysis

\( \text{C}_{12} \text{H}_{14} \text{O}_2 \text{NCl} \) requires C, 64.42; H, 6.31

Found C, 64.81; H, 6.48.

Cyclization of 2-p-Chlorophenylaminocyclohexanone

A mixture of the aminoketone (0.5 g.) and
p-chloroaniline hydrochloride (2 g.) was heated in an oil bath at 250° for one hour, and the resultant brown, semi-solid mass was thoroughly extracted with ether and freed from the insoluble hydrochloride by filtration. The filtrate was washed with dilute hydrochloric acid, water and bicarbonate solution, dried and evaporated when the crude 6-chlorotetrahydrocarbazole was obtained as a "sticky", dark brown solid. Recrystallisation from alcohol gave colourless plates

Yield 0.1 g. (22%) m.p. 140° - 145° (No depression with authentic 6-chlorotetrahydrocarbazole)

An attempt to effect ring closure by saturating a solution of the ketone (0.5 g.) in glacial acetic acid (10 ml.) with hydrobromic acid, and allowing the solution to stand overnight was unsuccessful, the 2-p-chlorophenylaminocyclohexanone being recovered unchanged on neutralisation of the acid mixture.

Preparation of 2-o-Chlorophenylaminocyclohexanone

2-Chlorocyclohexanone (5 g.), o-chloroaniline (7.9 g.) and sodium carbonate (3 g.) were boiled in alcohol (10 ml.) for 18 hours and the mixture was filtered and evaporated as in the previous experiment. No crystallisation took place even when all the alcohol had been evaporated, and the residue was distilled in vacuo. A small amount of excess o-chloroaniline (b.p. 85° - 90°/14 mm.) distilled first followed by the 2-o-chlorophenylaminocyclohexanone obtained as a colourless syrup which readily crystallised.
Yield 3.2 g. (38%) b.p. 175° - 185°/14 mm.
m.p. 51° - 54°.

Recrystallisation from light-petroleum (40° - 60°) gave large colourless prisms, m.p. 53° - 54°.

Analysis

\[ \text{C}_{12} \text{H}_{14} \text{ONCl} \text{ requires } \text{Cl}, 15.9 \]

Found Cl, 15.5.

A repetition of the condensation employing excess 2-chlorocyclohexanone improved the yield.

o-Chloroaniline (5 g.), 2-chlorocyclohexanone (7.8 g.) and sodium carbonate (3.1 g.) were boiled under reflux with alcohol (20 ml.) for 24 hours. Isolation of the intermediate as above gave a pale yellow syrup, b.p. 190° - 200°/15 mm; m.p. 51° - 53°; yield 5.3 g. (60%). The 2-o-chlorophenylaminocyclohexanone rapidly darkened in colour in the crude state, but was quite stable after recrystallisation from light-petroleum.

Preparation of 2-p-Bromophenylaminocyclohexanone

\[ \begin{align*}
\text{Br} & \quad \text{O} \\
\text{Cl} & \quad \text{Na}_2\text{CO}_3 \\
\text{NH}_2 & \quad \text{Br}
\end{align*} \]

p-Bromoaniline (6 g.) and 2-chlorocyclohexanone (7.2 g.) were condensed in boiling alcohol (20 ml.) over sodium carbonate (3 g.) for five hours in the usual manner. 2-p-Bromophenylaminocyclohexanone separated from the alcohol in long, colourless prisms on cooling.

Yield 5 g. (54%) m.p. 141° - 142°.
Recrystallisation from alcohol raised the m.p. to $143^\circ - 144^\circ$. (At $143^\circ$ the compound melted to a colourless liquid which decomposed to a dark crimson, resin-like substance at $230^\circ$, the decomposition temperature depending on the rate of heating).

**Analysis**

$C_{12}H_{14}O \cdot N \cdot Br$ requires Br, 30.8

Found Br, 29.8.

**Attempted cyclization of 2-p-Bromophenylaminocyclohexanone**

\[ \text{Br} \quad \text{O} \quad \text{N} \quad \text{Br} \quad \text{H} \quad \text{C} \quad \text{H} \quad \text{N} \quad \text{Br} \]

1. With p-bromoaniline hydrochloride

A mixture of the aminoketone (1 g.) and p-bromoaniline hydrochloride (0.8 g.) was heated on an oil bath at $150^\circ - 160^\circ$ for 30 minutes, but the resultant charred mass was only slightly soluble in ether and the extract on evaporation gave a viscous black syrup which failed to crystallise. The method of Julian and co-workers (J.A.C.S. 1945, 67, 1203) was also employed: 2-p-bromophenylaminocyclohexanone (1 g.) and p-bromoaniline (1.5 g.) were heated with 10% hydrochloric acid (2 d.) in an atmosphere of nitrogen at $150^\circ$ for two hours, and the residue was extracted with ether. The extract was washed in the usual way, dried and evaporated but the resultant brown syrup failed to give any 6-bromotetrahydrocarbazole on trituration or crystallisation.
2. **With p-bromoaniline**

Molecular amounts of the aminoketone and p-bromoaniline were mixed and heated at different temperatures. Below a critical temperature no reaction took place, but when this temperature was reached a vigorous decomposition set in and the mixture began to boil briskly at the same time darkening rapidly in colour. No 6-bromotetrahydrocarbazole could be isolated from the dark violet resin formed.

3. **With aniline hydrochloride**

The aminoketone (1 g.) and aniline hydrochloride (0.5 g.) were heated at 150° for 30 minutes as in (1), and the mixture was extracted with ether as previously. The extract on evaporation gave a brown solid, colourless plates from light-petroleum (60° - 80°) m.p. 95° - 97°; picrate, dark red needles from benzene, m.p. 143° - 145°. These m.ps. suggested that tetrahydrocarbazole (lit. m.p. 116°; picrate m.p. 147°) and not 6-bromotetrahydrocarbazole had been obtained, and this supposition was confirmed by a mixed m.p. with tetrahydrocarbazole which showed no depression.

4. **With glacial acetic acid and hydrobromic acid**

Hydrobromic acid was passed into a solution of 2-p-bromophenylaminocyclohexanone (1 g.) in glacial acetic acid (20 ml.) for one hour, but the aminoketone was recovered unchanged on neutralisation of the acid mixture.
5. With concentrated sulphuric acid

The aminoketone (0.5 g.) was dissolved in varying concentrations of hot sulphuric acid (1:1 vol., 1:2 vol. and 1:3 vol.) but in each case a brown gelatinous product of very indefinite m.p. was formed, and as this failed to give a picrate in benzene solution, it was not further investigated.

Preparation of 2-o-Bromophenylaminocyclohexanone

2-Chlorocyclohexanone (5 g.) and o-bromoaniline (8.1 g.) were condensed in boiling alcohol (20 ml.) with sodium carbonate (3 g.) in the usual manner. The resultant syrup would not crystallise and was divided into two portions prior to further purification. The first was distilled in vacuo but as soon as excess o-bromoaniline had been removed, further heating caused decomposition of the residue and gave a black resin similar to that obtained in the condensation without the carbonate (p.). The second half was freed from excess amine in a similar manner but the distillation was stopped before decomposition occurred and the brown syrupy product was crystallised from alcohol, the 2-o-bromo-phenylaminocyclohexanone separating in colourless prisms.

Yield 2 g. (40%) m.p. 66° - 69° (d. at 208°).

Analysis

C_{12} H_{14} O N Br requires N, 5.22; Br, 29.8

Found N, 5.05; Br, 28.4.

As in the case of the p-bromo isomer the
2-o-bromophenylaminocyclohexanone melted at 66° to a colourless liquid which decomposed on further heating, d.p. 208°.

Preparation of 2-(2' : 4'-Dichlorophenylamino)-cyclohexanone

2:4-Dichloroaniline and 2-chlorocyclohexanone were condensed in boiling alcohol with sodium carbonate as before. The intermediate ketone could not be distilled in vacuo and purification was effected as in the previous experiment by distilling off excess 2:4-dichloroaniline and crystallising the residue. The 2-(2': 4'-dichlorophenylamino)-cyclohexanone separated from light-petroleum (60° - 80°) in the form of colourless prisms

Yield 48% m.p. 81° - 82° (decomp. >500°)

Analysis

C_{12} H_{13} O N Cl_{2} requires N, 5.45; Cl, 27.5

Found N, 5.47; Cl, 27.0.

Attempted cyclization of 2-(2': 4'-Dichlorophenylamino)-cyclohexanone

The aminoketone (1 g.) and 2:4-dichloroaniline hydrochloride (1.5 g.) were heated at 200° for one hour, but the resultant dark brown syrup failed to give any 6:8-dichlorotetrahydrocarbazole on extraction with ether.
Condensation of o-Chloroaniline and 2-Chlorocyclohexanone in the presence of Sodium acetate

\[ \text{Cl} \quad \text{Cl} \quad \text{NH}_2 \quad \quad + \quad \quad \text{O} \quad \text{C} \quad \text{H} \quad \text{C} \quad \text{H} \quad \text{C} \quad \text{H} \quad \text{C} \quad \quad \text{NaAc} \quad \quad \rightarrow \quad \text{Cl} \quad \text{Cl} \quad \text{NH} \quad \text{C} \quad \text{H} \quad \text{C} \quad \text{H} \quad \text{C} \quad \text{H} \quad \text{C} \quad \text{H} \quad \text{C} \quad \text{H} \]

2-Chlorocyclohexanone (5 g.) was added dropwise to a boiling suspension of sodium acetate (4 g.) in o-chloroaniline (15 g.), and the resulting mixture was cooled and extracted with ether. The extract was washed in the usual way, dried and evaporated when the condensation product was obtained as a yellow syrup which readily crystallised.

Yield 4.2 g. (50%) m.p. 45° - 50°.
Recrystallisation from light-petroleum (40° - 60°) gave colourless prisms, m.p. 53° - 55°. No depression with 2-(o-chlorophenylamino)-cyclohexanone.
Condensation of α-Aminoketones and α-Halogenated Ketones with 2 : 4-Dinitrophenylhydrazine

These investigations were carried out to confirm the presence of the carbonyl group in the intermediate aminoketones prepared in the previous section, but in view of the somewhat unexpected results obtained it seemed advisable to describe this work in a separate section.

1. 2-α-Chlorophenylaminocyclohexanone

The aminoketone (0.6 g.) and 2 : 4-dinitrophenylhydrazine (0.5 g.) were condensed in alcohol containing sulphuric acid by Brady's method, and the orange suspension was boiled for two hours to ensure that the reaction was complete. The resultant scarlet compound, m.p. 208° - 210° (d.), had no definite crystalline form and was extremely insoluble. Purification by boiling with glacial acetic acid gave a scarlet solid m.p. 237° - 239° (d.)

Analysis

\[ C_{18}H_{18}O_{4}N_5 \text{Cl requires } N, 17.5 \]

\[ \text{Found } N, 23.1; \text{ no Cl present.} \]

The above condensation was repeated, but in this case the oily emulsion obtained by mixing alcoholic solutions of the two reactants was not heated. When the emulsion was shaken and rubbed with a glass rod a curdy orange solid, m.p. 143° - 150° separated from the solution, and analysis showed that this compound still contained chlorine. It was slightly soluble
in boiling glacial acetic acid but the product obtained on cooling had no definite crystalline form and melted over a wider range than the original compound - 160° - 178°. When the orange solid of m.p. 143° - 150° (0.2 g.) and 2 : 4-dinitrophenylhydrazine (0.1 g.) were boiled under reflux with alcohol (5 ml.) containing concentrated sulphuric acid (0.5 ml.) for two hours, a darkening in colour of the suspended solid was apparent, and a scarlet compound of m.p. 230° - 231° (d.). (No depression with compound analysed) was obtained.

2. 2-p-Bromophenylaminocyclohexanone

Solutions of 2-p-bromophenylaminocyclohexanone (1.3 g.) and 2 : 4-dinitrophenylhydrazine (1 g.) in alcohol containing sulphuric acid were mixed and the resultant orange suspension was boiled for two hours. The scarlet compound formed had no definite crystalline form and because of its insoluble nature recrystallisation was unsuccessful. Boiling with glacial acetic acid as in (1) gave a compound of m.p. 229° - 230° (d.).

Analysis

\[ C_{18}H_{18}O_4N_5Br \] requires N,15.6

Found N,23.2

Conclusion Although the two dinitrophenylhydrazine condensation products were obtained from intermediate ketones containing different halogen atoms, they both contain the same percentage of nitrogen. This suggests that elimination of the halogen from each
condensation product must be taking place during the reaction. That this was indeed the case, and that in fact the two products were identical was shown by carrying out a mixed melting point determination which showed no depression. The chemical structure of these condensation products, was determined by examination of the condensation of 2-chlorocyclohexanone and 2 : 4-dinitrophenylhydrazine outlined below.

3. 2-Chlorocyclohexanone

Condensation of 2-chlorocyclohexanone and 2 : 4-dinitrophenylhydrazine in alcohol by Allen's method gave a mass of orange prisms, m.p. 145° - 152° (d.); rosettes of orange prisms from tetralin, m.p. 158° (d.)

Analysis

C_{12} H_{13} O_{4} N_{4} Cl requires N,18.3; Cl,10.9

Found N,17.9; Cl,11.3.

An attempted recrystallisation from aqueous acetic acid indicated that a reaction was occurring in this solvent and this was verified as follows: 2-chlorocyclohexanone-2 : 4-dinitrophenylhydrazone (0.1 g.) was dissolved in glacial acetic acid (2 ml.) and water (3 drops) was added to the solution. On bringing the mixture to the boiling point the colour of the solution changed from orange to red, and on cooling after two minutes a red oil separated from the solution. Reheating effected crystallisation of this compound and gave a mass of small scarlet
needles, m.p. 235° - 238° (d.)

Analysis

Found  C, 45.73;  H, 3.52;  N, 24.3;  No Cl present.

This compound was also obtained by boiling a mixture of 2 : 4-dinitrophenylhydrazine (0.16 g.) and 2-chlorocyclohexanone-2 : 4-dinitrophenylhydrazone (0.25 g.) in glacial acetic acid (3 ml.). When the b.p. was reached the solution turned dark red, and cooling and reheating as above gave a scarlet solid m.p. 233° - 236° (d.).

Mixed melting point determinations with the condensation products obtained from 2-o-chlorophenylaminocyclohexanone and 2-p-bromophenylaminocyclohexanone showed that all these compounds melting between 230° and 235° were identical, and the structure opposite appears to be the only one which would explain their formation in these different condensation reactions.

C₁₈H₁₈Cl₁₂N₈ requires  C, 45.57;  H, 3.82;  N, 23.6.

4. w-Chloroacetophenone

w-Chloroacetophenone and 2 : 4-dinitrophenylhydrazine were condensed in alcohol by Allen's method to give orange needles of the dinitrophenylhydrazone, m.p. 214° - 215° (d.) (lit. 212°).

w-Chloroacetophenone dinitrophenylhydrazone (0.3 g.) and 2 : 4-dinitrophenylhydrazine (0.18 g.)
were boiled under reflux with glacial acetic acid (minimum amount required to dissolve reactants) but no darkening in colour was apparent in this case, the dinitrophenylhydrazone being recovered unchanged (m.p. 207° - 210°) even after 26 hours reflux.

The dinitrophenylhydrazone (0.15 g.) was dissolved in a mixture of water (5 drops) and enough glacial acetic to produce a homogeneous solution at the boiling point, but after six hours at this temperature no appreciable darkening of the solution had occurred. After 20 hours a dark red solid began to separate in small quantity, and at this stage further portions of the dinitrophenylhydrazone (0.15 g.), water (1 ml.) and glacial acetic acid were added and the solution was boiled for a further 48 hours. Filtration of the boiling liquid gave scarlet needles, yield 0.11 g.; m.p. 296° - 297°.

Analysis

\[ \text{C}_{20} \text{H}_{16} \text{O}_8 \text{N}_8 \text{ requires } \text{C}, 48.39; \text{H}, 3.25; \text{N}, 22.5 \]

Found \[ \text{C}, 48.26; \text{H}, 3.30; \text{N}, 21.6 \]

The dark brown filtrate deposited a small amount of bronze coloured scales, m.p. 197° - 200°, on cooling.

Analysis

Found N, 17.6

\[ \text{C}_{14} \text{H}_{12} \text{O}_5 \text{N}_4 \text{ requires } \text{N}, 17.7. \]
Condensation of Aminobenzoic Acids and Esters with 2-Chlorocyclohexanone

Preparation of Methyl tetrahydrocarbazole-8-carboxylate

2-Chlorocyclohexanone (5 g.) was added dropwise to methyl anthranilate (12 g.) at 140°, and the temperature was allowed to rise gradually to 160° during the addition. The dark brown mixture was maintained at 160° for 15 minutes, cooled, boiled with dilute hydrochloric acid (50 ml.) to remove the hydrochloride and excess amine and the residue was extracted with boiling ether. A dark brown insoluble resin was not investigated. The ether extract was washed with acid and bicarbonate solution in the usual manner, and the crude yellow product obtained on evaporation was purified by trituration with methyl alcohol.

Yield 2.9 g. (34%) m.p. 119° - 123°.

Recrystallisation from methyl alcohol gave colourless prisms of methyl tetrahydrocarbazole-8-carboxylate, m.p. 123° - 124° (lit. 124°).

Analysis

Calc. for C_{14}H_{15}O_{2}N N, 5.90

Found N, 6.11.

Picrate: brick-red needles from benzene, m.p. 130° - 132°.
Hydrolysis of Methyl tetrahydrocarbazole-8-carboxylate

The ester (0.31 g.) was boiled with ethyl alcohol (10 ml.) and sodium hydroxide (10 ml., 8%) for two hours and the solution was cooled and acidified.

Yield 0.29 g. (100%) m.p. 196° - 200°

Recrystallisation from benzene gave colourless prisms of 8-carboxytetrahydrocarbazole, m.p. 200° - 201° (lit. 205°); no depression with authentic specimen.

Preparation of Methyl tetrahydrocarbazole-6-carboxylate

Methyl p-aminobenzoate was prepared in 80% yield by catalytic hydrogenation of methyl p-nitrobenzoate (cf. Organic Synthesis Vol. VIII, p. 66) and 12 g. were condensed with 2-chlorocyclohexanone (5 g.) as in the previous experiment.

Yield 2.6 g. (30%) m.p. 153° - 156°.

Recrystallisation of the product from aqueous acetic acid gave colourless leaflets of methyl tetrahydrocarbazole-6-carboxylate, m.p. 155° - 157° (lit. 158°).

Hydrolysis of Methyl tetrahydrocarbazole-6-carboxylate

The ester (0.35 g.) was hydrolysed as above.

Yield 0.34 g. (100%) m.p. 275° - 276°.

Recrystallisation from glacial acetic acid gave colourless leaflets, m.p. 279° - 281° (lit. 282°); no depression with authentic 6-carboxytetrahydrocarbazole.

Condensation of 2-chlorocyclohexanone and o-aminobenzoic acid

2-Chlorocyclohexanone (5 g.) and o-aminobenzoic
acid (11 g.) were condensed at 150° as in the case of the ester. The crude product was extracted with boiling benzene to free it from the insoluble brown resin and the 8-carboxytetrahydrocarbazole crystallised from the extract in colourless prisms on cooling.

**Yield 2.8 g. (35%) m.p. 198° - 200° (lit. 203°)**

**Condensation of 2-chlorocyclohexanone and p-aminobenzoic acid**

2-Chlorocyclohexanone and p-aminobenzoic acid were condensed at 190° - 200° (just above the m.p. of the acid) but a very vigorous reaction took place and the product failed to give any tetrahydrocarbazole-6-carboxylic acid when treated in the usual way.

**Condensation of 2-chlorocyclohexanone and m-aminobenzoic acid**

1. 2-Chlorocyclohexanone (5 g.) was added slowly to m-aminobenzoic acid (11 g.) just above the m.p. (175° - 185°) but as in the previous experiment the reaction was very vigorous and the resultant viscous brown tar appeared insoluble in ether.

2. The same quantities of chloroketone and acid were dissolved in alcohol (70 ml.) and the solution was boiled under reflux for 18 hours. A considerable amount of m-aminobenzoic acid hydrochloride separated from the dark brown solution during this reflux period, and when the solution was finally evaporated and cooled, further crystallisation occurred; total yield 6 g. (92%), m.p. 288° (d).
To ensure that this material was all hydrochloride it was extracted with boiling water but no residue was obtained. The alcohol mother liquor was diluted with ether but only a small amount of the solute dissolved, a large quantity of a crimson, ether-insoluble resin separating. The ethereal solution was washed, dried and evaporated and the residue was crystallised twice from alcohol to give colourless prisms of 7 carboxytetrahydrocarbazole.

\[
\text{Yield 0.2 g. (2.5\%) m.p. } 285^\circ - 286^\circ \\
\text{(lit. } 287^\circ) 
\]

**Analysis**

Calc. for C\(_{13}\)H\(_{13}\)O\(_2\)N C, 72.55; H, 6.09

Found C, 72.20; H, 6.31.
Condensation of 2-Chloro-5-Methylcyclohexanone and Aniline

Inactive m-methylcyclohexanone was chlorinated in the presence of calcium carbonate by the method of Godchot and Bedos (Bull. Soc. Chim., 1926, 39, 90), and the mixture of cis- and trans- 2-chloro-5-methylcyclohexanone was separated by fractional distillation in vacuo. A separation of the isomers is not essential but this was carried out to compare the b.ps. with those of Godchot.

(i) Fraction b.p. 76° - 86°/12 mm. (lit. 80° - 86°/6 mm.)
(ii) Fraction b.p. 93° - 97°/12 mm. (lit. 90°/6 mm.)

The total yield was 50% of which 40% was the lower boiling isomer.

\[
\begin{align*}
\text{Condensation:} & \\
\text{Product:} &
\end{align*}
\]

The lower boiling 2-chloro-5-methylcyclohexanone (5 g.) was added slowly to boiling aniline (10 g.) and the mixture was cooled and treated with dilute hydrochloric acid (100 ml.). The brown insoluble portion was extracted with ether, dried and distilled in vacuo to give a pale yellow syrup which slowly crystallised.

Yield 2.4 g. (58%) b.p. 180° - 200°/16 mm.

Crystallisation from light-petroleum (60° - 80°) gave colourless prisms, m.p. 78° - 81° (softens at 75°)
Analysis

C_{13} H_{15} N requires C, 84.28; H, 8.16; N, 7.56

Found C, 83.90; H, 7.98; N, 7.50

Picrate: maroon needles from benzene, m.p. 116° - 126°.

The tetrahydrocarbazole (1 g.) and chloranil (2.67 g.) were boiled under reflux in xylene (30 ml.) for 20 hours and the solution was diluted with ether, washed several times with potassium hydroxide (4%) and dried. Evaporation gave the crude carbazole, (0.27 g., 27%) m.p. 219° - 229°; colourless plates from alcohol, m.p. 240° - 245°. The melting point range suggested that the compound was not pure and a portion was dissolved in benzene and passed through a short alumina column. The eluate gave colourless plates, m.p. 241° - 245° (softens at 239°) (No depression with authentic 2-methylcarbazole, m.p. 257° - 259°).

Analysis

C_{13} H_{11} N requires C, 86.14; H, 6.12; N, 7.73

Found C, 85.38; H, 6.12; N, 7.98

Picrate (prepared with specimen from alcohol):

orange needles from benzene m.p. 161° - 163° (softens at 155°). Decomposition of this picrate by passing its benzene solution over alumina gave colourless plates of indefinite m.p. (lit. 2-methylcarbazole picrate m.p. 167°).

Colour test: Both 2-methyl carbazole and the compound of m.p. 241° - 245° gave a bottle green colour with concentrated sulphuric acid and one drop of concentrated nitric acid.
An investigation of the condensation of 2-chlorocyclohexanone and substituted derivatives of aniline has revealed a promising method for the preparation of methyl-, dimethyl-, chloro- and carbethoxy derivatives of tetrahydrocarbazole. Although the method does not appear to be of such wide application as some of the existing methods for the synthesis of this heterocyclic compound, and the yields are generally lower, it has the advantage that the starting products are much more readily obtained.

A study of the cyclization of the intermediate halogen substituted 2-phenylaminocyclohexanones has shown that the conditions required for their ring closure are similar to those necessary for the indolisation of phenacylanilines. Since condensation of aniline and 2-chloro-5-methylcyclohexanone gives 2-methyl- instead of the expected 3-methyltetrahydrocarbazole it seems probable that the cyclization stage of this condensation takes place by a similar mechanism.

It has been shown that the halogen substituted 2-phenylaminocyclohexanones form dinitrophenylhydrazones with 2:4-dinitrophenylhydrazine, but simultaneously the halogen substituted phenylamino group is replaced by the 2:4-dinitrophenylhydrazino group, and the final product is α-2:4-dinitrophenyl-β-(2'-cyclohexanone 2:4-dinitrophenylhydrazone)-hydrazine. This structure has also been obtained by effecting the condensation of both the ketone group and the reactive halogen in 2-chlorocyclohexanone with
2 : 4-dinitrophenylhydrazine, and an analogous derivative has been obtained from 4-chloroacetophenone.
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PART II

STUDIES IN THE PYRIDOBENZIMINAZOLE SERIES
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INTRODUCTION

While a survey of the literature of the past twenty-five years reveals that much attention has been paid to the chemistry of 2-aminopyridine and the condensed ring systems derived from this heterocyclic base, the aim of the investigators in this field seems to have been the preparation of new ring systems rather than the assignment of precise structural formulae to these compounds. It is not surprising, therefore, to find that several of these investigators differ in their interpretation of the mechanism of the condensation reactions of 2-aminopyridine. This is especially true of the reaction with α-halogenated ketones which forms the major portion of this section of the thesis. Although the extensive investigations of Tschitschibabin on the condensation products obtained from the halogen derivatives of straight chain ketones have established that the resulting bicyclic products possess pyrimidazole ring structures, the results published by the only investigators of the analogous reaction with cyclic ketones of the cyclohexanone type are quite incompatible with the observations of Tschitschibabin. The present investigation was
undertaken in the hope that the results obtained might lead to a solution of this anomaly.

In 1951, a process for the manufacture of heterocyclic compounds was developed and patented by I.G. Farbenindustrie (I) which utilised the condensation reaction between derivatives of 2-aminopyridine (I) and 2-chlorocyclohexanone (II) for the synthesis of derivatives of the hitherto unknown 6:7:8:9 tetrahydro-2-carboline (III).

No mention is made in the patent, however, of the possibility of the 2-aminopyridine acting in its \(\alpha\)-pyridone-imine form (IV) and condensing with the 2-chlorocyclohexanone by the possible alternative route shown to give the isomeric pyrrole (1':2':1:2) - 4:5:6:7 - tetrahydro-benzimiazole.

That this alternative course for the reaction is in fact much more probable, is indicated by the very thorough study made by Tschitschibabin of the condensation products derived from 2-aminopyridine. In his preliminary investigations on the reaction
with methyl iodide (2), he showed that two types of N-methyl derivatives could be formed depending on the conditions employed in their preparation. When 2-aminopyridine and methyl iodide are allowed to react directly, and the quaternary salt (VI) formed is treated with silver oxide, the main reaction product is N-methyl-α-pyridone-imine (VII).

If, on the other hand, the sodium derivative of 2-aminopyridine (VIII) obtained by the action of sodamide on the base,

is condensed with methyl iodide, the isomeric 2-methylaminopyridine (IX) is formed.

In view of the existence of these two isomeric N-methyl derivatives, Tschitschibabin suggested that 2-aminopyridine itself

might be a tautomeric mixture of the normal amino compound (IX a) and the α-pyridone-imine form (VII a). The recent ultra-violet absorption measurements of Anderson and Seeger (3) lend no support to this
hypothesis, however, and as the dipole moment values of 4-substituted derivatives of pyridine obtained by Leis and Curran (4) rule out the possibility of the corresponding α-pyridone-imine being present in any appreciable amount in solutions of 4-aminopyridine, it seems probable that this will also be true in the case of the 2-isomer.

The existence of the two isomeric N-methyl derivatives of 2-aminopyridine indicates, nevertheless, that in reactions of this type it can be regarded as a tautomeric compound, and that the halogen may condense either with the hydrogen of the amino group or the hydrogen attached to the ring nitrogen. As the α-pyridone-imine form is convenient for the representation of several of the reactions of 2-aminopyridine, it will occasionally be employed during this discussion.

Further work by Tschitschibabin on the products obtained by condensation with α-halogenated ketones, esters and acid halides showed that 2-aminopyridine has little tendency to undergo ortho condensations involving the ϕ-carbon atom, but rather cyclizes to the iminazole ring structure in the formation of which both nitrogen atoms are involved. 2-Aminopyridine and chloroacetone (X) for example yield only 2-methylpyriminazole (XI), and none of the isomeric 3-methyl-7-azaindole (XII) formed by ring closure at the ϕ-carbon atom (5). In a similar fashion
bromoacetic ester (XIII) and chloroacetyl chloride (XIV) both give 2-keto-2,3-dihydropyrimidazole (XV) (6).

Reindel (7) and Sucharda (8) also studied the reaction with the α-halogenated acetic acid, but both assigned to their product the structure in which the β-carbon atom is involved in cyclization. Tschitschibabin demonstrated the falseness of this assumption, however, by isolating the intermediate 2-pyridone-imine-1-acetic acid (XVI) which cannot possibly cyclize to a 7-azaindole ring system. The structure of this intermediate was proved by its decarboxylation to the known N-methyl-α-pyridone-imine and its isolation led Tschitschibabin to the conclusion that the reactive halogen atom of these ketonic compounds tends to attack the ring nitrogen rather than the primary amino group. This hypothesis is supported by the absence of the theoretically possible 3-methylpyrimidazole (XVIII) in the product obtained by condensation of chloroacetone and 2-amino-pyridine.
If the halogen condensed with the amino group, the hypothetical intermediate 2-acetonylaminopyridine (XVII) would cyclize to 3-methylpyriminazole.

Although no proof of the position of this methyl substituent in the product obtained from 2-aminopyridine and chloroacetone is to be found in the work of Tschitschibabin, the investigations of Schmid and Bangler (9) on the corresponding phenyl derivative appear to furnish the necessary evidence. They showed that the compound XX, formed from 2-aminopyridine and acetophenone diethyl acetal (XIX), undergoes further condensation with the acetophenone to give α-dypnoneaminopyridine (XXI).

\[ \text{XIX} \quad \text{XX} \quad \text{XXI} \]

Treatment of this α-dypnoneaminopyridine with hydrochloric acid, effects cyclization to 2-phenylpyriminazole (XXII), identical with that obtained by condensation of 2-aminopyridine and chloroacetophenone (XXIII).
It is interesting to note that Goldfarb and his co-workers in Russia, who have recently been investigating the products derived from α-aminonicotine and α-halogenated ketones seem to be uncertain of the position of this substituent in the ring. They agree with Tschitschibabin that only one of the two possible pyriminazole derivatives is formed, but they hesitate to assign a definite position to the substituent. With α-aminonicotine (XXIV) and chloroacetone for example, they obtained a product (XXV) which they call 5-(N-methyl-α-pyrrolidyl) -2 (or 3) -methylpyriminazole (10), and with bromopyruvic ester, the corresponding 2 (or 3) - carbethoxy derivative (XXVI) (11) was formed

\[ R = \begin{array}{c}
\text{C}_3H_7 \\
\text{N} \\
\text{CH}_3
\end{array} \]

The most recent experimental results seem to indicate that the mechanism of the condensation reactions of 2-aminopyridine is not so straightforward as was originally believed, and that the ring nitrogen is not exclusively the centre of attack, as Tschitschibabin has suggested. This is exemplified by the results of Sharp (12), who was investigating
the condensation products of 2-aminopyridine and long chain alkyl iodides. By heating the two reactants in cymene, he obtained a mixture of the two possible products containing 75% - 85% of the more strongly basic N-alkyl-α-pyridone-imine (XXVII), and 25% - 15% of the isomeric 2-alkylaminopyridine (XXVIII). These results indicate, however,

\[ \text{XXVII} \quad \text{XXVIII} \]

that the ring nitrogen is the main centre of attack.

It seems probable that the first stage in the condensation between 2-aminopyridine and α-halogenated ketones is the formation of a quaternary salt (XXIX) at the ring nitrogen, and subsequent loss of the halogen acid and water according to the scheme suggested below, results in the formation of the pyriminazole ring.

\[ \text{XXIX} \]

This is the mechanism of the analogous reaction with α-picoline (XXX), also investigated by Tschitschibabin (13), but in this case the intermediate quaternary salt (XXXI) may be isolated.
Treatment of its aqueous solution with sodium bicarbonate effects dehydrohalogenation and cyclodehydration to a 2-substituted pyrrocoline (XXXII).

\[
\begin{align*}
XXX & \quad XXXI \\
XXX & \quad XXX II
\end{align*}
\]

The suggested quaternary salt formation as the first stage of the 2-aminopyridine condensations is in agreement with the general theory of salt formation in polyamines recently reviewed by Mann and Watson (14). Whilst they agree that the position of proton attack in the monocacidic 2-aminopyridine is uncertain, they point out that the cation formed by attack on the ring nitrogen would be stabilised by resonance between structures XXXIII and XXXIV, whereas this would not be possible if the cation had structure XXXV.

\[
\begin{align*}
XXXIII & \quad XXXIV \\
XXX & \quad XXXV
\end{align*}
\]

This review of the condensation reactions of 2-aminopyridine shows that while several of the papers in the literature are characterised by an uncertainty regarding the mode of condensation of the reactants, they all agree that the bicyclic ring compounds formed possess the pyriminazole ring structure. It seems highly probable, therefore,
that the products listed in the I.G. Farbenindustrie patent are derivatives of pyrido (1': 2': 1 : 2)-tetrahydrobenzimidazol, and not of tetrahydro-2-carboline as claimed by the patent. Although neither of these tetrahydro compounds has been prepared by any other method, the two parent compounds, in which both rings are aromatic have since been synthesised.

The alkaloids harmine and harmaline are derivatives of 3-carboline and Perkin and Robinson (15) synthesised the 2-isomer in the course of their studies on the constitution of these natural products. They condensed 2-chloropyridine (XXXVI) and o-phenylenediamine (XXXVII), and by the action of nitrous acid on the resultant \( N-\alpha \)-pyridyl \( o \)-phenylenediamine (XXXVIII), obtained 1-\( \alpha \)-pyridylbenzotriazole (XXXIX). This compound readily lost nitrogen on heating with zinc chloride, simultaneously cyclizing to 2-carboline (XL).
Pyrido (1': 2': 1 : 2) benziminazole was prepared by Morgan and Stewart (16), whilst investigating the condensation products of 2-amino-pyridine and aromatic nitro compounds containing reactive halogen atoms. With picryl chloride (XLI), 2-picrylaminopyridine (XLII) is formed, and this readily loses nitrous acid in boiling dimethylaniline giving 4 : 6-dinitropyridobenziminazole (XLIII). Removal of the two nitro groups in the usual manner, by reduction, diazotisation and boiling the tetrazotate in alcohol gives the parent base (XLIV), which Morgan and Stewart have called Pyrido (1': 2': 1 : 2) benziminazole, or 1 : 2 Pyrido-4 : 5-benzo-1 : 3-diazaline, the former name being used throughout this thesis.

In the first stage of this synthesis, the halogen of the picryl chloride may condense with the hydrogen attached to the ring nitrogen to form N-picryl-α-pyridone-imine (XLII a), but Morgan and Stewart, without giving any reason for their choice, prefer to regard it as acting in the manner shown.
The catalytic reduction of 4 : 6-dinitropyrido-
benzimiazole gives 4 : 6-diamino-3' : 4' : 5' : 6'-
tetrahydropyrido-(1' : 2' : 1 : 2)-benzimiazole and
despite increased hydrogen pressures, Morgan and
Stewart were unable to carry the reduction beyond
the tetrahydro stage.

Apart from these two syntheses, no other work
has been carried out on the chemistry of 2-carboline
or pyridobenzimiazole, and consequently nothing is
known of their substitution reactions. The
structures of both, however, suggest that their
derivatives might prove useful in the field of
chemotherapy, and when these potentialities have been
more fully examined, perhaps a wider range of
derivatives will become known.
PURPOSE AND GENERAL PLAN OF RESEARCH

The introductory section has made it clear that a doubt exists regarding the structure of the compounds whose preparation is described in the I.G. Farbenindustrie patent. The purpose of this research was to determine whether tetrahydrocarbolines or pyridotetrahydrobenzimidazoles are formed by condensation of 2-aminopyridine and its derivatives with 2-chlorocyclohexanone.

It seemed probable that the results of the following proposed lines of research would shed some light on this problem:

(1) Condensation of 2-chlorocyclohexanone and 3-substituted derivatives of 2-aminopyridine, which cannot possibly cyclize to the carboline ring system. The known 2-amino-3-methyl-(XLV), 2-amino-3-nitro-(XLVI) and 2-amino-3:5-dibromopyridine (XLVII) suggested themselves for this investigation.

\[
\begin{align*}
\text{XLV} & & \text{XLVI} & & \text{XLVII} \\
\begin{array}{c}
\begin{array}{c}
\text{N} \\
\text{CH}_3 \\
\text{NH}_2
\end{array}
\end{array} & & \\
\begin{array}{c}
\begin{array}{c}
\text{N} \\
\text{NO}_2 \\
\text{NH}_2
\end{array}\end{array} & & \\
\begin{array}{c}
\begin{array}{c}
\text{Br} \\
\text{Br} \\
\text{N} \\
\text{H}_2
\end{array}
\end{array}
\end{align*}
\]

It is to be noted, however, that although the tricyclic condensation products from these compounds must necessarily have pyridobenzimidazole structures, it is possible that the unsubstituted 2-aminopyridine might cyclize by the alternative route, and give tetrahydrocarboline.
(2) Comparison of the ultra-violet absorption spectra of the known pyridobenzimiazole structures obtained in (1), and the spectrum of the condensation product of 2-chlorocyclohexanone and unsubstituted 2-aminopyridine should throw light on the structure of the latter.

(3) Dehydrogenation of the product from 2-aminopyridine and 2-chlorocyclohexanone, if successful, should give the known 2-carboline or pyrido (1': 2': 1: 2) benzimiazole.

The main object of this investigation was therefore the determination of the ring structure of these compounds, but it was hoped that by carrying out the reaction as a two-stage process, and by attempting to condense the two N-methyl derivatives of 2-aminopyridine and 2-chlorocyclohexanone, some insight might be gained into the mechanism of the reaction.
DISCUSSION OF RESULTS

SECTION A.

Syntheses of Pyrido (1': 2': 1 : 2) 4 : 5 : 6 : 7- tetrahydrobenzimidazole and several of its substituted derivatives.

The condensation of 2-aminopyridine and 2-chlorocyclohexanone in boiling alcohol, and isolation of the product as described in the patent, gave a tricyclic condensation product apparently identical with that obtained by the German workers. It is interesting to note that this compound crystallises from organic solvents as the monohydrate of m.p. 56° - 58° and molecular formula C_{11}H_{14}ON_{2}, a fact not disclosed in the patent, where it was stated that crystallisation gave a compound of m.p. 95°. The hydrate was readily dehydrated in vacuo, however, the anhydrous base being obtained with m.p. 95° - 96°, and the change in weight resulting from this treatment corresponding approximately to the loss of one molecule of water. The anhydrous compound rapidly reverts to the monohydrate on exposure to the air, the change in weight again approximating to the uptake of one molecule of water. A closer examination of the melting of the hydrate showed that at 56° - 58° the solid melted to a cloudy liquid which did not clear until the water of crystallisation distilled off at 120°, the clear liquid crystallising in the anhydrous form on cooling.
A critical examination of the condensation of 2-aminopyridine and 2-chlorocyclohexanone under varying conditions has shown that the reaction time can be reduced, and the yield of product improved by carrying out the condensation at the boiling point of the amine in the absence of a solvent. The excess aminopyridine is readily removed by steam distillation, and the residual crude material gives the anhydrous base on distilling in vacuo.

The patent assigns a tetrahydrocarboline structure to this condensation product, but the ease with which 3-substituted derivatives of 2-aminopyridine were condensed with 2-chlorocyclohexanone under identical conditions to give 3-substituted derivatives of pyridotetrahydrobenzimidazole suggested that a similar cyclization might be occurring in the case of the unsubstituted aminopyridine.

3'-methylpyrido (1':2':1:2) 4:5:6:7 tetrahydrobenzimidazole (XLVIII) was prepared from 2-amino-3-methylpyridine and 2-chlorocyclohexanone by boiling the reactants in alcohol and isolating the condensation product as the hydrochloride, and also by carrying out the condensation in the absence of a solvent. The anhydrous compound obtained by this latter method readily crystallised from water as the dihydrate, which had been obtained by decomposition of the hydrochloride formed in the
2-Aminopyridine was brominated in sulphuric acid solution according to the method developed by Tschitschibabin (17), and the 2-amino-3:5-dibromopyridine obtained from the mixture of bromo compounds by extraction with light-petroleum, readily condensed with 2-chlorocyclohexanone in boiling alcohol to give 3':5'-dibromopyrido (1':2':1:2) - 4:5:6:7-tetrahydrobenziminazole (XLIX). In this case crystallisation gave the anhydrous base, which showed no tendency to form a hydrate. The 2-amino-5-bromopyridine formed in the bromination of aminopyridine was also condensed with 2-chlorocyclohexanone, but as this amine has no blocking substituent in the 3-position, the product may have either the 5'-bromopyrido (1':2':1:2) - 4:5:6:7-tetrahydrobenziminazole (L) or the 4-bromo-6:7:8:9-tetrahydro-2-carboline (LI) structure.

The nitration of 2-aminopyridine (18), like the bromination gives a mixture of two products, but the
separation of the 2-amino-3-nitro and 2-amino-5-nitropyridine in the mixture, by repeated fractional crystallisation from alcohol proved such a tedious and wasteful procedure, that the 3-nitro isomer was obtained pure only in sufficient quantity for one trial experiment. It had been hoped to attempt a separation of the isomers by chromatographic methods, but the comparatively low solubility of the mixture in the non-polar solvents most suitable for chromatographic adsorption indicated that the method might be even more tedious than the fractional crystallisation technique employed.

Conditions for the condensation of 2-amino-5-nitropyridine and 2-chlorocyclohexanone are given in the I.G. Farbenindustrie patent, and it was decided to apply this method to the 3-nitro isomer. Unfortunately the black mass obtained by heating the reactants at 120° failed to yield any condensation product on extraction with acid. Despite this failure, however, the 2-amino-5-nitropyridine and 2-chlorocyclohexanone were condensed under similar conditions, and extraction of the product gave a tricyclic ring compound of m.p. 214° - 215°, apparently identical with the product of m.p. 210° reported in the patent. As in the case of the monobromo condensation product,
Fig. 1.

Fig. 2.
this compound may be either the 5'-nitropyridotetrahydrobenziminazole (LII), or the 4-nitrotetrahydrocarboline (LIIL).

The results obtained from a comparison of the ultra-violet absorption of the known 3': 5'-dibromo pyridotetrahydrobenziminazole and the condensation product of 2-aminopyridine and 2-chlorocyclohexanone show clearly that even in the absence of a blocking substituent group, the cyclization of 2-aminopyridine takes place at the two nitrogen atoms giving pyridobenziminazole structures. The two curves, illustrated in Fig. 1, opposite, show that over a wavelength range of 2,000 - 4,000 Å, the two compounds exhibit almost identical absorption, the only difference being that in the case of the dibromo derivative, the absorption maxima occur at slightly longer wavelengths.

It might be argued that this wavelength shift is due to the change from the carboline to the pyridobenziminazole structure, but if we now consider the absorption curve of the monobromo compound, this objection loses much of its significance. The curve obtained for the condensation product of 2-amino-5-bromopyridine and 2-chlorocyclohexanone (L or LI) is shown along with the two measured above in Fig. 2, and the only feasible explanation of the similarity in form is obtained by assuming that each possesses the pyridobenziminazole structure, and that the gradual displacement of the absorption towards longer
wavelengths is a result of the successive bromination of the pyridine ring. The use of 3'-methylpyridotetrahydrobenzimiazole as a standard, rather than the 3':5'-dibromo compound would no doubt have given a curve more similar in shape to that of the unsubstituted pyridobenzimiazole, but the dibromo derivative was selected because of its easy purification, and the fact that it was required for comparison with the 2-amino-5-bromopyrididine condensation product.

It is worth noting at this point that whilst tetrahydrocarboline has not yet been prepared, and consequently its ultra-violet absorption spectrum has not been determined, the ultra-violet absorption curve of the fully aromatic 2-carboline is known (19). This differs considerably from the curves obtained with pyridotetrahydrobenzimiazoles, but no conclusions can be drawn from this fact since the dehydrogenation of the cyclohexene ring will in itself influence the absorption.

The correctness of the conclusions of these ultra-violet absorption studies was demonstrated by the results of dehydrogenation experiments on the pyridotetrahydrobenzimiazoles. It had been realised when this problem was originally commenced that the most expeditious method of proving the structure of this condensation product of 2-aminopyridine and 2-chlorocyclohexanone was to effect dehydrogenation to the known 2-carboline or to pyrido (1':2';1:2) benzimiazole, but preliminary trial experiments met
with no success. With chloranil, which has proved so successful in the dehydrogenation of tetrahydro-carbazoles (20), these basic ring compounds gave a dark red condensation polymer as soon as the solution in xylene was brought to the boiling point, and with palladised charcoal in boiling mesitylene (21), no dehydrogenation took place. By heating the condensation product of 2-aminopyridine and 2-chlorocyclohexanone with palladium on charcoal at 300°, however, a dehydrogenation product was isolated in 20% yield which appears to be identical with the pyrido (1' : 2' : 1 : 2) benziminazole synthesised by Morgan and Stewart (16).

It can therefore be stated that the condensation of 2-aminopyridine and its 3- and 5- substituted derivatives with 2-chlorocyclohexanone results in the formation of pyrido (1' : 2' : 1 : 2) - 4 : 5 : 6 : 7 - tetrahydrobenziminazole structures, and not tetrahydro-2-carboline as previous workers in this field have claimed.

In view of the results of recent studies on the cyclization of 6- substituted derivatives of 2-aminopyridine, however, there is a distinct possibility that ring closure in these cases will proceed via the α-carbon atom and give tetrahydro-carboline derivatives.

Lappin (22) has shown that the intermediate ethyl 2-pyridylaminomethylenemalonates (LV), formed
by condensing substituted 2-aminopyridines and ethoxymethylenemalonic ester (LIV) can cyclize to two types of products depending on the position of the substituent in the aminopyridine ring.

```
R
\[ \begin{array}{c}
\text{NH}_2 \\
\text{C}=\text{COOEt}
\end{array} \]
\[ \begin{array}{c}
\text{ELO-C=CH} \\
\text{C}=\text{COOEt}
\end{array} \]
\[ \begin{array}{c}
\text{C}=\text{COOEt} \\
\text{CH} \\
\text{C}=\text{COOEt}
\end{array} \]
\[ \begin{array}{c}
\text{OH} \\
\text{C}=\text{COOEt}
\end{array} \]
\[ \begin{array}{c}
\text{R} \\
\text{C}=\text{COOEt}
\end{array} \]
```

All substituted derivatives except those containing electron releasing group like the methoxy or methyl group in the 6-position gave the pyrido (1': 2': 1 : 2) pyrimidone structure (LVII), but in these special cases, the isomeric 1 : 8 - naphthyridine ring (LVI) was formed. Lappin attributes the failure of these 6-substituted derivatives to cyclize in the normal way, to the ortho steric effect of the 6-substituent, which prevents ring closure at the nitrogen atom. A similar effect has been reported by Hauser and Weiss (25) in the condensation of 2-aminopyridine and acetoacetic ester. Unsubstituted 2-aminopyridine and acetoacetic ester give the pyrido (1': 2': 1 : 2) pyrimidone (LVIII), but 2 : 6 - diaminopyridine gives the isomeric aminonaphthyridine (LIX). It is interesting to
note that in the case of the monoaminopyridine, the ester group is regarded as condensing with the primary amino group, whereas with the 2:6-diaminopyridine, the ketone group undergoes this condensation, and the ester group is involved in the cyclization on the p-carbon atom. Hauser and Weiss make no mention of this difference in mechanism of the two reactions, but as the isolation of the dianil (LX) was effected in the second case, there seems no doubt that their conclusions are justifiable.

The condensation of 2-chlorocyclohexanone and 2-amino-6-methylpyridine (LXI) was carried out at the boiling point of the latter, as in previous experiments of

LXI  
LXII  
LXIII
this type, and the condensation product (LXII or LXIII) isolated as the hydrochloride. In an attempt to decide whether this product was 6'-methylpyrido (1': 2': 1 : 2)-tetrahydrobenzimidazole (LXII) or 3-methyltetrahydrocarboline (LXIII), the parent base was oxidised with alkaline permanganate. Most of the compound was recovered unchanged, but a small amount was converted to a compound containing both a basic nitrogen and an acidic carboxyl group, the analysis of which indicates an empirical formula C_{7}H_{9}O_{2}N. The compound has apparently lost one nitrogen atom and acquired a carboxyl group as a result of oxidation, but further work will be necessary before the structure of this oxidation product can be established. Perhaps ultra-violet measurements on the original condensation product will indicate whether it possesses structure LXII or LXIII.

The attempted elucidation of the mechanism of the reaction between 2-chlorocyclohexanone and 2-aminopyridine by condensation of the two N-methyl derivatives of 2-aminopyridine with the chloroketone has been unsuccessful. It was hoped that if the first stage of the condensation was quaternary salt formation at the ring nitrogen followed by loss of hydrochloric acid,
it might be possible to isolate the N-(2'-cyclohexanone)-
N'-methyl-aminopyridine (LXIV) formed with 2-methyl-
aminopyridine. If, on the other hand, the reactive
chlorine condenses with the amino group, the isomeric
structure LXV might be obtained. The 2-methylamino-
pyridine, however, could not be condensed with 2-chloro-
cyclohexanone under the conditions found satisfactory
for 2-aminopyridine.

Attempts to condense N-methyl-α-pyridone-imine
with 2-chlorocyclohexanone resulted in the removal
of hydrochloric acid from the chloroketone, no
condensation reaction being detected.
SECTION B

Attempted preparation of 2-(2'-Pyridylamino)-cyclohexanone and its derivatives.

The generally accepted method of preparing derivatives of 2-aminopyridine with an alkyl or aryl substituent in the amino group, is to condense the sodium derivative of 2-aminopyridine with the required alkyl or aryl halide. In accordance with these ideas, the I.G. Farbenindustrie patent describes the preparation of 2-(2'-pyridylamino)-cyclohexanone (LXVI) from 2-sodiumaminopyridine and 2-chlorocyclohexanone. The present investigations on the condensation of 2-aminopyridine and 2-chlorocyclohexanone in the presence of alkali, however, have shown

![LXVI](image)

![LXVII](image)

that this intermediate compound is much more readily obtained by boiling the reactants in alcohol over sodium carbonate. The yield of product was only 30%, but the melting point of 147° - 149° is in close agreement with the value quoted (147°) for the intermediate obtained in the patent by the more complex sodamide method, for which no yield is given.

To ensure that this compound was not the isomeric N-(2'-cyclohexanone)-α-pyridone-imine (LXVII), its ultra-violet absorption spectrum was
Fig. 3.
determined and compared (Fig. 3) with the spectra of 2-methylaminopyridine and N-methyl-α-pyridone-imine recently measured by Anderson and Seeger (3). This comparison seems to furnish adequate proof that the halogen has condensed with the amino group of 2-aminopyridine, but this conclusion was verified by an examination of the reactions of the compound. The isomeric N-(2'-cyclohexanone)-α-pyridone-imine would be expected to undergo alkaline hydrolysis to N-(2'-cyclohexanone)-α-pyridone (LXVIII), in the same way as N-methyl-α-pyridone-imine gives N-methyl-α-pyridone (2),

\[
\text{HN} \quad \text{O} \\
\text{N} - \text{CH}_3 \quad \text{N} - \text{CH}_3
\]

When the compound of m.p. 147° - 149° was boiled with alcoholic sodium hydroxide, however, no ammonia evolution was detected, and instead

\[
\text{LXVIII} \quad \text{LXIX}
\]

of the α-pyridone compound, a product of molecular formula C_{11}H_{16}ON_{2} was formed. This suggested that the intermediate had undergone reduction in the alkali, and this was verified bysubjecting it to a Meerwein-Ponndorf reduction, the 2-(2'-pyridylamino)-cyclohexanol (LXIX) resulting from conversion of the
ketone to the secondary alcohol, being identical with the C\textsubscript{11}H\textsubscript{16}ON\textsubscript{2} structure obtained above. It seems as if this ketonic reduction in the presence of alcoholic sodium hydroxide can only be explained by assuming that traces of sodium ethoxide formed in the solvent have catalysed a hydrogen transfer of the Meerwein-Ponndorf type, the ketone being reduced to the secondary alcohol, at the expense of the ethyl alcohol oxidised to acetaldehyde.

Reduction of the ketone group in the compound of m.p. 147° - 149° by the modification of the Wolff-Kishner method recently introduced by Huang-Minlon (2\textsuperscript{4}), gave 2-cyclohexylaminopyridine (LXXII) identical with the product formed by condensation of 2-bromo-pyridine (LXX) and cyclohexylamine (LXXI), thus proving conclusively that condensation of 2-aminopyridine

\[ \text{Br} + \text{H}_2\text{N-C}_6\text{H}_4 - \text{C}_6\text{H}_{11} \rightarrow \text{H}_2\text{N-C}_6\text{H}_{11} \text{NH-C}_6\text{H}_{11} \]

LXX LXXI LXXII
and 2-chlorocyclohexanone in the presence of sodium carbonate gives 2-(2'pyridylamino)-cyclohexanone.

It is interesting that attempted reduction of 2-(2'-pyridylamino)-cyclohexanone with zinc and hydrochloric acid led to a cleavage of the molecule at the secondary amino group. 2-Aminopyrididine was identified as one of the reduction products, but the identity of the residue was not determined. This cleavage of amino ketones when reduced by Clemmensen's
method has also been reported by von Braun and Weissbach (25), who showed that \( \text{w-dimethylaminoacetophenone} \) gave ethylbenzene (LXXIV) and dimethylamine (LXXV)

\[
\begin{align*}
\text{LXXIII} & \quad \text{LXXIV} & \quad \text{LXXV} \\
\text{LXXIV} & \quad \text{LXXV}
\end{align*}
\]

and in view of their results it seems probable that \( 2-(2'-\text{pyridylamino})\)-cyclohexanone will form cyclohexane, in addition to the \( 2\)-aminopyridine mentioned earlier.

The condensation of \( 2\)-amino-3-methyl-, \( 2\)-amino-5-bromo- and \( 2\)-amino-3 : 5-dibromopyridine with \( 2\)-chlorocyclohexanone in the presence of alkali resulted in the formation of the corresponding

\[
\begin{align*}
\text{LXXVI} & \quad \text{LXXVII} & \quad \text{LXXVIII} \\
\text{LXXVII} & \quad \text{LXXVIII}
\end{align*}
\]

pyridobenzimidazoles, instead of the expected substituted derivatives of \( 2-(2'-\text{pyridylamino})\)-cyclohexanone. This cyclization of structures LXXVI, LXXVII and LXXVIII in boiling alcohol in the presence of sodium carbonate can only be explained by assuming that the ortho and para methyl and bromo substituents facilitate ring closure of \( 2-(2'-\text{pyridylamino})\)-cyclohexanone. Allen and his co-workers (26) observed a similar effect in attempting to obtain \( 2\)-acetoacetamino-3 : 5-dibromo-
pyridine (LXXIX) from 2-amino-3:5-dibromopyridine and acetoacetic ester.

Instead of the acetoacetamino derivative, they obtained structure LXXX due to cyclization of the intermediate, whereas 2-aminopyridine and acetoacetic ester under identical conditions had given 2-acetoacetaminopyridine (LXXXI) which could only be cyclized by employing drastic conditions.

Only in the case of unsubstituted 2-aminopyridine, therefore, was it possible to isolate the intermediate amino ketone by condensing with 2-chlorocyclohexanone in the presence of sodium carbonate. The resultant 2-(2'-pyridylamino)-cyclohexanone was readily cyclized to pyridotetrahydrobenziminazole.
in boiling acetic anhydride, and also in cold glacial acetic acid when the solution was saturated with hydrobromic acid, the cyclodehydration apparently being a hydrogen ion catalysed reaction.

This is in accordance with the theory proposed by Hauser and Weiss (23), who believe that the ring closure of carbonyl compounds of this type follows a mechanism analogous to that of other electrophilic substitutions into aromatic rings such as the Friedel-Crafts type of reaction. The cyclization on the ring nitrogen is explained by the resonance

\[ \text{LXXXII} \quad \text{LXXXIII} \]

of 2-aminopyridine among the above structures, and in particular by the evidence indicating that LXXXII makes the main contribution. If cyclization is preceded by polarisation of the carbonyl bond, the positively charged electrophilic carbon atom will satisfy its electron deficiency by ring closing at the negatively charged nitrogen. Although Hauser and Weiss do not enter into any detailed discussion of the reaction mechanism, it seems probable that they would regard the first step in this particular case as the polarisation of the carbonyl group in the resonance structure LXXXIV of 2-(2'-pyridylamino)-cyclohexanone.
Structure LXXXV resulting

\[\text{LXXXIV} \quad \text{LXXXV}\]

from this polarisation would cyclize to pyridotetrahydrobenzinazol because of the charge distribution mentioned earlier. It seems much more probable, however, that

\[\text{LXXXVI} \quad \text{LXXXVII}\]

in an acid medium, the first stage will be the addition of a proton to LXXXIV giving LXXXVI. This reaction destroys both the negative charge on the nitrogen, and consequently the driving force required for cyclization on the ring nitrogen as mentioned above, but at the same time it supplies the hydrogen necessary for ring closure, and does not necessitate the highly improbable migration of this hydrogen from the secondary amino group. In view of the removal of the negative charge on the nitrogen, the polarisation of the carbonyl group serves no useful purpose, and a simple enolisation of structure LXXXVI to LXXXVII, followed by abstraction of water by the acid mixture seems to be equally satisfactory in explaining the
cyclo dehydration.

This mechanism does not explain the failure to isolate structures LXXVI, LXXVII and LXXVIII by condensation of 2-chlorocyclohexanone and the corresponding aminopyridines in the presence of alkali, however, and it seems probable that further work will have to be carried out before these anomalous results find a suitable explanation.

The cyclization of certain 2-aminopyridine derivatives on the \( \beta \)-carbon atom is explained by Hauser and Weiss as being due to an activation of the 2-aminopyridine molecule by the substituent group causing structures LXXXVIII and LXXXIX to make a larger than usual contribution to the resonance of 2-aminopyridine, but this mechanism is highly speculative.
SECTION C

Condensation of 2-aminopyridine and its derivatives with bromoacetone and 3-chloroacetoephene.

These investigations were carried out prior to the successful dehydrogenation of pyridotetrahydrobenzimidazole discussed in Section A, with a view to obtaining a wider range of standard structures for the ultra-violet absorption comparison studies. The assignment of the pyridobenzimidazole structure to the condensation product of 2-aminopyridine and 2-chlorocyclohexanone is now based on chemical, as well as physical evidence, however, and the inclusion of this section in the thesis is justifiable only on the grounds that it covers the preparation of several new derivatives of pyriminazole.

By condensation of bromoacetone and 2-aminopyridine and its methyl, bromo and nitro substituted derivatives in boiling alcohol, the hitherto unknown 2 : 8-dimethyl- (XC), 2-methyl-5-bromo- (XCI), 2-methyl-5 : 8-dibromo- (XCII) and 2-methyl-5-nitropyriminazole (XCIII) have been readily obtained.
Fig. 4.
A comparison of the ultra-violet absorption of structures XC and XCI has shown (Fig. 4) that the displacement of the wavelength of maximum absorption occurs in these compounds as well, and as in this case, both contain a blocking group in the 3-position, the displacement can only be due to the substituent bromine atoms. As we would expect, the absorption of these compounds is very similar to that of the corresponding pyridotetrahydrobenzimidazoles, the main difference being that a single absorption maximum is present at 3,000 \( \AA \), instead of the double peaked maximum obtained previously with the pyridotetrahydrobenzimidazoles which can be regarded as 2 : 3-cyclohexenopyriminazoles.

The assignment of a pyridobenzimidazole structure to the condensation product of 2-aminopyridine and 2-chlorocyclohexanone merely on the similarity of the ultra-violet absorption spectra illustrated in Fig. 1, could be criticised on the grounds that the absorption of the isomeric tetrahydrocarboline might also be similar to dibromopyridotetrahydrobenzimidazole. As no methods are available for the preparation of 6 : 7 : 8 : 9-tetrahydrocarbolines, however, their ultra-violet absorption spectra could not be determined. In the pyriminazole field on the other hand, the isomeric structures formed by cyclization on the \( \mathbf{\alpha} \)-carbon atom have been prepared. Clemo and Swan (27), by ring closure of 2-acetylamino-3-methylpyridine (XCVI) with sodium ethoxide at 300°,
Fig. 5.
obtained 2-methyl-7-azaindole (XCV).

\[ \text{XCIV} \quad \text{XCV} \]

It had been hoped that whilst the ultra-violet absorption of 2:8-dimethylpyriminazole and pyridotetrahydrobenzimidazolone showed a marked similarity because of their similar structures, the absorption of 2-methyl-7-azaindole similar in structure to tetrahydro-2-carboline, would be quite different. This was not the case, however, and the similar nature of all three curves in Fig. 5 shows the difficulty of assigning a structure to pyridotetrahydrobenzimidazolone solely on the results of ultra-violet absorption measurements. The similarity in form of the absorption curves of the pyrimazoles and the corresponding pyridotetrahydrobenzimidazolones is readily explained by the transparent nature of the cyclohexene ring attached to the latter. When this ring is dehydrogenated to an aromatic ring as in pyridobenzimidazolone a difference in the absorption would be expected.
EXPERIMENTAL

INTRODUCTION

The introductory remarks made at the beginning of the experimental section of Part I apply to this section also.

The picrates of the pyridobenzimiazoles were found to be much less soluble in benzene than those of the carbazoles, and purification was generally effected prior to analysis by recrystallisation from a mixture of alcohol and glacial acetic acid, or from glacial acetic acid alone.
CONDENSATION OF 2-CHLOROCYCLOHEXANONE WITH 2-AMINOPYRIDINE AND ITS DERIVATIVES.

**Preparation of Pyrido (1': 2': 1 : 2)-4 : 5 : 6 : 7-tetrahydrobenzimidazole**

![](image)

1. In boiling alcohol (British patent 360,027)

(a) 2-Chlorocyclohexanone (10 g.) and 2-aminopyridine (7.1 g., 1 mol.) were refluxed in alcohol (40 ml.) for 12 hours, and the residue obtained on evaporation was taken up in acetic acid, and the solution extracted with ether. Addition of a saturated solution of sodium bichromate to the acid layer precipitated the orange salt of the condensation product. Decomposition of the salt with sodium hydroxide gave a brown oil which was extracted with alcohol-ether (1:1), dried and distilled in vacuo. A pale yellow syrup was obtained which rapidly crystallised.

Yield - 4.7 g. (33%) b.p. - 170° - 185°/12 mm.

m.p. - 60° - 85°.

A first recrystallisation from ether gave large colourless cubes, m.p. - 60° - 85°, but repetition gave cubes, m.p. 56° - 58° (pat. m.p. 95°).

**Analysis**

Calc. for C_{11}H_{12}N_{2} - C, 76.72; H, 7.02; N,16.3

Found C, 70.00; H, 7.50; N,15.4
Picrate: Yellow needles from alcohol-glacial acetic acid, m.p. 258° - 260°

Analysis

\[ \text{C}_{17} \text{H}_{15} \text{O}_{7} \text{N}_{5} \] requires N, 17.5

Found N, 17.4

While the method adopted for this trial condensation was exactly similar to that described in the patent, the analysis results indicate that the empirical formula of the product is \( \text{C}_{11} \text{H}_{14} \text{ON}_{2} \), and that only hydrochloric acid has been split out from the reactants

Calc. for \( \text{C}_{11} \text{H}_{14} \text{ON}_{2} \): C, 69.45; H, 7.42; N, 14.7.

Analysis of the picrate, however, gives a nitrogen percentage agreeing with the figure calculated for the picrate of a compound of molecular formula \( \text{C}_{11} \text{H}_{12} \text{N}_{2} \); a condensation product formed by loss of both hydrochloric acid and water from the reactants. It is also worth noting that although the melting point of the distillate is not sharp, two recrystallisations from ether give a product of sharp m.p., despite negligible loss in the recrystallisation process.

The isolation of the product by precipitation and subsequent decomposition of the sodium bichromate salt seems unnecessary, since any unreacted 2-amino-pyridine, the only possible side-product in the acid solution will also give a similar salt.
(b) 2-Chlorocyclohexanone (5 g.) and 2-aminopyridine (3.6 g.) were condensed in boiling alcohol (20 ml.) for 12 hours as in (a), but the residue obtained on evaporation was dissolved in water and the solution made alkaline with sodium hydroxide. The oil which separated was extracted with benzene and the dried benzene extract was chromatographed through an alumina column (18" X 1") with a 3 : 1 mixture of benzene and light-petroleum (100° - 120°) for development. No band separation was evident in ordinary or ultra-violet light, but the column as a whole showed a strong blue-violet fluorescence under the U/V lamp. The eluate was collected in 30 ml. portions, each of which on evaporation yielded varying amounts of the colourless condensation product obtained in (a)

<table>
<thead>
<tr>
<th>Total yield</th>
<th>3.0 g. (42%)</th>
<th>m.p. 56° - 58°</th>
</tr>
</thead>
<tbody>
<tr>
<td>Picrate</td>
<td>yellow needles</td>
<td>m.p. 260° - 261°</td>
</tr>
<tr>
<td>Methiodide</td>
<td>colourless needles</td>
<td>m.p. 256° - 258°</td>
</tr>
</tbody>
</table>

The patent reports a m.p. 257° for the methyl iodide quaternary salt of the "tetrahydrocarboline" prepared by this method.

2. At 150° - 160° in the absence of a diluent

2-Chlorocyclohexanone (5 g.) was added dropwise with stirring to 2-aminopyridine (10.6 g., 3 mols.) at 150° - 160°C. The temperature rose rapidly during the addition, the mixture darkened in colour, and began to boil gently. The resultant viscous brown syrup was dissolved in hot water, the solution made alkaline with sodium hydroxide and the oil which
separated was extracted with benzene. The brown syrup obtained on evaporation of the dried benzene solution resisted attempts at crystallisation, probably because of the excess 2-aminopyridine present, and purification was effected by the chromatographic method employed in 1 b. The condensation product was obtained as a buff coloured solid of m.p. 45° - 50°. Recrystallisation from a mixture of benzene and light-petroleum (60° - 80°) gave colourless cubes.

Yield - 1.2 g. (17%) m.p. 56° - 58°.

3. At the b.p. of 2-aminopyridine

2-Chlorocyclohexanone (8 g.) was added to 2-aminopyridine (11.4 g., 2 mols.) at the b.p. as in 2, and the mixture was refluxed gently for 15 minutes after all the chloroketone had been added. It was found that the excess 2-aminopyridine was much more readily removed by dissolving the product in water, making the solution alkaline with sodium hydroxide and distilling in steam until the distillate was free from aminopyridine. The residue was extracted with benzene, dried and distilled in vacuo to give the condensation product as a yellow syrup which slowly crystallised.

Yield - 7.4 g. (65%) m.p. 45° - 65°

Recrystallisation from an ether-light-petroleum mixture gave colourless cubes, m.p. 56° - 58°.

Repeat analysis

Found C, 69.74; H, 7.35; N, 15.2.

Mol. weight (M) - 174.
At this stage it was discovered that the pyridotetrahydrobenzimiazole was crystallising with one molecule of water of crystallisation, and therefore giving analysis results indicating a molecular formula $\text{C}_{11}\text{H}_{14}\text{ON}_{2}$.

Calc. for $\text{C}_{11}\text{H}_{12}\text{N}_{2}\text{H}_{2} \text{O}$: C, 69.45; H, 7.42; N, 14.7; M, 190

Found (i) C, 70.00; H, 7.50; N, 15.4

(ii) C, 69.74; H, 7.33; N, 15.2; M, 174

The presence of the water of crystallisation was indicated by the change in m.p. brought about by dehydration of the compound in vacuo, and the accompanying change in weight corresponding approximately to one molecule of water per mole of the pyridotetrahydrobenzimiazole. Approximately 0.1 g. of the hydrate was dehydrated in vacuo (ca. 20 mm.) over phosphorous pentoxide for 48 - 72 hour periods until the weight fell to a constant value, and finally dried in high vacuo (0.05 mm.) to ensure complete removal of water.

Wt. of crucible - 4.55297 g.

" " " + hydrate - 4.66003 g.

:. Wt. of hydrate - 0.10706 g.

Wt. of crucible after 72 hr. in vacuo - 4.65535 g.

" " " 120 " " " - 4.65441 g.

" " " 168 " " " - 4.65400 g.

" " " 240 " " " - 4.65382 g.

18 hr. in high vacuo - 4.65384 g.

:. Wt. of anhydrous compound - 0.10087 g.
Wt. of crucible after attaining equilibrium in atmosphere - 4.66410 g.

Gain in weight due to hydration - 0.01027 g.

Theoretical gain for one molecule of \( \text{H}_2\)O - 0.01054 g.

m.p. of anhydrous \( \text{C}_{11}\text{H}_{12}\text{N}_2 \) - 95° - 96° (pat. 95°)

m.p. of hydrate \( \text{C}_{11}\text{H}_{12}\text{N}_2\cdot\text{H}_2\text{O} \) 56° - 58° (loses water at 120° - 125°)

The patent assigns to this condensation product of 2-aminopyridine and 2-chlorocyclohexanone a tetrahydrocarboline structure, and quotes only the m.p. of the anhydrous substance making no mention of the fact that it takes up water readily to form a monohydrate. This water of crystallisation seems to be readily removed during the formation of the picrate, as the analysis of this compound is in close agreement with the theoretical figure for the anhydrous pyridotetrahydrobenziminazole.

Preparation of 5'-Methylyridine-(1': 2': 1: 2)-4: 5: 6: 7-tetrahydrobenziminazole

1. In boiling alcohol

2-Amino-3-methylpyridine (5 g.) and 2-chlorocyclohexanone (7.7 g., 1.2 mols.) were refluxed in alcohol (50ml.) for 28 hours, and the solvent was evaporated until the crystallisation of the hydrochloride of the condensation product commenced. Addition of ether in small quantities with shaking completed this partial precipitation.

Yield - 6.5 g. (65%) m.p. 235° - 237°
The hydrochloride (5 g.) was converted to the free base by dissolving in water and making the solution alkaline with sodium hydroxide, when the 3'-methylpyridotetrahydrobenzimidazole separated as a mass of colourless needles.

Yield 3.75 g. (90%) m.p. 60° - 61°

The compound was very soluble in the common organic solvents, but crystallised readily from water as the dihydrate in long colourless needles m.p. 58° - 61° (loses H₂O at 115°)

Analysis

C₁₂ H₁₄ N₂ · 2H₂ O requires C, 64.82; H, 8.16; N, 12.6

Found C, 64.33; H, 8.04; N, 12.7.

Picrate: yellow plates from alcohol, m.p. 155° - 158°

C₁₈ H₁₇ O₇ N₅ requires N, 18.1

Found N, 16.9, 17.3.

Dehydration in vacuo

Loss in weight on dehydration - 0.0115 g.
Gain " " hydration - 0.00567 g.

Theoretical change for two molecules H₂O - 0.00801 g.

2. At the b.p. of 2-amino-3'-methylpyridine

2-Chlorocyclohexanone (5 g.) was added dropwise with stirring to gently boiling 2-amino-3'-methylpyridine (9.6 g., 2 moles), and the product was treated as in the case of 2-aminopyridine. After removal of the excess amine by steam distillation, the residue was dried and distilled in vacuo to give the anhydrous 3'-methylpyridotetrahydrobenzimidazole as a pale yellow syrup which rapidly crystallised.
Yield 3.4 g. (48%) b.p. 230° - 240°/143 mm. m.p. 85° - 87°.

When this anhydrous 3'-methylpyridotetrahydrobenzimidazole was crystallised from water, the dihydrate, m.p. 52° - 54° (no depression with product from 1) separated in long colourless needles.

Condensation of 2-amino-6-methylpyridine and 2-chlorocyclohexanone.

There is the possibility that this 6-methyl group will exercise a steric effect and prevent ring closure at the nitrogen atom.

2-Amino-6-methylpyridine (4 g.) was heated to 160°, and the stirred liquid treated dropwise with 2-chlorocyclohexanone (5 g.). The mixture boiled gently during the addition period, and finally solidified to a hard yellow mass. Recrystallisation from alcohol-ether gave the condensation product hydrochloride in the form of colourless prisms.

Yield 4.5 g. (55%) m.p. >300°

Analysis Found  C,62.38; H,6.81; N,12.7; Cl,16.33
C_{12}H_{15}N_{2}Cl requires  C,64.71; H,6.79; N,12.6; Cl,15.92

Decomposition of the salt with sodium hydroxide gave a yellow oil which was extracted with ether and dried. Evaporation gave the parent base as a yellow syrup which gradually crystallised.
Yield 2.3 g.  

m.p. 51° - 53°.

Recrystallisation from ether gave yellow prisms, m.p. 51° - 53°.

Analysis  

<table>
<thead>
<tr>
<th>Substance</th>
<th>Required</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₁₂H₁₄N₂</td>
<td>C, 77.58; H, 7.74; N, 15.0</td>
<td>C, 73.43; H, 7.63; N, 14.7</td>
</tr>
<tr>
<td>C₁₂H₁₄N₂.2H₂O</td>
<td>C, 77.58; H, 7.74; N, 15.0</td>
<td>C, 73.79; H, 7.74; N, 14.4</td>
</tr>
</tbody>
</table>

Picrate: long yellow prisms from alcohol-glacial acetic acid, m.p. 204° - 206°.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Required</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₁₈H₁₇O₂N₅</td>
<td>N, 16.8</td>
<td>N, 16.4</td>
</tr>
</tbody>
</table>

Oxidation of condensation product

The base (1 g.), water (30 ml.) and 2N. sodium carbonate (1 ml.) were brought to the boiling-point, and the emulsion was treated dropwise with potassium permanganate (120 ml., 1%). Filtration, extraction with ether, and evaporation of the dried extract gave a brown syrup which failed to crystallise, but which readily formed a picrate in benzene solution, m.p. 160° - 190°. Two recrystallisations from alcohol-glacial acetic acid gave yellow prisms, m.p. 189° - 199°, the melting point of which was not depressed on mixing with the picrate of the initial condensation product.

The ether extracted aqueous layer on evaporating almost to dryness at room temperature deposited a felt of colourless needles, m.p. 165° - 166°, which crystallised readily from water, m.p. 167° - 168°.

Analysis  

<table>
<thead>
<tr>
<th>Substance</th>
<th>Required</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₇H₉O₂N</td>
<td>C, 60.41; H, 6.52; N, 10.1</td>
<td>C, 61.31; H, 6.72; N, 10.4</td>
</tr>
</tbody>
</table>
The compound dissolved in boiling water but appeared to be negligibly soluble in the cold. It dissolved readily in cold sodium hydroxide and acid, however, and probably contains both a carboxyl and basic nitrogen grouping.

**Bromination of 2-Aminopyridine**

2-Aminopyridine (20 g.) was brominated in sulphuric acid by the method of Tschitschibabin (Chem. Zentr., 1923, III, 1021), and the mixture of 2-amino-5-bromo- and 2-amino-3:5-dibromopyridine was separated by extraction with light-petroleum (80° - 100°) in which the former is only slightly soluble. Repeated recrystallisations from alcohol and benzene respectively gave the 2-amino-3:5-dibromopyridine as buff coloured needles, m.p. 104° - 106° (lit. 105°); and the 2-amino-5-bromopyridine as colourless plates, m.p. 137° - 138° (lit. 137°).

**Preparation of 3':5'-Dibromopyrido-(1':2':1:2)-4:5:6:7-tetrahydrobenzimidazole**

2-Amino-3:5-dibromopyridine (5 g.) and 2-chlorocyclohexanone (4 g., 1½ mols.) were refluxed in alcohol (30 ml.) for 26 hours. Evaporation of the solvent and addition of ether precipitated the hydrochloride of the dibromopyrididotetrahydrobenzimidazole which was dissolved in water and treated with sodium hydroxide to yield the parent base

Yield 2.4 g. (37%) m.p. 153° - 156°.
Recrystallisation from light-petroleum \((100^\circ\text{C} - 120^\circ\text{C})\) gave colourless needles of the dibromo compound, m.p. \(159^\circ\text{C} - 160^\circ\text{C}\)

**Analysis**

\[
\begin{align*}
C_{11}H_{10}N_2Br_2 & \text{ requires } C, 40.00; H, 3.05; N, 8.49; Br, 48.42 \\
& \text{ Found } C, 40.51; H, 3.45; N, 8.43; Br, 47.90.
\end{align*}
\]

**Picrate:** yellow needles from alcohol-glacial acetic acid, m.p. \(167^\circ\text{C} - 169^\circ\text{C}\).

\[
\begin{align*}
C_{17}H_{13}O_7N_5Br_2 & \text{ requires } N, 12.4 \\
& \text{ Found } N, 12.5.
\end{align*}
\]

**Preparation of 5'-Bromopyrido-(1':2';1:2)-4:5:6:7-tetrahydrobenzimidazole.**

1. **In boiling alcohol**

2-Amino-5-bromopyridine (5 g.) and 2-chlorocyclohexanone (5.8 g., \(\frac{1}{2}\) mols.) were condensed in boiling alcohol as in the previous experiment.

**Yield of hydrochloride** 7.3 g. (83%) m.p. \(260^\circ\text{C} - 262^\circ\text{C}\).

Decomposition of an aqueous solution of the hydrochloride with sodium hydroxide gave the 5'-bromopyridotetrahydrobenzimidazole

**Yield** 5.8 g. (90%) m.p. \(148^\circ\text{C} - 149^\circ\text{C}\).

The base crystallised readily from light-petroleum \((100^\circ\text{C} - 120^\circ\text{C})\) in small colourless prisms, m.p. \(148^\circ\text{C} - 149^\circ\text{C}\).

**Analysis**

\[
\begin{align*}
C_{11}H_{11}N_2Br & \text{ requires } C, 52.60; H, 4.42; N, 11.2; Br, 51.82 \\
& \text{ Found } C, 52.85; H, 4.40; N, 10.3; Br, 51.19.
\end{align*}
\]
Picrate: yellow needles from glacial acetic acid, m.p. 264\(^\circ\) - 265\(^\circ\) (d)

\[ C_{17} H_{14} O_{7} N_{5} Br \] requires N, 14.6

Found N, 16.4, 13.7.

2. In the absence of a diluent.

2-Amino-5-bromopyridine (1.5 g.) was treated dropwise at 160\(^\circ\) - 170\(^\circ\) with 2-chlorocyclohexanone (1.2 g., 1 mol.) as in previous experiments of this type. A vigorous reaction set in and the mixture boiled briskly during the addition, eventually setting to a semi solid mass which was maintained at 160\(^\circ\) - 170\(^\circ\) for 15 minutes. The product was dissolved in hot dilute hydrochloride acid and filtered, neutralisation of the filtrate precipitating the 5'-bromopyridotetrahydrobenzimazol as a brown oil which rapidly crystallised.

Yield 1.7 g. (73%) m.p. 138\(^\circ\) - 142\(^\circ\)

No depression with product from 1.

Nitration of 2-aminopyridine

2-Aminopyridine was nitrated in sulphuric acid according to the method of Phillips (J. Chem. Soc. 1941, 12), but the separation of the 2-amino-3-nitropyridine and 2-amino-5-nitropyridine by repeated fractional crystallisation from alcohol proved such a tedious and wasteful process that the 3-nitro isomer was obtained only in very small yield. The higher melting 5-nitro isomer, however, which is less soluble in alcohol was readily obtained by allowing
the mixture to crystallise from this solvent. When
the bulk of the 2-amino-5-nitropyridine had been
removed, the mother liquor was evaporated and the
residue was extracted with light-petroleum (100° -
120°) to give the 2-amino-5-nitropyridine:
2-amino-5-nitropyridine - yellow leaflets from
alcohol, m.p. 186° - 188° (lit. 188°).
2-amino-3-nitropyridine - yellow plates from light-
petroleum (100° - 120°), m.p. 158° - 160° (lit. 162°).

Attempted condensation of 2-amino-3-nitropyridine and
2-chlorocyclohexanone.

The conditions employed for this trial
condensation were those outlined in the patent for
the analogous reaction with 2-amino-5-nitropyridine.

2-Amino-3-nitropyridine (1.2 g.) and 2-chloro-
cyclohexanone (1.1 g., 1 mol.) were melted together,
and the temperature of the mixture was gradually
raised. At 120° - 130° a vigorous reaction
commenced and the reactants began to boil briskly,
at the same time darkening considerably in colour.
The black coloured residue remaining when the
reaction had subsided, however, failed to yield any
3'-nitropyridotetrahydrobenzimidazole on repeated
extraction with hydrochloric acid.

Preparation of 5'-Nitropyrido-(1': 2': 1 : 2)-4 : 5 :
6 : 7-tetrahydrobenzimidazole.

![Chemical structure](image)
2-Amino-5-nitropyridine (3.0 g.) and 2-chlorocyclohexanone (2.9 g., 1 mol.) were warmed together as in the previous experiment, and the residual mass obtained after the reaction had subsided was maintained at 130° for two hours. The black coloured product was dissolved in boiling dilute hydrochloric acid (25 ml.), charcoaled and filtered. On making the filtrate alkaline with sodium hydroxide, a pale brown solid of indefinite m.p. separated, but recrystallisation form alcohol (charcoal) gave the 5'-nitropyridotetrahydrobenziminazole as a mass of orange-yellow needles.

Yield 1.4 g. (30%) m.p. 214° - 215° (pat. 210°)

Analysis

Calc. for C₁₁ H₁₁ O₂ N₃ C, 60.81; H, 5.10; N, 19.5.
Found   C, 60.61; H, 5.11; N, 19.5.

Picrate: yellow needles from alcohol-glacial acetic acid, m.p. 216° - 219° (d).

\[
\text{C}_{17} \text{H}_{14} \text{O}_{9} \text{N}_6 \quad \text{requires N, 18.8}
\]

\[
\text{Found } \quad \text{N, 18.2.}
\]

Attempted dehydrogenation of Pyridotetrahydrobenziminazole and its derivatives.

Several trial experiments with chloranil in boiling xylene showed that pyridotetrahydrobenziminazole and its 3': 5'-dibromo and 5'-nitro
derivatives all gave an insoluble red resinous product as soon as the xylene solution was brought to the boiling point. The following method employing 5% palladised charcoal (cf. Horning, Horning & Walker. J.A.C.S. 1948, 70, 3935) was found to be effective in the case of the unsubstituted pyridotetrahydrobenzimidazole, however.

The freshly distilled base (1 g.) and palladised charcoal (0.5 g.) were heated in a metal bath at 300° for six hours, and the residue was thoroughly extracted with boiling acetone. The solid obtained on evaporation (0.9 g.) had a very indefinite melting point, and it was decided to attempt purification by chromatographic methods. A solution in benzene (40 ml.) was washed through an alumina column (24" X 1"), benzene being used for development. A distinct separation into two main bands was achieved, an upper pale green practically non-fluorescent band surmounting a colourless strongly violet fluorescent band. When a distinct separation of the bands was discernible in ultra-violet light, the column was dried and cut, each extruded portion being extracted with a mixture of alcohol and benzene. The extract of the lower colourless band yielded a small amount of the starting product on evaporation, but the upper band gave a pale green, somewhat sticky solid of m.p. 120° - 150°. Recrystallisation from benzene gave long, needle-shaped prisms of pyridobenzimidazole, slightly green in colour despite the use of charcoal.
in the recrystallisation.

Yield 0.2 g. (20%) m.p. 176° - 177° (lit. 178°).

Analysis

<table>
<thead>
<tr>
<th></th>
<th>Found</th>
<th>Calc. for C_{11}H_{8}N_{2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>78.50; H, 4.63; N, 17.1</td>
<td>C, 78.54; H, 4.79; N, 16.7</td>
</tr>
</tbody>
</table>

Preparation of N-methyl-α-pyridone-imine

\[
\text{2-Aminopyridine (20 g.) and methyl-iodide (34 g.) were allowed to react at room temperature as recommended by Tschitschibabin (Ber. 1921, 54, 817). The methiodide obtained after the very vigorous reaction had abated was recrystallised from alcohol.}
\]

Yield 26 g. (48%) m.p. (after drying in vacuo) 148° - 150° (lit. 149° - 150°).

Decomposition of the salt (24 g.) in water with silver oxide by Tschitschibabin's method, and evaporation and distillation of the residue gave the N-methyl-α-pyridone-imine as a pale yellow syrup which darkened rapidly in the atmosphere.

Yield 5 g. (46%) m.p. 145° - 147°/80 mm. 118° - 120°/25 mm. (lit. 108°/16 mm.)

Analysis

<table>
<thead>
<tr>
<th></th>
<th>Calc. for C_{6}H_{8}N_{2}</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>66.64; H, 7.45; N, 25.9</td>
<td>C, 65.12; H, 7.60; N, 25.3</td>
</tr>
</tbody>
</table>

Picrate: yellow prisms from alcohol-glacial acetic acid, m.p. 202° - 204° (lit. 201°)

Benzoyl derivative: colourless prisms from light-
petroleum (100° - 120°), m.p. 68° - 70° (lit. 70°).

**Attempted condensation of 2-chlorocyclohexanone and N-methyl-α-pyridone-imine.**

N-Methyl-α-pyridone-imine (4 g.) and 2-chlorocyclohexanone (5 g., 1 mol.) were refluxed in alcohol (25 ml.) for three hours. Evaporation of most of the solvent and addition of ether initiated precipitation of a colourless hydrochloride.

**Yield 2.4 g.  m.p. 108° - 110°.**

Recrystallisation from alcohol gave colourless prisms, m.p. 110° - 112°. (Tschitschibabin reports a m.p. 110° for the hydrochloride of N-methyl-α-pyridone-imine).

**Analysis**

Found  C, 44.00; H, 6.72; N, 16.7

C₆H₈N₂HCl requires  C, 49.81; H, 6.27; N, 19.4

C₆H₈N₂HCl.H₂O requires  C, 44.52; H, 6.82; N, 17.2.

These results indicate that no condensation reaction has taken place, but instead, the imino compound has removed the elements of hydrochloric acid from the 2-chlorocyclohexanone. Tschitschibabin (Ber. 1921, 54, 819) reports the preparation of this N-methyl-α-pyridone-imine hydrochloride and quotes a m.p. 110° in agreement with the above figure, but the chlorine analysis which he carried out gave no indication that the hydrochloride crystallised as a monohydrate. In view of the more complete analysis given above, however, it must be assumed that N-methyl-α-pyridone-imine hydrochloride crystallises with one
molecule of water of crystallisation.

A repetition of the trial condensation in alcohol in the presence of sodium carbonate again gave the pyridone-imine hydrochloride, the organic compound evidently being a stronger base than sodium carbonate. When the hydrochloride itself was refluxed with 2-chlorocyclohexanone for lengthening periods up to 20 hours, no reaction occurred.

**Preparation of 2-Methylaminopyridine**

After several unsuccessful attempts to prepare 2-methylaminopyridine by the methods of Tschitschibabin (Ber., 1928, 61, 427 and 2215), the procedure of Seeger and Anderson (J.A.C.S. 1949, 71, 340) was adopted.

2-Bromopyridine (20 g.) and a 33% W/W solution of methylamine in alcohol (11.8 g.) were heated in a sealed tube at 150° for twelve hours. The resultant semi-solid mass was heated with sodium hydroxide and extracted with ether, and the extract was dried and distilled. A pale yellow distillate smelling strongly of 2-bromopyridine was obtained.

**Yield** 11 g. (94%)  **b.p.** 192° - 196° (lit. 200°)

**Picrate:** yellow needles from glacial acetic acid,  
**m.p.** 192° - 193° (lit. 190°).

**Calc.** for **C₁₂H₁₁O₇N₅** N, 20.8  
**Found**  N, 20.4.

Seeger and Anderson give no method for the removal of 2-bromopyridine from the product, and it would seem advisable to use excess methylamine.
Attempted condensation of 2-Methylaminopyridine and 2-chlorocyclohexanone.

2-Methylaminopyridine (2.7 g.) and 2-chlorocyclohexanone (3.5 g.) in alcohol (12 ml.) were boiled under reflux for five hours, and the solution was evaporated and cooled. No crystallisation occurred, and on addition of ether a brown oil separated. The solution was again evaporated, and the residue was warmed with sodium hydroxide and extracted with ether. The extract gave a pale yellow syrup (2.7 g.) which readily formed a picrate, m.p. 193° - 194°, whose m.p. was not depressed by admixture with the picrate of 2-methylaminopyridine.

A repetition of the condensation at the b.p. of the methylaminopyridine resulted in copious hydrochloric acid evolution, the mixture simultaneously darkening rapidly in colour.

Isolation of the product as above, again gave unchanged 2-methylaminopyridine; picrate m.p. 192° - 193°, along with a dark coloured, ether insoluble syrup which was not investigated.
**SECTION B**

Condensation of 2-Aminopyridine and its Derivatives with 2-Chlorocyclohexanone in the presence of Sodium Carbonate

*Preparation of 2-(2'-Pyridylamino)-cyclohexanone*

![Chemical structure](image)

2-Chlorocyclohexanone (5 g.), 2-aminopyridine (4.5 g.) and sodium carbonate (3 g.) (reactants in mol. ratio 2 : 2.5 : 3) were boiled under reflux with alcohol (15 ml.) for three hours. Filtration and evaporation of the solvent gave a colourless, flocculent precipitate of 2-(2'-pyridylamino)-cyclohexanone.

**Yield 2.1 g. (30%) m.p. 145° - 147°.**

Recrystallisation from alcohol gave fine colourless needles, m.p. 147° - 149° (pat. 147°).

**Analysis**

Calc. for C₁₁H₁₄ON₂ C, 69.45; H, 7.42; N, 14.7

Found C, 69.05; H, 7.46; N, 15.2.

**Dinitrophenylhydrazone:** rosettes of small orange needles from alcohol-glacial acetic acid, m.p. 164° - 165° (d). This derivative was prepared by Brady's method and appears to consist chiefly of the hydrosulphate of the dinitrophenylhydrazone.

**Analysis**

C₁₇H₂₀O₈N₆S requires N, 18.0; S, 6.84
Found  N,16.4; S,6.13.

The mother liquor from the original crystallisation was evaporated and the residue was distilled in vacuo to discover if any of the isomeric N-(2'-cyclohexanone)-α-pyridone-imine had been formed in addition to the 2-(2'-pyridylamino)-cyclohexanone. The only products obtained were excess 2-aminopyridine (b.p. 110°-120°/56 mm.), and a fraction, b.p. 210°-220°/56 mm., which gradually solidified to a product whose m.p. was not depressed by mixing with pyrido (1': 2': 1 : 2)-tetrahydrobenzimidazole.

Although the weakly basic properties of this condensation product support the contention that it possesses the 2-(2'-pyridylamino) cyclohexanone structure, it was decided to carry out several experiments to ensure that it was not the isomeric N-(2'-cyclohexanone)-α-pyridone-imine.

**Attempted hydrolysis with sodium hydroxide**

![Diagram](image)

The intermediate compound (0.7 g.), sodium hydroxide (5 g.) and water (5 ml.) were brought to the boiling-point and enough alcohol was added to produce a homogeneous solution (cf. Tschitschibabin Ber. 1921, 54, 819; hydrolysis of N-methyl-α-pyridone-imine).

There was no evidence of ammonia evolution at
the boiling-point, but the mixture was refluxed for nine hours, diluted with water and extracted with ether. Evaporation of the dried extract yielded a brown oil which crystallised on trituration with alcohol to give a colourless solid, m.p. 154° - 156°. Recrystallisation from alcohol gave colourless rhombic plates, m.p. 157° - 158°.

**Analysis**  Found C,68.26; H,8.38; N,14.4.

The high nitrogen percentage excludes the possibility of hydrolysis of an imino group, and the increased figure for hydrogen suggests some form of reduction, probably at the ketone group. The corresponding secondary alcohol \( \text{C}_{11} \text{H}_{16} \text{ON}_2 \) requires C,68.71; H,8.39; N,14.6.

**Reduction of Ketone Group in 2-(2'-Pyridylamino)cyclohexanone by the method of Meerwein and Ponsdorf.**

![Chemical reaction diagram]

As the commercial aluminium isopropoxide used in the reduction was found to have undergone considerable decomposition, the following method had to be adopted. Aluminium isopropoxide (20 g.) was extracted at the b.p. for several minutes with dry isopropyl alcohol (60 ml.), and the solution obtained on filtering was added to the ketone (1.5 g.). The mixture was brought to the b.p. and kept refluxing gently until acetone could no longer be detected in the distillate.
A Hahn partial condenser (Organic Reactions, Vol. II, p. 197) was used to allow distillation of acetone with minimum loss of isopropyl alcohol, methanol instead of the recommended ethanol being found more efficient in effecting this separation. After one hour the distillate no longer gave a precipitate with the 0.2% dinitrophenylhydrazine test reagent, and the residue left after evaporation of the alcohol was boiled for several minutes with 10% sodium hydroxide (60 ml.). The reduction product remained as a colourless solid.

Yield 1.3 g. (86%) m.p. 150° - 160° (not raised by recrystallisation from alcohol)

A mixed m.p. with the product obtained by the sodium hydroxide treatment of 2-(2'-pyridylamino)-cyclohexanone showed no depression.

Attempted reduction of the Ketone group in 2-(2'-Pyridylamino)-cyclohexanone by Clemmensen's method.

\[
\text{[Diagram of reaction]} \quad \text{Zn} + \text{HCl} \rightarrow \text{[Product]} 
\]

A solution of the ketone (1 g.) in alcohol (40 ml.) was added in 5 ml. portions to zinc amalgam (ca 25 g.) in water (3 ml.) and concentrated hydrochloric acid (7 ml.) at reflux temperature, concentrated hydrochloric acid (10 ml.) being gradually added simultaneously. (cf. Organic Reactions Vol. I, p. 164). On completion of the addition,
the mixture was boiled for seven hours. Decantation of the acid layer followed by neutralisation with caustic soda and extraction with ether gave a pale yellow solid. Crystallisation from light-petroleum (100° - 120°) gave colourless needles, m.p. 130° - 142°. Mixed m.p. with starting product - no depression.

A repetition of the reduction in the absence of alcohol was also attempted. The ketone (2.5 g.) in water (25 ml.) and concentrated hydrochloric acid (55 ml.) was boiled with zinc amalgam (ca. 25 g.) for ten hours, concentrated hydrochloric acid being added in 25 ml. portions every three hours. Treatment as previously gave a yellow syrup which failed to crystallise Yield - 1.5 g.

The syrup readily formed a picrate, yellow needle-shaped prisms from alcohol-glacial acetic acid, m.p. 218° - 221° (d); and a benzoyl derivative, colourless needles from alcohol, m.p. 167° - 169°; the melting points of which suggested that the reduction product was 2-aminopyridine (lit. picrate, m.p. 217°; dibenzoyl derivative, m.p. 167.5° - 169°). This was confirmed by analysis of the benzoyl derivative,

Found C,75.48; H,4.71; N,9.77
Calc. for dibenzoylaminopyridine C,75.50; H,4.67; N,9.27

and a mixed melting point determination with authentic dibenzoylaminopyridine which showed no depression.
Reduction of 2-(2'-Pyridylamino)-cyclohexanone by
the Wolff-Kishner method.

To avoid the use of a sealed tube in the
decomposition of the hydrazone, the modification of
the Wolff-Kishner method developed by Huang-Minlon
(J.A.C.S. 1946, 68, 2487) was adopted. The ketone
(2.8 g.), sodium hydroxide (2 g.) and 90% hydrazine
hydrate (5 ml.) were refluxed with trimethylene
glycol (40 ml.) for one hour, and excess hydrazine and
water were distilled off until the temperature of the
boiling liquid reached 200°. The residual solution
was boiled for four hours, cooled and diluted with
water when the reduction product crystallised as a
mass of colourless plates.

Yield 0.9 g. (35%) m.p. 125° - 126°.

Extraction of the mother liquor with ether
failed to increase the yield of this reduction
product, which would appear to be 2-cyclohexylamino-
pyridine (lit. m.p. 123° - 124°).

Preparation of 2-Cyclohexylaminopyridine

Although Bergstrom (J. Org. Chem., 1946, 11,
244) has shown that 2-cyclohexylaminopyridine can be
prepared by heating 2-bromopyridine and cyclohexyl-
amine in a sealed tube at 180°, it was decided to
attempt the condensation by refluxing the reactants
together under atmospheric pressure.

A mixture of 2-bromopyridine (5 g.) and cyclohexylamine (9.5 g., 3 mols.) was boiled for six hours, and the cooled mixture was dissolved in pyridine (10 ml.) and warmed with powdered sodium hydroxide to decompose any cyclohexylamine hydrobromide present. Evaporation of the pyridine and excess cyclohexylamine, and distillation of the residue gave a considerable amount of unchanged 2-bromopyridine (b.p. 105° - 110°/44 mm.), and only a small amount of condensation product which solidified in the side arm of the distillation flask.

Yield 0.8 g. (14%) m.p. 125° - 126° (lit. 123°-124°).

Recrystallisation from light-petroleum (80° - 100°) gave clusters of colourless needles, m.p. 125° - 126°.

Analysis

Found C,74.82; H,8.79
Calc. for C_{11}H_{16}N_{2} C,74.96; H,9.15
Benzoyl derivative: colourless needles from alcohol, m.p. 129° - 130°.

Found C,77.00; H,7.13; N,9.76
C_{18}H_{20}ON_{2} requires C,77.11; H,7.19; N,9.99
Picrate: yellow needles from alcohol-glacial acetic acid, m.p. 185° - 187°.

Found N,17.2
C_{17}H_{19}O_{7}N_{5} requires N,17.3

A mixed melting-point of this authentic 2-cyclohexylaminopyridine and the reduction product
obtained in the previous experiment gave no depression, proving that the reduction had indeed given 2-cyclohexylaminopyridine, and also that the intermediate ketone has the 2-(2'-pyridylamino)-cyclohexanone structure and not the alternative, isomeric pyridoneimine form.

**Attempted preparation of 2-(6'-Methyl-2'-pyridylamino)-cyclohexanone.**

2-Amino-5-methylpyridine (2.5 g.), 2-chlorocyclohexanone (4.6 g., 1½ mol.) and sodium carbonate (1.9 g., 1½ mol.) were heated in boiling alcohol (20 ml.) for three hours. Filtration and evaporation gave a brown syrup which failed to crystallise, and which was purified by chromatography through alumina (18" X 1") with benzene. Development of the column showed no band separation, but collection of the eluate in 30 ml. portions proved that a separation into two main fractions had occurred. One consisted chiefly of unchanged 2-amino-5-methylpyridine and a 2-chlorocyclohexanone degradation product which was not further investigated. It readily decolourised alkaline potassium permanganate in the cold and is probably Δ2-cyclohexenone. The second fraction crystallised from the benzene solution as a mass of colourless needles.

Yield 2.0 g. (46%) m.p. 59° - 61°.

A mixed melting point with 3'-methylpyridotide-tetrahydrobenzimidazole showed no depression.
indicating that cyclization of the intermediate compound has occurred.

**Attempted preparation of 2-(5'-Bromo-2'-pyridylamino)-cyclohexanone.**

Preliminary experiments showed that no appreciable reaction had occurred after three hours in boiling alcohol and the reflux period was therefore increased. 2-Amino-5-bromopyridine (5.8 g.), 2-chlorocyclohexanone (6.4 g.) and sodium carbonate (2.5 g.) were heated in boiling alcohol (25 ml.) for twelve hours, and the syrupy residue obtained on evaporating the filtered mixture was dissolved in chloroform and dried. Evaporation gave a brown very viscous syrup which only partly dissolved in boiling ether leaving a black tarry residue. From the ether extract 5'-bromopyridotetrahydrobenzimidazole crystallised as colourless prisms showing that cyclization had again taken place.

*Yield 1.5 g. (17%) m.p. 147° - 148°.*

**Attempted preparation of 2-(3': 5'-Dibromo-2'-pyridylamino)-cyclohexanone.**

2-Amino-3': 5'-dibromopyridine (2.8 g.), 2-chlorocyclohexanone (2.2 g.) and sodium carbonate (0.9 g.) were refluxed in alcohol (15 ml.) for eighteen hours and the condensation product isolated as before. Colourless needles of 3': 5'-dibromopyridotetrahydrobenzimidazole separated from the ether on cooling.

*Yield 1.1 g. (30%) m.p. 159° - 160°.*
Conclusion  The results of these condensations in the presence of sodium carbonate indicate that only in the case of unsubstituted aminopyridine is it possible to isolate the intermediate 2-(2'-pyridylamino)-cyclohexanone.

Cyclization of 2-(2'-Pyridylamino)-cyclohexanone

1. In acetic anhydride (Brit. patent 360,027).

   The ketone (0.9 g.) and acetic anhydride (1.6 g.) were boiled for three hours, and the mixture was cooled and poured into water. Neutralisation of the solution with sodium carbonate caused the separation of a brown oil which slowly crystallised. Extraction of the dried solid with light-petroleum (40° - 60°) gave the tricyclic pyridotetrahydrobenzimazole as colourless cubes, m.p. 56° - 58° which did not depress the m.p. of the specimen prepared previously.

   The petroleum insoluble residue crystallised from alcohol in the form of yellow prisms, m.p. 158° - 159°.

Analysis  Found C, 73.07; H, 6.52; N, 7.27.

   The nature of this compound has not yet been discovered.

2. In acetic acid saturated with hydrobromic acid (cf. France, Tucker and Forrest J. 1945, 9.)

   The ketone (2.5 g.) was dissolved in glacial acetic acid (25 ml.) and dry hydrobromic acid was bubbled through the cold solution for one hour. Neutralisation of the acid mixture with sodium hydroxide and extraction of the resultant emulsion
with ether gave the pyridotetrahydrobenzimidazole as colourless cubes:

Yield 2.1 g. (64%) m.p. 54° - 58°.
SECTION C

Condensation of Bromoacetone and W-Chloroacetophenone with 2-Aminopyridine and its Derivatives

Bromination of acetone

Acetone (50 ml.) in acetic acid solution was treated with bromine (36 ml.) (Organic Synthesis Vol. X p. 12), and the bromoacetone obtained as a colourless, strongly lachrymatory liquid which darkened considerably on long exposure to the air.

Yield 21 g. (21%) b.p. 55° - 58°/35 mm. (lit. 40° - 42°/15 mm.)

Preparation of 2-Methylpyriminazole

Bromoacetone (15 g.) in alcohol (20 ml.) was treated with 2-aminopyridine (10 g.) according to the method of Tschitschibabin (Ber. 1926, 59, 2054), and the 2-methylpyriminazole obtained as a pale yellow syrup which tended to assume a pink colour on exposure to the air.

Yield 1.5 g. (10%) b.p. 134° - 136°/15 mm. (lit. 148° - 150°/20 mm.)

Analysis

Found C, 71.91; H, 6.81; N, 21.3
Calc. for C₈H₈N₂ C, 72.71; H, 6.10; N, 21.2
Preparation of 2:8-Dimethylpyriminazole

In view of the low yield obtained in the previous experiment the procedure of Tschitschibabin was modified, a longer period of reflux being tried.

2-Amino-3-methylpyridine (5 g.) and bromoacetone (6.3 g., 1 mol.) were refluxed in alcohol (30 ml.) until the smell of bromoacetone could scarcely be detected (ca. 25 hours).

Evaporation of the alcohol and addition of ether precipitated the 2:8-dimethylpyriminazole hydrochloride as a pale yellow mass.

Yield 3.4 g. (80%) m.p. 248° - 250°.

Decomposition of its aqueous solution with sodium hydroxide gave a mass of colourless needles of the free base.

Yield 4 g. (62%) m.p. 42° - 45°.

The 2:8-dimethylpyriminazole was very soluble in the common organic solvents, only crystallising from light-petroleum (40° - 60°) when most of the solvent had evaporated to give colourless crystals which rapidly assumed a pink tinge. The base crystallised readily from water, however, as long colourless needles, (m.p. 42° - 45°) which only turned pink after exposure to the air for several days.
Analysis

Found C, 61.65; H, 7.51; N, 16.4
C₉H₁₀N₂, 1½H₂O requires C, 62.41; H, 7.57; N, 16.2
C₉H₁₀N₂, H₂O requires C, 65.84; H, 7.36; N, 17.1
C₉H₁₀N₂, 2H₂O requires C, 59.32; H, 7.74; N, 15.4

Picrate: yellow prisms from alcohol-glacial acetic acid, m.p. 192° - 194°.

C₁₅H₁₃O₇N₅ requires N, 18.7

Found N, 18.8

Loss in weight on dehydration 0.01784 g.
Gain in weight on hydration 0.00296 g.
Theoretical gain for uptake of 1½ molecules of water 0.00302 g.

Preparation of 2-Methyl-6 : 8-dibromopyriminazole

2-Amino-3 : 5-dibromopyridine (5 g.) and bromoacetone (2.8 g.) were refluxed in alcohol (30 ml.) for 40 hours. At this stage some of the condensation product had separated from the boiling solution as the hydrobromide. Cooling and addition of ether completed this crystallisation, the salt being obtained as a mass of pale yellow needles.

Yield 5.2 g. (76%) m.p. >300°.

Decomposition of the salt (2.4 g.) with alkali gave 2-methyl-6 : 8-dibromopyriminazole, which crystallised from light-petroleum (100° - 120°) in
clusters of small, colourless needles.

**Yield 1.8 g. (88%) m.p. 144° - 145°**

**Analysis**

<table>
<thead>
<tr>
<th>Found</th>
<th>C, 32.28; H, 5.27; N, 9.71; Br, 55.01</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₈H₆N₂Br₂ requires C, 33.13; H, 2.09; N, 9.66; Br, 55.11</td>
<td></td>
</tr>
</tbody>
</table>

(This has obviously been a faulty hydrogen analysis).

**Picrate:** yellow prisms from alcohol-glacial acetic acid, m.p. 198° - 200°.

Found N, 13.3

**C₁₄H₉O₇N₅Br₂ requires N, 13.5.**

**Preparation of 2-Methyl-6-bromopyrimidazole**

2-Amino-5-bromopyridine (5 g.) and bromoacetone (4 g.) were condensed as in the previous experiment.

**Yield of hydrobromide 4.9 g. (58%)**

**m.p. 210° - 220°.**

The 2-methyl-6-bromopyrimidazole was obtained by treatment of a solution of the salt (2.5 g.) with sodium hydroxide.

**Yield 1.2 g. (72%) m.p. 96° - 98°.**

Recrystallisation from light-petroleum (60° - 80°) gave small, colourless needles, m.p. 102° - 103°.

**Analysis**

<table>
<thead>
<tr>
<th>Found</th>
<th>C, 45.30; H, 3.57; N, 12.4; Br, 58.56</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₈H₇N₂Br requires C, 45.53; H, 3.34; N, 13.3; Br, 57.86</td>
<td></td>
</tr>
</tbody>
</table>

**Picrate:** yellow needles from alcohol-glacial acetic acid, m.p. 226° - 228° (d).

Found N, 16.2

**C₁₄H₁₀O₇N₅Br requires N, 15.9.**

**Preparation of 2-Methyl-6-nitropyrimidazole**

2-Amino-5-nitropyridine (3 g.) and bromoacetone
(3 g.) were condensed in alcohol as previously.

Yield of hydrobromide 3.0 g. (54%) m.p. >300°.

A portion of the salt (2.8 g.) was converted to the free base as before.

Yield 2.0 g. (100%) m.p. 193° - 195°.

Recrystallisation from alcohol gave yellow needles of the 2-methyl-6-nitropyrimidazole, m.p. 197° - 199° (slight decomp.).

Analysis

Found C, 54.01; H, 3.75; N, 23.2

C₈H₇O₂N₃ requires C, 54.24; H, 3.98; N, 23.7

Picrate: yellow plates from alcohol-glacial acetic acid, m.p. 181° - 184° (d).

Found N, 20.2

C₁₄H₁₀O₉N₆ requires N, 20.7.

Preparation of 2-Phenylpyrimidazole

2-Aminopyridine (3.1 g.) and chloroacetophenone (5 g.) were refluxed in alcohol (30 ml.) for 28 hours. (cf. Tschitschibabin Ber. 1926, 59, 2051; Schmid and Bangler Ber. 1926, 59, 1362). Evaporation of the alcohol led to the crystallisation of a small amount of a colourless solid (ca 0.1 gm.); long slender needles, m.p. 114° - 116°. Recrystallisation from a mixture of alcohol and ether did not raise the melting point.
Analysis

**Found** C, 58.21; H, 6.05; N, 10.21; Cl, 13.09

\[ \text{C}_{13} \text{H}_{10} \text{N}_{2}, \text{HCl} \cdot 2\text{H}_{2}\text{O} \text{ requires } C, 58.53; H, 5.67; N, 10.2; \text{Cl}, 13.29. \]

Despite further evaporation, no more solid crystallised, and the residual brown syrup was dissolved in water and the solution was made alkaline with sodium hydroxide. 2-Phenylpyriminazole separated as a brown oil which gradually crystallised, and the crude product was recrystallised from aqueous alcohol, pale brown needles being obtained

**Yield** 2.0 g. (32%)  
**m.p.** 134° - 136°  
**(lit. 135.5°, 140°)**

A second recrystallisation from alcohol (charcoal) gave colourless 2-phenylpyriminazole, m.p. 134° - 136°.

**Analysis**

**Found** C, 80.00; H, 5.32

**Calc. for** \[ \text{C}_{15} \text{H}_{10} \text{N}_{2} \text{N}, 80.39; H, 5.19 \]

**Picrate:** yellow needles from glacial acetic acid,  
**m.p.** 228° - 229° (d., sinters at 200°).

**Found** N, 17.6, 15.4

\[ \text{C}_{19} \text{H}_{15} \text{O}_{7} \text{N}_{5} \text{ requires } N, 16.6. \]

**Preparation of 2-Phenyl-8-methylpyriminazole**

\[
\begin{align*}
\begin{array}{ccccc}
\text{NH}_2 & & \text{CO-CH}_3 & \\
\text{Cl} & & \text{Cl} & & \text{Cl}
\end{array}
\end{align*}
\]

2-Amino-3-methylpyridine (5 g.) and \( \text{w-} \)chloro-acetophenone (7.5 g.) were melted together, and the temperature of the melt was gradually raised. At
130° a vigorous reaction commenced, and the mixture was maintained at this temperature for two hours. The resultant yellow syrup was dissolved in dilute hydrochloric acid and the 2-phenyl-8-methylpyriminazol e precipitated by addition of sodium hydroxide. Recrystallisation of the resultant pale yellow solid from light-petroleum (100° - 120°) gave colourless, elongated prisms of the base.

Yield 4.8 g. (50%) m.p. 108° - 110°

Analysis

Found C, 80.42; H, 5.93; N, 13.5

C_{14}H_{12}N_{2} requires C, 80.71; H, 5.81; N, 13.5

Picrate: yellow needles from alcohol-glacial acetic acid, m.p. 240° - 241° (d., sinters at 210°)

Found N, 15.9

C_{20}H_{15}O_{7}N_{5} requires N, 16.0.

Preparation of 2-Methyl-7-azaindole

2-Amino-3-methylpyridine (6 g.) was acetylated with acetic anhydride (10 g.) as described by Seide (Ber. 1924, 57, 1804), and the product obtained on distillation (b.p. 176° - 178° / 35 mm.) was crystallised from benzene.

Yield of 2-acetylamino-3-methylpyridine 5.5 g. (66%)

m.p. 62° - 66° (lit. m.p. 64°).

The acetylamino-picoline (7.5 g.) was ring
closed by heating with sodium ethoxide at 360° in an atmosphere of nitrogen according to the method of Clemo and Swan (J. 1945, 603).

Yield of 2-methyl-7-azaindole 0.4 g. (6%) m.p. 134° - 135° (lit. 136°).

Picrate: yellow needles from acetone m.p. 224° - 225° (d) (lit. 229°).
Measurement of Absorption Spectra

All spectra were determined with a Spekker Ultra-Violet Photometer (Hilger Ltd.), the actual spectra being recorded by photographic methods. This instrument uses two light paths, one of which passes through a solution of the absorbing substance and the other through the solvent itself, and the photograph obtained consists of a pair of spectra in close juxtaposition. The instrument is so designed that at points of equal intensity in these two spectra, the "density" drum reading controlling the size of the aperture in front of the solvent cell gives directly the value of $\log_{10} \frac{I_0}{I}$. By taking a series of photographs with the drum set to different "density" values, and searching out the points of equality of the two spectra, it is possible to obtain a number of values of $\log_{10} \frac{I_0}{I}$ for a wide range of wavelengths. In regions of special interest, and in the immediate neighbourhood of maxima and minima it is possible to obtain greater accuracy by selecting a concentration which enables the maximum number of "density" values to be used.

The concentrations employed varied with the compounds being examined, but for each compound at least three determinations were carried out using approximately 0.0005 M, 0.00025 M and 0.0001 M solutions. Alcohol was used as a solvent in all cases, and this was purified by drying and distilling over potassium hydroxide. The specimens
examined were those which had been used for analyses.

The molecular extinction coefficients, \( \epsilon \), were calculated from the equation

\[
\epsilon = \frac{\log_{10} \frac{I_0}{I}}{c \times l}
\]

where \( \log_{10} \frac{I_0}{I} \) is the density drum reading, \( c \) the concentration of solute in gm. mols/litre, and \( l \) the length of the cell = 1 cm.

The graphs obtained by plotting \( \log \epsilon \) against wavelength were photographed to avoid duplication, and in these, the individual points are not shown for the sake of clarity.
SUMMARY

An examination of the ultra-violet absorption spectra and the dehydrogenation of the products obtained by condensation of 2-aminopyridine and its derivatives with 2-chlorocyclohexanone has shown that these compounds are derivatives of the cyclic diazaline, Pyrido (1': 2': 1 : 2)-benzimazolone, and not of 2-Carboline as stated in a Patent dealing with this condensation. The preparation of 2-(2'-Pyridylamino)-cyclohexanone, the intermediate amino ketone in this condensation, by condensing the reactants in the presence of sodium carbonate has shown that it is not necessary to prepare compounds of this type by isolation of the sodium derivative of 2-aminopyridine. The cyclodehydration of this intermediate to Pyrido (1': 2': 1 : 2)-4 : 5 : 6 : 7-tetrahydrobenzimazolone has been found to be an acid catalysed reaction, but the mechanism of the direct reaction in which hydrochloric acid and water are split out simultaneously remains unsolved.

Several new members of the pyriminazole series have been prepared, and in two cases their absorption spectra determined and compared with that of 2-methyl-7-azaindole.
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