THE FORMATION AND CHEMISTRY
OF SOME HETEROCYCLIC AMINE OXIDES

by

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TO MY PARENTS
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INTRODUCTION

General Object of Investigation

The formation of amine oxides has aroused great interest since it was first discovered by Meisenheimer\(^1\) in 1926. In the field of pyridines, quinolines and isoquinolines only one possible product from the peroxidation of amine to amine oxide, can be formed. However, if one considers the diazines, there arises the possibility in many cases of more than one isomer which could be formed and this leads to the problem of their isolation and identification.

Following the discovery\(^2\) of carcinogenic and carcinostatic properties in the compound 4-nitroquinoline N-oxide (1), an interest in this type of compound has been maintained at the Chester Beatty Institute.

![Chemical Structure](image)

(1)

The present work has been carried out under the auspices of a British Empire Cancer Campaign Grant for the investigation of heterocyclic amine oxides related to (1). The compounds which have been synthesised, have been sent to the Chester Beatty Institute for biological evaluation.

The purpose of this investigation has been to prepare a
variety of simple cinnolines and to peroxidise them. The isolation of the mixture of oxides, their separation and identification, has been carried out. The effect of some substituents in the ring on the ratio of oxides has been investigated; synthetic problems have reduced the scope of this part of the investigation. In particular, the nitration of the separate oxides and the determination of the position of the nitro group in each isomer has been attempted. The comparison of the nitration position in the simple base and the effect of peroxidation on the nitrocinnolines has also been investigated.

Since there appeared to be some positive information from their biological evaluation, the area of investigation has been extended to the preparation of benzo[c]cinnoline, its oxides and their nitration products. The positive identification of the position of N-oxidation has been postulated by the degradative oxidation of one of the benzenoid rings. The use of an activating or deactivating substituent in the benzo[c]cinnoline molecule would influence the site of ring oxidation. Further decarboxylation would lead to an identifiable substituted cinnoline oxide.
The use of spectroscopic methods for the identification of the different isomers has been of paramount importance and both nuclear magnetic resonance spectroscopy and mass spectrometry have played a major part. The use of spectroscopy has involved the use of labelled compounds and a series of deuterated cinnolines and their oxides have been prepared.

HISTORICAL BACKGROUND

The cinnoline ring system was first discovered by V. von Richter in 1883.\(^3\) Cinnoline (2) is a heterocyclic bicyclic base containing two vicinal nitrogen atoms. It is benzo[c]pyridazine and is numbered conventionally.

It is the least well known of the family of the condensed bicyclic aromatic compounds having two nitrogen atoms in the one ring. The nitrogen atoms may be ortho as in cinnoline and phthalazine (3), meta as in quinazoline (4), or para as in quinoxaline (5).
Three fairly general methods have been known for some time for the preparation of the cinnoline nucleus. Each one of these involves the formation of the pyridazine ring by the cyclisation of aryldiazonium compounds containing an unsaturated grouping in the ortho position. More recently another method of general application to the formation of substituted cinnolin-4(1H)ones has been reported and has been widely applied in the synthesis of cinnolines.

a. From o-aminophenylpropionic acids.

The first synthesis of the cinnoline was reported by von Richter who did not obtain the parent compound in sufficient purity for elementary analysis. The diazonium chloride (7) obtained from o-aminophenylpropionic acid (6) was heated to 70°C in aqueous solution. Cooling caused separation of 3-carboxycinnolin-4(1H)one (8), which, on heating above its melting point, liberated carbon dioxide and cinnolin-4(1H)one (9) was liberated in nearly theoretical yield. Distillation of (9) with zinc dust furnished a small amount of a basic oil which was assumed to be cinnoline.
This preparation of cinnolin-4(1H)-one was repeated by Busch and Klett\textsuperscript{5} although in poor yield and this was converted to cinnoline via 4-chlorocinnoline (10) by Busch and Rast.\textsuperscript{6} An alternative route to cinnoline from (9) has been reported by Alford and Scholfield.\textsuperscript{7} This involved the preparation of (10), conversion of this to 4-tosylhydrazinocinnoline (12) and treatment of (12) with sodium carbonate at 95°C. This method was to prove of great use in experiments to be discussed later.

\begin{align*}
\text{(9)} & \xrightarrow{\text{POCl}_3} \text{(10)} \\
\text{(10)} & \xrightarrow{\text{Fe}, \text{H}_2\text{SO}_4} \text{(11)}
\end{align*}

\begin{align*}
\text{(9)} & \xrightarrow{\gamma_3 = \rho(\text{H}, \text{C}_6\text{H}_5\text{SO}_2^-)} \text{(10)} \\
\text{(10)} & \xrightarrow{\text{Ts.NH.NH}_2} \text{(11)} \\
\text{(11)} & \xrightarrow{\text{H}_2\text{O}} \text{(12)}
\end{align*}

\begin{align*}
\text{(12)} & \xrightarrow{\text{Na}_2\text{CO}_3, \text{H}_2\text{O}} \text{(2)}
\end{align*}

**b. o-aminophenylethylene**

The second general method for the synthesis of cinnolines is the only one which does not involve a route through (9). It was first shown by Widman\textsuperscript{8} that by allowing a diazonium salt of 3-amino-4-isopropenylbenzoic acid (13) to stand at room temperature,
it underwent ring closure to 4-methylcinnoline-7-carboxylic acid (15).

\[ \text{Stoermer}^9 \text{ extended this method to the synthesis of 4-arylcinnolines and it has become known as the Widman-Stoermer reaction.} \]

Investigation of the scope and mechanism of this reaction by Simpson and his co-workers\(^ {10} \) has shown that the ring closure is more or less ionic in nature and is induced by the polarization of the diazonium salt (16). The presence of an electron-releasing group \( R_1 \) is essential for the polarization to be set up. The presence of an electron absorbing group will retard this mechanism and when \( R_2 = \text{COOH} \) cyclisation will not take place. The reaction goes quite rapidly and is seemingly independent of the geometric configuration of the groups around the ethylenic linkage. In this reaction the cyclisation is always in
competition with the nucleophilic replacement of the diazonium group by a hydroxyl group and when \( R_2 = \text{Ph} \), a Pschorr\(^{11} \) reaction may take place with the formation of a phenanthrene. The formation of the cinnoline is favoured by low temperatures. An example of a Pschorr reaction is shown below.

\[
\begin{align*}
\text{HCl} & \quad \text{NaNO}_2 \\
\end{align*}
\]

\[
\begin{align*}
\text{NH}_2 & \quad \text{COOH} \\
\text{C}_6\text{H}_5 & \quad \text{C}_6\text{H}_5 \\
\end{align*}
\]

\[
\begin{align*}
\text{NH}_2 & \quad \text{COOH} \\
\text{C}_6\text{H}_5 & \quad \text{C}_6\text{H}_5 \\
\end{align*}
\]

\[
\begin{align*}
\text{HCl} & \quad \text{NaNO}_2 \\
\end{align*}
\]

\[
\begin{align*}
\text{NH}_2 & \quad \text{COOH} \\
\text{C}_6\text{H}_5 & \quad \text{C}_6\text{H}_5 \\
\end{align*}
\]

c. From o-aminoacetophenones

The synthesis of 4-cinnolin-(1\( H \))ones from diazotised o-aminoacetophenones was discovered fairly recently by Borsche and Herbert\(^{12} \) and expanded by Simpson and his co-workers.\(^{13} \)

\[
\begin{align*}
\text{R}_5 & \quad \text{COCH}_3 \\
\text{R}_5 & \quad \text{COCH}_3 \\
\text{NH}_2 & \quad \text{NH}_2 \\
\text{R}_3 & \quad \text{R}_3 \\
\end{align*}
\]

\[
\begin{align*}
\text{R}_5 & \quad \text{COCH}_3 \\
\text{R}_5 & \quad \text{COCH}_3 \\
\text{NH}_2 & \quad \text{NH}_2 \\
\text{R}_3 & \quad \text{R}_3 \\
\end{align*}
\]

\[
\begin{align*}
\text{R}_5 & \quad \text{COCH}_3 \\
\text{R}_5 & \quad \text{COCH}_3 \\
\text{NH}_2 & \quad \text{NH}_2 \\
\text{R}_3 & \quad \text{R}_3 \\
\end{align*}
\]

The reaction has several points of interest. The formation of cinnoline is favoured by the presence of electron-attracting groups at \( C_3 \) and \( C_5 \) (i.e. \( R_3 = \text{NO}_2 \), etc.). The diazotisation is
also best done in concentrated acid solution since the yield of cinnolin-4(1H)one is low in dilute acid especially when no substituent is present. This low yield is due again to the strongly competing reaction of phenol formation. The reactivity of the diazonium cation towards ring closure probably results from the inductive or resonance displacement of electrons from the nitrogen towards the benzene ring. This reduces the electron density at the β nitrogen of the diazonium group and increases the ability of the donor group to add at this site and produce a cyclic molecule. The presence of strong acid helps to provide enolization of the carbonyl group which is important. The Borsche synthesis can be represented as occurring through an acid-catalysed enolization of the carbonyl group leading to the cyclisation and formation of cinnolinone.
A new synthesis by Barber leads to the formation of cinnolin-4(1H)one. However, this has very wide scope for the production of substituted cinnolines. The difference in this method is the preforming of the C-N-N-C bonds before cyclisation; the latter occurs by Friedel-Crafts acylation reaction of the di-acid chloride to give the 3-carboxycinnolin-4(1H)one derivative (21) as shown.

In the intermediates, the phenylhydrazone structures rather than the tautomeric azo structures have been adopted by Barber on the basis of spectral evidence put forward by Arison. In this he showed that peaks in the N.M.R. spectrum of diethyl -phenylhydrazo-oxaloacetate in dueterochloroform could be assigned to proton of N-H.

A synthetic route of limited use has been put forward by Moore who showed the formation of 3,4-disubstituted cinnolines by the reaction of acidic reagents on the relevant phenylhydrazone. The preparation of 3,4-diphenylocinnoline (23) was accomplished by
the reaction of 75-80% (w/w) sulphuric acid on benzil monophenyl-
hydrazone (22).

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

This reaction was further examined by Allen \(^{16}\) who described a
modified procedure for the synthesis and reported the failure of
cyclisation for the monophenylhydrazone of phenylglyoxal to give
4-phenylcinnoline. In this case only largely sulphonated
material was obtained. This type of reaction has only had limited
exploitation. The reaction conditions are rather strong and very
like the Skraup synthesis for quinolines where boiling strong
\(\text{H}_2\text{SO}_4\) solutions are also used as the cyclising reagents. The
cyclisation is in direct competition with the hydrolysis of the
phenylhydrazone.

The synthesis of a number of 3-substituted and 3,4-disub-
stituted cinnolines (25) has been described in a series of papers
by Baumgarten.\(^{17,18,19}\). The condensation of reagents such as
nitromethane or ethyl acetoacetate with diazotised o-aminobenzaldehyde
or o-aminoacetophenone gave the corresponding phenylhydrazone (24).
Cyclisation, which competed with hydrolytic cleavage, was achieved
using dilute base or using alumina and acetone which gave an increased yield. Here again, there were some difficulties which included competitive hydrolysis from water formed from the reaction of acetone and the alumina, reaction of the phenylhydrazone with acetone, difficulty in separating the products from the alumina and the slowness of the reaction. An alternative method for cyclisation, used in certain cases, was the anion exchange resin Amberlite IRA-400 in tetrahydrofuran solution. Cyclisation would not take place under these conditions with the phenylhydrazones of diazotised anthranilic acids.

\[ \text{R-HC}_{6}H_{5} \xrightarrow{\Delta \text{NaOH}} \text{RCOR} \]

\[ \text{R-HC}_{6}H_{5} + \text{CH}_{3}\text{NO}_{2} \xrightarrow{\Delta \text{NaOH}} \text{RCOR} \]

\[ \text{R-HC}_{6}H_{5} \xrightarrow{\text{Al}_{2}O_{3} \text{Acetone}} \text{RCOR} \xrightarrow{\text{NO}_{2}} \]

The Tautomerism of Cinnolin-4(1H)one.
In the preceding discussion the cinnolinone structure (27) has been preferred to the phenolic structure (26). The reasons for this are outlined as follows. Simpson and his co-workers have examined the U.V. spectra of a number of substituted 4-hydroxy-cinnolines to try and elucidate the tautomeric forms present. They have shown that it exists mainly as (27) but as much as 30% (26) may be present in alcoholic solution. It has been shown that alkyl and halogen substituents give rise to a mixture of tautomers but electron-withdrawing substituents present lead to the existence of the cinnolinone form (27) only.

Infra red spectral evidence for this structure has been reported by S.F. Mason. By interpreting the infrared spectra of a number of N-heterocyclic hydroxy compounds, he has shown that compounds with a hydroxyl group α or γ to a ring nitrogen atom absorb in the N-H and C=O stretching vibration regions both in the solid state and in chloroform or carbon tetrachloride solution and so possess principally an amide structure. The principal absorptions for cinnolin-4(1H)one have $\nu_{\text{max}} = 3422 \text{ cm}^{-1}$ and $1638 \text{ cm}^{-1}$. From this evidence the representation will be as the cinnolin-4(1H)one tautomer in this work.

**Amine Oxides**

The formation of amine oxides from the heterocyclic tertiary amines such as pyridine, quinoline and isoquinoline, has been known for about forty years. The methods used by Meisenheimer involved the use of perbenzoic acid on the tertiary amine and purification of the oxide through its picrate. For large scale
work this method was unwieldy and a simple method involving the use of hydrogen peroxide was required.

Most of the early work in this field was done by Ochiai in Japan and independently by van den Hertog in Holland. Ochiai established that amine oxides of the pyridine and quinoline series can be obtained in good yield using hydrogen peroxide as an oxidant if one adds to the reaction mixture, a carboxylic acid as catalyst. The most suitable method for use is the action of 30% hydrogen peroxide on the tertiary amine in glacial acetic acid solution at 70 - 80°C. The conditions for these amine oxidations have been worked out mainly from experiments on the pyridine and quinoline series, but their application has been found to be suitable for other series of heterocyclic amines. The reacting species is probably peracetic acid which is in equilibrium with hydrogen peroxide and acetic acid, or the hydroxyl cation.

Three possible N-oxides could be formed from a cinnoline as shown: a 1-oxide (28), a 2-oxide (29), or a 1,2-dioxide (30).
The first recorded work on the direct N-oxidation of simple cinnolines was by Atkinson and Simpson, who investigated the action of hydrogen peroxide on several \( \text{I-arylcinnoline} \) and in each case an N-oxide was formed. At that time it was suggested that the N-oxide formed was a 1-oxide, but this is open to doubt in the light of evidence produced in later years.

Most of the work done, however, has been reported in the last five or six years with Japanese workers appearing to be the main investigators in this field. The advent of chromatographic techniques and nuclear magnetic resonance spectroscopy has assisted considerably in the identification of N-oxidation products formed.

Ogata and his co-workers described the syntheses and structural studies on cinnoline, \( \text{4-methylcinnoline} \) and other substituted cinnoline N-oxides. Cinnoline (2) was readily converted to a mixture of its isomeric mono-N-oxides, cinnoline 1-oxide (31) and cinnoline 2-oxide (32), on treatment with hydrogen peroxide and acetic acid.

\[
\text{Cinnoline (2)} \xrightarrow{\text{AcOH, } 30^\circ\text{C}, \text{H}_2\text{O}_2, \text{70}^\circ\text{C}} \begin{array}{c}
\text{Cinnoline 1-oxide (31)} \\
\text{Cinnoline 2-oxide (32)}
\end{array}
\]

The separation of isomers was achieved by chromatography on alumina using benzene followed by chloroform as solvent for elution. The ratio of 1-oxide to 2-oxide isolated was found to be 1:2 but from
n.m.r. studies the ratio found was later shown to be 1:1.4. 4-Methylocinnoline was treated in the same way with the resultant ratio of isomers isolated being 1:2 with confirmation of this by n.m.r. spectroscopy.

At the time that the present research project was commenced, no evidence of the formation of cinnoline dioxides by direct oxidation had been obtained, although benzo[c]cinnoline di-N-oxides had been prepared by other methods.26

During the course of this work, 4-methylocinnoline di-N-oxide (35) was prepared by direct N-oxidation, and the preparation and proof of structure reported briefly.27
Subsequently Suzuki has confirmed the formation of cinnoline di-N-oxide (36) during the oxidation of cinnoline. By using much stronger conditions than those already applied, a compound was identified as (36) along with the usual formation of (31) and (32). The identification of the di-N-oxide was by chemical and physicochemical means. Although the di-N-oxide could also be represented as a dinitroso compound, the properties exhibited, i.e. stability, lack of colour, high melting point, do not agree with the presence of a free nitroso group, as had been apparent in the note of Palmer and Russell.

Suzuki and his co-workers have also shown that the amount of 2-oxide produced was greater than that of 1-oxide for substituted cinnolines such as 4-methoxycinnoline and 4-chlorocinnoline.

Loudon and Tennant in a review on ortho-substituted nitrobenzenes reported the preparation of 4-cyano-3-hydroxycinnoline 1-oxide (37). The interest in this preparation is that it provided a direct route to a cinnoline oxide. o-Nitrophenylacetamide does not undergo cyclodehydration and o-nitrophenylcyanoacetamide (38) which is better equipped to provide an anion is readily cyclised in the presence of warm aqueous sodium hydroxide to the product (37).

\[
\text{(38)} \xrightarrow{\text{NaOH}} \text{(37)}
\]
The benzo[c]cinnoline N-oxide synthesis is the best known method of introducing an N-oxide directly. The preparation of benzo[c]-cinnoline (39) and its N-oxides is different from that of the simple cinnoline series. By varying the strength and amount of reducing agent it is possible to prepare from the same starting material, 2,2'-dinitro-biphenyl (33), the dioxide (34), the monoxide (40), or the parent base itself; further reduction leads to the dihydrobenzo[c]cinnoline (41) and finally 2,2'-diamino-biphenyl (42).
The standard method of preparing (34) is by reduction with zinc dust and acetic acid. The general method for preparing (40) is by reduction of (33) with sodium sulphide and this reaction gives a good yield. It has been shown by Suzuki recently that by heating (40) with acetic acid and 30% hydrogen peroxide at 120°C, it is possible to isolate some dioxide (34).
Methyl Anthranilate

o-Aminophenyl, Dimethyl Carbinol
**DISCUSSION**

**4-Methylcinnoline**

The preparation of 4-methylcinnoline (44a) by the Widman-Stoermer method was described in two different papers. It was found that using the conditions employed by Atkinson and Simpson, when diazotisation was carried out at 0-5°C, evolution of nitrogen occurred together with change from a dark green to red solution during the actual diazotisation. This change of colour signified a negative coupling reaction and the consequent formation of only phenolic material. To ensure that diazotisation might be carried out properly and the coupling reaction allowed to occur slowly, the reaction temperature for the diazotisation was lowered to -8°C to -12°C and after diazotisation the mixture allowed to stand at 0°C to -5°C for two days; the reaction was thus allowed to occur and go slowly to completion. After two days at 0°C, gentle warming at 60°C of the by now, red solution made sure that the reaction had gone fully to completion. In view of this experiment, it was found advisable in all subsequent diazotisations of a similar type to employ a reaction temperature of about -10°C rather than 0°C → -5°C. The diazotisation occurred much more completely and cyclisation took place with very little side product formation. At 0°C there tended to be side products in the form of oils and tars which reduced the overall yield of cyclised product.

The Widman-Stoermer synthesis stemmed from originally either an o-aminoketone or an o-aminoester. The Grignard reaction on this with an alkyl halide followed by dehydration led to the appropriate o-aminophenyl-ethylene in the simple case. It was found in the
- Isopropenyl Aniline

- Methylcinnolone
preparation of these intermediates that the reactions went so well that there was little need to purify them. It was quite possible to use the crude products without loss of yield. The completeness of the Grignard reaction was shown from the n.m.r. spectrum of the crude product by comparison with that of the starting material. Further to this comparison of the infrared spectra showed the complete loss of any peak in the carbonyl region, together with a large OH peak at 3500-3300 cm\(^{-1}\) for the tertiary alcohol. The dehydration stage, again from the n.m.r. spectrum, showed the crude product to be sufficiently pure to carry on. The infrared spectrum showed the loss of large OH peak and a sharp doublet at \(\nu_{\text{max}} = 3500\text{ and }3400\text{ cm}^{-1}\) for a primary amine group.

In order to prepare other 3- and 4- substituted cinnolines, it was decided to extend this synthesis. In the case of methyl anthranilate, interest was aroused as to the nature of the final product on treatment with an alkyl halide other than methyl iodide. The Grignard reaction with ethylmagnesium bromide went very smoothly to give eventually a crystalline solid product. The n.m.r. spectrum showed the presence of two identical ethyl groups and the formation of a tertiary alcohol from the ester was confirmed by the complete absence of a carbonyl group and the presence of a large hydroxyl peak in the infrared spectrum. The dehydration of this product was accomplished quite readily using \(\text{P}_2\text{O}_5\) and dry benzene. The infrared spectrum of this product showed the removal of the hydroxyl peak and the presence of a primary amine. The n.m.r. spectrum was very complex but from the integral which was in the ratio of 4:1:2:8 (low field to high field) it could be shown that a hydrogen from a carbon \(\alpha\) to the OH group had been lost to give a structure
of the type (43).

\[
\begin{align*}
\text{CH}_2 & - \text{CH}_3 \\
\text{NH}_2 & \\
\text{(43)}
\end{align*}
\]

\[
\begin{align*}
\text{R}_1 & = \text{CH}_3, \text{R}_2 = \text{H} \\
\text{R}_1 & = \text{C}_2 \text{H}_5, \text{R}_2 = \text{CH}_3 \\
\text{R}_1 & = \text{CH}_3, \text{R}_2 = \text{CH}_3 \\
\text{R}_1 & = (\text{CH}_3)_3 \text{C}, \text{R}_2 = \text{H} \\
\text{(44)}
\end{align*}
\]

The complexity of the n.m.r. spectrum obtained from this compound, however, suggested that geometric isomers and possibly other isomers were present. Treatment with acid followed by rebasification failed to produce any significant difference in the form of the spectrum so that it was probable that very little terminal olefin was present. Diazotisation of the amine produced only one product, 4-ethyl-3-methylcinnoline (44b) after the same work-up procedure as for 4-methylcinnoline.

It had already been shown that 3,4-dimethylcinnoline (44c) could be prepared from o-aminopropiophenone by Grignard reaction with methylmagnesium iodide followed by dehydration and diazotisation. The synthesis of (44c) was achieved in a like manner using o-aminoacetophenone and ethylmagnesium bromide.

Again the formation of the amino-olefin gave a complex n.m.r. spectrum which was due to presence of geometric and position isomers. On diazotisation the final yield obtained was in the same order as that obtained by Szniai and his co-workers.

The preparation of cinnolines by this route was hampered by the difficulty of preparing o-aminoacetophenone. Nitration of acetophenone gave mainly the meta derivative and the ortho derivative
only in small yield. Reduction of this to the aminoacetophenone was achieved with difficulty. The preparation of substituted o-aminoacetophenones was reported by the oxidation of 2,3-dimethylindoles with substituents in the benzene ring, and Atkinson, Simpson and Taylor reported the preparation of o-aminoacetophenone from 1-acetyl, 2,3-dimethyl indole by oxidation with chromic acid in acetic acid solution. Recently, however, a much better method has been reported by Dalby which involved the preparation of o-formaminoacetophenone. This involved the oxidation of 3-methylindole with sodium periodate at room temperature over twenty-four hours. Chromatography of the extracted oil from the reaction gave the crystalline o-formaminoacetophenone in good yield and hydrolysis with an equal amount of ethanol, concentrated hydrochloric acid and water gave the o-aminoacetophenone in good yield after removal of ethanol, basification and extraction. On the large scale which was required, it was found impracticable to chromatograph the product from the oxidation. The hydrolysis was carried out directly on the oil obtained from the oxidation. This led to a certain amount of tar formation but on working up, distillation of the final product led to an overall yield of about 50% o-aminoacetophenone.

\(4\text{-t-Butylcinnoline (44d)}\)

The preparation of \(4\text{-t-butylcinnoline (44d)}\) was carried out starting with o-aminoacetophenone and t-butylmagnesium chloride. In order to obtain 100% conversion from the ketone to the tertiary alcohol, it was necessary to use a 5:1 excess of Grignard reagent and to recycle the reaction using a further 5:1 excess of Grignard reagent. The dehydration of the tertiary alcohol provided
some unforeseen difficulties. The usual methods employed for dehydration in this series of reactions failed to work and it was finally necessary to heat the oil neat with 25% KHSO₄ at 180°C. Distillation of the water produced was carried out during heating. After extraction of the product it was shown to be about 75% olefin. Chromatography on alumina eventually yielded a separation. The oil could not be distilled to give absolutely pure product for fear of rearrangement of the tertiary-butyl group. From the n.m.r. spectrum it was found that a certain amount of rearrangement had already taken place since there were some small peaks in the methyl region besides the main t-butyl peak. The possible reluctance at dehydration may be due to the steric hindrance created by the bulky t-butyl group. Although there should be free rotation about a single C-C bond, the presence of an ortho substituent and the bulky group may have held the hydroxyl group in a relatively inaccessible position.

Diazotisation of the product obtained, was carried out and after three days the reaction mixture was basified and continuously extracted with ether to give a red oil. Extraction of this oil with boiling light petroleum (b.p. 60-80) failed to give any product, unlike the other cinnoline syntheses. Chromatography on alumina gave a yellow band on elution with 10% CHCl₃ in benzene which yielded a reddish oil. This was rechromatographed and the spectrum of the product obtained was much cleaner than that of the earlier products. Attempts to crystallise the product failed. However, from the n.m.r. spectrum obtained, there was every confidence that the product was the one required. The peaks could be assigned to the different protons and the integral was in order. The peaks
in the aromatic region were in the same relative positions as for 4′-methylcinnoline (I4a) except for one of the aromatic protons which was displaced downfield slightly. This could be explained in terms of a slight downfield shift for 5-\(H\) due to it being next to a large group on 4-\(C\). The t-butyl group showed as a singlet at 8.35T.

**Substituents in the Benzene Ring**

In many cases, the introduction of a substituent in the benzene ring involved the synthesis firstly of a tri-substituted benzene with the required substituent in the correct position relative to an aminogroup and carbonyl group ortho to one another. Attempts to form a bromine-substituted 4′-methylcinnoline directly only gave resinous products and it was necessary to prepare such a compound from methyl anthranilate (45) with bromine substituted in the appropriate position. 6-Bromo-4′-methylcinnoline (47) thus required the preparation of methyl 5-bromoanthranilate (46). Here bromination was probable in the 3- or 5-position particularly the latter. To induce substitution in the 5-position only (para to the amino group) a Schiff's base was formed using anhydrous chloral and this created only para-directing substitution in (45). The preparation of (47) from (46) was quite straightforward from this stage using the Widman-Stoermer method.
The preparation of a 4-methylcinnoline with a methyl-substituent in the benzene ring required a lengthy synthesis. To prepare 4,6-dimethylcinnoline (54), p-toluidine was first converted to 5-methylisatin (49) by the usual procedure involving hydroxylamine hydrochloride, chloral hydrate and then sulphuric acid. Oxidation of the isatin with 30% hydrogen peroxide and sodium hydroxide gave the 5-methylantrianilic acid (50). Esterification of the acid with methanol and dry HCl gave the required methyl 5-methylantranilate (51), and this was converted to (54) in the normal way. Similarly o-toluidine gave 7-methylisatin (52) and methyl 3-methylantranilate (53) from which 4,8-dimethylcinnoline (54) was prepared.

In the case of nitro-substituents, direct nitration of 4-methyl-
Cinnoline led to an 8-nitro derivative (55a) in about 35% yield. This was the only isolated product. 3,4-Dimethylcinnoline and 4-ethyl-3-methylcinnoline also gave only 8-nitro derivatives in 45% and 83% yield respectively.

\[
\begin{align*}
&(\text{55a}) \\
&(\text{55})
\end{align*}
\]

4-t-butylcinnoline, on nitration also gave a product which was believed to be the 8-nitro derivative (55d), but this was not proved conclusively. The analysis of the compound prepared was not in agreement with the theoretical requirements. The compound was most insoluble in most solvents and an n.m.r. spectrum failed to give a recognisable spectrum apart from the presence of a singlet at 8.35 ppm which could be attributed to the t-butyl group. The aromatic region was uninterpretable.

Attempts to prepare 4-methyl-6-nitrocinnoline by different methods failed. Isatin was nitratated to 5-nitroisatin by the method of Sumpster and Jones and the methyl 5-nitroanthranilate obtained from this. The Grignard reaction with methyl magnesium iodide failed due to the insolubility of the nitroester in the solvents required for the reaction.

4-methyl-6-nitrocinnoline 2-oxide (56) was prepared as shown later, by nitration of the 4-methylcinnoline-2-oxide. Deoxygenation of (56) was tried using phosphorus trichloride in chloroform,
triethyl phosphite and neat phosphorus trichloride and each time starting material was recovered unchanged. The probable explanation for the difficulty in deoxygenation was the withdrawal of the electrons, necessary for the deoxygenation, from the oxygen by the nitro-group. It is possible to draw a canonical structure (56a) with a full double bond between nitrogen and oxygen. In this case the lone pair of electrons required for formation of the intermediate in the deoxygenation were unavailable. From the extreme stability of the oxide towards the deoxygenating agents it seemed that the oxygen was very unreactive. The compound recrystallised from phosphorus trichloride, showing how little addition reaction occurred.

The preparation of 8-nitro-4-phenylcinnoline was proposed. However, it could not be prepared by direct nitration as this would probably occur preferentially in the 4-phenyl group. The best way to prepare this compound was to start with the nitro-group in the relevant position. The Grignard reaction between 2-amino-3-nitro-acetophenone (prepared (as shown later) from 4-methyl-8-nitroquinoline) and phenylmagnesium bromide was carried out. This required stronger conditions than normal and a ratio of 4:1 of Grignard reagent to ketone. Eventually after recycling twice a small amount of solid was obtained which gave an analysis and spectral properties in agreement with that required for the tertiary
alcohol. The Grignard reaction had taken place successfully on the deactivated ketone. The nitro-group's presence required much stronger conditions and this raised the danger of the formation by coupling reaction of diphenyl since the Grignard reagent was already present in excess. The yield was so small that it was not possible to proceed further with this reaction.

Cinnoline

A direct cyclisation to cinnoline (2) itself has not been reported. Two methods for the preparation of (2) have been used. The preparation of (2) has been reported in a six stage synthesis from methyl anthranilate (45). 4-Methylcinnoline (44a) was prepared in three stages by the Widman-Stoermer reaction and condensed with benzaldehyde to give a quantitative yield of 4-styrylcinnoline (57). The oxidation of (57) with potassium permanganate was carried out according to the literature but a yield of only 35% of 4-carboxycinnoline (58) was obtained compared with a reported 82% yield. The separation of the product from the manganese dioxide in the large scale reaction was found to be quite difficult and even removal of the manganese dioxide with sulphur dioxide after the major extraction with base did not provide more product. The decarboxylation of (58) went quite smoothly according to the literature to give cinnoline (2) as a green oil.
Barber's method\textsuperscript{4} for the preparation of cinnolin-4(1H)one (9) followed by Alford and Scholfield's method for conversion to (2) was more practical. The preparation of 4-chlorocinnoline (10) was carried out using a few slightly different variations of starting materials. It was found, however, that by using a mixture of phosphorus oxychloride and phosphorus pentachloride at 140 °C according to Leonard and Boyd\textsuperscript{41} that the best results were obtained for the preparation of (10). The reaction mixture required very careful neutralisation as the formation of an intractable tar was prevalent, as reported, if the pH was taken above 5. The 4-chlorocinnoline (10) was converted to the 4-toluenesulphonylhydrazinocinnoline (11) by treatment with p-toluenesulphonylhydrazide in warm chloroform. This on treatment with aqueous sodium carbonate at 95 °C gave after filtration and extraction cinnoline (2) as an oil.
Deuterated Cinnolines

The preparation of cinnoline (2) with deuterium instead of hydrogen in certain positions of the ring was required for the investigation of the mass spectrum of the parent compound. The introduction of a deuterium atom at C-3, C-4 and C-8 in the cinnoline nucleus was carried out. The introduction of deuterium at the other positions appeared to be beyond the scope of the present investigation.

The primary step for the introduction of deuterium at C-3 was the exchange of deuterium for hydrogen in the carboxyl group of 3-carboxycinnolin-4(1H)one (8). Repeated boiling of (8) with deuterium oxide followed by high vacuum distillation of the water gave the deuterated compound with 100% conversion. Decarboxylation of this with Dowtherm at 220°C gave the corresponding cinnolinone with the deuterium attached to C-3. The compound appeared quite stable and impervious to further exchange, as expected. Conversion of the cinnolinone to the cinnoline via Alford and Scholfield's method retained the deuterium atom at C-3 without dilution. Formation of the 4-chloro-3-deuterocinnoline and the 4-toluenesulphenylhydrazino-derivative was carried out; the latter with aqueous sodium carbonate gave 3-deuterocinnoline, as shown by mass spectrometry.

By using anhydrous sodium carbonate in deuterium oxide for the decomposition of the toluenesulphenylhydrazide above, a 4-deuterium atom was introduced, the product being identified as 3,4-dideuterocinnoline by mass spectrometry. In a similar way 4-deuterocinnoline was prepared from 4-chlorocinnoline (10) by treatment of the toluenesulphenylhydrazide with anhydrous sodium
carbonate in deuterium oxide. In all three cases, 3-deutero-,
3,4-dideutero-, and 4-deuterocinnoline, it was shown that the
conversion to the deuterated derivative was complete and the
compound quite stable.

The introduction of deuterium into the cinnoline ring system
at C-8 required a different technique. It was introduced by the
reductive diazotisation of 8-amino-4-methylcinnoline with trideutero-
hypophosphorous acid. The amine was first shaken with deutero-
chloroform and deuterium oxide to convert NH₂ to ND₂ and was then
dissolved in trideuterohypophosphorous acid (whose synthesis is
given later). The diazotisation was carried out at 0°C using a
solution of sodium nitrite in deuterium oxide. Treatment of the
diazotised solution with a further 15:1 molar ratio of acid to
amine at 0°C completed the reaction to give 8-deutero-4-methyl-
cinnoline. The formation of the amine salt with the hypophosphorous
acid was quite in order as it is a strong monobasic acid. It was
reported that amines were generally deaminated with 5 moles of
hypophosphorous acid but the yields were increased by using 10
to 15 moles of acid.

3-Deutero-4-trideuteromethylcinnoline (59)

The synthesis of 3-deutero-4-trideuteromethylcinnoline (59)
was carried out using trideuteromethyl iodide in a Grignard
reaction with methyl anthranilate (45). The formation of the
tertiary alcohol (60) went quantitatively and from the total
absence of methyl proton absorption in the n.m.r. spectrum of the
product it appeared there was no exchange of hydrogen for deuterium.
The dehydration to the pentadeuteroisopropenylaniline (61) was
carried out by treatment of the tertiary alcohol with phosphorus
pentoxide in dry benzene. Owing to an error, the protons of the amino and hydroxyl groups were not exchanged with deuterium prior to the dehydration; some reintroduction of protons thus occurred, as shown from the nuclear magnetic resonance absorption. The extent of deuterium labelling at the olefin stage was about 70%. The theoretical amount of labelling, based upon total equilibration of three protons and six deuterons, is 66%. The n.m.r. spectrum suggested random distribution of hydrogen and deuterium in the 3- and 4- positions. Cyclisation of the olefin to the cinnoline was carried out in 98% D$_2$SO$_4$ containing dry sodium nitrite and it was hoped that further equilibration with the solvent would remove the remaining protons incorporated earlier. However, no further deuterium enrichment was obtained.

\[\text{(60)} \quad \text{P}_2\text{O}_5\text{, Benzene} \quad \text{(61)} \quad \text{D}_2\text{SO}_4, \text{NaNO}_2 \quad \text{(59)}\]

4-Methylcinnoline with $^{15}$N enrichment

With the advent of $^{15}$N n.m.r. spectroscopy it was thought that by labelling one of the nitrogens it would be possible to distinguish between the 1-oxide and 2-oxide of 4-methylcinnoline (44a) by means of the different signals created by a tertiary and a quarternary nitrogen, and also to ascertain more information about the nature of the N-atoms in the N-N-O system. It was possible to prepare 4-methylcinnoline with a $^{15}$N enrichment from the commercially available potassium phthalimide which contained 30% $^{15}$N. The n.m.r.
spectrum of the phthalimide in trifluoracetic acid showed a doublet attributable to $^{15}\text{N}-\text{H}$ with $J_{^{15}\text{N}-\text{H}}$ of 97 c/s. It has been reported by Bernheim and Batiz-Hernandez that the coupling constant attributable to $^{15}\text{N}-\text{H}$ in $^{15}\text{NH}_2$ was 61•2 c/s. More recently the coupling constants of $^{15}\text{N}$-labelled hydrazones have been examined and it was found that $J_{^{15}\text{N}-\text{H}}$ was in the region of 89 to 94 c/s.

The preparation of $^{15}\text{N}$ enriched 6-methylcinnoline involved the synthesis of anthranilic acid from the phthalimide using sodium hypochlorite and then esterification of the acid using diazomethane. Unfortunately the use of diazomethane led to a certain amount of N-methylation as well as the esterification. The ester was then converted to the cinnoline by the Widman-Stoermer reaction and the cinnoline obtained purified by chromatography.
Preparation of Trideuterohypophosphorous acid

The deuterated hypophosphorous acid required for the preparation of 8-deutero-4-methylcinnoline was prepared from 50% aqueous hypophosphorous acid by evaporation of the aqueous solution to dryness to give the anhydrous acid, on shaking with deuterium oxide and further evaporation under high vacuum, a partially deuterated acid was obtained as shown by the reduction in intensity of the proton resonance signals for the acid. The process of dilution with deuterium oxide and evaporation was then repeated until all hydrogen atoms had been replaced by deuterium atoms.

The n.m.r. spectrum of hypophosphorous acid \( \left( \text{H}_2\text{PO}_2 \right) \) showed peaks at \(-1.68\) and \(7.65\) attributable to the hydrogen joined to phosphorus. The coupling constant \( J_{\text{P-H}} \) was thus 560 c/s, which was in agreement with earlier work\(^5,6\) which recorded \( J_{\text{P-H}} = 561 \pm 8 \) c/s. When the exchange process was virtually complete the doublet appeared as a double 1,1,1 triplet having \( J = 560 \) c/s and \( J = 6 \) c/s. This small coupling arose from the \( ^2\text{H} - ^1\text{H} \) coupling from the residual \( \text{D-O-P-D} \) in the \( \text{D}_3\text{PO}_2 \). After multiplication by the ratio of the gyromagnetic constants for proton to deuteron \( \gamma_\text{H}/\gamma_\text{D} = 6.51\) this gave for \( \text{H-O-P-H} \) \( J_{\text{H,H}} = 39.1 \) c/s. This figure was much larger than the geminal coupling constant recorded\(^7\) for \( \text{H}_3\text{P} \) \( (J_{\text{H,H}} = 13.2 \) c/s measured from \( \text{HPD}_2 \), which has \( J_{\text{H,D}} = 2.03 \pm 0.7 \) c/s) and \( \text{P}_2\text{H}_4 \) \( (J_{\text{H,H}} = 12 \pm 4 \) c/s).\(^8\) Although this is not surprising since phosphorus\(^V\) compounds, usually have larger \( \text{P-H} \) coupling constants than phosphorus\(^\text{III}\) compounds,\(^6\) this appears to be the first reference to a geminal \( J_{\text{H,H}} \) in phosphorus\(^V\) compounds.
Synthesis of Amine Oxides

Cinnoline N-oxides

The general method outlined by Ogata and his co-workers, involving the use of acetic acid and 30% hydrogen peroxide at 70°C, was used for the synthesis of the amine oxides from the free base. Oxidation of cinnoline itself, was found to give a mixture of isomers, cinnoline 1-oxide (31) and cinnoline 2-oxide (32), in the ratio of 1:2 as was found in the literature. However, it was found that in chromatographing the mixture, elution with benzene removed the 1-oxide but it only required 30% chloroform in benzene to remove the 2-oxide. Further elution with a stronger solvent mixture of 75% chloroform in benzene gave a small portion of yellow solid which had melting point 215°C. This yellow solid could not be fully identified but it was suspected that it was possibly slightly impure cinnolin-4(1H)one (9) whose melting point is 225°C. The solid was not soluble enough for a n.m.r. spectrum but an infrared spectrum showed a peak in the carbonyl region at 1660 cm⁻¹. This suggested that the product was not cinnoline 1,2-dioxide (36) which was subsequently reported to be found as one of the products of reaction by Suzuke and his co-workers, but rather the cinnolinone; although the melting point of the dioxide was not recorded in the literature.

4-Methylcinnoline N-oxides

The oxidation of 4-methylcinnoline by the action of acetic acid and 30% hydrogen peroxide gave the mixture of mono-N-oxides. The method used was essentially that of Ogata and the ratio of isomers formed was found to be for 4-methylcinnoline 1-oxide (62) to
4-Methylcinnolone 1-oxide

4-Methylcinnolone 2-oxide
4-methylicinnoline 2-oxide (63) approximately 1:2.5 while the literature reported a ratio of 1:2. It was found again that in chromatographing the mixture, the removal of (62) and (63) required less change in eluant than reported. (62) was eluted with benzene as reported but (63) was eluted with only 25% chloroform in benzene. It was noticeable that the 1-oxide was not stable to prolonged exposure to light and turned blue very quickly. However, there was no appreciable difference in the infrared or n.m.r. spectrum or melting point before or after this phenomenon occurred. The 2-oxide, on the other hand, appeared to be quite stable to light and on standing for several months, the sample exhibited the same spectra and melting point as before.

The formation of a third product from the oxidation of 4-methylicinnoline (44a) was rather unexpected. Microanalysis of the product definitely indicated the presence of two oxygens in the molecule from the empirical formula C<sub>9</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub> obtained. The molecular weight obtained by vapour-pressure osmometry was 172 and from mass spectrometry the parent peak was at m/e = 176. The mass spectrum also showed strong peaks at P-16<sup>+</sup> and P-32<sup>+</sup> respectively due to the loss of oxygen atoms. The presence of the bicyclic aromatic nucleus followed from the n.m.r. and ultraviolet spectra. At this point several structures for the compound could be postulated.
4-Methylcinnoline 1,2-dioxide
The compound was shown not to be a cinnoline N-oxide monohydrate, (which might be suggested by analogy with quinoline and isoquinoline whose oxides both form hydrates,¹) by results obtained from n.m.r. and mass spectrometry and also the ultraviolet spectrum in 95% ethanol. The 4-hydroxymethylcinnoline N-oxide structures could be eliminated by the presence in the n.m.r. spectrum of a peak at 7.4. The hydroxy-4-methylcinnoline N-oxides and 4-methylcinnolin-3(2H)one 1-oxide would show the presence of hydroxyl or carbonyl absorption and none was observed. Also no peaks were shifted by treatment with deuterium oxide. Of the remaining possibilities only 4-methylcinnoline 1,2-dioxide (35) and the pair of isomeric 4-methyl-N-peroxycinnolines need be considered.

The peroxycinnoline structure was ruled out on the basis of the stability of the compound which appeared unchanged and quite stable to air after several months; also the mass spectrum showed a peak corresponding to the loss of $\text{HONO}$ from the molecule with the retention
of one nitrogen and one oxygen atom. This could be more readily interpreted in terms of the 1,2-dioxide than either of the isomeric peroxides.

### Ultraviolet Spectra of 4-Methylcinnoline N-oxides

<table>
<thead>
<tr>
<th>Compound</th>
<th>( \lambda_{\text{max}} ) (nm)</th>
<th>( \log E_{\text{max}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-oxide</td>
<td>220, 263, 315, 360</td>
<td>4.36, 4.12, 3.58, 3.75</td>
</tr>
<tr>
<td>2-oxide</td>
<td>224, 262, 357</td>
<td>4.42, 4.57, 3.54</td>
</tr>
<tr>
<td>1,2-dioxide</td>
<td>236, 275, 348</td>
<td>4.42, 4.60, 3.85</td>
</tr>
</tbody>
</table>

1. All spectra in 95% ethanol.

Consideration of the ultraviolet spectra of the oxidation products from the reaction showed firstly that there was no ring-fission and further that there was a slight bathochromic shifts of peaks in the unknown compared with the 1-oxide and 2-oxide. This indicated a greater extent of conjugation which would be due to the further addition of a pair of electrons.

### Infrared Spectra of 4-Methylcinnoline N-oxides

<table>
<thead>
<tr>
<th>Compound</th>
<th>( \nu_{\text{max}} ) (cm(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-oxide</td>
<td>1360, 1395, 1420</td>
</tr>
<tr>
<td>2-oxide</td>
<td>1370, 1395, 1420</td>
</tr>
<tr>
<td>1,2-dioxide</td>
<td>1350, 1395, 1425, 1420</td>
</tr>
</tbody>
</table>

1. In chloroform solution.

The infrared spectrum of the compound showed no absorptions attributable to either an hydroxyl or carbonyl grouping and only major absorptions comparable with the 1-oxide (62) and 2-oxide (63) in the 1300 to 1420 cm\(^{-1}\) region. The two peaks in the 1390 to 1410 cm\(^{-1}\)
region of the infrared spectra of the cis dimers of aromatic nitroso compounds \(^4^9\) prepared from the monomer,\(^5^0\) have been assigned to the \(N(\bar{\sigma}) = \bar{\sigma}(\bar{\sigma})\)-group. Benzo[c]cinnoline 5,6-dioxide (34) is anomalous in this respect and has peaks at 1342 cm\(^{-1}\) and 1399 cm\(^{-1}\); this may be the result of a structure approximating to a biphenyl, with a bridging \(N(\bar{\sigma}) = \bar{\sigma}(\bar{\sigma})\)-group having little aromaticity in the heterocyclic ring, since cis azomethane \(-1,2\)-dioxide and also some related compounds\(^5^1\) have \(\nu_{\text{max}}\) 1342 and 1399 cm\(^{-1}\). Either assignment might be applied to the compound from the infrared spectral evidence. Apart from dismissing structures with hydroxy or carbonyl groups present, the infra red spectra were rather inconclusive.

**Proton Chemical Shifts (\(\gamma\))\(^1\)**

<table>
<thead>
<tr>
<th>Compound</th>
<th>(\gamma)-Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-oxide</td>
<td>1.3, (H-8); 1.83, (H-3); 2.1, (H-5,6,7); 7.4, (4-Me).</td>
</tr>
<tr>
<td>2-oxide</td>
<td>1.9, (H-3); 2.2, (H-3,5,6,7); 7.36, (4-Me).</td>
</tr>
<tr>
<td>1,2-dioxide</td>
<td>1.7, (H-8); 1.9, (H-3); 2.2, (H-5,6,7); 7.4, (4-Me).</td>
</tr>
</tbody>
</table>

1. All spectra in CDCl\(_3\) solution with T.M.S. as internal standard.

The n.m.r. spectrum of the compound provided several points of evidence for the structure by comparison with the spectra of the parent base, the 1-oxide, and the 2-oxide. The doublet at 7.40\(\gamma\) with \(J = 1.2\) c/s showed that the 4-methyl group was unaffected by the oxidation and was still coupled to H-3 which was located as a poorly resolved 1,3,3,1 quartet with \(J = 1.2\) c/s. From this alone, the presence of a cinnolinone type structure could be ruled out. The multiplet at 1.65\(\gamma\) which represented one proton from the integral was attributed to H-8 by comparison with the parent base which had a multiplet at 1.50\(\gamma\) attributable to H-8. H-3 was shifted upfield relative to the parent base to the same extent as the 1-oxide and
2-oxide. The overall number of protons was unchanged compared with the parent base and thus the oxygen atoms were attached to the nitrogens. The downfield shift of H-8 relative to its position in the 2-oxide and upfield relative to that in the 1-oxide would suggest the presence of substituents at both nitrogens which had a slight counterbalancing effect on the chemical shift of H-8.

From the evidence at hand, the structure of the compound must be 4-methylcinnoline-1,2-dioxide (35). It is regarded as a dioxide and not a dinitroso compound on the basis of its stability, high melting point, (172°C on Kofler block), and lack of reactivity and colour. Suzuki and his co-workers have subsequently managed to prepare cinnoline-1,2-dioxide (36) itself, by heating at 120°C instead of 70°C. They are in full agreement with the proposition that the compound prepared is a dioxide rather than a dinitroso compound.

The di-N-oxides of pyridazine and its benzodervatives are of theoretical interest because of the formal unit positive charge on each nitrogen atom and the degree to which it may be spread to other parts of the ring. The best known compounds possessing the unit \( \hat{\mathrm{N}(\bar{\mathrm{O}})} = \hat{\mathrm{N}}(\bar{\mathrm{O}}) \) - are the dimers of nitroso compounds and benzo[c]cinnoline-5,6-dioxide (34) prepared by the reduction of 2,2'-dinitrobiphenyl (33). Direct formation of compounds of these type by the oxidation of the \(-N=N-\) system does not seem to have been established, although a possible, but unlikely, case is the formation of a di-N-oxide from 1,10-diaminobenzo[c]cinnoline; the dioxide in this case is thought to be the 4,9- or 4,10- rather than the 4,5-dioxide.

There are three possible sequences leading to the 1,2-dioxide (35): (a) Synchronous addition at both 1 and 2 positions.
(b) Addition at the 1-position followed by further oxidation at the 2-position. (c) The reverse of (b). On the basis of an experiment tried on 4-methylcinnoline 2-oxide (63), this last suggested method may be excluded. (63) was treated with further portions of 30% hydrogen peroxide and acetic acid at 70°C for eight hours and at the end of this time the starting material was recovered in almost 100% yield.

On the other hand (62), on treatment with further 30% hydrogen peroxide and acetic acid furnished mainly starting material but a small amount of material was obtained which was identified as the 1,2-dioxide (35) when compared with the properties of an authentic sample. From this it may be concluded that an intermediate stage may be the preparation first of the 1-oxide followed by further addition at the 2-position to give the 1,2-dioxide. The synchronous addition at both positions at once must be ruled as unlikely, but cannot be excluded.

The effects of ultraviolet light on the two mono-N-oxides are quite different. On extended irradiation the 2-oxide (63) in absolute ethanol has proved to be quite stable but the 1-oxide (62) on irradiation for two days changed to the 2-oxide. A comparative photoarrangement has been reported for quinoxaline 1-oxide to 2-hydroxyquinoxaline\(^{54}\) and for quinoline N-oxide to carbostyril.\(^{55}\) A possible pathway for the rearrangement is outlined below.

![Chemical structures](image-url)
The intermediate (64) postulated would be of the same type as that isolated by the reaction of light on 5,5-dimethyl-1-pyrroline 1-oxide (65) which gives a stable oxiran (66), although this is thermally rearranged to 5,5-dimethylpyrrolid-2-one (67) on prolonged heating.

The stability of 4-methylcinnoline 2-oxide (63) can further be emphasised by its failure to react with acetic anhydride under conditions where 3-methylpyridine 1-oxide has been shown to give 3-methylpyridin-2-(1H)one. The preparation of a 3-hydroxy compound would have served as a proof of structure for the 2-oxide.

Attempts to react 4-methylcinnoline 2-oxide (63) and 1,2-dioxide (35) with methyl iodide and methylene diiodide respectively both gave back starting materials although in each case an interesting phenomenon was observed which led to the belief that some reaction might have occurred. In each case there was a sharp change in the colour of the starting material. (63) was obtained as sky blue needles while (35) was obtained as orange needles.

**Oxides of Labelled Cinnolines**

The oxidation of 4-deuterocinnoline was carried out in a similar manner to that of cinnoline itself and a mixture of mono-N-oxides was obtained which was separated by chromatography on alumina. Sufficient amounts of the pure 1-oxide and 2-oxide were obtained for the purposes.
of identification by n.m.r. spectroscopy and for mass spectrometry.

Similarly 3-deutero-4-trideuteromethylcinnoline was oxidised but on chromatography of the mixture only a pure sample of the 2-oxide was isolated. Repeated chromatography failed to achieve a separation of the 1-oxide from 2-oxide, present as an impurity although the 1-oxide was shown to be present in the mixture from the n.m.r. spectrum.

$^{15}$N labelled 4-methylcinnoline was oxidised with 30% hydrogen peroxide and acetic acid to give a mixture of 1-oxide and 2-oxide. These were separated by chromatography to give products 1-oxide to 2-oxide in ratio 1:2.5. At the time of writing neither results from the mass spectrometry or from the $^{15}$N n.m.r. spectroscopy were known.

Formation of Oxides from Substituted Cinnolines

The oxidation of 6-bromo-4-methylcinnoline (147) and 4,6-dimethylcinnoline (148) were carried out according to Ogata's method but the work-up procedure required was different from before. In each case a solid precipitate was obtained on basification of the reaction mixture.

6-Bromo-4-Methylcinnoline N-oxides

In the case of the 6-bromo-4-methylcinnoline N-oxides the separation of the isomers was never completely achieved. The 60 Mc./s n.m.r. spectrum of the mixture was very degenerate and very little information could be obtained. However, a 100 Mc/s spectrum was obtained and this showed there to be a mixture of isomers. It was possible to obtain an indication of the ratio of isomers from the presence of H-8 of the 1-oxide downfield. From this the ratio of 1-oxide to 2-oxide was found to be 1:2.6.
4,6-Dimethylcinnoline N-oxides

The oxidation of 4,6-dimethylcinnoline (48) gave a precipitate on basification of the reaction mixture. Recrystallisation of this solid gave a single compound which was shown to be the 2-oxide from the n.m.r. spectrum. Extraction of the basic aqueous phase eventually gave another solid which was identified as the 1-oxide from the n.m.r. spectrum. Thus in this case it was possible to effect an almost total separation of the isomers on basification of the reaction mixture. The isomer ratio by weight was 1-oxide to 2-oxide, 1:2.5.

3- and 4-Substituted Cinnoline N-oxides

The effect of substituents in the 3- and 4- positions has been quite noticeable. The oxidation of 3,4-dimethylcinnoline (44c) and 4-ethyl-3-methylcinnoline (44b) produced a mixture of two compounds, in both cases the 2-oxide (68) and the 1,2-dioxide (69). It was found that in both these reactions no 1-oxide was isolated at all, and the amount of 1,2-dioxide (14 and 10% respectively) was much greater than in the case of 4-methylcinnoline (44a).

![Diagram](https://via.placeholder.com/150)

The oxidation of cinnolines with electron-withdrawing groups at position 3 or 4 has produced only one isomer in each case. 4-Methyl-3-nitrocinnoline (70) on oxidation gave only one product which was...
identified as the 1-oxide (71) by the downfield shift of one proton relative to its position in the parent compound. This was characteristic of H-8 next to a 1-oxide. This product could be rationalised by the fact that the nitro-group at C-3 would draw \( \pi \)-electrons away from N-2 with the resultant pull of the lone pair towards the nitrogen. This would reduce its availability for N-oxidation and enhance the reactivity at the 1-position. The reaction at N-2 would also be affected by the steric hindrance of the nitro-group. In the case of 4-carboxycinnoline (58), the oxidation again provided only one product which was identified from the n.m.r. spectrum as the 2-oxide (72) by the absence of H-8 downfield as a multiplet on its own. The formation of a 2-oxide would be consistent with the electron-withdrawing properties of the carboxyl group deactivating N-1.

From the oxidations carried out, it seems that generally with electron-releasing substituents, the formation of a 2-oxide is much more prevalent than that of a 1-oxide, and that a ratio of about 2.5:1 is obtained. The effect of a nitro-group or some other such electron-withdrawing group and a methoxy group in the carbocyclic ring requires further investigation.
(55) \[ \text{R} \]
\[ \text{R} \]
\[ x \]
\[ -11 \] 
\[ z \]
\[ (55) \]
\[ \text{RCHRH} \]
\[ \text{R} \]
\[ \text{H} \]
\[ \text{c} \]
\[ \text{R} \]
\[ \text{H} \]
\[ \text{c} \]
\[ \text{R(} \]
\[ \text{H} \]
\[ \text{c} \]
\[ \text{-L.} \]
\[ \text{R} \]
\[ \text{a} \]
\[ \text{R1} = \text{CH} \text{3}, \text{R2} = \text{H} \]
\[ \text{b} \]
\[ \text{R1} = \text{C}, \text{H} \text{5}, \text{R2} = \text{CH} \text{3} \]
\[ \text{c} \]
\[ \text{R1} = \text{CH} \text{3}, \text{R2} = \text{H} \]
\[ \text{d} \]
\[ \text{R1} = \text{CH} \text{3}, \text{R2} = \text{CH} \text{3} \]
\[ \text{e} \]
\[ \text{R1} = \text{C}, \text{H} \text{5}, \text{R2} = \text{CH} \text{3} \]
\[ \text{f} \]
\[ \text{R1} = \text{CH} \text{3}, \text{R2} = \text{CH} \text{3} \]
\[ \text{g} \]
\[ \text{R1} = \text{CH} \text{3}, \text{R2} = \text{CH} \text{3} \]

(73)
(74) \[ \text{R} = \text{CH} \text{3} \]
(75) \[ \text{R} = \text{C} \text{2} \text{H} \text{5} \]

(76)

(74)
Oxidation of Nitrocinnolines

The oxidation of 4-substituted-8-nitrocinnolines was expected to give as the main product the corresponding 2-oxide since the formation of the 1-oxide was less likely on the grounds of steric hindrance. However, the product obtained on oxidising 4-methyl-8-nitrocinnoline (55a) was shown not to be an oxide but rather a cinnolinone. Observation of the n.m.r. spectrum showed the complete loss of the methyl group; the infrared spectrum showed the presence of a carbonyl group, a secondary amine group, and the nitro-group. This led to the conclusion the product must be 8-nitrocinnolin-4(1H)-one (73). This was confirmed by comparison of spectra with an authentic sample of (73) prepared by diazotisation and direct cyclisation of 3-nitro-2-aminoacetophenone (74). The mixed melting point also showed no depression.

The oxidation of 4-ethyl-3-methyl-8-nitrocinnoline (55c) again showed this phenomenon by giving a cinnolinone as product. This was identified as 3-methyl-8-nitrocinnolin-4(1H)one (73b) by comparison with a sample prepared from 2-amino-3-nitropropiophenone (75).

From these reactions it was possible to put forward three different methods for the formation of the 8-nitrocinnolin-4(1H)ones. It could either have occurred by a substitution reaction, or by a successive oxidation of the 4-substituted group or by breaking the C-3 - C-4 bond and ring closure with exclusion of C-3. The reactions above did not give a clear answer to the formation as it was possible to postulate all three routes for the formation. 3,4-Dimethyl-8-nitrocinnoline (55b) was prepared as described earlier and treatment with 30% hydrogen peroxide and acetic acid gave 3-methyl-8-nitrocinnolin-4(1H)one identical with that prepared from (75). From this
result it was clear that C-3 must be retained throughout the whole reaction and the heterocyclic ring is not broken at any point of the reaction. To confirm this the oxidation of 4-t-butyl-8-nitrocinnoline (55d) was attempted. If the ring breaking and reclosure had any validity, in this case there could be no ring closure after the opening because of the t-butyl group; furthermore stepwise oxidation of the t-butyl group would be less likely. The other possibilities were that (73a) would be formed or no reaction would take place due to steric hindrance of the t-butyl group. It was found after oxidation that from the n.m.r. spectrum the t-butyl group was still present but the product of reaction was not fully identified.

Before considering the mechanism of these oxidations it is appropriate to mention that the oxidation of 5-nitrocinnoline and 8-nitrocinnoline has been carried out by Suzuki and his co-workers. They showed that the oxidation of 5-nitrocinnoline provided a mixture of 1- and 2-oxide as well as 4-nitroindazole. The 8-nitrocinnoline yielded only 2-oxide and 7-nitroindazole and if the time of reaction was extended a small amount of (73a). The comparison of these reactions with those of the corresponding nitroquinolines showed that 5-nitroquinoline 1-oxide was formed in good yield but 8-nitroquinoline gave rather the 3-hydroxy compound. A similar type of reaction was reported to occur with 6-nitroquinoline where the action of 30% hydrogen peroxide and acetic acid at 80°C gave a mixture of 6-nitroquinoline N-oxide (41%), 3-hydroxy-6-nitroquinoline (1%) and 3-hydroxy-6-nitroquinoline N-oxide (27%). The small amount of the 3-hydroxy-6-nitroquinoline was explained by the fact that it readily gave the oxide on treatment with further hydrogen peroxide and acetic acid and was only produced as an intermediate which was then further reacted.
on by the oxidising mixture.

Further comparison between the reactions of quinolines and cinnolines was carried out in the present work by the oxidation of 4-methyl-8-nitroquinoline (76), which produced (74) in small yield. In this case the oxidation created the fragmentation of the heterocyclic ring unlike the cinnoline series, with fracture of the C-3 to C-4 and N-1 to C-2 bonds.

The postulated pathways have been given in scheme opposite. Route C may be ruled out on the evidence from the oxidation of 3,4-dimethyl-8-nitrocinnoline. It is difficult to decide between route A or B. The oxidation of t-Butyl derivative and the resultant product could be explained in terms of both. The failure to remove the t-Butyl group in terms of A would be caused by the failure to oxidise the t-butyl group. In terms of B the failure would be due to plain steric hindrance.
Nitration of Cinnoline N-oxides

The nitration of cinnoline 1-oxide (31) has certain similarities and differences in comparison with the nitration of quinoline 1-oxide. It has been reported\(^\text{60}\) that the 4-nitro derivative is formed on heating quinoline 1-oxide at 70°C with mixed acid but at 0 to 100°C a mixture of 5- and 8-nitro derivatives are formed. The formation of a nitro derivative at a \(\beta\) position occurs with benzoyl nitrate in chloroform giving 3-nitroquinoline 1-oxide.

It was found that by using the same mixed acid nitrating conditions at low temperature, only 4-nitrocinnoline 1-oxide was obtained in 30% yield although Suzuki\(^\text{60a}\) has reported the formation of 4,5-dinitrocinnoline 1-oxide and 5-nitrocinnoline 1-oxide in trace amounts along with the 4-nitro derivative. From this result it seems that the nitration of (31) may be achieved much more easily. The directing influence of the N-oxide function and the presence of a second nitrogen in the ring lead to the direct nitration at the 4-position while more forcing conditions are required for quinoline 1-oxide.

The nitration\(^\text{61}\) of cinnoline 2-oxide (32) with mixed acids has been found to give a mixture of mononitro derivatives and these have been identified as the 5-, 6-, and 8-nitro derivatives. The ratio of isomers formed was reported to be dependent on reaction time, temperature and concentration of sulphuric acid present. Nitration of benzoyl nitrate gave a 5-nitro derivative in 1.5% yield with 95% recovery of starting material after a week at room temperature.

The nitration of some substituted cinnoline 2-oxides has been carried out here under similar conditions using mixed acids or sulphuric acid and potassium nitrate. In the case of 4,6-dimethyl-
cinnoline 2-oxide the starting material was recovered almost quantitatively. 4-Methylcinnoline 2-oxide (63) gave a mixture of two isomers, the 6-nitro (76a) and 8-nitro (77a) derivatives in 27% and 4% yield respectively while 4-ethyl-3-methylcinnoline 2-oxide (68b) gave a mixture of 6-nitro (76b) and 8-nitro (77b) derivatives in 31% and 16% yield respectively. In the nitration of (68b) the mother liquor from the recrystallisation of (76b) on evaporation to dryness showed two meta doublets in its n.m.r. spectrum which could not be accounted for in terms of (76b). The position of these doublets far downfield suggested the possible presence of a 6,8-dinitro derivative but no further product was isolated.

\[
\begin{align*}
(63) & \quad R_1 = \text{H, } R_2 = \text{H} \\
(68b) & \quad R_1 = \text{C}_8\text{H}_5, R_2 = \text{H} \\
(76a) & \quad R_1 = \text{C}_8\text{H}_5, R_2 = \text{H} \\
(77a) & \quad R_1 = \text{C}_8\text{H}_5, R_2 = \text{H} \\
(76b) & \quad R_1 = \text{C}_8\text{H}_5, R_2 = \text{C}_8\text{H}_5 \\
(77b) & \quad R_1 = \text{C}_8\text{H}_5, R_2 = \text{C}_8\text{H}_5.
\end{align*}
\]

The electronic effect of the cinnoline nucleus is to direct substituents to both the 5- and 8-positions. It has already been shown that 4-substituted cinnolines are only nitrated in the 8-position with increasing yield as the size of the substituent is increased. From this it would be expected that the cumulative effect of both the electronic effect of the cinnoline ring and the orientating effect of the 2-oxide function in these 4-substituted cinnolines would be such that the 8-nitro derivative would be produced in greatest
yield. Although a greater yield of 8-nitro derivative was obtained from (68b) than (63), the 6-nitro derivative was formed as the largest single product and it is significant that in the case where there was already a 6-substituent no product was formed at all. The directing influence of the N-oxide function amphi to itself is the greatest single influence and controlling factor in the nitration of the 2-oxides.
Quaternisation of Cinnolines

The position of quaternisation in the cinnolino series has been in dispute for some time as to whether it occurs at N-1 or N-2. This has been investigated at length by Ames and his co-workers. They have shown that quaternisation takes place mainly at N-2. It has been shown recently too, that the site of protonation is N-2 in cinnoline (2) as well as the site of quaternisation by spectroscopic studies on cinnolinium perchlorate (78a) and methylcinnolinium perchlorate (78b).

\[ \text{(78)} \]

\[ \text{(79)} \]

The first synthesis of a quaternary methiodide from 4-methylcinnoline was reported by Atkinson and Simpson. They reported that the product was mainly the 1,4-dimethylcinnolinium iodide. However, on repeating this experiment it was found that a mixture of two isomers was obtained from the n.m.r. spectrum, in the ratio of 10:1. After two recrystallisations a pure product was obtained with only one isomer present. A comparison with the spectra of 4-methylcinnoline 1-oxide (62) and 2-oxide (63) was made. A consideration of the 4-methyl group in each of these showed that the methyl peak in (63) was 0.05 downfield compared with (62). However since the electronic effect of the quaternary group was opposite to that of N-oxide group, the positions of the 4-methyl peaks should be reversed.
and the 4-methyl peak for the 2-quaternary salt would be upfield of that in the 1-quaternary salt. In the quaternisation reaction the dominant isomer had the methyl peak upfield of the minor isomer. From this it appeared that the formation of 2,4-dimethylcinnolinium iodide (79a) was by far the greater isomer. This was in agreement with the findings of Ames on the methylation of substituted cinnolines. This was also in agreement with the trend to form more of the two isomer than the one isomer for cinnolines with electron-donating groups at C-4 as was the case with the amine oxides. The synthesis was also carried out of the quaternary salt from 4-methylcinnoline with trideuteromethyl iodide and the major isomer, 2-trideuteromethyl-4-methylcinnolinium iodide (79b) isolated. The mass spectra of (79a) and (79b) were both obtained and are described later.
Reaction of Ethyl Magnesium Bromide on 4-Methylcinnoline

The Grignard reagent was prepared from ethyl bromide and magnesium in dry ether and 4-methylcinnoline (4μa) added in dry benzene. There was an immediate colour change from grey to dark red and this remained throughout the time of reflux. On work-up an oily grey solid was obtained and this was shown to be a mixture. Recrystallisation from benzene gave a pure white crystalline solid of melting point 198°C. The mother liquor on evaporation produced some impure (4μa). The actual structure of this compound has not been fully proved. A molecular weight of 190 was obtained from mass spectrometry which was in agreement with the empirical formula obtained from analysis, C_{11}H_{14}N_{2}O. The compound was quite stable to strong heating with palladium charcoal and sublimed to give the starting material unchanged with melting point still 198°C.

The infrared spectrum showed a strong peak at ν_max = 3280 cm⁻¹ which could be attributed to a secondary amine stretch or a free hydroxyl stretch. There was also a strong peak at ν_max = 955 cm⁻¹ which could be assigned to an aliphatic N-oxide N-O stretch. The n.m.r. spectrum in trifluoroacetic acid showed that the 4-methyl group was still present as a singlet but moved up field which showed that the environment at C-4 had been changed. The addition of another group at C-4 was most probable and the ethyl group appeared to be the group. The CH₂ peaks appeared to be more than a quartet and were possibly coupled to a further proton. The spectrum also showed a broad peak at 17 which was assigned to a single proton from the integral. This might either be assigned to C-3 or C-8.

From the molecular weight the Grignard reagent has added on to
the molecule and the magnesium halide has been hydrolysed. There are several possible structures for the product depending on the site of addition. The two most favoured structures come either from a 1,4-addition or a 3,4-addition. A 2,3 addition is unlikely since it would require a quinoid structure for the benzenoid ring. This may be ruled out on the basis of the compound's stability and lack of colour. The formation of dihydrocinnolines has been shown to give a 1,4 addition product. This would lead to a structure (80) in the case of this compound.

Similarly to the 1,4-dihydrocinnolines, the product is colourless. It exhibits a peak at 1630 cm$^{-1}$ in the infrared spectrum in Nujol. However, the n.m.r. spectrum cannot unequivocally be explained in terms of this structure (80) since the hydroxyl group will not have the same electronic effect as an N-oxide on the 8-position and it is not clear to which proton the low field broad peak can be assigned. A point in favour of this structure is found in the mass spectrum where a (P-17)$^+$ ion and (P-16)$^+$ ion are found. 1-Hydroxy-quinolin-4-one (99) which can tautomerise to the corresponding N-oxide, showed$^{31}$ (P-17)$^+$ as the base peak and the (P-16)$^+$ ion in 42% abundance. The abundance of the (P-17)$^+$ and (P-16)$^+$ ions in the product were of the same relative abundance.
The other possible structure may be explained in terms of a 3,4-addition followed by hydrolysis to give (81) and then a 1,3-allylic shift of the hydrogen followed by a tautomeric shift to give the cinnolinone structure (82). The infrared spectrum may be explained in terms of this structure but the low field peak in the n.m.r. spectrum cannot be explained in terms of H-8 since it should have a spectrum similar to a primary amine such as aniline where the aromatic protons are all up field.

It has not yet been established which is the true structure of this compound, although (80) is the more probable, and a comparison with other reactions of the same type will need to be investigated to provide further information.
Benzo[c]cinnoline Series

The main synthetic routes to benzo[c]cinnoline (39), benzo[c]cinnoline 5-oxide (40) and benzo[c]cinnoline 5,6-dioxide (34) from 2,2'-dinitrobiphenyl (33) have been known for a long time now. It was found that the sodium sulphide reduction of (33) proceeded extremely well with the formation of the product (40) in good yield. However, attempts to prepare (34) by reduction of (33) with zinc dust and caustic potash produced mainly starting material when the reaction was carried out according to the literature method, although a small yield of the required product was obtained. It was found that by increasing the time of reaction, the reducing agent was powerful enough to reduce the starting material directly to (39). The oily product obtained by extraction, after removal of the zinc dust and ethanol, was purified quite readily by chromatography on alumina to give a reasonable yield of (39). It was found that the preparation of the dioxide was best carried out by peroxidation of the monoxide at 120°C. It was found to give approximately a 25% yield and recovery of about 30% starting material.

The main interest in the benzo[c]cinnoline series was in the nitrated compounds since one of the compounds sent to the Chester Beatty Institute for testing for chemotherapeutic properties showed some activity against tumour growth. The nitration of benzo[c]cinnoline (39) has been quite thoroughly investigated. The nitration of (39) with a mixture of fuming nitric acid and concentrated sulphuric acid at 0°C produced a mixture of isomers which were separated to give almost equal amounts of the 1-nitro (83) and 4-nitro (84) isomers. This was consistent with the literature reports in which only (83) and (84) have been isolated using these reagents. The nitration
follows the same pattern as that of cinnoline itself which is
nitrat ed at the 5- and 8-positions under similar conditions.

The nitration of the monoxide (40) has produced conflicting
results in the past. The work of King and King\textsuperscript{32} has come under
severe criticism. Using their method for nitration, fuming nitric
acid at 90\textdegree C it was found that the product obtained was not 2-nitro-
benzo[c]cinnoline 6- or (5)-oxide (85) as they claimed. Analysis
of the product led to the belief that it must be a dinitrobenzo[c]-
cinnoline mono-N-oxide (86). The n.m.r. spectrum, even at 100 mc/s,
however failed to give a clear indication of the position of the
substituents. In this reaction no other product was isolated.
The actual constitution of this product is still in doubt but the
general consensus of opinion both here and in the earlier work is
that it is a dinitro monoxide although Arcos, Arcos and Miller\textsuperscript{68}
thought it might be a dinitro dioxide. The product (86) is most
probably 1,7-dinitrobenzo[c]cinnoline 6 (or 5)-oxide rather than the
2,4-dinitro derivative, since it would be expected that the second
nitro group would enter the unsubstituted ring. If the 2,4-dinitro
derivative was formed it would be possible to pick out two meta
doublets or even broad singlets well downfield in the n.m.r. spectrum
but these have not been observed.

The nitration of benzo[c]cinnoline 5-oxide (40) with fuming
nitric acid at 30\textdegree C produced a mononitro derivative which was shown
to be (85) by reduction to 2-aminobenzo[c]cinnoline.\textsuperscript{69} A small by-
product was isolated which compared satisfactorily with the reported
isolation of a 2-nitrobenzo[c]cinnoline 5,6-dioxide (87). Nitration
of (40) by mixed acids gave a mixture of two products, a 1-nitro (88)
and 4-nitro (89) derivative. The oxidation of 1-nitrobenzo[c]cinnoline
(83) has been shown to give two isomeric monoxides, the higher melting of which corresponds to (88) from the nitration of (40). The different products obtained on nitration of (40) may be due to the effect of the presence of sulphuric acid. The absence of sulphuric acid leads to a less protonated species and the actual nitration may take place by a different species.

An attempt was made to nitrate benzo[c]cinnoline 5,6-dioxide directly using fuming nitric acid. The product obtained was highly insoluble and had melting point 255°C but it was not possible to tell if there was a mixture or one product present.

The oxidation of benzo[c]cinnoline to pyridazine-tetracarboxylic acid is well known and attempts were made to oxidise (86) by the same method. The monoxide dissolved in pyridine to give a dark green solution, but there was an immediate change of colour to red and reaction with the formation of a precipitate when caustic potash was added, even before the potassium permanganate was added. The eventual black product isolated, melted at a relatively low temperature 130°C but it could not be characterised at all. The interesting effect of base on (86) led to treating it with ethanolic caustic potash under reflux for one hour. Again the red colouration was characteristic of the reaction and the precipitate obtained was very insoluble and high melting. From this it was concluded that one of the nitro groups must be quite labile and be replaced quite readily by a hydroxy group to give a cinnolinone type of molecule. This would account for both the very high melting point and insolubility.

Attempts to deoxygenate (86) with phosphorus trichloride gave starting material. The whole field of nitrobenzo[c]cinnoline oxides was hampered by the very high insolubility of the molecules. This
made it difficult to separate the products, and to obtain reasonable n.m.r. spectra was almost impossible due to the low concentration of solutions which could be used.
The theoretical interpretation of observed shifts is in fact more difficult than it might at first appear. Thus Pople\textsuperscript{90,91} has developed a theory of chemical shifts in which the screening constant \((\sigma_A^A)\) for an atom \(A\) in a molecule is given by

\[
\sigma_A = \sigma_A^A + \sigma_A^P + \sigma_{AB} + \sigma_A, \text{ ring}
\]

where \(\sigma_A\) is given by \(H_A = H_0(1 - \sigma_A)\) = observed field for the resonance of \(A\).

The various terms in the equation are defined as follows:

(I) \(\sigma_A^d\) is a diamagnetic contribution from the electrons of atom \(A\); it is a function of the number of electrons surrounding the nucleus and the electron density at their average radius from the nucleus.

(II) \(\sigma_A^P\) is a paramagnetic contribution from the electrons of atom \(A\). The magnetic field causes mixing of the ground and excited states of the molecule; the expression from which \(\sigma_A^P\) has been evaluated for molecular environments involves an inverse third power of the average radius of the electrons, the energy differences between the various molecular orbitals and the bond orders of the molecule.

(III) \(\sigma_{AB}\) depends on the magnetic anisotropy of the neighbouring atoms (B); in this situation departures from cylindrical symmetry in the electron distribution nearby, lead to the magnetic susceptibility of the neighbouring group varying in different directions. The effect decreases with the inverse third power of the distance, but is strongly directional depending upon the cosine of the angle between the direction of the dipole being considered and the vector to the appropriate proton.
(IV) $\sigma_{\text{ring}}$ refers to the effects of ring currents in the molecule. If the ring current in two related molecules is not the same, the one with the lower current will show a proton resonance shift to higher field. This will affect all protons in the molecule identically.

Very little work has been reported for the detailed calculations of $\sigma$ for heterocycles. The main exception is for pyridine where it was shown that replacement of the C-H dipole by an N: atom could account for most of the observed difference in the chemical shifts of the $\alpha$, $\beta$, and $\gamma$ protons of pyridine relative to benzene. The effect was shown to occur through three factors, the magnetic anisotropy of the nitrogen atom, the local dipole of the nitrogen atom lone pair and the $\pi$-electron density at the ring carbon atoms. The first two factors are of approximately equal importance. The remainder was attributed to $\pi$-electron density, assuming the constant of proportionality of proton chemical shifts and charge being 10 p.p.m. per unit of charge, as is often done.

From the point of view of the present work, detailed calculations such as these would not be possible at this stage; however, the separate effects of magnetic anisotropy and dipole of the N: and N - O groups and electron density are discussed below.

The spectrum of pyridazine 1-oxide (90) has been interpreted and a complete assignment of the proton signals achieved, in a paper by Ogata and his co-workers. To do this it was necessary to examine a number of substituted derivatives and it was found that the presence of a chloro- or methyl group had little effect on the chemical shifts of the protons relative to the unsubstituted...
pyrazidazine 1-oxide (90). The n.m.r. spectrum of 3,6-dichloropyridazine 1-oxide had two doublets at 2.177 and 2.787 which were assigned to H-4 and H-5; (90) also had peaks at 2.177 and 2.787 but in both compounds it was impossible to distinguish which was H-4 or H-5.

The distinction between H-3 and H-6 in (90) was made by comparing the spectrum with that of pyrazine (91), pyrazine mono-N-oxide (92) and pyrazinedi-N-oxide (93); (91) and (93) showed singlets at 1.377 and 1.997 respectively, and (92) showed two quartets at 1.487 and 1.827. From this it was suggested that a proton attached to a carbon adjacent to the N=O group showed its signal peak at a higher field than a proton attached to carbon adjacent to a tertiary nitrogen. From this the peaks at 1.467 and 1.747 in (90) were assigned to H-3 and H-6 respectively. It was observed that the signal for H-3 had a broader peak with less resolution than the sharp peaks observed for H-6. *

The assignment of H-4 and H-5 in (90) was completed by consideration of the spectra of 3-chloro-4-methyl- and 3-chloro-5-methylpyridazine 1-oxides. These displayed no signals corresponding to H-3 and were thus considered as 1-oxides. Thus the assignment of the signal at 2.177 to H-5 and at 2.787 to H-4 in (90) was achieved.

It was thus shown that the protons in (90) exhibited signals in the order \( \gamma \) H-3 < H-6 < H-5 < H-4. Once this was

* The effect of \( ^{14}N \) having a quadrupole moment means that asymmetry of the electron charge distribution about the nucleus will result in the broadening of the signal. Thus a tertiary nitrogen is likely to give a broadened signal while a quaternary nitrogen will give a much sharper signal.
achieved it was possible to distinguish between pairs of isomeric N-oxides, separated from reaction mixtures by chromatography.

\[
\begin{align*}
(90) & \quad \begin{array}{c}
0.897 \\
1.107 \\
1.265 \\
1.598
\end{array} \\
(91) & \quad \begin{array}{c}
0.868 \\
1.265
\end{array} \\
(92) & \quad \begin{array}{c}
0 \\
N
\end{array} \\
(93) & \quad \begin{array}{c}
0 \\
N
\end{array}
\end{align*}
\]

It has been reported\(^7\) that there is a relationship between chemical shift and the local \(\pi\) -electron distributions in aromatic molecules. With the exception of C-6, the above order of shielding of the ring protons was in good agreement with a calculation\(^7\) of the local \(\pi\) -electron densities in the pyridazine 1-oxide molecule. Calculations showed that C-6 had the highest \(\pi\) -electron density and thus the proton attached to C-6 should be the most shielded one. The observed deshielding of this proton might be explained by the magnetic anisotropy effect of the N-O group.

This effect may be explained by the fact that protons may experience shielding effects caused by electronic circulations which originate in other parts of the molecule. The currents in the same molecule will not affect the shielding of a proton if averaged to zero by rapid rotation about a single bond. In a relatively rigid molecule such currents can either affect the shielding or deshielding of a proton. These effects depend on the orientation of the proton to the induced magnetic currents. In the case of pyridazine 1-oxide, quinoline 1-oxide, cinnoline 1-oxide and other 1-oxides, the position of the N-O bond is such relative to the ring that an induced diamagnetic current is set up which causes deshielding of the ortho-
and peri-protons respectively.

The assignment of each proton in the simple pyridazine 1-oxide has led to further studies in the benzodiazine N-oxide series using the information already obtained. By comparison of the spectra of cinnoline 1-oxide, 3-chlorocinnoline 1-oxide and 3-methoxy-4-chlorocinnoline 1-oxide, together with information gained from the spectrum of (90), it was possible to assign the doublet at 1.67 ppm to H-3 and the doublet at 2.50 ppm to H-4 for cinnoline 1-oxide. The spectrum also showed a multiplet at 1.33 ppm which was assigned to H-8, consistent with the anisotropic effect of the N-O group at N-1. On the other hand, cinnoline 2-oxide exhibited an AB quartet as the lowest peaks in the spectrum; these were assigned to H-3 and H-4. The high field part of this quartet was further slightly coupled to another proton and was thus due to H-4; since this splitting was due to long range spin coupling of H-4 with H-8. This long range spin coupling between protons of different rings in an aromatic compound has been demonstrated in quinolines between H-4 and H-8, and in benzofurans and indanes between H-3 and H-7. All the J values obtained were about 1 Hz. The lower part of the quartet was thus due to H-3.

The use of n.m.r. spectroscopy has been of prime importance in the present work in the assignment of structures to different isomers of substituted cinnoline N-oxides. The identification has been made by consideration of the change in chemical shifts of protons in the amine oxide relative to their chemical shifts in the parent amine. The measurement of the chemical shifts has been carried out with the intention of making a quantitative determination
of the effect of N-oxidation on chemical shift. The Japanese workers did not always work at fixed concentrations and the results here have been determined for infinite dilution to avoid inter-molecular effects.

The chemical shifts reported in the tables have all been measured, relative to an internal standard tetramethylsilane, in c/s downfield from T.M.S. (8 units). All spectra were measured at 60 M c/s in deuterochloroform as solvent. The individual shifts were measured at infinite dilution by taking the spectra of dilute solutions of known concentration and extrapolation of the results to zero concentration. References to changes in chemical shift between the parent amine and the oxide were made as $\Delta \delta$ (amine shift - oxide shift) in c/s., positive for an upfield shift and negative for a downfield shift.
<table>
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<tr>
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<th>H-1</th>
<th>H-2</th>
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<td>492</td>
<td>+18</td>
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Pyridazines

A comparison of pyridazines and its 3- and 4-methyl derivatives, shows that the methyl group leads to an upfield (+ ve) shift of all protons of about 9 c/s and 11 c/s respectively. The electron-releasing properties of the methyl group appear to be slightly more effective in the 4-position than in the 3-position; furthermore the methyl group is no less effective on the position meta to itself than those ortho or para. The same effect occurs with the 3- or 4-positions of quinolines when compared with their 2-methyl derivatives. 76

Position 4  + 8 c/s (o)  3  + 10 c/s (o)
5  + 8 c/s (m)  5  + 11 c/s (o)
6  + 10 c/s (p)  6  + 12 c/s (m)

In the N-oxide series, comparison with the corresponding methyl compound shows that the effect of the methyl group is much more variable; thus if all the compounds are regarded as 1-oxides, the average upfield shift by a methyl group varies as follows: - 3-methyl 17 c/s, 4-methyl 11 c/s, 5-methyl 12 c/s, and 6-methyl 14 c/s. The variation in effects of a methyl group also vary markedly, the 5- and 4-positions being most effected (average 17 c/s and 14 c/s respectively) while the positions (6- and 3-) adjacent to the nitrogen atoms are less effected (11 c/s and 10 c/s
respectively). These two effects show that a methyl group adjacent to nitrogen is the more effective as an electron releasing agent.

While the introduction of a methyl group in place of a hydrogen atom can rightly be regarded as a minor perturbation of the ring, the introduction of an N-oxide cannot, since there is an increase in the number of \( \pi \)-electron centres (to seven) and the number of \( \pi \)-electrons to eight. There will thus be a marked change in the molecular orbitals, and a marked change in the electron distribution. Given these reservations, the comparison of an azine with the corresponding N-oxide can be valuable, if the chemical shift data show a consistent trend on the shifts of protons within the ring. These trends will arise from the summation of various effects, not all of them acting in the same direction.

The overall effect of N-oxidation on the pyridazines, both on the parent compound and the four methyl substituted N-oxides leads to the following generalisations (the compounds all being considered as 1-oxide): \( H-3 = + 40 \pm 2 \) c/s; \( 4'-H = + 21 \pm 4 \) c/s; \( H-5 = - 15 \pm 5 \) c/s; and \( H-6 = + 55 \pm 5 \) c/s, the "errors" here representing the maximum deviation from the average. Thus three of the resonances undergo an upfield shift and one downfield. The
low dipole moment of pyridine N-oxide\textsuperscript{22} has been interpreted by Ochiai\textsuperscript{22} as evidence of electron release (A and B) from the N-oxide to the ring, rather than electron attraction (C and D).

The pyridazine monoxides can be represented by a range of canonical formulae in which the second nitrogen carries either positive or negative charge.

In view of the greater electronegativity of oxygen relative to nitrogen, and the stability of oxygen anions together with that of nitrogen cations, the N=N=O group is more likely to behave as $\overset{+}{N} = \overset{-}{N} = O$ or $\overset{-}{N} = N = O$ rather than $\overset{-}{N} = \overset{+}{N} = O$, $\overset{-}{N} = N = O$ etc.

For the present compounds it is clear that upfield shifts are the most frequently observed, and it is clear that two out of the four shifts can be ascribed to negative charge densities at the positions ortho or para to the N-oxide. However, the observation that H-3 and H-5 give shifts of opposite sign make an electron density explanation inadequate. A positive explanation of the
upfield shift for H-3 might be found by considering the resonance structures (90a) and (90b). In (90a) the negative charge on N-2 is the result of an additional electron which is accommodated in a p-orbital perpendicular to the plane of the ring i.e. is equivalent to a high $\pi$-electron density at the nitrogen atom. This would have very little added effect on the chemical shift of H-3. However, in (90b), the presence of a positive charge on N-2 would result in the lone pair of electrons in plane being drawn towards the nitrogen with resultant increase of s character of the $sp^2$ lone pair orbital. This in turn would lessen the effect of the lone pair on the adjacent H-3 with a resultant upfield shift. Since the net overall effect was an upfield shift, it appears that this process could be the dominant factor in controlling the direction of the chemical shift for H-3.

The upfield shift for H-4 can be ascribed to the increase of electron density at C-4 due to electron migration from the N-oxide group. The magnetic anisotropy of the N-oxide group which lies in the same axis with H-4 would lead to an upfield shift of the resonance. The net effect is the sum of these. Similarly H-6 would experience an upfield shift due to the electron density increase at C-6. The anisotropic effect of the N-O group, acting in the opposite direction, however, would be expected to reduce this to a much smaller change on a purely electron density approach. That the effect is much larger than that on H-4 shows that the approach is limited in value.
### CHEMICAL SHIFTS (δ c.p.s.) AND CHEMICAL SHIFT CHANGES (Δδ c.p.s.)

<table>
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<tr>
<th>COMPOUND</th>
<th>H₃</th>
<th>H₄</th>
<th>H₈δ</th>
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<th>4-CH₂</th>
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<td>δ</td>
<td>Δδ</td>
<td>δ</td>
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<tr>
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<td>-4</td>
<td>161</td>
<td>+17</td>
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</table>
Cinnolines

The hypothetical changes from naphthalene to quinoline and isoquinoline and from these to cinnoline occur by replacement of a C-H group by N. These will have the effect of introducing changes in the distribution of the \(-\)electron density and of introducing extra magnetic effects in the rings. These changes can be expected to alter the observed proton chemical shifts in both rings, but to influence those nearest the nitrogen atoms most.

Direct comparison of naphthalene with quinoline and isoquinoline leads to the following substituent effects.

A nitrogen in the 1-position, \(H-2 = -83\) c/s, \(H-3 = +13\) c/s, \(H-8 = -13\) c/s; a nitrogen in the 2-position, \(H-1 = -59\) c/s; \(H-3 = -79\) c/s.

For cinnoline the figures are not additive in \(H-3\) and \(H-8\), as expected, but there are some parallel trends.
One of the most interesting observations is the difference in chemical shift of H-8 in cinnoline and quinoline; the difference (Δ = quinoline - cinnoline) of -18 c/s shows the effect of the β nitrogen atom in the former. For quinoxaline the effect (S = quinoline - quinoxaline) is very much less at +2 c/s; this contrast can best be described as a direct magnetic effect rather than a mesomeric or inductive effect, since first principles suggest that the extra nitrogen atom in cinnoline and quinoxaline should behave similarly at the 8-position.

**Cinnoline Oxides**

In cinnoline 1-oxide (31), the chemical shift changes for H-3 and H-4, +65 c/s and +17 c/s respectively, were similar to the changes experienced by H-3 and H-4 in pyridazine 1-oxide (90) although the effect on H-3 is much larger in the cinnoline. It is interesting to compare the upfield shift of H-3 in cinnoline 1-oxide with quinoline 1-oxide where H-3 is unaffected; the position of H-4 in the latter is uncertain as it lies under the multiplet of the 5-, 6- and 7-protons.

In cinnoline 2-oxide (32) the chemical shift changes were quite distinct from those of the 1-oxide. Again H-3 had an upfield shift of +65 c/s but H-4 had a downfield shift of -20 c/s. The changes were comparable with H-6 and H-5 respectively in pyridazine 1-oxide which were in the same relative positions. The direction and size of change were in the same order for both compounds. A further comparison here is with isoquinoline 2-oxide where both H-1 and H-3 are upfield of those in the parent base by +24 c/s and +18 c/s respectively. Unfortunately H-4 is not resolved in the
multiplet of the 5-, 6-, 7-, 8-protons. Even in quinoline 1-oxide, the proton (H-2), adjacent to the N-oxide lies upfield (+ 20 c/s) of that in the base.

In the cinnoline series, the additional interest of the chemical shift changes of H-8 was investigated. The use of H-8 relative to its position in the parent amine was the most important factor in the identification of the isomeric N-oxides. In the 1-oxide (31), H-8 experienced a downfield shift change of - 16 c/s; this downfield shift change was ascribed to the anisotropic effect of the N-O group. In quinoline 1-oxide the corresponding change in H-8 was - 40 c/s.

In cinnoline 2-oxide (32), H-8 was shifted upfield by > + 40 c/s; in isoquinoline 2-oxide, H-8 was not directly observed but from the very degenerate 4-, 5-, 6-, 7-, 8-protons, which largely occur as a broad singlet, it would seem as if it was only slightly effected at most.

Although the N-oxidation produced a much larger effect on H-8 in quinoline than cinnoline, the substituent effects for the "synthesis" of cinnoline 1-oxide from quinoline via quinoline 1-oxide or via cinnoline lead to self consistent data as shown. Similarly the same observation can be made for the case of H-3 in cinnoline 2-oxide from isoquinoline via isoquinoline 2-oxide or via cinnoline as shown. Thus the substituent groupings do lead to additive increments.

The chemical shift changes for 4-methylcinnoline 1-oxide (62) and 2-oxide (63) were comparable with the corresponding unsubstituted cinnoline 1-oxide (31) and 2-oxide (32). In both (62) and (63), H-3 was shifted upfield by + 60 c/s, while the shift changes for H-8
although smaller were in the same direction as the corresponding cinnoline 1-oxide (31) and cinnoline 2-oxide (32). 4-methyl-cinnoline 1,2-dioxide (35) also exhibited a chemical shift change of + 60 c/s for H-3 while H-8 was also moved upfield by 12 c/s. It was found in all three cases, for (62), (63) and (35) that the methyl group experienced a small upfield change of approximately 5 c/s.

From these it was possible to identify the products from the oxidation of 3,4-dimethylcinnoline (44b) and 4-ethyl-3-methyl-cinnoline (44c). The characteristic upfield shift of > + 25 c/s for H-8 has identified the presence of a 2-oxide in each case. However, the other product obtained in each case although identified as 1,2-dioxide gave variable shift change which was found to decrease with increase of size of substituents in the heteroring. The effect of oxidation on the 3-methyl group was quite marked. In both cases (44b) and (44c), on oxidation there was a substantial upfield shift of about + 18 c/s. This was caused by the same effect which produced the large upfield shift on H-3 in the unsubstituted cinnolines.

From these results it was possible to establish the identity of an N-oxide for a cinnoline with either H-4 or H-8; but since the change for H-3 was comparable for both 1- and 2-oxides it was only considered as means of identification of the formation of an N-oxide.
### CHEMICAL SHIFTS (δ c.p.s.) AND CHEMICAL SHIFT CHANGES (Δδ c.p.s.)

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**Phthalazines**

In the phthalazine series, on oxidation of phthalazine (3) to its mono-N-oxide, the spectrum of the product showed two singlet signals with $\Delta \delta = +23$ c/s and $+53$ c/s. Closer examination of the peaks showed a broad peak at the lower field signal and a sharp peak at the upper field signal. These were consistent with protons next a tertiary and quaternary nitrogen respectively. Comparison with the pyridazine series which showed $H-3$, with broad signal, $\Delta \delta = +40$ c/s, and $H-6$, with sharp signal, $\Delta \delta = +56$ c/s. From this the large change was attributed to $H-1$, next to the N-oxide group in phthalazine 2-oxide and the smaller change was attributed to $H_4$, next to the tertiary nitrogen.

**Pyrazines and Benzo pyrazines**

In the pyrazine and quinoxaline series, a general effect was found in that protons adjacent to a tertiary nitrogen experienced shifts of from 7 to 11 c/s while the protons adjacent to the N-O group experienced a shift upfield between three and four times as great. The difference in chemical shift changes for the two types of proton were due to the opposing effects of the tertiary and quaternary nitrogens.

In the case of the unsubstituted pyrazine mono-N-oxide (92) and pyrazine 1,4-dioxide, the sum of the individual changes was greater for the mono-N-oxide than for the change in the dioxide. In the dioxide $\Delta \delta (H-2) = \Delta \delta (H-3) = +35$ c/s but in the monoxide $\Delta \delta (H-2) = +31$ c/s and $\Delta \delta (H-3) = +9$ c/s. However, in the quinoxaline series, the sum of the individual changes was found to be almost the same as for the change in the dioxide. $\Delta \delta (H-2) = ...$
\[ \Delta \delta(H-3) = 34 \text{ c/s}, \text{ while in 1-oxide} \Delta \delta(H-2) = +25 \text{ c/s and} \]
\[ \Delta \delta(H-3) = +7 \text{ c/s}. \]

In the case of the oxidation products of 2-methyl pyrazine, confusion was caused in the literature where a wrong assignment of the isomeric N-oxides was made. On preparation of the two isomeric N-oxides by the method of Kloesch and Gumprecht, two products were obtained, a solid m.pt. 145-146°C and a solid m.pt. 91-92°C.

![Diagram](image-url)

According to their report, 2-methylpyrazine 1-oxide (94) melted at 145-146°C and the 4-oxide (95) at 91-92°C. From the n.m.r. spectrum observation of the shape of the peaks and the chemical shifts of the individual protons suggested that their assignment should be reversed. Their proof of structure was based on the reaction with acetic anhydride. 2-Methylpyrazine 1-oxide was reported to give 2-hydroxymethylpyrazine on hydrolysis of the acetate. The product m.pt. 91°C which was obtained was treated with acetic anhydride and the product obtained was 2-hydroxymethylpyrazine from the n.m.r. spectrum. This suggested that the product m.pt. 91-92°C was (94), and not (95) as they had suggested.

Klein and Berkowitz also disagreed with the results of Kloesch and Gumprecht. They claimed the formation of only one
monoxide (95) in two different melting forms and put forward as proof, spectral data, and the reaction with phosphorus oxychloride which gave an identical product with both compounds. These workers, however, failed to isolate both monoxides which were formed.

In 1964, Gumprecht\textsuperscript{30} reported in a footnote to a further paper on pyrazine mono-N-oxides that the two isomeric N-oxides had been wrongly assigned and that (94) had m.pt. 91-92\textdegree C.
MASS SPECTROMETRY OF AMINE OXIDES

The application of mass spectrometry to the identification of amine oxides is of considerable importance. It is not always easy to establish the presence of an N-oxide function in a molecule by means of infrared spectroscopy since the N-O stretching frequency for aromatic amine oxides occurs in the fingerprint region between 1400 cm\(^{-1}\) and 1250 cm\(^{-1}\). The use of mass spectrometry can overcome this difficulty.

It has been shown by Bryce and Maxwell\(^{81}\) that in the case of quinoline N-oxides of general structure (96), the mass spectra indicated that the parent ions were present in 70-100% of the base peak intensity.

Further to this, they showed that in all the spectra there was an abundant (P-16\(^+\)) ion (15-40%) corresponding to the loss of a single oxygen atom from the molecule. Comparison with spectra of the type (97) showed that (P-16\(^+\)) ions in (97) were of 0 \(\rightarrow\) 0.4% abundance; in this case the very small ions arose from within the nitro group. Loss of a single oxygen atom from a molecular ion has been observed for nitro compounds, anthraquinones and epoxides. The largest losses are in the order of 6-8% and most are under 3%.

The scope of this method for the detection of N-oxides was found by determining the mass spectra of some other compounds.
They found that abundant parent ions were observed and in the case of phenazine di-N-oxide the \((P-16)^+\) ion was the base peak. The spectra of these phenazine di-N-oxides also showed abundant \((P-32)^+\) ions corresponding to the loss of two oxygen atoms. Large \((P-16)^+\) ions were observed for azoxybenaene (38%) and 4-nitropyridine 1-oxide (68%). The spectra of a substituted 2-hydroxy-isoquinolin-3-one (98) and a substituted 1-hydroxy-quinolin-4-one (99) both of which could tautomerise to the corresponding N-oxide showed \((P-16)^+\) ions of 44% and 42% respectively. The preferred form from infra-red spectroscopy \(^{82}\) is the hydroxy-ketone form and (99) showed \((P-17)^+\) as the parent ion.

The results have shown that the \((P-16)^+\) ion is generally more abundant for N-oxides than for any other type of molecular ion losing one oxygen atom. It may thus be taken as a guide to the presence of a N-oxide function in the molecule.

However, Grigg and Odell \(^{83}\) have reported that the abundance of the \((P-16)^+\) ion can be considerably affected by substituents in an ortho position as in the 2-alkylpyridine N-oxides. The base peaks of these have been shown to be the \((P-OH)^+\) ions. They have also reported that \(\Delta^1\)-pyrroline N-oxides, in sharp contrast to the aromatic N-oxides show much smaller amounts (about 1-10%) of \((P-16)^+\) ions, and hence the \((P-16)^+\) ion is not of diagnostic value.
for these compounds.

From this it may be concluded that large (P-16)$^+$ ions are not characteristic of the N-oxide function in all cases but may be of some diagnostic value in aromatic N-oxides.

The fragmentation of molecules when bombarded with electrons is frequently complex. This arises from the fact that the molecules are in an excited state, owing to the electron bombardment energy, and hence normal patterns of bond cleavage are not always observed. Owing to the high vacua in mass spectrometers, the reactions are normally unimolecular, although occasionally ion-molecule reactions are observed. The fragmentation pattern for the decomposition of an ion $m_1^+$ to an ion $m_2^+$, frequently leads to the observation of a broad peak (a metastable ion) in the mass spectrum whose position is given by $m^* = m_2^2/m_1$; the presence of such an ion defines the process $m_1^+ \rightarrow m_2^+ + x$ where $x$ is a neutral molecule, radical or atom.

The general fragmentation pattern of nitrogen heterocycles is of relevance here; the cracking patterns from the mass spectra of pyridine and the simple methylpyridines are well established and show the parent ion to be the base peak. However, the size of the (P-1) ion relative to the parent ion increases with the number of substituent groups. The parent ion in pyridines must be formed by the ionisation of one of the non-bonding electrons attached to the nitrogen since the ease of ionisation of electrons is $n > \pi > \sigma$.

In the benzoazine series the mass spectra of quinoline and isoquinoline are very similar. The heterocyclic ring is most readily broken. In both cases the molecular ion is the base peak
and the dominant processes are \((P)^+ \rightarrow (P-1)^+\) and \((P)^+ \rightarrow (P-27)^+\); i.e. loss of an hydrogen atom or loss of HCN. The other important ions formed are \(C_6H_4^+, C_4H_3^+, C_4H_2^+,\) and \(C_3H_3^+\), the last three of which also appear in the decomposition of pyridine. The most probable structures which can be attributed to these are that \(C_6H_4^+\) is probably the cation of benzyne (100): \(C_4H_3^+\) may be represented by both an open structure identical with that of a protonated diacetylene (101) or a cyclic structure identical to the cyclobutadiene cation less a hydrogen atom (102): \(C_4H_2^+\) is best represented as the cation (103), identical with that formed from diacetylene by the loss of one \(\pi\) electron, since a cyclic structure is less likely because of strain: \(C_3H_3^+\) is best represented by the cyclopropenyl cation with 2 \(\pi\) electrons (104).

An investigation of the mass spectra of cinnoline and its N-oxides, including deuterated samples for tracing decomposition pathways, has been carried out. No previous work is reported for this group of compounds. The principal ions (>1% of the parent peak) are indicated in the tables of spectra of the different samples investigated. The parent ion is the base peak in nearly all the samples.

**Cinnoline**

In cinnoline, the base peak is the parent ion; this is characteristic of an azine, with the electron loss probably coming from one of the non-bonding pairs. The di-cation of the parent ion is present in the spectrum but only in trace amount. Its presence may be confirmed by an ion at \(m/e = 65.5^+\) which corresponds to \((^{12}C_7^{13}C_1^{1H_6}^{14}N_2)^{++}\); since the \(m/e\) abundance ratios \(131^+\) to \(130^+\)
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and 65·5⁺ to 65⁺ are approximately equal, most of the m/e = 65⁺ ion is the \((1^2\text{C}_8\text{H}_6\text{N}_2)^{++}\) ion. The formation of this cation is of interest since it is almost certainly 1,2-cinnolyne (105a).

The major ions appear at m/e = 130⁺, 102⁺, 76⁺, 51⁺. The decomposition of the parent ion may be followed by metastable ions which show that the following processes occur:

\[
\begin{align*}
\text{C}_8\text{H}_6\text{N}_2^+ \rightarrow & \rightarrow \text{C}_8\text{H}_6^+ + \text{N}_2^+ \rightarrow \text{C}_6\text{H}_4^+ + \text{C}_2\text{H}_2^+ \\
\text{m/e} = 130^+ & \rightarrow \text{m/e} = 102^+ & \text{m/e} = 76^+ \\
\text{C}_4\text{H}_3^+ + \text{C}_2\text{H}^+ & \rightarrow \text{m/e} = 51^+
\end{align*}
\]

In most of these processes the assignment of a formula to a particular m/e is unambiguous except for \((P-28)^+\) which could be \((P-\text{N}_2)^+\) or \((P-\text{C}_2\text{H}_4)^+\) where P is the parent ion; high resolution measurements confirmed the former as expected. The other major ions for which no \(m^e\) is observed are at m/e = 50⁺, 39⁺. These are \(\text{C}_4\text{H}_2^+, \text{C}_2\text{H}_3^+\) respectively.

3-Deuterocinnoline and 4-Deuterocinnoline

The major ions appear at m/e = 131⁺, 103⁺, 77⁺, 76⁺, 51⁺, 50⁺. Decomposition of the parent ion is observed by the following processes
There are no observable metastable ions for processes leading to
m/e = 51+ and 50+, but possible decompositions from 77+ and 76+
may be outlined as,

\[ \text{C}_6\text{H}_3\text{D}^+ \rightarrow \text{C}_4\text{H}_2\text{D}^+ + \text{C}_2\text{H}_2 \quad \text{C}_6\text{H}_3\text{D}^+ \rightarrow \text{C}_4\text{H}_2^+ + \text{C}_2\text{HD} \]

m/e = 77+ \quad m/e = 51+ \quad m/e = 77+ \quad m/e = 50+

The further decomposition of 78+, 77+, 70+ is probably the
same as for the monodeutero compounds in the case of 77+ and 76+
while the decomposition of 78+ may be outlined as follows:

**3α-Dideuterocinnoline**

The major ions appear at m/e = 132+, 104+, 78+, 77+, 76+, 52+, 51+, 50+. Decomposition of the parent ion by the following processes occurs by the observed metastable ions.

\[ \text{C}_8\text{H}_4\text{D}_2\text{N}_2^+ \rightarrow \text{C}_8\text{H}_4\text{D}_2^+ + \text{N}_2 \quad \text{m}^+ = 58.5 \quad \text{C}_6\text{H}_2\text{D}_2^+ + \text{C}_2\text{H}_2 \]

m/e = 132+ \quad m/e = 104+ \quad m/e = 78+

\[ \text{C}_6\text{H}_2\text{D}^+ + \text{C}_2\text{HD} \quad \text{C}_6\text{H}_4^+ + \text{C}_2\text{D}_2 \]

m/e = 77+ \quad m/e = 76+
The principal loss from the molecular ion in all these compounds is a molecule of nitrogen. In the monodeutero compounds for m/e=103, C\textsubscript{6}H\textsubscript{5}D\textsuperscript{+}, the ratio of abundances of m/e = 76\textsuperscript{+} to 77\textsuperscript{+} formed on decomposition of m/e = 103\textsuperscript{+} is about 1:1. This would tend to suggest a migration of the deuterium atom to give total equivalence of hydrogen and deuterium around the ring and thus random loss of hydrogen or deuterium. This leads to an almost equal chance of the formation of C\textsubscript{6}H\textsubscript{4}\textsuperscript{+} or C\textsubscript{6}H\textsubscript{3}D\textsuperscript{+}. In the case of the dideutero compound for m/e = 104\textsuperscript{+}, the ratio of possible decomposition products m/e = 76\textsuperscript{+}, 77\textsuperscript{+}, 78\textsuperscript{+} is 1:1:5:1. This leads to a greater chance of losing C\textsubscript{2}HD from C\textsubscript{6}H\textsubscript{4}D\textsubscript{2}\textsuperscript{+} than C\textsubscript{2}H\textsubscript{2} or C\textsubscript{2}D\textsubscript{2}.

Some of the obvious structures for the C\textsubscript{6}H\textsubscript{6}\textsuperscript{+} ions are a, b, c. In view of the behaviour of the deutero compounds, if the ions a or b are involved it seems that randomisation of the deuterium positions occur.

**4-Methylcinnoline**

The major ions appear at m/e = 114\textsuperscript{+}, 115\textsuperscript{+}, 89\textsuperscript{+} and 63\textsuperscript{+}. A major decomposition route of the parent ion may be followed by the presence of metastable ions which confirm the following degradations

\[
\begin{align*}
\text{C}_{6}\text{H}_{5}\text{N}_{2}^{+} & \xrightarrow{m^*=91.8} \text{C}_{6}\text{H}_{7}^{+} + \text{N}_{2}^{+} + \text{H} & \text{m}^* = 68.8 & \text{C}_{7}^{+} + \text{C}_{2}\text{H}_{2}^{+} \\
\text{m/e}=114^{+} & \text{m/e}=115^{+} & \text{m/e}=89^{+}
\end{align*}
\]

\[
\begin{align*}
\text{m}^* = 114.6 & \text{C}_{5}\text{H}_{3}^{+} + \text{C}_{2}\text{H}_{2}^{+} \\
\text{m/e}=63^{+}
\end{align*}
\]
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Confirmation of \( m/e = 115^+ \) being \( \text{C}_9\text{H}_7^+ \) has been obtained by high resolution measurements which thus fixes \( 89^+ \) as \( \text{C}_7\text{H}_5^+ \) and \( 63^+ \) as \( \text{C}_5\text{H}_3^+ \).

Other degradations which have been confirmed by the presence of metastable ions are:

\[
\begin{align*}
\text{C}_9\text{H}_8\text{N}_2^+ & \quad m/e = 56.3 \rightarrow \text{C}_7\text{H}_6^+ \\
\text{m/e} &= 144^+ \\
\text{C}_9\text{H}_7^+ & \quad m/e = 88.6 \rightarrow \text{C}_8\text{H}_5^+ \\
\text{m/e} &= 115^+
\end{align*}
\]

In 4-methylcinnoline there is a strong parent ion and the presence of a di-cation can be detected from the ratio of abundances of peaks at 145 to 144 and 72.5 to 72. This shows the presence of 4-methyl-1,2-cinnolyne (105b).

The species at \( m/e = 130^+ \) is of interest, since it arises (as shown by high resolution measurement) from the loss of a nitrogen atom. If the extent of rearrangement during the expulsion of the nitrogen atom is small, then a structure similar to the (P-1) cation from 3-methylindole might be expected and it seems that the latter is the quinolinium ion formed by ring expansion. The spectrum of \( 15_N \) enriched 4-methylcinnoline will help to ascertain which nitrogen is lost from molecular ion.

There are two possible structures for the highly abundant \( \text{C}_9\text{H}_7^+ \) ion which are compatible with the formation of an abundant dipositive ion (\( m/e = 57.5^+ \)) and with the structures of the aromatic precursors. These are the indenyl cation (106) and the phenylcyclopropenium cation (107). The formation of either of these ions from 4-methylcinnoline implies substantial rearrangement of
Scheme B:

\[ \text{m/e} = 144^+ \]

\[ \text{m/e} = 115^+ \]

\[ \text{m/e} = 115^+ \]

(106)

\[ \text{m/e} = 89^+ \]

(108)

\[ \text{m/e} = 63^+ \]

(109)
the hydrogen atoms attached to the hetero ring.

\[ \text{(106)} \quad \text{(107)} \]

The \( \text{C}_9\text{H}_7^+ \) ion, formed in high abundance in the mass spectrum of indene, is readily interpreted in terms of (106) where complete delocalisation of the \( \pi \) electron cloud is achieved. A comparison of the spectra of indene and \( \mu \)-methylcinnoline below \( m/e = 115^+ \) shows the similarity is striking and it is most likely that \( m/e = 115^+ \) may be represented by (106). A possible route to this is outlined in Scheme B.

The ions at \( m/e = 89^+ \) and \( 63^+ \), \( \text{C}_7\text{H}_5^+ \) and \( \text{C}_5\text{H}_3^+ \), are probably closely related to the \( \text{C}_7\text{H}_7^+ \) and \( \text{C}_5\text{H}_5^+ \) cations which occur in the spectra of many aromatic hydrocarbons. Thus if as is generally accepted, \( \text{C}_7\text{H}_7^+ \) is the tropylum cation and \( \text{C}_5\text{H}_5^+ \) is the cyclopentadienyl cation, then \( \text{C}_7\text{H}_5^+ \) and \( \text{C}_5\text{H}_3^+ \) are probably their 1,2-dehydro derivatives, whose classical structures are (108) and (109) respectively.

A number of other hydrocarbon ions are observed in the range \( m/e = 39^+ \) to \( 75^+ \) and these arise most probably from the decomposition of the carboxylic ring.

\textit{8-Deutero-\( \mu \)-methylcinnoline}

The major ions are at \( m/e = 145^+ \), \( 144^+ \), \( 116^+ \), \( 115^+ \), \( 90^+ \), \( 89^+ \), \( 64^+ \), \( 63^+ \). From the n.m.r. spectrum, there was a very small
percentage of undeuterated material present. This explains the presence of peaks at m/e = 114+ and 115+ which are both very abundant ions in the undeuterated compound.

The major decomposition route can be shown by the observed metastable ions:

\[ \text{C}_9\text{H}_7\text{DN}_2^+ \xrightarrow{m^* = 92.8} \text{C}_9\text{H}_6\text{D}^+ + \text{N}_2 + \text{H} \]
\[ m/e = 114^+ \quad m/e = 116^+ \]
\[ \xrightarrow{m^* = 69.8} \text{C}_7\text{H}_2\text{D}^+ + \text{C}_2\text{H}_2 \]
\[ m/e = 90^+ \]
\[ \xrightarrow{m^* = 45.5} \]

\[ \text{C}_5\text{H}_3^+ + \text{C}_2\text{H}_2 \xrightarrow{m^* = 89} \text{C}_7\text{H}_5^+ + \text{CHD} \]
\[ m/e = 63^+ \quad m/e = 89^+ \]

The other decomposition step which is possible here has no observed metastable ion:

\[ \text{C}_7\text{H}_4\text{D}^+ \xrightarrow{m/e = 90^+} \text{C}_5\text{H}_3^+ + \text{CHD} \]
\[ m/e = 63^+ \]

The parent ion at 114+ is again an abundant ion and the dication is observable at m/e = 72.5+. From the strong peak at m/e = 116+, the structure here is C\text{H}_6\text{D}^+ and on degradation the peaks at m/e = 90+ and 89+ are of almost equal abundance which represent the loss of either C\text{H}_2 or C\text{H}D respectively. These losses are more readily accounted for by a structure like (106). The ratio of m/e = 64 to 63 in the deutero compound is almost double that in the undeuterated compound which indicates an equal possibility of the retention or loss of a deuterium atom in the degradation.

It is apparent that in the case of the cinnolines, the heteroatom ring decomposes more readily as is the case with other heteroaromatic compounds.
The Cinnoline N-oxides

In all the cinnoline N-oxides considered, the parent ion is the most abundant ion. These ions no doubt contain one unpaired non-bonding electron, as do the cinnoline cations but it is not possible to assign the relative amounts of positive charge to the nitrogen, oxygen and surrounding carbon atoms. The formation of an abundant (P-16)$^+$ ion is easily interpreted in terms of the classical substructure $\overset{\cdot}{N} = \overset{\cdot}{N} (\overset{\cdot}{O}^-)\cdot$, and this representation is used in the present work.

For both the 1-oxides and 2-oxides an important fragmentation path proceeds through the formation of the deoxygenated cations; many of the ions of lower m/e than these can thus be attributed to decompositions similar to those of the parent bases. In comparison with the parent ions (P)$^+$, the abundance of the (P-O)$^+$ ions show marked variations for the different series. In the 4-CH$_3$ series, (P-O)$^+$ for 1-oxide is 49% and for 2-oxide, 15.6%; in the 4-H series, for the 1-oxide, 9.6%, and the 2-oxide, 15.1%; and in the 4-D series, for the 1-oxide, 19.2%, and the 2-oxide 24.6%. Thus the presence of the methyl group is of importance either to the relative stabilities of the parent ions or to the ease of deoxygenation relative to the other modes of decomposition. The high proportion of (P-O)$^+$ in the 4-methyl 1-oxide spectrum is suggestive of the latter since the electron-releasing nature of the 4-CH$_3$ group will be most strongly felt at N=1 and this will be of assistance to loss of the oxygen atom.
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Scheme C

\[ \begin{align*}
R=H & \quad m/e=119^+ \\
R=CH_3 & \quad m/e=133^+ \\
CH_3CO^+ & \quad m/e=43^+
\end{align*} \]
Cinnoline 1-oxide

The major ions appear at m/e = 146⁺, 130⁺, 119⁺, 116⁺, 102⁺, 92⁺, 90⁺, 89⁺, 76⁺, 63⁺ and 50⁺.

The presence of metastable ions indicates the following decompositions.

\[
\begin{align*}
C_7H_5NO^+ & \rightarrow C_6H_4O^+ & C_8H_6^+ & \rightarrow C_6H_4^+ \\
m/e=119^+ & \quad m/e=92^+ & m/e=102^+ & \quad m/e=76^+
\end{align*}
\]

\[
\begin{align*}
C_7H_5^+ & \rightarrow C_5H_3^+ & C_7H_6^+ & \rightarrow C_7H_5^+
\\m/e=89^+ & \quad m/e=63^+ & m/e=90^+ & \quad m/e=89^+
\end{align*}
\]

High resolution measurements confirm the ions at m/e = 102⁺ as C₈H₆⁺, 92⁺ as C₆H₄O⁺, 90⁺ an equal mixture of C₇H₆⁺ and C₆H₄N⁺, and 89⁺ as C₇H₅⁺.

Other possible decompositions that may take place but for which there are no observed metastable ions are as follows:

\[
\begin{align*}
C_8H_6N_2O^+ & \rightarrow C_8H_6N_2^+ \rightarrow C_8H_6^+ + N_2 \\
m/e=146^+ & \quad m/e=130^+ & \quad m/e=102^+
\end{align*}
\]

\[
\begin{align*}
C_8H_6N_2O^+ & \rightarrow C_7H_5NO^+ + HCN \\
m/e=146^+ & \quad m/e=119^+
\end{align*}
\]

The parent ion appears as the strongest ion at m/e = 146⁺.

The ion at m/e = 130⁺ is due to the loss of the oxygen atom. The next ion considered at m/e = 119⁺ indicates the loss of HCN from the molecule. It is probably attributable to the ease of alternative processes to deoxygenation. The possible structure for this ion is the anthranil cation leading to the further loss of HCN to give the ion m/e = 92⁺, C₆H₄O⁺ as shown in Scheme C. Further confirmation of the formation of a C-4 to O bond is the formation
of CH₃CO⁺ (high resolution measurement) at m/e = 43⁺ in the spectrum of 4-methylcinmolone 1-oxide (see below).

The peak at m/e = 102⁺ indicated the loss of N₂O from the parent ion. The two most reasonable structures for the resulting C₈H₆⁺ ion are the benzocyclobutadiene (110) and the cyclo-octa-3,5,7-trien-1-yne (111) cations; the loss of acetylene to give C₆H₄⁺, presumably the benzyne cation was suggestive of the former.

The 90⁺ ion has been shown to be a 1:1 mixture of C₆H₄N⁺ and C₇H₆⁺. It seems probable that the formation of C₆H₄N⁺ occurs from C₆H₆N⁺ → C₆H₄N⁺ + C₂H₂. Direct formation from the parent ion by simultaneous loss of NO and C₂H₂ seems less likely in view of the extensive rearrangement which would have to take place.

The 89⁺ ion is very abundant and may be formed by direct loss of NO and HCN from the parent ion, or by successive loss in either order of these groups. No metastable ions have been observed for the process leading to C₇H₅⁺ in this case. A possible structure for this has already been postulated.

The ions of lower m/e are formed by the subsequent fragmentation of the carbocyclic ring and structures for these have already been postulated.
**4-Deuterocinnoline 1-oxide**

The principal ions appear at \( m/e = 147^+, 131^+, 103^+, 92^+, 90^+, 77^+, 76^+, 64^+, 63^+, 51^+, 50^+ \).

The presence of metastable ions indicates the following decomposition processes:

\[
\begin{align*}
\text{C}_7\text{H}_4\text{DNO}^+ & \quad m/e=70.5 \quad \text{C}_6\text{H}_4^+ & \quad m/e=92^+ \\
m/e=120^+ & \quad m/e=103^+ & \quad m/e=77^+
\end{align*}
\]

\[
\begin{align*}
\text{C}_8\text{H}_5\text{D}^+ & \quad m/e=57.5 \quad \text{C}_6\text{H}_3\text{D}^+ \\
m/e=103^+ & \quad m/e=77^+ & \quad m/e=64^+
\end{align*}
\]

\[
\begin{align*}
\text{C}_7\text{H}_4\text{D}^+ & \quad m/e=56.1 \quad \text{C}_6\text{H}_4^+ \\
m/e=103^+ & \quad m/e=76^+ & \quad m/e=90^+ & \quad m/e=63^+
\end{align*}
\]

The other major decompositions which may take place but for which there are no observed metastable ions are:

\[
\begin{align*}
\text{C}_8\text{H}_5\text{DN}_2\text{O}^+ & \quad \text{C}_8\text{H}_5\text{D}^+ + 0 \quad \text{C}_8\text{H}_5\text{D}^+ + \text{N}_2 \\
m/e=147^+ & \quad m/e=131^+ & \quad m/e=103^+
\end{align*}
\]

\[
\begin{align*}
\text{C}_8\text{H}_5\text{DN}_2\text{O}^+ & \quad \text{C}_8\text{H}_5\text{DNO}^+ + \text{H}_2\text{CN} \\
m/e=147^+ & \quad m/e=120^+
\end{align*}
\]

The individual ions in the 4-deutero compound are very similar to those for the parent cinnoline 1-oxide. The parent ion is the strongest ion at \( m/e = 147^+ \). The ion at \( m/e = 120^+ \) can again be attributed to an anthranil cation where \((R = D)\) in Scheme C as a process \( 120^+ \rightarrow 92^+ \) is found leading to \( C_6H_4O^+ \).

The \( m/e = 103^+ \) ion gives two products on degradation, ions at \( m/e = 77^+ \) and \( 76^+ \), the latter being formed in greater abundance. This supports the assignment of a structure of form (110) for \( C_8H_6^+ \) and \( C_5H_5D^+ \).
There is almost equal abundance of ions at $m/e = 63^+$ and $64^+$ which is suggestive of the structure of $m/e = 90^+$, $C_7H_4D^+$, being of type (108).

**4-Methylcinnoline 1-oxide**

The principal ions appear at $m/e = 160^+$, $134^+$, $115^+$, $89^+$, $63^+$, $50^+$, which is suggestive of the structure of $m/e = 90^+$, $C_7H_4D^+$, being of type (108). There are very few observable metastable ions to identify decomposition processes. The loss of oxygen from the parent ion to give $C_9H_8N_2^+$, the 4-methylcinnoline cation, and the presence of similar ions to those in the spectrum of 4-methylcinnoline suggest that a major decomposition pattern is the same as for 4-methylcinnoline after loss of the oxygen.

Other ions which are of interest are at $m/e = 133^+$ and $43^+$. The presence of $m/e = 133^+$, $C_8H_7NO^+$, may be attributed to the loss of HCN from the parent ion. The abundance of this ion is not as great as that of $m/e = 119^+$ in 4-H compound, or $m/e = 120^+$ in 4-D compound but the structure for this ion is most probably the 3-methylanthranil cation (as in Scheme C). Compelling evidence for this structure comes from the presence of a strong $m/e = 43^+$, $CH_3CO^+$ ion which is negligible in the others although they display HCO$^+$ and DCO$^+$ ions respectively, but to a smaller extent.

**Cinnoline 2-oxide**

The major ions appear at $m/e = 146^+$, $130^+$, $116^+$, $102^+$, $90^+$, $89^+$, $76^+$, $63^+$, and $50^+$.

A major decomposition pattern has been established by the presence of metastable ions:


\[ C_6H_6N_2O^+ \xrightarrow{m^e=71.2} C_6H_4^+ \xrightarrow{m^e=56.6} C_6H_4^+ + C_2H_2 \xrightarrow{m^e=33.0} \]
\[ m/e=146^+ \quad m/e=102^+ \quad m/e=76^+ \]

\[ C_4H_2^+ + C_2H_2 \]
\[ m/e=50^+ \]

Also \[ C_8H_6N^+ \xrightarrow{m^e=68.3} C_7H_5^+ + HCN \xrightarrow{m^e=146^+} C_5H_3^+ + C_2H_2 \]
\[ m/e=116^+ \quad m/e=89^+ \quad m/e=63^+ \]

Other possible decomposition steps for which there are no observed metastable ions are:

\[ C_8H_6N_2O^+ \xrightarrow{m/e=146^+} C_8H_6N_2^+ \quad C_8H_6N_2O^+ \xrightarrow{m/e=130^+} C_8H_6N^+ + NO \]
\[ m/e=130^+ \quad m/e=146^+ \quad m/e=116^+ \]

The parent ion \( m/e = 146^+ \) is the most abundant ion in the spectrum, and leads to the ion at \( m/e = 130^+ \) by the loss of oxygen.

The ion at \( m/e = 116^+ \) occurs by the loss of NO from the parent ion to give \( C_6H_6N^+ \). The most obvious structure for the \((P-NO)^+\) ion is the \((P-l)^+\) ion of indole (112). The decomposition of this indolyl cation with loss of HCN to give ion at \( m/e = 89^+ \), \( C_7H_5^+ \), and then further loss to \( C_5H_3^+ \), is corroborated by the presence of appropriate metastable ions. The structures of these ions at \( m/e = 89^+ \) and \( 63^+ \) have already been discussed.

The ion at \( m/e = 102^+ \), \( C_8H_6^+ \), is brought about by loss of \( N_2O \) from the parent ion. The further fragmentation pattern, as outlined is the same as for cinnoline, itself.

The ion at \( m/e = 90^+ \) may be due to two possible species, \( C_7H_6^+ \) or \( C_6H_4N^+ \). The presence of a possible metastable ion at \( 88.0 \) is suggestive of the former, but both may be present. The ion \( C_7H_6^+ \) may arise by loss of \( GN_2O \) from the parent ion while \( C_6H_4N^+ \) will arise from the loss of \( C_2H_2NO \). Possible structure for these are indicated.
**1-Deuterocinnoline 2-oxide**

The major ions appear at m/e = 147+, 131+, 117+, 103+, 90+, 89+, 77+, 76+, 64+, 63+, 51+, 50+.

The presence of metastable ions was not observed in the spectrum but the major decomposition steps must be similar to those for cinnoline 2-oxide. The possible decomposition steps are:

\[
C_{8}H_{5}DN_{2}O^{+} \rightarrow C_{8}H_{5}D^{+} + N_{2}O \rightarrow C_{6}H_{3}D^{+} + C_{2}H_{2} \text{ or } C_{6}H_{4}^{+} + C_{2}HD
\]

m/e=147+  m/e=107+  m/e=77+  m/e=76+

\[
C_{6}H_{3}D^{+} \rightarrow C_{4}H_{2}^{+} + C_{2}HD \text{ or } C_{4}HD^{+} + C_{2}H_{2}^{+}
\]

m/e=77+  m/e=50+  m/e=51+

\[
C_{8}H_{5}DN_{2}0^{+} \rightarrow C_{8}H_{5}DN^{+} + NO \rightarrow C_{7}H_{4}D^{+} + HCN
\]

m/e=147+  m/e=117+  m/e=90+

\[
\rightarrow C_{5}H_{2}D^{+} + C_{2}H_{2} \text{ or } C_{5}H_{3}^{+} + C_{2}H_{2}
\]

m/e=64+  m/e=63+. 

The parent ion is the most abundant ion and the decomposition pathway from C_{8}H_{5}D^{+} at m/e = 103+ gives an equal abundance of ions at m/e = 77+ and 76+. There is thus an equal chance of the loss of C_{2}H_{2} or C_{2}HD from C_{8}H_{5}D^{+}.

The decomposition of the parent ion via the indolyl cation is apparent also from the presence of peaks at 117+, 90+, 64+ and 63+.

**1-Methylcinnoline 2-oxide**

The major ions appear at m/e = 160+, 144+, 131+, 115+, 103+, 90+, 89+, 77+, 63+. High resolution measurements have shown that the ions at m/e = 131+ are C_{9}H_{7}O^{+}; 115+ are C_{9}H_{7}^{+}; 103+ are C_{8}H_{7}^{+}; 90+ are a 1:1 mixture of C_{7}H_{6}^{+} and C_{6}H_{4}^{+}; 89+ are C_{7}H_{5}^{+}; 77+ are C_{6}H_{5}^{+}. 

The major decomposition steps are confirmed by the presence of metastable ions.

\[ \text{C}_9\text{H}_8\text{N}_2\text{O}^+ \xrightarrow{m/e=107.5} \text{C}_9\text{H}_7^+ + \text{N}_2 \text{H} \]
\[ \text{C}_9\text{H}_8\text{N}_2\text{O}^+ \xrightarrow{m/e=66.1} \text{C}_8\text{H}_7^+ + \text{CH}_2\text{N}_2\text{O} \]

Other processes which possibly take place but for which there are no observed metastable ions are:

\[ \text{C}_9\text{H}_8\text{N}_2\text{O}^+ \rightarrow \text{C}_9\text{H}_5^+ + \text{C}_2\text{H}_2 \]

The parent ion \( \text{C}_9\text{H}_8\text{N}_2\text{O}^+ \), \( m/e = 160^+ \) is the most abundant ion. The ion at \( m/e = 131^+ \) is formed by the loss of oxygen to give the 4-methylcinnoline cation, \( \text{C}_9\text{H}_8\text{N}_2^+ \). The ion at \( m/e = 131^+ \) is formed by the extrusion of a nitrogen molecule and a hydrogen atom. This requires a migration of the oxygen atom to carbon from N-2. The direction of migration is most probably towards C-3 or further round the heteroring rather than across N-1 to C-8; in the latter case the 4-CH\(_3\) group does not appear likely to be a strong influence on the process. Possible structures for the \((\text{P-N}_2)^+\) and \((\text{P-N}_2\text{H})^+\) cations are the 3-methylbenzofuran (113) and benzopyrylium (114) cations respectively.

* The methylfurans readily lose a hydrogen atom in the mass spectrometer; this has been ascribed to the formation of pyrylium (115) ions rather than methylenefurans (116). Methylbenzofurans would be expected to behave in the same manner.
The ion at $m/e = 115^+$ is the C$_9$H$_7^+$ ion, the indenyl cation, which is also formed in great abundance in 4-methylcinnoline itself. The decomposition of this ion leads to $m/e = 89$, C$_7$H$_5^+$ and C$_5$H$_3^+$ both of which have established structures.

The ion at $m/e = 103^+$ is C$_8$H$_7^+$; this is brought about by loss of CHN$_2$O from the parent ion. Possible processes for the formation of this ion are the simultaneous loss of HCO + N$_2$ or (N$_2$ + CO + H), or an extension of the $P^+ \rightarrow (P-N_2H)^+$ sequence or loss of C-8a as shown (117).

In the absence of $^{13}$C labelling at C-3 and C-8a, direct evidence is absent.

The ion at $m/e = 77^+$, C$_6$H$_5^+$, comes from C$_8$H$_7^+$ by loss of acetylene.

**4-Methylcinnoline 1,2-dioxide**

The major ions appear at $m/e = 176^+$, 160$^+$, 144$^+$, 133$^+$, 115$^+$, 104$^+$, 103$^+$, 90$^+$, 89$^+$, 77$^+$, 63$^+$, 43$^+$.

The following decompositions may occur from the observed metastable ions:
\[ \text{Other decompositions which may take place but for which there are no observed metastable ions are:} \]

\[ \text{C}_9\text{H}_8\text{N}_2\text{O}_2^+ \rightarrow \text{C}_9\text{H}_7^+ + \text{C}_8\text{H}_7^+ \]

\[ \text{C}_9\text{H}_8\text{N}_2\text{O}_2^+ \rightarrow \text{C}_9\text{H}_7^+ + \text{C}_8\text{H}_7^+ \]

\[ \text{The presence of a very abundant ion at } m/e = 133^+ \text{ and also of one at } m/e = 143^+ \text{ leads to the formation of the 3-methylanthalanatin cation from the parent ion with loss of HCNO and then further decomposition to give } m/e = 143^+, \text{ CH}_3\text{CO}^+. \text{ In this way the dioxide behaves like 1-methylcinnoline 1-oxide. The primary loss of oxygen in HCNO is from the 2-position. However, the ion at } m/e = 160^+ \text{ is more likely to be the cation of the 2-oxide with loss of oxygen from the one position. This may be confirmed from the processes shown above. The process, } m/e = 160^+ \rightarrow 117^+ \text{ with loss of HCNO must surely only arise from the 2-oxide while the other processes are prominent in the decomposition of the 2-oxide. Thus the dioxide may behave either as a 1-oxide or as a 2-oxide.} \]

\[ \text{The presence of the ions at lower } m/e \text{ is brought about by processes which have already been described. The ion at } m/e = 104^+ \text{ however, which is very abundant could possibly be } \text{C}_6\text{H}_8^+, \text{ C}_7\text{H}_6\text{H}^+, \text{ or } \text{C}_7\text{H}_4^+. \text{ No direct high resolution measurements were made on this ion and direct evidence of its structure has not been found.} \]
The Mass Spectra of 3-Deutero-4-trideuteromethylcinnoline (59) and its 2-oxide

Owing to some back exchange of hydrogen for deuterium, the sample used for the mass spectrum was only about 70% deuterated in the required 3- and 4-positions. This created a range of ions instead of a strong C$_9$H$_4$D$_4$N$_2$ parent ion. After allowing for $^{13}$C isotope contributions, the ratio of peak heights for (59) from 144$^+$ to 149$^+$ was as follows.

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<td>148</td>
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<td>C$_9$H$_4$D$_4$N$_2$</td>
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<td>28.9</td>
<td>C$_9$H$_6$D$_2$N$_2$</td>
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<td>C$_9$H$_7$DN$_2$</td>
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<tr>
<td>144</td>
<td>2.0</td>
<td>C$_9$H$_8$N$_2$</td>
</tr>
</tbody>
</table>

The ratio of 148$^+$ to 149$^+$ was 100:17 which was greater than could be explained by an isotope contribution. The abnormally large (P+1)$^+$ ion could not be explained other than in terms of an ion-molecule interaction, or further incorporation of deuterium. From the spectrum it was shown that the ion at m/e = 147$^+$ was most abundant and this represented the presence of three deuterium atoms spread between position 3 and 4. Each stage of the decomposition paths for the compounds was made up of a series of peaks, in the same ratio as those at m/e = 145$^+$, 146$^+$, 147$^+$, 148$^+$.

The oxidation of (59) to its 2-oxide provided a surprising result. The spectrum showed only ions at m/e = 160$^+$, 161$^+$, 162$^+$, 163$^+$ in the parent ion region, and the ion at m/e = 163$^+$ was the $^{13}$C
From this it was shown that there was less deuterium in the oxide than in the cinnoline. Exchange must have taken place during the oxidation process. The same phenomenon did not take place with 4-deuterocinnoline 1-oxide or 2-oxide, as, in both these products there was only a very small (P=1)$^+$ ion.

In the acidic conditions of the reactions direct exchange of hydrogen for deuterium is unlikely in the azine ring. The exchange probably takes place through a protonated species which leads to two possibilities as shown. The more obvious choice is (A) which would lead to complete exchange of 4-CD$_3$ to give 4-CH$_3$ with retention of 3-D. The most abundant ion in the oxide has only one deuterium atom. Although it is reported that the major isomer formed by protonation of 4-methylcinnoline is probably the 2-protonated species, in the reversible equilibrium of the reaction the smaller amount of 1-protonated cinnoline could lead to this exchange.

The degradation of the parent ions showed a repetition of the three peaks at smaller m/e with the ratio of the lightest increasing relative to the others. The ratio at m/e = 115$^+$, 116$^+$, 117$^+$ after $^{13}$C contributions had been taken into account was 51:95:15. The larger amount of m/e = 115$^+$ was due to the loss of deuterium from the deuterio-oxides as well as the degradation of P$^+$ = 160$^+$ which did not contain deuterium. This would support the possible exchange
Scheme A since the loss of deuterium from C-3 would lead to a larger m/e = 115\textsuperscript{+} contribution in the mixture from the mono-deutero oxide. The general pattern of degradation to lower m/e fragments was the same as for 4-methylcinnoline and its 2-oxide.

2.\textit{h}-Dimethylcinnolinium iodide (79a) and \textit{h}-methyl-2-trideutero-methylcinnolinium iodide (79b)

The spectrum of (79b) contained a (P + 1)\textsuperscript{+} peak whose intensity was too large after allowing for 1\textsuperscript{3}C contributions. No other explanation other than a possible ion-molecule reaction can be found for this. The (P/P-1)\textsuperscript{+} ratio for (79a:79b) is different; there is more loss of hydrogen from (79a), 83% v. 58%. Thus apparently some hydrogen is lost from N-CH\textsubscript{3} in (79a). Since the fragmentation pattern is very similar below 1\textsuperscript{44} for (79a) and (79b) and also is similar to that of 4-methylcinnoline it seems likely that (P-1)\textsuperscript{+} does not relate to loss of H\textsuperscript{+} from 4-CH\textsubscript{3} but is more probably a loss of H\textsuperscript{+} from C-3.

By consideration of the peaks at m/e=1\textsuperscript{44} and 1\textsuperscript{45} it can be shown that two different processes are taking place with equal probability. In (79a), m/e = 1\textsuperscript{44} is large and is either C\textsubscript{9}H\textsubscript{8}N\textsubscript{2}\textsuperscript{+}, (P-CH\textsubscript{3})\textsuperscript{+}, or C\textsubscript{10}H\textsubscript{10}N\textsuperscript{+}, (P-NH)\textsuperscript{+}. In (79b), m/e = 1\textsuperscript{44} is large and is either (P-CD\textsubscript{3})\textsuperscript{+}, or (P-ND\textsubscript{2})\textsuperscript{+}; clearly C\textsubscript{9}H\textsubscript{8}N\textsubscript{2}\textsuperscript{+} is more probable in each case. In (79a), 1\textsuperscript{45} is very small and only the isotope of 1\textsuperscript{44}, while in (79b), 1\textsuperscript{45} is large, and is either (P-CHD\textsubscript{2})\textsuperscript{+} or (P-NH\textsubscript{3})\textsuperscript{+}. (P-CHD\textsubscript{2})\textsuperscript{+} is much more probable and would be (P-H-CD\textsubscript{2})\textsuperscript{+} while in (79a) this would give m/e = 1\textsuperscript{44} by (P-H-CH\textsubscript{2})\textsuperscript{+} again. Thus the scheme as shown demonstrates the value of deuteration in
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the identification of two different processes.

In both spectra, the peaks at 127\(^+\) and 128\(^+\) are very abundant while they are very small in 4-methylcinnoline. The possible explanation of these peaks is the presence of 1\(^+\) and H\(_2\)I\(^+\).

The ions at m/e = 115\(^+\) and 116\(^+\) are present and are C\(_9\)H\(_7\)\(^+\) by analogy with 4-methylcinnoline for 115, and C\(_9\)H\(_8\)\(^+\) or C\(_9\)H\(_6\)D\(^+\) for (79a) or (79b) respectively at 116\(^+\). The ions of lower m/e are similar to 4-methylcinnoline except for m/e = 36\(^+\) and 42\(^+\) but there are no obvious points of significance for these.
EXPERIMENTAL PROCEDURES

1. Melting points were taken on a Gallenkamp melting point apparatus (M.F.-370) and are uncorrected.

2. Microanalyses were by Weiler and Strauss of Oxford and by Dr. Minnis of A.H. Baird Ltd., Edinburgh.

3. N.M.R. spectra were recorded on a Perkin-Elmer R.10 (60 Mc/s) nuclear magnetic resonance spectrometer using tetramethylsilane as an internal standard.

4. Mass spectra were recorded on an A.E.I. M.S.9 double-focussing mass spectrometer by Mr. W.H. Wolstenholme.

5. Infrared spectra were taken on a Unicam S.P.200 Spectrophotometer.

6. Solutions were dried over anhydrous sodium sulphate.

7. Chromatography was carried out on alumina (Type H, supplied by Peter Spence and Sons, Ltd., Widnes).
EXPERIMENTAL SECTION

1. Preparation of Cinnolines

4-Methylcinnoline (44a)

Preparation of o-aminophenyl, dimethyl-carbinol

Methyl iodide (360g.) was slowly added with stirring to magnesium (60g.) in dry ether (1100 ml.). After addition the mixture was stirred for 30 minutes. Methyl anthranilate (75g.) in dry ether (750 ml.) was added and the mixture stirred under reflux for one hour. After cooling, the reaction mixture was poured into ice-cold ammonium chloride solution and the aqueous solution extracted with ether (3 x 200 ml.). After drying, the solvent was removed to give a light red oil (75g.). The infrared spectrum had broad band $\nu_{\text{max}} = 3500-3300 \text{ cm}^{-1}$. It showed no absorption in carbonyl region. The n.m.r. spectrum in CCl$_4$ showed peaks at 3.4 $\gamma$, multiplet, 4 aromatic protons; 6.10 $\gamma$, broad singlet, NH$_2$ + OH; 8.65 $\gamma$, singlet, two identical CH$_3$ peaks.

Preparation of o-isopropenyl aniline

o-Aminophenyl, dimethyl carbinol (75g.) was heated under reflux with P$_2$O$_5$ (150g.) and dry benzene (750 ml.) for three hours. After cooling, the reaction mixture was made alkaline to pH 9 with ice-cold dilute ammonia solution. Extraction with ether, (4 x 100 ml.), drying and removal of solvent gave a dark red oil (58g.). The infrared spectrum had doublet $\nu_{\text{max}} = 3500$ and 3400 cm$^{-1}$ primary amine present. The n.m.r. spectrum in CCl$_4$ had peaks at 3.3 $\gamma$, multiplet, 4 aromatic...
protons; 4.85 γ, doublet, J = 12 c/s, C = CH₂; 6.25 γ, singlet, NH₂; 7.43 γ, singlet, CH₃.

Preparation of 4-methylcinnoline (4h)

o-isopropenyl aniline (36g.) was added to concentrated HCl (60 ml.) and 2NHCl (240 ml.). The mixture was cooled to -10°C and a solution of sodium nitrite (15.3g.) in water (50 ml.) added dropwise with stirring while keeping the temperature below -8°C. The diazotised solution was stirred for a further hour at -10°C and then kept at 0°C for three days. The reaction mixture was heated to 60°C for ten minutes and then neutralised with aqueous sodium carbonate. The aqueous solution was extracted with ether, (6 x 200 ml.). Drying and removal of the solvent left a dark green oil. This oil was repeatedly extracted with boiling light petroleum (b.pt. 60-80) from which the 4-methylcinnoline crystallised in yellow needles. m.pt. 72°C. Lit. m.pt. 72-73°C.

Yield = 18g. (46%) Lit. yield = 46% Theory.

The n.m.r. spectrum in CCl₄ had peaks at 1.0 γ, singlet, H-3; 1.6 γ, multiplet, H-8; 2.25 γ, multiplet, H-5, H-6, H-7; 7.42 γ, singlet, 4-CH₃.

4-Ethyl-3-methylcinnoline (4h)

Preparation of o-aminophenyl, diethyl carbinal

Ethyl bromide (215 ml.) was added to magnesium (60g.) in dry ether (1100 ml.) with stirring. Methyl Anthranilate (75g.) in dry ether (750 ml.) was added and the reaction mixture refluxed with stirring for one hour. The product obtained after
decomposition and extraction, was a reddish oil which eventually
gave a solid. Recrystallization from benzene gave white crystals.
m.p.t. 58-59°C. Yield = 85g. - Quantitative.
The infrared spectrum in nujol had broad peak $\nu_{\text{max}}$ 3500-3300 cm$^{-1}$.
The n.m.r. spectrum in CCl$_4$ had peaks at 3.37; multiplet, 4 aromatic
protons; 6.05 $\gamma$, singlet, NH$_2$ +OH; 8.15 $\gamma$, quartet, J = 8 c/s,
CH$_2$ group; 9.25 $\gamma$, triplet, J = 8 c/s, CH$_3$ group.

Preparation of 3-(o-aminophenyl)pent-2-ene (43)

o-Aminophenyl, diethyl carbinol (85 g.) was dehydrated by
refluxing with P$_2$O$_5$ (180g.) and dry benzene (900 ml.) for three
hours. Basification and extraction with ether (3 x 200 ml.) gave
a red oil (51 g.). (70% yield).
The infrared spectrum had sharp doublet $\nu_{\text{max}}$ 3500 and 3400 cm$^{-1}$.
The n.m.r. spectrum in CCl$_4$ was very complex but the overall
integral was in ratio 4:1:2:8 (low field to high field) which
accounted for all the protons.

Preparation of 4-ethyl-3-methylcinnoline (144b)

Diazotisation of 3-(o-aminophenyl)pent-2-ene (51g.) in
concentrated HCl (70 ml.) and 2 NH$_3$Cl (280 ml.) at -10°C with
sodium nitrite (17.8g.) in water (100 ml.) gave after three days,
on basification and extraction with ether (6 x 200 ml.) an oily
solid. Extraction of this with boiling light petroleum (b.p.t.
60-80) gave yellow needles. m.p.t. 78°C.
The n.m.r. spectrum in CCl$_4$ had peaks at 1.72 $\gamma$, multiplet, H-8;
2.35 $\gamma$, multiplet, H-5, 6, 7; 7.0 $\gamma$, quartet, J = 8 c/s, 4-CH$_2$;
7.12 $\gamma$, singlet, 3-CH$_3$; 8.75 $\gamma$, triplet, J = 8 c/s, 4-CH$_3$. 
Yield = 25g.  46% of Theory.

\[ \text{C}_{11}\text{H}_{12}\text{N}_{2} \] Requires C, 76.7; H, 7.0; N, 16.3%.

Found C, 76.7; H, 6.9; N, 17.0%.

Preparation of o-aminoacetophenone

Skatole (71g.) in methanol (1100 ml.) was added slowly with stirring to sodium periodate (250g.) in water (1350 ml.). The reaction mixture was stirred for one day and then the methanol was distilled off. The aqueous solution was extracted with dichloromethane, and after drying and removal of the solvent, a dark tarry oil was obtained (60g.). This was heated with concentrated HCl, ethanol, water (each 250 ml.) to reflux for one hour. The ethanol was distilled off and the residue basified with sodium carbonate. Extraction with ether, gave on drying removal of solvent a tarry oil (45g.). Distillation of this gave a light oil (34g.) b.pt. 124°C at 11 mm.Hg.

The infrared had peaks at \( \nu_{\text{max}} \) 3500 cm\(^{-1}\) and 3400 cm\(^{-1}\); primary amine group; \( \nu_{\text{max}} \) 1680 cm\(^{-1}\); carbonyl group.

Overall yield from skatole = 45%.

3,4-Dimethylcinnoline (44c)

Preparation of o-aminophenyl, ethyl, methyl carbinol


The Grignard reaction on o-aminoacetophenone (19g.) in dry ether (200 ml.) with ethyl bromide (65g.), magnesium 15.1g.) in dry ether (250 ml.) gave on work up a red oil (24g.).

Quantitative Yield
The infrared spectrum had broad peak at $\nu_{max} \approx 3500 \text{ cm}^{-1}$ - $3300 \text{ cm}^{-1}$.

The n.m.r. spectrum in CCl$_4$ had peaks at 3.20 $\gamma$, multiplet, 4 aromatic protons; 6.25 $\gamma$, singlet, NH$_2$ + CH; 8.05 $\gamma$, quartet, $J = 8$ c/s, -CH$_2$; 8.45 $\gamma$, singlet, CH$_3$ from methyl group; 9.20 $\gamma$, triplet, $J = 8$ c/s, -CH$_3$ from ethyl group.

Preparation of 2-(o-aminophenyl)but-2-ene

o-Aminophenyl, ethyl, methyl carbinol (24g.) was refluxed with toluene (210 ml.) and iodine (0.1g.) for four hours and the water formed, azetroped out. The toluene was then removed by distillation and the residual oil distilled under reduced pressure. This gave oil (15g.) b.pt. 105-110°C at 12 mm. Hg. (lit. b.pt. 100-110 at 10 mm. Hg.).

The infrared spectrum showed doublet at $\nu_{max} \approx 3500$ and 3400 cm$^{-1}$.

Preparation of 3,4-dimethylcinnoline (hyc)

Diazotisation of 2-(o-aminophenyl)but-2-ene (15g.) in 2N HCl (120 ml.) at $-10^\circ$C was carried out with sodium nitrite (6g.) in water (40 ml.). After three days the reaction mixture was basified and continuously extracted with ether. Removal of the solvent after drying gave a yellow solid. Recrystallization from light petroleum (b.pt. 60-80) gave yellow crystals m.pt. 119-120°C. (Lit. m.pt. 119-120°C).

The n.m.r. spectrum in CCl$_4$ had peaks at 1.65 $\gamma$, multiplet, H-8; 2.25 $\gamma$, multiplet, H-5, 6, 7; 7.12 $\gamma$, singlet, 3-CH$_3$; 7.42 $\gamma$, singlet, 4-CH$_3$.

Yield = 11.2g. 70% of Theory. Lit. Yield = 72% of Theory.
14-t-Butylcinnoline (14d)

Preparation of o-aminophenyl, t-butyl, methyl carbinol

The Grignard reagent was prepared from freshly prepared t-butyl chloride (70g.), magnesium (18g.) and dry ether (350 ml.). o-Aminoacetophenone (20.5g.) was added in dry ether (200 ml.) and the reaction mixture refluxed for one hour. On work up this produced a red oil (21g.) which showed about 60% conversion. The whole material was recycled using the same quantity of Grignard reagent. This gave red oil (20g.).

The infrared spectrum showed total loss of carbonyl peaks and had broad peak at 3500-3300 cm$^{-1}$.

Preparation of 2,2-dimethyl-3-(o-aminophenyl)pent-3-ene

o-Aminophenyl, t-butyl, methyl carbinol (20g.) was boiled with toluene (250 ml.). This gave unchanged starting material. The tertiary alcohol (20g.) was refluxed with P$_2$O$_5$ (40g.) in dry benzene (400 ml.) but this gave back starting material. Alcohol (1.3g.) was heated at 180°C with KHSO$_4$ (14g.) for fifteen minutes. This showed 50% conversion. The remainder (18.7g.) was heated with KHSO$_4$ (2g.) for one hour at 180°C. There was no conversion. The alcohol was then reheated with KHSO$_4$ (5g.) for ninety minutes during which water (2 ml.) was distilled off. Basification and extraction of the aqueous product with chloroform (3 x 50 ml.) gave a dark red tarry product. This showed 75% conversion to the olefin from the infrared spectrum. The tarry oil was chromatographed on alumina and elution with 10% ether in benzene gave a red oil which was shown to be a mixture of isomeric products from the n.m.r. spectrum. Crude yield = 9g. The product was not distilled.
Preparation of 4-t-butylcinnoline (44a)

Diazotisation of the olefin (9g.) in 2 N HCl (100 ml.) was carried out at 0°C with sodium nitrite (3g.) in water (15 ml.). After three days at 0°C, the aqueous solution was basified and continuously extracted with ether. This gave an oil which would not crystallise. Boiling with light petroleum gave no crystalline product. The oil was chromatographed on alumina. Elution with 10% chloroform in benzene gave a red oil. This oil was rechromatographed but on removal of the solvent, a crystalline solid could not be obtained. Yield = 2.5g. 28% Yield.
The n.m.r. spectrum in CCl₄ had peaks at 0.8 γ, singlet, H-3; 1.55 γ, multiplet, H-5, H-8; 2.25 γ, multiplet, H-6, H-7; 8.35 γ, singlet, 4-t-Bu.

6-Bromo-4-methylcinnoline

Preparation of Methyl 5-bromoanthranilate (46)

Anhydrous chloral (58.3g.) was added slowly to methyl anthranilate (50g.) with external cooling to give a glass. This was dissolved in acetic acid (500 ml.) and the stirred solution cooled to 10-15°C. Dry bromine (52g.) was added dropwise to keep the temperature below 15°C. On completion of the addition, a precipitate was evolved. This was left for twelve hours, filtered and washed with acetic acid (2 x 50 ml.). The bromohydrate was decomposed with aqueous sodium carbonate and the liberated ester filtered and dried. Recrystallization from dilute methanol gave white crystals (18.9g.) m.pt. 58.60°C. Lit. m.pt. 71.6°C.
A large amount of oily residue remained after evaporation of
methanolic solution to dryness.

The infrared spectrum of the solid in nujol had $\nu_{\text{max}} = 3450$ and $3350 \text{ cm}^{-1}$-NH$_2$ and $\nu_{\text{max}} = 1700 \text{ cm}^{-1}$ carbonyl group from ester. The n.m.r. spectrum in CCl$_4$ had peaks at 2.1 $\gamma$, doublet, H-6; 2.73 $\gamma$, quartet, H-4; 3.51 $\gamma$, doublet, H-3; 4.30 $\gamma$, singlet, NH$_2$; 6.17 $\gamma$, singlet, -OMe.

Preparation of 2-amino-5-bromophenyl, dimethyl carbinol

Methyl 5-bromoanthranilate (18.8g.) in dry ether (150 ml.) was added to the Grignard reagent prepared from methyl iodide (5.8g.), magnesium (9.7g.) and dry ether (125 ml.). The reaction mixture was stirred under reflux for one hour. The product obtained was a red oil which crystallised on standing to give orange needles m.pt. 63-64°C. Yield 19g. Quantitative Yield. The infrared spectrum in nujol had broad peak at $\nu_{\text{max}} 3500-3300 \text{ cm}^{-1}$.

The n.m.r. spectrum in CCl$_4$ had peaks at 2.95 $\gamma$, doublet, H-6; 3.05 $\gamma$, quartet, H-4; 3.75 $\gamma$, doublet, H-3; 5.80 $\gamma$, broad singlet, NH$_2$ + OH; 8.55 $\gamma$, singlet, two CH$_3$ group.

Preparation 4-bromo-2-isopropenylaniline

The tertiary alcohol (19g.) was heated under reflux with P$_2$O$_5$ (40g.) and dry benzene (200 ml.) for three hours. After basification and extraction, a red oil was obtained (14.2g.) 80% Yield. The infrared spectrum had sharp doublet at $\nu_{\text{max}} 3450 \text{ cm}^{-1}$ and 3350 cm$^{-1}$. 
Preparation of 6-bromo-4'-methylcinnoline (47)

4-Bromo-2-isopropenylaniline (14.2 g.) in concentrated HCl (13 ml.) and 2 NHCl (55 ml.) was diazotised at -10°C with sodium nitrite (3.2 g.) in water (15 ml.). After the addition the mixture was kept at -10°C for one hour and then 0°C for three days. Basification with sodium carbonate followed by extraction with ether (6 x 50 ml.) gave on removal of the solvent, an oily solid. This gave a brown solid m.pt. 125°C on extraction light petroleum (b.pt. 60-80). Recrystallization from benzene gave orange prisms m.pt. 128-9°C. Yield = 3.7 g. % Yield = 25%

C<sub>9</sub>H<sub>7</sub>BrN<sub>2</sub> Requires C, 48.4; H, 3.1; Br, 35.8; N, 12.6%
Found C, 48.4; H, 3.1; Br, 35.8; N, 12.4%

The n.m.r. spectrum in CCl<sub>4</sub> had peaks at 0.95 γ, singlet, H-3; 1.65 γ, doublet, J = 9 c/s, H-8; 1.95 γ, doublet, J = 2 c/s, H-5; 2.18 γ, quartet, J = 2, 9 c/s, H-7; 7.35 γ, singlet, 4=CH<sub>3</sub>.

6,6-Dimethylcinnoline (48)

Preparation of 5-methylisation<sup>39</sup> (49)

Isonitrosoaceto-<i>p</i>-toluidine (95 g.) was added slowly to concentrated H<sub>2</sub>SO<sub>4</sub> (400 ml.) at 50°C. After addition the temperature was raised to 80°C for ten minutes, the solution then was cooled and poured on to ice. The precipitate formed was filtered off and dried to give red powder (75 g.) m.pt. 180°C. (Lit. m.pt. 174-183°C). % Yield = 90%.

Preparation of 5-methylanthranilic acid (50)

5-Methylisatin (75 g.) was dissolved in 5% NaOH (500 ml.) at room temperature and 30% H<sub>2</sub>O<sub>2</sub> (100 ml.) added dropwise with stirring.
After one hour the solution was made acid to pH4 and the precipitate formed was filtered off and dried (50g.). 66% Yield m.pt. = 168°C (Lit. m.pt. 175°C)

Preparation of Methyl 5-methylantranilate (51)

Methanol (250 ml.) was saturated with dry HCl (130g.). The acid (50g.) dissolved in the minimum of hot methanol, was added and the mixture refluxed for two hours. The solution was saturated again with dry HCl and then further refluxed for ninety minutes. The methanol was distilled off and the residue basified and extracted with ether (5 x 200 ml.). Removal of the solvent gave an oil which solidified on cooling. This was recrystallised from methanol to give white plates m.pt. 61°C. (Lit. m.pt. 62°C) Yield = 28.5g.  % Yield = 52%.

Preparation of (2-amino-5-methylphenyl), dimethyl carbinol

Ester (27.5g.) in dry ether (300 ml.) was added with stirring to the Grignard reagent, prepared from methyl iodide (120g.), magnesium (20g.) and dry ether (250 ml.), and the reaction mixture refluxed for one hour. Decomposition of the reaction mixture followed by extraction with ether (6 x 200 ml.) gave a red oil (25.5g.) % Yield = 90%.

The infrared spectrum had broad band ν max 3500-3300 cm⁻¹. It showed no carbonyl absorption.

Preparation of 2-isopropenyl-α-toluidine

The tertiary alcohol (25.5g.) was refluxed with P₂O₅ (50g.) in dry benzene (250 ml.) for three hours. Cooling, basification
and extraction with ether, produced a dark red oil which was used directly for the diazotisation.

\[ \text{Yield} = 17.59 \text{ g.} \quad \% \text{Yield} = 78\% \]

The infrared spectrum had sharp doublet at $\nu_{\text{max}} 3450 \text{ cm}^{-1}$ and $3350 \text{ cm}^{-1}$.

**Preparation of 4,6-dimethylcinnoline (48)**

2-isopropenyl-p-toluidine (17.59 g.) in concentrated HCl (26.6 ml.) and 2 NHCl (106 ml.) was diazotised at $-10^\circ \text{C}$ with a solution of sodium nitrite (6.8 g.) in water (25 ml.). After addition, the reaction mixture was kept at $0^\circ \text{C}$ for three days. The reaction mixture was basified and extracted with ether to give an oily solid. Exhaustive extraction with boiling light petroleum (b.pt. 60-80) gave yellow needles m.pt. 75-76°C.

\[ \text{Yield} 9.5 \text{ g.} \quad \% \text{Yield} = 50\% \]

$\text{C}_{10}\text{H}_{10}\text{N}_2$ **Requires** C, 76.0; H, 6.3; N, 17.7%.

**Found** C, 75.8; H, 6.3; N, 17.4%.

The n.m.r. spectrum in CDCl$_3$ had peaks at 0.95 $\gamma$, singlet, H-3; 1.65 $\gamma$, doublet, $J = 9$ c/s, H-8; 2.40 $\gamma$, multiplet, H-5 and H-7; 7.40 $\gamma$, broad peak, two CH$_3$ groups. Expansion of this methyl region showed 4-CH$_3$ to be downfield of 6-CH$_3$.

**4,8-Dimethylcinnoline (54)**

**Preparation of 3-methylantranilic acid**

7-methylisation (120 g.) were dissolved in 2N NaOH (700 ml.) and 30% H$_2$O$_2$ (200 ml.) added with stirring at room temperature. Stirring was continued for one hour after addition and then the solution was cooled and filtered. The filtrate was brought to
pH4 and the precipitate formed was filtered and dried. m.pt. 167°C. Lit. m.pt. 172°C.

Yield 87g; % Yield = 70%.

Preparation of methyl 3-methylantranilate (53)

3-Methylantranilic acid (105g.) in methanol (500 ml.) was added to a saturated methanol-dry HCl solution and refluxed for one hour. After further saturation with dry HCl and refluxing for one hour, the methanol was distilled off and the residue made basic with sodium carbonate. Extraction with ether, gave an oily solid.

Yield = 32.5g. % Yield = 28%.

The n.m.r. spectrum in CDCl₃ had peaks at 2.28 γ, quartet, J = 2, 8 c/s, H-6; 2.95 γ, quartet, J = 2.8 c/s, H-4; 3.52 γ, triplet, J = 8 c/s, H-5; 4.10 γ, singlet, NH₂; 6.02 γ, singlet, -OMe; 7.98 γ, singlet, 3-CH₃.

Preparation of 2-Amino-3-methylphenyl, dimethyl carbinol.

The ester (32.5g.) in dry ether (350 ml.) was added to Grignard reagent prepared from methyl iodide (144 g.) magnesium (24g.) and dry ether (450 ml.). The product obtained was a red oil (23.4g.) % Yield = 74%.

The infrared spectrum had broad peak at \( \gamma_{\text{max}} = 3500 - 3300 \text{ cm}^{-1}. \)

Preparation of 2-isopropenyl-6-methylaniline

The dehydration of the tertiary alcohol (23.4g.) was carried out using P₂O₅ (50g.) and benzene (250 ml.). The product obtained
was a dark red oil (15.1g.) % Yield = 72%.
The infrared spectrum had sharp doublet at $\nu_{\text{max}}$ 3500 and 3400 cm$^{-1}$.

**Preparation of 4,8-dimethylcinnoline (54)**

2-isopropenyl-6-methyleniline (15.1g.) in concentrated HCl (23 ml.) and 2NHCl (92 ml.) was diazotised at $-10^\circ$C with sodium nitrite (5.6g.) in water (25 ml.). After three days, the product obtained on basification and extraction was an oil. Extraction of this oil boiling light petroleum gave only an oil. The oil was chromatographed on alumina and a yellow band was developed with benzene as eluent. Removal of the solvent gave a solid which was recrystallised from light petroleum (b.pt. 60-80) to give yellow cubes m.pt. 90-91°C. Yield 0.5g.

C$_{10}$H$_{10}$N$_2$ \textbf{Requires} C, 76.0; H, 6.3; N, 17.7%.

\textbf{Found} C, 76.1; H, 6.2; N, 17.6%.

The n.m.r. spectrum in CCL$_4$ had peaks at 1.0 $\gamma$, singlet, H-3; 2.45 $\gamma$, multiplet, H-5, 6, 7; 7.08 $\gamma$, singlet, 8-CH$_3$; 7.38 $\gamma$, singlet, 4-CH$_3$.

**Attempted Preparation of 4-methyl-6-nitrocinnoline**

**Preparation of 5-nitroisatin (140)**

Isatin (25g.) in concentrated H$_2$SO$_4$ (112g.) was cooled to 0°C. Fuming nitric acid (30g.) was added dropwise with stirring to keep the temperature about zero. The reaction mixture was allowed to stand for thirty minutes and then poured on to ice. The yellow precipitate was filtered, washed and dried. m.pt. 250°C. (Lit. m.pt. 254-255°C).

Yield = 26.2g. % Yield = 80%. Lit. % Yield = 86%.
Preparation of 5-nitroanthranilic acid

5-nitroisatin (7g.) was dissolved in 10% NaOH (150 ml.) and 30% H₂O₂ (15 ml.) added dropwise with stirring at room temperature. After one hour the mixture was filtered and acidified to pH4. The precipitate formed was filtered and dried. Recrystallisation from ethanol gave yellow needles m.pt. 278°C. Lit. m.pt. 277-278°C.

Yield = 6.0g. % Yield = 89%.

Preparation of Methyl 5-nitroanthranilic acid

5-Nitroanthranilic acid (35g.) was added to methanol (700 ml.). To this suspension was added an ethereal diazomethane solution (9.6g. in 500 ml. of ether) in 10-20 ml. portions. The suspension gradually went into solution and the reaction mixture was left overnight. The ether and methanol were distilled off to leave an orange residue. This was neutralised with aqueous sodium carbonate to give a red solution and a buff precipitate. The precipitate was filtered and dried. m.pt. 215°C.

Yield = 31g. % Yield = 82%.

The n.m.r. spectrum in dimethyl sulphoxide had peaks at 1.30γ, doublet, J = 2 c/s H-6; 1.75γ, quartet, J = 2.8 c/s, H-4; 2.0γ, broad peak, -NH₂; 2.93γ, doublet, J = 8 c/s, H-5; 5.95γ, singlet, -OCH₃.

Attempted Grignard Reaction on Methyl 5-nitroanthranilic acid

The Grignard reagent was prepared from methyl iodide (100g.), magnesium (16.2g.) in dry ether (300 ml.). The ester (31g.) was suspended in ether (500 ml.) and added in 10-20 ml. portions and the reaction mixture refluxed with stirring for 18 hours. After this
time, the mixture still in the form of a suspension was cooled and decomposed on ammonium chloride solution. The solid was filtered off and shown to be largely unchanged ester. There was no evidence of the Grignard reaction having taken place.

Preparation of Nitrocinromines

Preparation of 4-methyl-8-nitrocinromine (55a)

4-Methylcinromine (3g.) was added to concentrated H₂SO₄ (12 ml.) at 0°C with stirring and then cooled to -8°C. A nitrating mixture of concentrated H₂SO₄ (5 ml.) and nitric acid (d 1.5) (1.1 ml.) was added dropwise with stirring, keeping the temperature below 0°C. The solution was stirred at 0°C for thirty minutes and then at 20°C for two hours. The solution was poured on to ice and neutralised to pH 7 with dilute ammonia. The brown solid formed was filtered off, dried and recrystallised from methanol to give dark green crystals m.pt. 136°C. Lit. m.pt. 137-138°C.

Yield = 1.28g. % Yield = 33% Lit % Yield = 35%.

The n.m.r. spectrum in CDCl₃ had peaks at 0.7γ, singlet, H-3; 2.0γ, multiplet, H-5, 6, 7; 7.24γ, singlet, 4-CH₃.

Preparation of 4-Ethyl-3-methyl-8-nitrocinromine (55b)

4-Ethyl-3-methylcinromine (7.3g.) was added to concentrated H₂SO₄ (25 ml.) and a nitrating mixture of concentrated H₂SO₄ (10 ml.) and HNO₃ (d.1.5) (2.3 ml.) added under the same conditions as above. On neutralisation, a yellow precipitate was formed, which was filtered and dried. This was recrystallised from methanol to give light green crystals m.pt. 102-103°C.

Yield = 7.7g. % Yield = 83%.
C_{11}H_{11}N_{3}O_{2}  \text{ Requires } C, 60.8; H, 5.1; N, 19.3%.

Found  C, 60.9; H, 4.8; N, 19.4%.

The n.m.r. spectrum in CDCl$_3$ had peaks at 1.65 $\gamma$, quartet, $J = 2$, 8 c/s, H-7; 1.95 $\gamma$, quartet, $J = 2$, 8 c/s, H-5; 2.15 $\gamma$, triplet, $J = 8$ c/s, H-6; 6.85 $\gamma$, quartet, $J = 7$ c/s, 4-CH$_2$; 7.0 $\gamma$, singlet, 3-CH$_3$; 8.70 $\gamma$, triplet, $J = 7$ c/s, -4-CH$_3$.

Preparation of 3,4-dimethyl-8-nitrocinclline (55b)

3,4-Dimethylcinnoline (5.5g.) was treated as before with concentrated H$_2$SO$_4$ (20 ml.) and a nitrating mixture of concentrated H$_2$SO$_4$ (8.3 ml.) and HNO$_3$ (1.80 ml.). The precipitate formed on neutralisation was filtered and dried. Recrystallisation from methanol gave orange crystals. m.pt. 150-151°C.

Yield = 2.6g.  \% Yield = 45%.

C$_{10}$H$_9$N$_3$O$_2$  \text{ Requires } C, 59.1; H, 4.5; N, 20.7%.

Found  C, 58.8; H, 4.4; N, 19.8%.

The n.m.r. spectrum in CDCl$_3$ had peaks at 1.77 $\gamma$, quartet, $J = 2$, 8 c/s, H-7; 2.0 $\gamma$, quartet, $J = 2$, 7.5 c/s, H-5; 2.25 $\gamma$, triplet, H-6; 7.02 $\gamma$, singlet, 3-CH$_3$; 7.31 $\gamma$, singlet, 4-CH$_3$.

Preparation of 4-t-butyl-8-nitrocinclline (55d)

4-t-butylcinnoline (0.75g.) was cooled in an ice bath and concentrated H$_2$SO$_4$ (3 ml.) added slowly to keep temperature at 0°C. A nitrating mixture of concentrated H$_2$SO$_4$ (1.2 ml.) and fuming HNO$_3$ (0.27 ml.) was added with stirring. After standing for two hours the mixture was poured on to ice and a precipitate formed. This was filtered off and dried to give a brown solid (0.33g.)
m.pt. 195°C. Basification of the filtrate yielded no more product.

The n.m.r. spectrum in T.F.A. had peaks at 2.0 γ, multiplet, H-5, 6,7; 8.35 γ, singlet –h-t-Bu.

Preparation of (2-amino-3-nitrophenyl), methyl, phenyl carbinol

A Grignard reagent was prepared from bromobenzene (2.15 ml.) and magnesium (0.5g) in dry ether (100 ml.). 2-Amino-3-nitroacetophenone (3.75g.) was added in benzene (50 ml.) and dry ether (50 ml.). After addition the reaction mixture was refluxed for one hour. On decomposition, the starting material was obtained. The reaction was repeated using a 3.5:1 excess of Grignard reagent to ketone. After addition of the ketone, the reaction mixture was refluxed for four hours. Decomposition of the reaction mixture gave an oil containing an excess of bromobenzene. This excess was distilled off and the remaining oil chromatographed on alumina.

Elution with benzene gave broad band which produced only biphenyl. Elution with ether gave dark red solution which on evaporation gave a red oil which was then chromatographed.

Elution with benzene gave no product. Elution with 25% ether in benzene gave a small portion of oil followed by a broad yellow band which on elution gave a solid. Recrystallisation of this from benzene gave orange crystals. m.pt. 141-142°C. Yield 0.3g.

\[ \text{C}_{14}^\text{H}_{11}^\text{N}_{2}^\text{O}_3 \] Requires C, 65·4; H, 5·4; N, 10·8%.  

found C, 65·1; H, 5·5; N, 10·8%.

The n.m.r. spectrum in CDCl₃ had peaks at 1.95 γ, quartet, J = 1.5,
9 c/s, H-4; 2.5 γ, quartet, J = 1.5, 8.5 c/s, H-6; 2.7 γ, singlet - Phenyl group; 3.05 γ, broad singlet, -NH₂; 3.4 γ, triplet with small split on central peak, H-5; 7.3 γ, broad peak, -OH; 8.1 γ, singlet, -CH₃.

Preparation of 4-methyl-3-nitrocinoline

-o-Aminoacetophenone (34g.) in concentrated HCl (26 ml.) was added to concentrated HCl (16.5 ml.), water (40 ml.) and ice (40g.) at 0°C. A solution of sodium nitrite (44g.) in water (20 ml.) was added dropwise with stirring.

A solution of nitromethane (12.25g.) in ethanol (40 ml.) was added to NaOH (8g) in water (2 l.) and ice (800 g.). The diazonium solution was added to this with rapid stirring and the stirring continued until a precipitate formed. Filtration and drying gave an orange solid (49g.) m.pt. 168°C.

This solid (49g.) was dissolved in acetone (2 l.) and alumina (500g.) added. The mixture was stirred for sixty hours. Filtration and extraction of the alumina with acetone (2 x 200 ml.) gave a dark red solid on removal of the solvent. Recrystallisation of this solid from ethanol gave 7.5g. of starting material insoluble in boiling alcohol and after charcoaling the boiling filtrate, ten lustrous needles (2.5g.) m.pt. 182°C. Lit. m.pt. 183°C.

The residue was chromatographed on alumina but only gave mixtures of starting material and product. The ratio of starting material to product was greater after chromatography.

The n.m.r. spectrum in CDCl₃ had peaks at 1.35 γ, multiplet, H-8; 1.90 γ, multiplet, H-5, 6, 7; 7.15 γ, singlet, 4-CH₃.
Preparation of Cinnoline

a. From 4-Methylcinnoline\(^{34}\) (44a)

**Preparation of 4-Styrylcinnoline (57)**

4-Methylcinnoline (23g.), benzaldehyde (82 ml.) and anhydrous zinc chloride (10.5g.) were refluxed for five hours. On cooling a yellow precipitate was formed after treatment with benzene (100 ml.) and 2N HCl (100 ml.). The solid was washed and converted to free base by shaking with 3N NaOH (200 ml.). The solid obtained was recrystallised from methanol to give yellow needles m.pt. 124°C. Lit. m.pt. 113-8°C.

Yield = 39g. \(\%\) Yield = 100%.

**Preparation of 4-carboxycinnoline (58)**

4-Styrylcinnoline (39g.) was suspended in water (420 ml.) and pyridine (420 ml.), at 0°C and KMnO\(_4\) (69g.) added in portions over ninety minutes keeping the temperature below 2°C. The mixture was stirred for three hours at room temperature and then filtered and the filtrate concentrated to about 400 ml. at 50°C. Acidification gave a precipitate which was dried. The mixed acids formed were shaken with ether for one hour and the precipitate filtered, washed with ether and dried to give green powder m.pt. 195°C. Lit. m.pt. 195°C.

Yield = 9.8g. \(\%\) Yield = 35%.

**Preparation of Cinnoline (2)**

4-Carboxycinnoline (9.8g.) was heated with benzophenone (50g.) under nitrogen for ninety minutes at 150°C. The reaction mixture was dissolved in ether (350 ml.) and extracted with 1N HCl (4 x 50 ml.).
The HCl extracts were washed with ether, and then basified with potassium carbonate. Extraction with ether gave on drying and removal of the solvent a light yellow oil.

Yield = 5g. % Yield = 67%.

The n.m.r. spectrum in CCl₄ had peaks at 0.70 ppm, doublet, J = 6 c/s, H-3; 1.55 ppm, multiplet, H-8; 2.20 ppm, multiplet, H-5,6,7; 2.25 ppm, doublet, J = 6 c/s, H-4.

b. from Aniline

Preparation of Diethyl mesoxalate phenylhydrazone

A slurry of aniline hydrochloride from aniline (100g.) and concentrated HCl (270 ml.) was diazotised at 0°C with sodium nitrite (76g.) in water (180 ml.). The filtered diazonium solution was added with stirring to a mixture of diethyl malonate (172 ml.), ethanol (2.2 l.), anhydrous sodium acetate (200g.) and water (320 ml.) at 0°C. Stirring was continued for five hours and then the ethanol was distilled off. Extraction of the aqueous solution with ether gave a red oil. The crude product was suitable for the next stage.

Yield = 250g. % Yield = 95%.

Preparation of Mesoxalic acid phenylhydrazone

The ester (250g.) in boiling ethanol (590 ml.) was hydrolysed with 2N NaOH (590 ml.) over thirty minutes. The ethanolic solution was filtered and neutralised with concentrated HCl. The precipitated acid was recrystallised from ethyl acetate to give yellow needles. m.pt. 162°C. Lit. m.pt. 162-163°C.

Yield = 150g. % Yield = 72%.
Preparation of Mesoxalyl chloride phenylhydrazene

The acid (18g.) was treated with excess thionyl chloride in dry chloroform (100 ml.). After refluxing for ninety minutes, the solution was cooled to give precipitate. This was filtered to give orange crystals m.pt. 136°C. Lit. m.pt. 135-136°C.

Yield = 14.5g. % Yield = 64.5%.
The infrared spectrum had $\nu_{\text{max}} = 1740$ cm$^{-1}$, acid chloride carbonyl group.

Preparation of 3-carboxycinnolin-4(1H)one (8)

The acid chloride (14.5g.) was suspended in ethylene dichloride (95 ml.) and titanium tetrachloride (7 ml.) was added with stirring, keeping the temperature below 95°C. After heating for six hours at 95°C, the residue was extracted with NaOH and acidification of this extract gave a brown precipitate m.pt. 246°C. This solid was stirred with concentrated HNO$_3$ overnight, poured on to ice and the precipitate, filtered, washed and dried. Recrystallisation from acetic acid gave small prisms m.pt. 261°C. Lit. m.pt. 265°C.

Yield = 7.5g. % Yield = 75%.

Preparation of cinnolin-4(1H)one (9)

The product (8) (5g.) was heated with Dowtherm (20g.) at 200°C for ninety minutes. On cooling the residue was treated with ether and filtered. The residue was recrystallised twice from acetic acid to give product m.pt. 210°C.

Yield = 2.5g. % Yield = 65%.
Preparation of 4-chlorocinnoline \(^{10}\) 

Cinnolin-4(1H)one (5 g.) was heated with \(\text{PCl}_5\) (9.2 g.) and \(\text{POCl}_3\) (10.5 ml.) at 140°C for thirty minutes. The mixture was cooled, poured on to ice, and brought to pH5 with sodium acetate. Extraction with ether (4 x 50 ml.) gave, after washing with sodium carbonate solution, drying and removal of solvent, a green oil. Extraction of the oil with boiling light petroleum (b.pt. 80-100) gave a yellow solid m.pt. 72°C. Lit. m.pt. 73-74°C.

Yield 1.1 g. \(\%\) Yield = 20%.

Preparation of 4-toluenesulphonylhydrazinocinnoline \(^{12}\)

4-Chlorocinnoline (1.1 g.) in \(\text{CHCl}_3\) (3 ml.) was added to tosylhydrazide (2.75 g.) in warm \(\text{CHCl}_3\) (80 ml.) and gently warmed. The flask was stoppered and left for one week. The yellow solution turned red and deposited pink crystals.

Yield = 2.0 g. \(\%\) Yield = 100%.

Preparation of cinnoline \(^{2}\)

The product (12) (0.39 g.) was heated at 95°C with anhydrous sodium carbonate (0.6 g.) and water (3 ml.). Filtration and extraction of the filtrate with ether (4 x 20 ml.) gave on removal of the solvent, a red oil.

Yield = 0.1 g. \(\%\) Yield = 80%.

The n.m.r. spectrum in \(\text{CCl}_4\) was the same as previously reported.
Preparation of Deuterated Cinnolines

Preparation of 3-deuterocinnolin-4(1H)one

3-Carboxycinnolin-4(1H)one (3g.) was heated with D$_2$O (5 ml.) under anhydrous conditions. The water formed was distilled off under high vacuum and the solid reheated with further D$_2$O (5 ml.). The removal of water was repeated. Dowtherm (20g.) was added and the mixture heated to >220°C on an oil bath. The internal temperature was checked and shown to be greater than 180°C. On cooling the solid mass was extracted with ether (4 x 100 ml.) and the residue left was a pale solid.

Yield = 1.0g.

The infrared spectrum had $\nu_{\text{max}} = 2200$ cm$^{-1}$, C-D band. It showed no carboxyl peaks.

Preparation of 4-chloro-3-deuterocinnoline

3-Deuterocinnolin-4(1H)one (1g.) was refluxed with PCl$_5$ (1.5g.) and POCl$_3$ (2 ml.) for thirty minutes at 140°C. The work up procedure as before was carried out to give yellow needles m.pt. = 72°C.

Yield 0.34g. % yield = 30%.

The n.m.r. spectrum in CDCl$_3$ had peaks at 1.35 $\gamma$, multiplet H-8; 1.90 $\gamma$, multiplet, H-5,6,7. The integral was in ratio 1:3.

Preparation of 3-deutero-4-tosylhydrazinocinnoline (12a)

4-Chloro-3-deuterocinnoline (0.34g.) and tosyl hydrazide (0.55g.) were warmed with CHCl$_3$ (20 ml.). The red solid formed after a week was filtered off.

Yield = 0.5g. % Yield = 75%.
Preparation of 3-deuterocinnoline

The product (12a) (0.2g.) was heated with anhydrous sodium carbonate (0.1g.) and water (3 ml.) at 95°C for thirty minutes. The work procedure, as before, gave red oil.

Yield 0.06g. % Yield = 70%.

The n.m.r. spectrum in CDCl₃ had peaks at 1.50 γ, multiplet, H-8; 2.10 γ, multiplet, H-4, 5, 6, 7. The integral was in ratio of 1:4. There was no peak at 1.0 showing absence of H-3.

Preparation of 3,4-dideuterocinnoline

The product (12a) (0.25g.) was heated with anhydrous sodium carbonate (0.5g.) and D₂O (4 ml.) at 95°C for thirty minutes. This gave a red oil.

Yield = 0.07g. % Yield = 68%.

The n.m.r. spectrum in CDCl₃ had peaks at 1.50 γ, multiplet, H-8; 2.25 γ, multiplet, H-5, 6, 7. The integral was in ratio of 1:3.

Preparation of 4-deuterocinnoline

4-Tosylhydrazinocinnoline (2.05g.) was heated with anhydrous sodium carbonate (4.1g.) and D₂O (10 ml.) at 95°C for thirty minutes. This gave a red oil.

Yield = 0.52g. % Yield = 69%.

The n.m.r. spectrum in CDCl₃ had peaks at 0.77 γ, singlet, H-3; 1.50 γ, multiplet, H-8; 2.25 γ, multiplet, H-5, 6, 7. The integral was in ratio 1:1:3.
Preparation of 8-deutero-4-methylcinnoline

50% Hypophosphorous acid (4 ml.) was evaporated to dryness on high vacuum pump, D_2O (2 ml.) added, the mixture shaken, and the water removed. This was repeated with further D_2O (2 ml.). The n.m.r. spectrum of 50% H_3PO_2 neat, with t-BuOH as standard, had doublet, J = 560 c/s, centred at 2.74 γ. The n.m.r. spectrum showed almost complete absence of these peaks. Very small peaks as 1:1:1 triplet with J = 6 c/s were observed.

8-amino-4-methylcinnoline (0.175g.) was shaken with CDCl_3 and D_2O. The n.m.r. spectrum showed replacement of NH_2 by ND_2. The solvents were removed and the amine dissolved in D_3PO_2 (1.5ml.). Sodium nitrite (0.08 g.) dried over P_2O_5 was dissolved in the minimum of D_2O. The amine salt was cooled to 0°C and diazotised with this mixture. A further portion of D_3PO_2 (1 ml.) in D_2O (1 ml.) was added to complete the reaction. The reaction mixture was allowed to stand at 0°C for one day. Basification, followed by extraction with ether (4 x 10 ml.) gave an oil. Extraction with boiling light petroleum (b.p.t. 60-80) gave colourless crystals m.p.t. 70-71°C. Yield = 0.05g. % Yield = 31%.

The n.m.r. spectrum in CDCl_3 had 0.9 γ, singlet, H-3; 2.10 γ, multiplet, H-5, 6, 7; 7.35 γ, singlet, 4-CH_3.

Preparation of Di-trideuteromethyl, o-aminophenyl carbinol (60)

The Grignard reagent was prepared from trideuteromethyl iodide (18g.), magnesium (3g.) in dry ether (100 ml.). Methyl anthranilate (3.75g.) in dry ether (50 ml.) was added and the mixture stirred under reflux for one hour. Decomposition was carried out with ammonium chloride in the minimum of water.
Extraction of the aqueous solution with ether (4 x 100 ml.) gave a red oil.

Yield 3.8g.  Quantitative Yield

The infrared spectrum had $\gamma_{\text{max}} = 3500-3300 \text{ cm}^{-1}$, $\text{OH}$ band; 2245 cm$^{-1}$, O-D band. There was no carboxyl absorption. The n.m.r. spectrum in CDCl$_3$ had peaks at 3.20 $\tau$, multiplet, 4 aromatic protons; 6.20 $\tau$, broad singlet, NH$_2$ + OH groups.

Preparation of o-Pentadeuteroisopropenyl aniline (61).

The tertiary alcohol (3.8g.) was heated with P$_2$O$_5$ (6g.) and dry benzene (60 ml.) for one hour. Basification and extraction with ether gave a red oil.

Yield = 1.1g.

The infrared spectrum had $\gamma_{\text{max}} = 3450$ and 3350 cm$^{-1}$, $\text{NH}_2$ group. The n.m.r. spectrum in CDCl$_3$ had small peaks in the methyl region.

Preparation of 3-deutero-4-trideuteromethylcinnoline (59)

The dehydration product (1g.) in D$_2$SO$_4$ (0.6 ml.) and D$_2$O (1 ml.) were stirred at 0° C for ninety minutes. Sodium nitrate (0.6g.) in D$_2$O (10 ml.) was added dropwise with stirring at 0° C. The solution was diluted with D$_2$O (20 ml) and left for three days. The reaction mixture was neutralised with NaOH (0.6g.) in D$_2$O (3 ml.). Extraction of the reaction mixture with benzene (8 x 30 ml.) gave an oil. Extraction with boiling light petroleum gave orange crystals m.pt. 71-72° C.

Yield = 0.37g.  % Yield = 33%.

The n.m.r. spectrum showed a mixture of deuterated to undeuterated material in ratio of 2:1.
Preparation of $^{15}$N containing cinnolines

**Preparation of Anthranilic Acid with 30% $^{15}$N enrichment**

Potassium phthalimide (10g.) was added to a stirred solution of NaOH (2.7g.) in water (26 ml.) and the temperature raised to 30°C to effect complete solution. The solution was cooled to -5°C and a solution of NaOH (4.8g.) in water (10 ml.) was added. A 15% solution of sodium hypochlorite (70 ml.) was added with stirring and ice was added to keep the temperature below 15°C. Stirring was continued for two hours and an excess of hypochlorite maintained by further small additions. After two hours, the excess hypochlorite was removed by careful addition of sodium bisulphite solution. Activated carbon was added and the pH brought to 6-8 by slow addition of concentrated HCl, keeping the temperature at 20°C. The mixture was filtered and the precipitate washed with water (2 x 5 ml.). The filtrates were combined, sodium dithionite (0.2g.) added, and concentrated HCl added until the pH was 3.6-3.7. The precipitated acid was filtered and dried.

Yield = 6g. % Yield = 81%.

**Preparation of Methyl Anthranilate with $^{15}$N enrichment**

Anthranilic acid (6g.) in methanol (100 ml.) was treated with diazomethane in ether. The removal of the solvents gave an oil. A small amount of solid was removed by taking the oil up in chloroform, filtering and then removing the solvent. This gave oil.

Yield = 4.2g. % Yield = 65%.

The n.m.r. spectrum showed two peaks in 6γ region, one of which was 0-Me peak. The other was attributed to N-Me peak.
Preparation of 4-methylcinnoline with $^{15}\text{N}$ enrichment

The Grignard reagent was prepared from magnesium (3.5g.) and methyl iodide (20g.) in dry ether (62 ml.). The ester (4.2g.) in dry ether (40 ml.) was added. This gave oil (4.18g.). This was heated with $\text{P}_2\text{O}_5$ (8g.) in benzene (40 ml.) for three hours. Basification and extraction with ether gave o-isopropenyl aniline as an oil (2.8g.).

The amine (2.8g.) was dissolved in concentrated HCl (4.6 ml.) and 2N HCl (17.4 ml.). This gave a slight precipitate which was removed by filtration. The filtrate was cooled to $-10^\circ\text{C}$ and diazotised with sodium nitrite (1.18g.) in water (5 ml.). The reaction mixture was kept at $0^\circ\text{C}$ for two days and finally warmed at $60^\circ\text{C}$ for 10 minutes. Neutralisation with sodium carbonate followed by extraction with ether, gave on removal of the solvent an oil which was chromatographed on alumina. Elution with benzene and recrystallisation of the resultant oily solid from light petroleum gave yellow needles m.pt. 71-72$^\circ\text{C}$.

Yield = 1.5g. \% Yield from amine = 50\%. 
Preparation of Cinnoline N-oxides

The preparation of the N-oxides was carried out using the general method of Ogata and his co-workers.\textsuperscript{25}

Preparation of Cinnoline 1-oxide (31) and 2-oxide (32)

Cinnoline (4.8 g.) was warmed with acetic acid (25 ml.) and 30\% hydrogen peroxide (12.5 ml.) at 70°C for three hours. A further amount of 30\% hydrogen peroxide (12.5 ml.) was added and heating continued for three hours. The solution was evaporated to half volume and a further quantity of acetic acid (25 ml.) and 30\% hydrogen peroxide (12.5 ml.) added. The whole process was repeated twice. After evaporation to a small volume the solution was neutralised with sodium carbonate and extracted with chloroform (3 x 100 ml.). The chloroform extract was washed with ferrous sulphate solution till no change occurred in the colour of the ferrous solution. The chloroform solution was dried and the solvent removed to give a solid (3.43 g.). This was taken up in the minimum of benzene and chromatographed on alumina.

Elution with 100\% benzene gave yellow solid. Recrystallisation from benzene-light petroleum gave yellow needles m.p. 106-107°C. (Lit. 110-111°C).

Cinnoline 1-oxide (31) Yield = 0.80 g.

Elution with 33\% CHCl\textsubscript{3} in benzene gave a white solid. Recrystallisation from benzene gave white needles m.p. 122-123°C. Lit. m.p. 123-126°C.

Cinnoline 2-oxide (32) Yield = 1.70 g.

Elution with 75\% CHCl\textsubscript{3} in benzene gave small amount of yellow solid m.p. 215°C. An n.m.r. spectrum was not obtained because of insolubility.
Preparation of 4-methylcinnoline 1-oxide (62), 2-oxide (63) and 1,2-dioxide (35)

4-Methylcinnoline (10g.) was treated with acetic acid and hydrogen peroxide at 70°C as described. This gave on evaporation of chloroform extracts, a mixture (7g.). This solid was taken up in benzene and chromatographed on alumina.

Elution with 50% light petroleum in benzene gave reddish solid which on recrystallisation from benzene-light petroleum gave light yellow needles m.pt. 94-95°C. Lit. m.pt. 95-96°C. for 4-methylcinnoline 1-oxide.

Yield = 1.3g.

Elution with 25% CHCl₃ in benzene gave a white solid which on recrystallisation from benzene gave white needles m.pt. 147-148°C. Lit. m.pt. 150-151°C for 4-methylcinnoline 2-oxide.

Yield 3.5g.

Elution with 75% CHCl₃ in benzene gave reddish solid which was recrystallised from benzene to give pale orange needles m.pt. 171-172°C.

Yield = 0.35g.

C₉H₅N₂O₂ Requires C, 61.3; H, 4.5; N, 15.9%.

Found C, 61.2; H, 4.5; N, 15.6%.

The n.m.r. spectrum in CDCl₃ had peaks at 1.70 γ, multiplet, H-8; 1.90γ, singlet, H-3; 2.20γ, multiplet, H-5, 6, 7; 7.4γ, singlet, 4-CH₃.

Preparation of 4-deuterocinnoline 1-oxide and 2-oxide

4-Deuterocinnoline (0.45g.) was treated with acetic acid (2.5 ml.) and 30% hydrogen peroxide (1.5 ml.) at 70°C. After three hours a further (1 ml.) of peroxide was added. The reactants
were heated for 15 hours, cooled, basified with sodium carbonate and extracted with chloroform (3 x 25 ml.). The chloroform solution was washed carefully with ferrous sulphate solution, dried and the chloroform removed to give an oil. The n.m.r. spectrum showed a mixture was present and no splitting of the 3-proton showing intactness of deuterium in 4-position.

The oil was chromatographed on alumina. Elution with benzene gave a small amount of yellow solid (0.05 g.), m.p.t. 108°C. The n.m.r. spectrum in CDCl$_3$ showed peaks at 1.40 \( \gamma \), multiplet, H-8; 1.70 \( \gamma \), singlet, H-3; 2.25 \( \gamma \), multiplet, H-5, 6, 7.

This confirmed presence of 1-oxide.

Elution with 10% CHCl$_3$ in benzene gave yellow solid (0.1 g.), m.p.t. 124°C. The n.m.r. spectrum in CDCl$_3$ had peaks at 1.83 \( \gamma \), singlet, H-3; 2.25 \( \gamma \), multiplet H-5, 6, 7, 8. This was consistent with presence of 2-oxide.

Preparation of N-oxides of 3-deutero-4-trideuteromethylcinnoline

The cinnoline (0.3 g.) was heated with acetic acid (4 ml.) and 30% hydrogen peroxide (1 ml.) at 70°C for eight hours. On dilution and basification, extraction with chloroform gave a small amount of oily solid. The solid was taken up in benzene and chromatographed on alumina.

Elution with benzene gave a mixture of oxides. Attempts to separate by further chromatography and fractional crystallisation failed.

Elution with 10% CHCl$_3$ in benzene gave a pure sample of the 2-oxide.
The n.m.r. spectrum of this in CDCl$_3$ had peaks at 1.90 ppm, small peak, H-3; 2.20 ppm, multiplet, H-5, 6, 7, 8.

**Preparation of 4-methylcinnoline 1-oxide and 2-oxide with $^{15}$N enrichment**

4-Methylcinnoline (1g.) was treated at 70°C for eight hours with acetic acid (5 ml.) and 30% hydrogen peroxide (2 x 2.5 ml.). After dilution the aqueous solution was neutralised with sodium carbonate. Extraction with chloroform gave a dark solid. This solid was taken up in the minimum of benzene and chromatographed on alumina. Elution with benzene gave a yellow solid, which was recrystallised from benzene-light petroleum to give yellow needles m.pt. 92°C.

Yield of 1-oxide = 0.14 g.

Elution with 30% CHCl$_3$ in benzene gave a white solid which was recrystallised from benzene to give white needles m.pt. 142°C.

The yield of 2-oxide = 0.37 g.

**The N-oxidation of 6-Bromo-4-methylcinnoline (47)**

6-Bromo-4-methylcinnoline (10g.) was treated with acetic acid (50 ml.) and 30% hydrogen peroxide (25 ml.) at 70°C according to Ogata's method. After evaporation to a small volume, the solution was basified and produced a large precipitate which was filtered and dried (8g.). The filtrate gave no further product on extraction. The solid was recrystallised from ethanol to give orange powder m.pt. 205°C. The n.m.r. spectrum at 60 M c/s was very degenerate and indicated only one product.
An n.m.r. spectrum in CDCl₃ at 100 Mc/s however, showed there was a mixture of mono-N-oxides. From the 8-protons, it was shown that ratio of 1-oxide to 2-oxide was 1:2.5.

Preparation of 4,6-Dimethylcinnoline 1-oxide and 2-oxide.

4,6-Dimethylcinnoline (7.6 g.) was heated with acetic acid (35 ml.) and 30% hydrogen peroxide (18 ml.) at 70°C according to Ogata's method. After evaporation to a small volume, the solution was basified, this gave a precipitate which was filtered and dried. This was recrystallised from benzene to give straw-coloured needles m.pt. 230-231°C.

Yield = 3.2 g.

The n.m.r. spectrum in CDCl₃ had peaks at 1.90 Ɣ, broad singlet, H-3; 2.20 Ɣ, doublet, H-8; 2.35 Ɣ, multiplet, H-5 and H-7; 7.40 Ɣ, singlet, 4-CH₃; 7.42 Ɣ, singlet 6-CH₃.

This confirmed the presence of 4,6-dimethylcinnoline 2-oxide.

The filtrate was treated separately. It was extracted with chloroform (3 x 50 ml.) and this gave after drying and removal of the solvent a brown solid. This was recrystallised from benzene-light petroleum to give white needles m.pt. 160-161°C.

Yield = 1.39 g.

The n.m.r. spectrum in CDCl₃ had peaks at 1.45 Ɣ, doublet, H-8;
1.907, singlet, H-3; 2.407, multiplet, H-5 and H-7; 7.427, singlet, 4-CH₃; 7.447, singlet, 6-CH₃.

This confirmed the presence of 4,6-dimethylcinnoline 1-oxide.

Preparation of 4-Ethyl-3-methylcinnoline 2-oxide (68b) and 1,2-dioxide (69b)

4-Ethyl-3-methylcinnoline (12g.) was heated with acetic acid (60 ml.) and 30% hydrogen peroxide (30 ml.) at 70°C according to Ogata's method. After basification and extraction with chloroform, removal of the solvent gave a solid (7.5g.). This was taken up in benzene and chromatographed on alumina.

Elution with 20% CHCl₃ in benzene gave a yellow solid (3.2g.) which was recrystallised from benzene-light petroleum to give white crystals m.p. 98-99°C.

The yield was 2.65g.

C₁₁H₁₂N₂O₂ Requires C, 70.2; H, 6.4; N, 14.9%.

Found C, 70.2; H, 6.4; N, 14.8%.

The n.m.r. spectrum in CDCl₃ had peaks at 2.37, multiplet, -4 aromatic protons; 6.887, quartet, J = 8 c/s, 4-CH₂; 7.357, singlet, 3-CH₃; 8.357, triplet, J = 8 c/s, 4-CH₃.

This was 4-ethyl-3-methylcinnoline 2-oxide.

Elution with 40% CHCl₃ in benzene gave an orange solid on removal of the solvent (1.5g.). This was recrystallised from benzene to give orange needles m.p. 171-172°C.

Yield = 0.85g.

C₁₁H₁₂N₂O₂ Requires C, 64.7; H, 5.9; N, 13.7%

Found C, 64.8; H, 5.7; N, 13.6%.

The n.m.r. spectrum in CDCl₃ had peaks at 1.607, multiplet, H-8;
2.20 \( \gamma \), multiplet, H-5, 6, 7; 6.95 \( \gamma \), quartet, \( J = 8 \) c/s, 4-CH\(_2\);
7.32 \( \gamma \), singlet, 3-CH\(_3\); 8.70 \( \gamma \), triplet, 4-CH\(_3\).

This was 4-ethyl-3-methylcinnoline 1,2-dioxide.

**Preparation of 3,4-Dimethylcinnoline 2-oxide (68a) and 1,2-dioxide (69a)**

3,4-Dimethylcinnoline (4.4g.) was heated at 70°C with acetic acid (20 ml.) and 30% hydrogen peroxide (10 ml.) according to Ogata's method. After extraction with chloroform, removal of the solvent gave an oily solid. This was taken up in the minimum of benzene and chromatographed on alumina.

Elution with 10% CHCl\(_3\) on benzene gave a white solid which was recrystallised from benzene and this gave white needles m.pt. 160-1°C.

Yield 1.0g.

**C\(_{10}\)H\(_{10}\)N\(_2\)O**

*Requires* C, 68.9; H, 5.8; N, 16.1%.

*Found* C, 68.9; H, 5.6; N, 15.6%.

The n.m.r. spectrum in CDCl\(_3\) had peaks at 2.37 \( \gamma \), multiplet, H-5, 6, 7, 8; 7.4 \( \gamma \), singlet, both 3-CH\(_3\) and 4-CH\(_3\). This confirmed the presence of 2-oxide.

Elution with 40% CHCl\(_3\) in benzene gave a yellow solid which on recrystallisation from benzene gave yellow crystals m.pt. 171-172°C.

Yield 0.8g.

**C\(_{10}\)H\(_{10}\)N\(_2\)O**

*Requires* C, 63.1; H, 5.3; N, 14.7%.

*Found* C, 63.3; H, 6.0; N, 14.6%.

The n.m.r. spectrum in CDCl\(_3\) had peaks at 1.70 \( \gamma \), multiplet, H-8; 2.30 \( \gamma \), multiplet, H-5, 6, 7; 7.36 \( \gamma \), singlet, 3-CH\(_3\) and 4-CH\(_3\). This confirmed the presence of 1,2-dioxide.
Preparation of 4-Methyl-3-nitrocinclolone 1-oxide (71)

4-Methyl-3-nitrocinclolone (0.8 g.) was warmed with acetic acid (25 ml.) and 30% hydrogen peroxide (3 ml.) at 70°C for six hours and then further hydrogen peroxide (3 ml.) was added. Heating was continued overnight. The solution was evaporated to a small volume and diluted when a precipitate was formed. This was filtered and dried. Recrystallisation from ethanol gave orange crystals m.pt. 170°C.

Yield 0.39 g. % Yield = 35%

C₉H₇N₃O₃
Requires C, 52.7; H, 3.4; N, 20.5%
Found C, 52.3; H, 3.6; N, 20.3%

The n.m.r. spectrum in T.F.A. had peaks at 1.10 γ, multiplet, H-8; 1.70 γ, multiplet, H-5,6,7; 7.0 γ, singlet, 4-CH₃.

Preparation of 4-carboxycinclolone 2-oxide (72)

4-Carboxycinclolone (5.5 g.) was heated at 70°C with acetic acid (25 ml.) and 30% hydrogen peroxide (13 ml.) at 70°C according to Ogata's method. After evaporation to a small volume, a precipitate was formed which was filtered and dried m.pt. 242°C.

Yield = 0.95 g. % Yield = 15%

C₉H₆N₂O₃
Requires C, 56.8; H, 3.2; N, 14.7%
Found C, 56.4; H, 3.2; N, 15.0%

The n.m.r. spectrum in D.M.S.O. showed peaks at 1.40 γ, singlet, H-3; 2.10 γ, broad singlet; 4-aromatic protons.

The filtrate from above was extracted with chloroform (3 x 100 ml.) and the extract washed with ferrous sulphate solution. This gave on removal of the solvent, a green solid (2.5 g.) m.pt. 195°C. This was shown to be unchanged starting material.
Reactions on $4$-Methylcinnoline N-oxides

The action of Acetic Anhydride on $4$-Methylcinnoline 2-oxide (63)

The 2-oxide (*) and acetic anhydride (*) were refluxed for one hour in an atmosphere of nitrogen. The acetic acid was distilled off and a few drops of water added. The reaction mixture was warmed at $80^\circ C$ for thirty minutes and then evaporated to dryness. The oil left was taken up in benzene and chromatographed on alumina. Elution with benzene followed by $50\%$ CHCl$_3$ in benzene gave on removal of the solvent black crystalline material. This was recrystallised from benzene-light petroleum to give black crystals m.pt. $143-144^\circ C$.

Elution with more polar solvents gave no further product. The product obtained had the same spectra as the starting material.

Reaction of Acetic Acid/Hydrogen Peroxide on $4$-methylcinnoline 1-oxide (62)

$4$-Methylcinnoline 1-oxide (0.5g.) was treated with acetic acid and hydrogen peroxide at $70^\circ C$ according to Ogata's method. After basification, extraction with chloroform ($3 \times 25$ ml.) gave an oil. This was taken up in benzene and chromatographed on alumina.

Elution with $30\%$ chloroform in benzene gave yellow solid (0.2g.) m.pt. $94^\circ C$.

The n.m.r. spectrum in CDCl$_3$ was identical with starting material.

Elution with $50\%$ chloroform in benzene followed by $75\%$ chloroform in benzene gave orange solid (0.05 g.) m.pt. $172^\circ C$.

The n.m.r. spectrum in CDCl$_3$ had peaks at $1.65 \gamma$, multiplet, $H-8$; $1.90 \gamma$, singlet $-H-3$; $2.20 \gamma$, multiplet, $-H-5, 6, 7$; $7.42 \gamma$, singlet $-4Ch_3$. 
This orange solid was thus identified as 4-methylcinnoline 1,2-dioxide (35).

Reaction of Acetic Acid/Hydrogen Peroxide on 4-methylcinnoline 2-oxide (63)

4-Methylcinnoline 2-oxide (0.5g.) was treated with acetic acid and 30% hydrogen peroxide at 70°C according to Ogata's Method. Basification with sodium carbonate was followed by extraction with chloroform (3 x 50 ml.). The chloroform extract was washed with ferrous sulphate solution, dried and evaporated to dryness. The residue was a solid m.pt. 145°C. Their residue was taken up in benzene and chromatographed on alumina. Elution with benzene followed by 25% chloroform in benzene, gave a product (0.35g.) m.pt. 145°C. This gave no depression on mixed m.pt. with starting material.

Elution with increasingly stronger solvents gave no further product.

Effect of U.V. light on 4-methylcinnoline (44a)

4-Methylcinnoline (0.2g.) in spectroscopic alcohol (3 ml.) was irradiated with light from Hanovia U.V.S. 500/A. medium pressure mercury arc with a filter and heat filter interposed. After five hours the sample was evaporated to dryness and solid obtained. m.pt. 72°C. Starting material had m.pt. 72-73°C.

Effect of U.V. light on 4-methylcinnoline 1-oxide (62)

4-Methylcinnoline 1-oxide (0.13g.) in spectroscopic alcohol
(3 ml.) was irradiated for five hours under the same conditions as above. On evaporation of solvent this gave a green solid m.pt. 92°C. Starting material had white crystals m.pt. 94°C. The solid was taken up in spectroscopic alcohol (3 ml.) and irradiated for a further 27 hours as before and then a further nineteen hours with only the heat filter. Evaporation gave a solid m.pt. 130°C - 135°C.

The n.m.r. spectrum in CDCl₃ on expansion of the aromatic region showed it to be very similar to that of 4-methylcinnoline 2-oxide and quite different from the 1-oxide.

Reaction of Methyl Iodide on 4-methylcinnoline 2-oxide (63)

4-Methylcinnoline 2-oxide (0.5g.) in ethanol (4 ml.) and methyl iodide (2g.) were refluxed for four hours. The solution was cooled and flooded with ether, to give green crystals m.pt. 148°C. These were recrystallised from ethyl acetate-alcohol to give sky blue needle crystals (0.14g.) m.pt. 149-150°C. From the n.m.r. spectrum in CDCl₃ this product was shown to be starting material.

Reaction of Methylene Diiodide on 4-Methylcinnoline 1,2-dioxide (35)

4-Methylcinnoline 1,2-dioxide (0.15g.) in ethanol (5 ml.) and methylene diiodide (0.25g.) were allowed to reflux for four hours. The precipitate formed on cooling was filtered and dried to give straw coloured crystals m.pt. 170-174°C. Starting material had m.pt. 171-172°C.
The N-oxidation of Nitrocinnolines

Preparation of 8-nitrocinnolin-4(1H)one (73a)

a. 4-Methyl-8-nitrocinnoline (1g.) was heated at 70°C with acetic acid (5 ml.) and 30% hydrogen peroxide (3 ml.) according to Ogata's method. On evaporation of solvent chloroform after work-up procedure, there remained a small amount of yellow solid. This was recrystallised from ethanol to give yellow needles m.pt. 170°C.

Yield = 0.2g.  % Yield = 20%.

The infrared spectrum in chloroform had $\nu_{\text{max}} = 3380$ cm$^{-1}$, -N-H group; 1642 cm$^{-1}$, - quinone type of carbonyl group; 1542 cm$^{-1}$ and 1310 cm$^{-1}$, -NO$_2$ Group.

The n.m.r. spectrum in CDCl$_3$ had peaks at $1.30\gamma$, multiplet; $2.0\gamma$, singlet; $2.5\gamma$, multiplet. There was no peak in the methyl region.

b. From 2-Amino-3-nitroacetophenone (74)

2-amino-3-nitroacetophenone (0.79g.) was dissolved in acetic acid (7 ml.) and 80% H$_2$SO$_4$ (2.3 ml.) and cooled to 0°C. Sodium nitrite (0.319g.) was added slowly and then the mixture was allowed to stand for thirty minutes at 0°C. It was finally heated at 70-75°C for one hour. Dilution of the cooled solution with water (25 ml.) gave a dark red precipitate which was filtered, dried and recrystallised from ethanol to give needles m.pt. 180-187°C.

Lit. m.pt. 185-186°C.

Yield = 0.2g.  % Yield = 28%.

Preparation of 3-Methyl-8-nitrocinnolin-4(1H)one (73b)

a. 4-Ethyl-3-methyl-8-nitrocinnoline (7.5g.) was heated at 70°C with acetic acid (38 ml.) and 30% hydrogen peroxide (19 ml.)
according to Ogata's method. On evaporation of the aqueous solution to a small volume and neutralisation, a precipitate was formed which was filtered off and dried. This was recrystallised from ethanol to give yellow needles m.pt. 235-236°C. Lit. 238-239°C.

Yield = 3.5g. % Yield = 44%.

C₉H₇N₃O₃ Requires C, 52.7; H, 3.5; N, 20.4%.

Found C, 52.4; H, 3.7; N, 20.6%.

The infrared spectrum in chloroform had \( \nu \max = 3350 \text{ cm}^{-1} \), N-H group; 2450 cm\(^{-1}\), -CH₃ group; 1610 cm\(^{-1}\), quinone type group; 1540 cm\(^{-1}\), -NO₂ group.

The n.m.r. spectrum in T.F.A. had peaks at 1.00 \( \gamma \), triplet, H-5 and H-7; 2.25 \( \gamma \), multiplet, H-6; 7.36 \( \gamma \), singlet, 3-CH₃.

b. From 3,4-Dimethyl-8-nitrocinnoline (55b)

3,4-Dimethyl-8-nitrocinnoline (2.5g.) was heated at 70°C with acetic acid (12 ml.) and 30% hydrogen peroxide (6 ml.) according to Ogata's method. On basification, no precipitate was formed. The aqueous solution was extracted with chloroform (3 x 50 ml.); the extract washed with ferrous sulphate solution, dried, and the solvent removed to give a yellow solid. This was recrystallised from ethanol to give yellow needles m.pt. 235°C.

Yield = 0.579g. % Yield = 23%.

The infrared spectrum in chloroform had \( \nu \max = 3300 \text{ cm}^{-1} \); 2950 cm\(^{-1}\); 1630 cm\(^{-1}\); 1540 cm\(^{-1}\).

The n.m.r. spectrum in T.F.A. had peaks at 1.0 \( \gamma \), triplet, H-5, H-7; 2.20 \( \gamma \), multiplet, H-6; 7.35 \( \gamma \), singlet, 3-CH₃.
Nitration of Cinnoline N-oxides

The Nitration of 4-Methylcinnoline 2-oxide (63)

a. 4-Methyl-6-nitrocinnoline 2-oxide (76a)

The 2-oxide (1g.) was heated at 90°C for two hours with concentrated H₂SO₄ (5 ml.) and concentrated HNO₃ (5 ml.) and then poured on to ice. The precipitate formed was filtered, washed and dried. Extraction of the filtrate gave no further product. Recrystallisation of the solid from dimethylformamide gave white needles m.pt. 235°C.

Yield = 0.35g. % Yield = 27%

C₉H₇N₃O₃ Requires C, 52.7; H, 3.4; N, 20.4%

Found C, 52.5; H, 3.4; N, 18.8%

The n.m.r. spectrum in T.F.A. had peaks at 0.827, doublet, J = 2 c/s, H-5; 1.207, quartet, J = 2, 9 c/s, H-7; 1.207, singlet, H-3; 1.607, doublet, J = 9 c/s, H-8; 7.07, singlet, 4-CH₃.

b. 4-Methyl-8-nitrocinnoline 2-oxide (77a)

The filtrate from the dimethylformamide recrystallisation was evaporated to dryness. The residue was taken up in boiling acetone, filtered and the filtrate evaporated to dryness. The residue was recrystallised twice from methanol to give light fawn needles m.pt. 231-232°C.

Yield 0.05g. % Yield = 0.91%

C₉H₇N₃O₃ Requires C, 52.7; H, 3.4; N, 20.4%

Found C, 52.4; H, 3.3; N, 19.0%

The n.m.r. spectrum in T.F.A. had peaks at 1.157, singlet, H-3; 1.507, multiplet, H-5 and H-7; 1.917, triplet, J = 8 c/s, H-6, 7.057, singlet, 4-CH₃.
Attempted Nitration of 4,6-Dimethylcinnoline 2-oxide

4,6-Dimethylcinnoline 2-oxide (1.8 g.) was added to concentrated H$_2$SO$_4$ (5.8 ml.) and warmed to 60°C. Potassium nitrate (0.72 g.) was added slowly to keep temperature at 60°C. After addition, the mixture was heated at 60°C for three hours, then cooled and poured on to ice. The precipitate obtained was filtered and dried (1.6 g.). Recrystallisation from acetone gave m.pt. 230-231°C. A mixed melting point with the starting material had no depression.

The Nitration of 4-Ethyl-3-methylcinnoline 2-oxide

a. 4-Ethyl-3-methyl-6-nitrocinnoline 2-oxide (76b)

The 2-oxide (0.75 g.) was heated at 90°C with a mixture concentrated H$_2$SO$_4$ (4 ml.) and concentrated HNO$_3$ (4 ml.) for two hours. The solution was cooled, poured on to ice and the precipitate filtered off. The precipitate was recrystallised from benzene-light petroleum to give solid m.pt. 145-150°C. This was shown to be a mixture from n.m.r. spectrum. The solid and filtrate were recombined and chromatographed on alumina. Elution with benzene gave yellow band which was developed and evaporation of the solvent gave a yellow solid. Recrystallisation of this from benzene gave yellow needles m.pt. 194°C.

Yield = 0.3 g.  % Yield = 31%.

$\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}_3$ Requires C, 56.6; H, 4.7; N, 18.0%

Found C, 56.5; H, 4.6; N, 17.8%.

The n.m.r. spectrum in CDCl$_3$ had peaks at 1.23 $\gamma$, doublet, $J = 2.5$ c/s, H-5; 1.55 $\gamma$, quartet, $J = 2.5$, 9 c/s, H-7; 2.05 $\gamma$, doublet, $J = 9$ c/s, H-8; 6.8 $\gamma$, quartet, $J = 8$ c/s, 4-CH$_2$; 7.32 $\gamma$, singlet, 3-CH$_3$; 8.60 $\gamma$, triplet, $J = 8$ c/s, 4-CH$_3$. 
b. 4-Ethyl-3-methyl-8-nitrocinnoline 2-oxide (77b)

A second fraction was taken from the column immediately after elution of the yellow band. On removal of the solvent, a white solid was obtained. This was recrystallised from benzene to give white needles m.pt. 196°C.

Yield = 0.15g. % Yield = 16%

\[ \text{C}_{11}\text{H}_{11}\text{N}_3\text{O}_3 \]

Requires C, 56.6; H, 4.7; N, 18.0%

Found C, 56.8; H, 4.7; N, 17.6%

The n.m.r. spectrum in CDCl$_3$ had peaks at 1.97, quartet, $J = 1.5$, 8 c/s, H-7; 2.07, quartet, $J = 1.5$, 8 c/s, H-5; 2.267, triplet, $J = 8$ c/s, H-6; 6.847, quartet, $J = 8$ c/s, H-CH$_2$; 7.377, singlet, 3-CH$_3$; 8.66, triplet, $J = 8$ c/s, H-CH$_3$.

The filtrate from fraction 1 on evaporation to dryness showed extra peaks which were not accounted for in terms of isomers separated. Two meta doublets at 1.087 and 1.317 were shown. No other product however could be isolated.

Preparation of 4-nitrocinnoline 1-oxide

Cinnoline 1-oxide (0.5g.) was added slowly to a mixture of concentrated H$_2$SO$_4$ (2.75 ml.) and concentrated HNO$_3$ (2.75 ml.) at 0°C. The mixture was left at room temperature for eight hours and then heated at 50°C for one hour, cooled and poured on to ice. The precipitate formed was filtered, washed and dried. This was re-crystallised from acetone to give green needles m.pt. 162-163°C. Lit. m.pt. 161-162°C.

Yield = 0.2g. % Yield = 30%.
Preparation of Quaternary Salts

Preparation of 2,4-Dimethylcinnolinium Iodide

4-Methylcinnoline (1g.) in ethanol (6.25 ml.) and methyl iodide (2g.) were refluxed for four hours. On cooling a brown precipitate was formed which was recrystallised from ethyl acetate-ethanol to give brown needles m.pt. 205°C. Lit. m.pt. 207°C.

Yield = 1.36g. % Yield = 68%.

Preparation of 6-Bromo-2,4-Dimethylcinnolinium Iodide

6-Bromo-4-methylcinnoline (1g.) in ethanol (9 ml.) and methyl iodide (3.5g.) gave after reflux for four hours, a brown solid. This was recrystallised from ethyl acetate-ethanol to give dark brown crystals m.pt. 187°C.

Yield = 1.2g. % Yield = 74%.

Preparation of 2,4,6-Trimethylcinnolinium Iodide

4,6-Dimethylcinnoline (0.4g.) in ethanol (5 ml.) and methyl iodide (1.1g.) were refluxed for four hours. Recrystallisation of the cooled precipitate from ethyl acetate-ethanol gave green powdery crystals m.pt. 181-182°C.

Yield = 0.56g. % Yield = 75%.
Preparation of 2,3-Dimethyl-4-ethylcinnolinium Iodide

4-Ethyl-3-methylcinnoline (1 g.) in ethanol (8 ml.) and methyl iodide (4 g.) were refluxed for five hours. The cooled precipitate was recrystallised from ethyl acetate-ethanol to give orange needles m.pt. 165-166°C.

Yield = 1.3 g. % Yield = 73%.

C_{12}H_{15}IN_{2} Requires C, 45.9; H, 4.8; I, 40.4; N, 8.9%

Found C, 46.3; H, 4.9; I, 40.4; N, 9.4%.

Preparation of 4-Methyl-2-trideuteromethylcinnolinum Iodide (79b)

4-Methylcinnoline (0.75 g.) in ethanol (4.5 ml.) and trideuteromethyl iodide (2 g.) were refluxed for four hours. The precipitate formed on cooling was recrystallised from ethyl acetate-ethanol to give brown needles m.pt. 201°C.

Yield = 1.0 g. % Yield = 67%.

Preparation of 2,4-Dimethylcinnolinium methosulphate

4-Methylcinnoline (1.33 g.) in methanol (6 ml.) and dimethyl sulphate (1 ml.) were refluxed gently for ninety minutes. After cooling, the methanol was distilled off leaving a tarry solid. This was recrystallised from methanol-ethyl acetate to give purple needle crystals m.pt. 216°C. Yield = 1.2 g. % Yield = 48%.

C_{11}H_{12}N_{2}O_{4}S Requires C, 48.9; H, 5.2; N, 10.3; S, 11.9%

Found C, 48.5; H, 5.0; N, 9.8; S, 12.4%
Reaction of Ethylmagnesium Bromide on 4-Methylicinnoline

Ethyl bromide (6 ml.) was added to dry magnesium (1.32 g.) in dry ether (50 ml.). 4-Methylicinnoline (4 g.) in dry benzene (50 ml.) was added with stirring and the reaction mixture refluxed for one hour. After decomposition of the complex, extraction with ether (3 x 100 ml.) followed by benzene (3 x 100 ml.) gave a dark grey solid. This was taken up in boiling benzene to give a white solid. The mother liquor from this was boiled down to dryness and shown to contain impure 4-methylicinnoline. The white solid was recrystallised from benzene to give white needles m.pt. 198°C.

Yield = 0.8 g.

The molecular weight was shown to be 190 from mass spectrum.

C_{11}H_{14}N_{2}O  

Requires  C, 69.5;  H, 7.2;  N, 14.7%

Found  C, 70.0;  H, 7.2;  N, 13.5%

The infrared spectrum in nujol had \( \nu_{max} = 3300 \text{ cm}^{-1}; 1620 \text{ cm}^{-1} \). The n.m.r. spectrum in T.F.A. had peaks at 1.1 \( \gamma \), broad singlet, 2.6 \( \gamma \), multiplet; 6.25 \( \gamma \), quartet, \( J = 8 \text{ c/s} \), -CH\text{2}; 8.15 \( \gamma \), singlet, -CH\text{3}; 8.50 \( \gamma \), triplet, \( J = 8 \text{ c/s} \), -CH\text{3}. 
Benzo[c]cinnolines

Preparation of Benzo[c]cinnoline (39)

2,2'-Dinitrobiphenyl (17.5 g.) was dissolved in boiling 90% ethanol (350 ml.) and 40% aqueous KOH (15 ml.) added. The solution was stirred under reflux while zinc dust (52.5 g.) was added and then stirred for a further four hours. Filtration gave a red solution, which on cooling gave no precipitate. The filtrate was evaporated to a small volume, diluted with water and extracted with chloroform (3 x 100 ml.). The dried extract gave a blackish oil which crystallised out on cooling. The product was taken up in benzene and chromatographed on alumina. Elution with benzene-ether gave a solid on removal of solvent. The solid was recrystallised from benzene to give yellow cubes m.pt. 156°C. Lit. m.pt. 150°C.

Yield = 7.5 g. % Yield = 57%

Preparation of Benzo[c]cinnoline 5-oxide (40)

2,2'-Dinitrobiphenyl (30 g.) was dissolved in ethanol (550 ml.) with warming and a mixture of sodium sulphide (60 g.) and sodium hydroxide (12 g.) in water (100 ml.) added dropwise with refluxing and stirring. The mixture was allowed to reflux gently for four hours and then the ethanol was distilled off and the residue poured into water (1 l.). The precipitate formed, was filtered off and dried. It was recrystallised from ethanol to give buff needles m.pt. 135-137°C. Lit. m.pt. 136-138°C.

Yield = 23 g. % Yield = 95%
Preparation of Benzo[c]cinnoline 5,6-dioxide 66(34)

a. From 2,2'-dinitrobiphenyl (33)

2,2'-Dinitrobiphenyl (10g.) was dissolved in boiling ethanol (200 ml.) and 40% KOH (6 ml.) added. Zinc dust (30g.) was added over ten minutes and the mixture was stirred with refluxing for twenty minutes. The mixture was filtered hot and the filtrate allowed to cool. This gave two distinct types of crystal which were separated by hand. One fraction melted at 124°C, → starting material. The other fraction was recrystallised from ethanol twice to give fawn plates m.pt. 238°C. Lit. m.pt. 240°C.

Yield = 1.3g. % Yield = 16%

b. From Benzo[c]cinnoline 5-oxide 28(40)

Benzo[c]cinnoline 5-oxide (6g.), acetic acid (30 ml.) and 30% hydrogen peroxide (30 ml.) were heated at 120°C for eight hours. On cooling a small amount of yellow crystals were filtered off. These were recrystallised from ethanol to give needles m.pt. 124°C. The filtrate was evaporated to a small volume and treated with water. This gave a precipitate which was filtered, dried and recrystallised from ethanol to give fawn plates m.pt. 238°C.

Yield 1.4g. % Yield = 23%

Preparation of 1-Nitrobenzo[c]cinnoline 67(83)

Benzo[c]cinnoline (16.5g.) was added slowly to a stirred mixture of fuming HNO₃ (27.5 ml.) and concentrated H₂SO₄ (82.5 ml.) at -3°C. Stirring was continued at 0°C for seven hours and then the solution was poured on to ice and the pH brought to 7 with
concentrated ammonia solution. The precipitate formed was filtered, washed and dried. Soxhlet extraction of the solid with light petroleum (60-80) gave a yellow powder on removal of the solvent. The powder was recrystallised from benzene to give yellow crystals m.pt. 160°C. Lit. m.pt. 162°C.

Yield = 7.5g. % Yield = 37%.

The remaining black residue was recrystallised from acetic acid to give black powder m.pt. 230°C. l-Nitrobenzo[c]cinnoline m.pt. 237-238°C.

Yield = 8g. % Yield 40%.

Oxidation of 1-Nitrobenzo[c]cinnoline

1-Nitrobenzo[c]cinnoline (5g.) was heated with acetic acid (25 ml.) and 30% hydrogen peroxide (12 ml.) at 70°C for twelve hours. On cooling the precipitate formed was filtered, dried and recrystallised from benzene to give yellow crystals m.pt. 238°C. Lit. m.pt. 245°C.

Yield 1.8g. % Yield = 35%.

The filtrate was diluted to give a further precipitate containing the other isomer in an impure state m.pt. 178°C. Recrystallisation from benzene failed to raise this.

Nitration of Benzo[c]cinnoline 5-oxide (40)

Preparation of 2-Nitrobenzo[c]cinnoline 6-oxide

Benzo[c]cinnoline 5-oxide (19.6g.) was added to fuming nitric acid (150 ml.) with stirring, the temperature being kept below 40°C. After one hour, the solution was poured on to ice and the precipitate formed was filtered and dried. The yellow solid obtained was re-
crystallised from dimethyl formamide to give yellow needles
m.p.t. 262°C. Lit. m.p.t. 265-269°C.

\[ C_{12}H_{7}N_{3}O_{3} \]

**Requires** C, 59.9; H, 2.9; N, 17.4%

**Found** C, 59.5; H, 2.8; N, 17.6%

The n.m.r. spectrum in T.F.A. had peaks at 0.4 \( \gamma \), doublet; 1.05 \( \gamma \),

broad singlet; 1.25 \( \gamma \), quartet; 1.75 \( \gamma \), multiplet.

The dimethyl formamide filtrate from A was diluted to give a

further precipitate. This was recrystallised from aqueous dimethyl-

formamide followed by acetic acid to give a light yellow solid

m.p.t. 253°C.

Yield = 1 g.

Lit. m.p.t. = 258-259°C for 2-nitrobenzo[c]cinnoline 5,6-dioxide

(87).

The n.m.r. spectrum in T.F.A. had peaks at 0.9 \( \gamma \), doublet; 1.38 \( \gamma \),

quartet; 2.40 \( \gamma \), multiplet.

Preparation of a Dinitrobenzo[c]cinnoline N-oxide (86)

Benzo[c]cinnoline 5-oxide (20g.) and fuming HNO\(_3\) (140 ml.) were

heated at 90°C for three hours. The cooled dark brown solution was

poured on to ice to give a yellow precipitate. This was filtered

and washed with water, then alcohol and ether. The solid was re-

crystallised from nitromethane to give light green powder

m.p.t. 262°C.

Yield = 13 g.

\[ C_{12}H_{6}N_{4}O_{5} \]

**Requires** C, 50.3; H, 2.1; N, 19.5%

**Found** C, 49.6; H, 2.4; N, 19.4%

The infrared spectrum in nujol had \( \nu_{\text{max}} = 1535 \text{ cm}^{-1}, 1340 \text{ cm}^{-1} \),
- Nitro group.

\[ \nu_{\text{max}} = 1405 \text{ cm}^{-1}, 1385 \text{ cm}^{-1}; \text{-N} \rightarrow \text{O group.} \]

**Nitration of Benzo[c]cinnoline 5,6-dioxide (34)**

Benzo[c]cinnoline 5,6-dioxide (0.38g.) was heated under reflux with fuming nitric acid (8 ml.) for eight hours. The solution was poured on to ice and the bright yellow precipitate obtained was filtered and dried (0.33g.) m.pt. 253-256°C.

A 100 MHz n.m.r. spectrum showed there to be a mixture whose components could not be separated.

**Reactions of the Dinitrobenzocinnoline mono-N-oxide (86)**

a. with POCl₃

The oxide (6g.) was suspended in chloroform (50 ml.) and phosphorus trichloride (12 ml.) added. The reagents were heated under reflux for one hour. The chloroform was distilled off and the residue poured on to ice. This gave a yellow-green precipitate m.pt. 260-263°C. This was unchanged starting material.

b. with KMnO₄

The oxide (2g.) was dissolved in pyridine (40 ml.) to give a dark green solution and 10% KOH (20 ml.) was added slowly. This immediately produced a red precipitate. A 4% solution of KMnO₄ (120 ml.) was added with shaking. Gradually the red colour changed to brown with the formation of manganese dioxide. The reaction mixture was warmed in a water bath for one hour and then filtered. The solution was evaporated to a small volume and then taken to
pH4. A small amount of solid was obtained m.pt. 130-140°C. An attempt to recrystallise this failed. The solid was not positively identified.

c. with Ethanol KOH

The oxide (0.5g.) was refluxed with a solution of ethanol (20 ml.) and KOH pellets (2g.) in water (20 ml.) for one hour. The ethanol was distilled off. The remaining solution was diluted with water and the black precipitate formed, filtered off. This had m.pt. > 330°C. The black solid was not positively identified.

Preparation of Amine-oxides for N.M.R. Spectroscopy

Pyridazine 1-oxide$^{78}$(90)

Pyridazine (4g.), acetic acid (100 ml.), and 30% hydrogen peroxide (7 ml.) were heated at 70°C for one day. The solution was evaporated to a small volume, diluted and neutralised. Extraction with chloroform (3 x 50 ml.) gave an oil (0.4g.). The n.m.r. spectrum in CDCl$_3$ had peaks at 1.45 $\gamma$, H-3; 1.74 $\gamma$, H-6; 2.15 $\gamma$, H-5; 2.78 $\gamma$, H-4.

3-Methylpyridazine 1-oxide and 2-oxide

The compounds were prepared by method of Ogata and Kano. Chromatography of the mixture of isomers gave on elution with benzene, 3-methyl pyridazine 2-oxide, m.pt. 83°C. Lit. m.pt. 83-84°C. Elution with benzene/chloroform gave 3-methylpyridazine 1-oxide m.pt. 65-66°C. Lit. m.pt. 68-69°C.
Phthalazine 2-oxide

Phthalazine (0.75 g.) was treated with acetic acid (5 ml.) and 30% hydrogen peroxide (3 ml.) for eight hours at 70°C. The solution was evaporated to half volume diluted and neutralised. Extraction with chloroform (3 x 25 ml.) gave a solid which was recrystallised from benzene to give yellow crystals (0.39 g.) m.pt. 141°C. Lit. m.pt. 143°C.

Pyrazine 1-oxide (92) and Pyrazine 1,4-dioxide (93)

Pyrazine was oxidised according to method of Koelsch and Gumprecht.78 Pyrazine 1-oxide was obtained as white needles from benzene m.pt. 112-113°C. Lit. m.pt. 113-114°C. Pyrazine 1,4-dioxide was obtained as white needles from methanol m.pt. 280°C. Lit. m.pt. 285-295°C.

2-Methylpyrazine 1-oxide (94) and 2-Methylpyrazine 4-oxide (95)

The preparation of these compounds was carried out by method of Koelsch and Gumprecht.78 The solid obtained on oxidation was extracted with light petroleum (30-40). On cooling, white crystals were deposited. These were filtered off and recrystallised from ether to give white needles m.pt. 91°C. The n.m.r. spectrum in CDCl₃ had peaks at 1.53, singlet; 1.57, doublet; 7.42, singlet.

The filtrate was evaporated to dryness to give an oil which was chromatographed on alumina. Elution with benzene gave a mixture of isomers. Elution with 50% CHCl₃ in benzene gave a solid. This was recrystallised from benzene to give white needles m.pt. 46°C. The n.m.r. spectrum in CDCl₃ had peaks at 1.65, doublet; 2.00, singlet; 2.05, doublet; 7.48, singlet.
Quinoxaline 1-oxide

Quinoxaline 1-oxide was prepared according to the method of Landquist. The product obtained on N-oxidation of quinoxaline was recrystallised from cyclohexane to give colourless needles m.pt. 122°C. Lit. m.pt. 122-123°C.

Quinoxaline 1,4-dioxide

Quinoxaline 1,4-dioxide was prepared from quinoxaline according to method of Landquist. The product obtained was recrystallised from ethanol to give orange needles m.pt. 240°C. Lit. m.pt. 241-243°C.
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4 Methylcinnoline-1,2-dioxide

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Department of Chemistry, Edinburgh University

The di-N-oxides of pyridazine or its benzo derivatives are of theoretical interest owing to the formal unit positive charge upon each nitrogen atom, and the degree to which this can be spread to other parts of the molecule. The best known compounds possessing the unit \( -N(\bar{O})=N(\bar{O})- \) are the dimers of nitroso compounds,\(^1\) prepared from the monomer,\(^2\) and benzoylcinnoline-5,6-dioxide prepared from 2,2'-dinitrobiphenyl by reduction.\(^3\) Direct formation of compounds of these types by the oxidation of the \(-N=N-\) system does not seem to have been established although a possible, but unlikely, case is the formation of a di-N-oxide from 1,10 diamino-benzoylcinnoline;\(^4\) this dioxide was thought to be the 4,9- or 4,10- rather than the 4,5-dioxide.

We report now the preparation of 4-methylcinnoline-1,2-dioxide as yellow needles, m.p. 168-9 ° (m.p. 172 ° on Köfler block). It is formed as a by-product (in about 4% yield) during the oxidation of 4-methylcinnoline to the mixture of mono-N-oxides by the action of hydrogen peroxide and acetic acid. The method used was essentially that of Ogata and co-workers,\(^5\) and the ratio of mono-N-oxides given by them has been confirmed. A comparison of the spectral properties of the 1-oxide, 2-oxide and 1,2-dioxide is shown in the Table. The 1,2-dioxide was obtained from the mixture by chromatography on alumina after elution with 50% chloroform in benzene, following the removal of the 1-oxide (with benzene) and the 2-oxide with 25% chloroform in benzene. Microanalysis and molecular weight (by vapour pressure osmometry) indicated the presence of a second oxygen atom in the molecule, leading to the formula \( \text{C}_9\text{H}_8\text{N}_2\text{O}_2 \) (Found: C, 61·2; H, 4·5; N, 15·6; M, 172. \( \text{C}_9\text{H}_8\text{N}_2\text{O}_2 \) requires C, 61·3; H, 4·5; N, 15·9%; M, 176). These conclusions were confirmed by mass spectrometry.

![Diagram](image)

The formation of a di-N-oxide by direct oxidation could proceed by either further oxidation of a mono-oxide, or synchronous formation direct from the free base. Since N-oxidation is normally considered to be an electrophilic reaction both routes appeared unlikely, and various alternative structures for the product \( \text{C}_9\text{H}_8\text{N}_2\text{O}_2 \) were considered. The presence of the bicyclic aromatic nucleus follows from the p.m.r. and ultraviolet spectra. That the compound was not a cinnoline-N-oxide monohydrate (suggested by analogy with other amine oxides) was shown by the p.m.r. and mass spectrometry results and also the ultraviolet spectrum in 95% ethanol. The 4-(hydroxy-methyl)-cinnoline-N-oxides were eliminated by the p.m.r. absorption at 7 4 ppm; the hydroxy-4-methylcinnoline-N-oxides and 4-methylcinnolin-3(2H)one-1-oxide would show the presence of OH or C=O absorption in the infrared region (none was observed); no p.m.r. peaks were altered by treatment with isotope.

### Table: Spectral Properties of 4-Methylcinnoline oxides

<table>
<thead>
<tr>
<th>Compound</th>
<th>( \lambda_{\text{max.}} ) (mμ)</th>
<th>( \nu_{\text{max.}} ) (cm(^{-1}))</th>
<th>Proton Chemical Shifts (( \tau ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-oxide</td>
<td>220, 263, 315, 360(^4)</td>
<td>1360, 1395, 1420</td>
<td>1-3(8H); 1-83(3H); 2-17 7-4(4Me)</td>
</tr>
<tr>
<td>2-oxide</td>
<td>224, 262, 357(^5)</td>
<td>1370, 1395, 1420</td>
<td>1-9(3H); 2-29; 7-36(4Me)</td>
</tr>
<tr>
<td>1,2-dioxide</td>
<td>236, 275, 348(^6)</td>
<td>1350, 1405, 1420</td>
<td>1-7(8H); 1-9(3H); 2-27 7-4(Me)</td>
</tr>
</tbody>
</table>

### Footnotes to Table

1. In 95% ethanol
2. In CHCl\(_3\)
3. In CDCl\(_3\) (about 0·5 molar solutions)
4. log \( \epsilon_{\text{max.}} \) 4·36; 4·12; 3·85 respectively
5. log \( \epsilon_{\text{max.}} \) 4·42; 4·57; 3·54 respectively
6. log \( \epsilon_{\text{max.}} \) 4·42; 4·60; 3·85 respectively
7. Three protons as multiplet
8. Four protons as multiplet

We report now the preparation of 4-methylcinnoline-1,2-dioxide as yellow needles, m.p. 168-9 ° (m.p. 172 ° on Köfler block). It is formed as a by-product (in about 4% yield) during the oxidation of 4-methylcinnoline to the mixture of mono-N-oxides by the action of hydrogen peroxide and acetic acid. The method used was essentially that of Ogata and co-workers,\(^5\) and the ratio of mono-N-oxides given by them has been confirmed. A comparison of the spectral properties of the 1-oxide, 2-oxide and 1,2-dioxide is shown in the Table. The 1,2-dioxide was obtained from the mixture by chromatography on alumina after elution with 50% chloroform in benzene, following the removal of the 1-oxide (with benzene) and the 2-oxide with 25% chloroform in benzene. Microanalysis and molecular weight (by vapour pressure osmometry) indicated the presence of a second oxygen atom in the molecule, leading to the formula \( \text{C}_9\text{H}_8\text{N}_2\text{O}_2 \) (Found: C, 61·2; H, 4·5; N, 15·6; M, 172. \( \text{C}_9\text{H}_8\text{N}_2\text{O}_2 \) requires C, 61·3; H, 4·5; N, 15·9%; M, 176). These conclusions were confirmed by mass spectrometry.

![Diagram](image)

The formation of a di-N-oxide by direct oxidation could proceed by either further oxidation of a mono-
D₂O. Of the remaining possibilities only 4-methylcinnoline-1,2-dioxide (I) and the pair of isomeric 4-methyl-N-peroxycinnolines (II) for example need to be seriously considered. The last is eliminated by the stability of the compound; specimens have been shown to be stable in air for several months at least; they are apparently unaffected by light, in contrast to 4-methylcinnoline-1-oxide the colourless crystals of which rapidly turn blue on standing in air (cf. cinnoline itself which melts to a green liquid on standing).

The mass spectrum of the compound shows a peak corresponding to the loss of HCN from the molecule, that is, one oxygen atom is retained; this is most readily interpreted in terms of a 1,2-dioxide rather than either of the isomeric peroxides. Positive evidence for the structural assignment is the two low field peaks at 1.7 τ and 1.9 τ in the p.m.r. spectrum; these must arise from the 8H and 3H of a cinnoline respectively, since the former is a not completely resolved octet, while the latter is a poorly resolved 1,3,3,1-quartet (J=1.2 c.p.s.) consistent with the presence of 3CH-4Me; the methyl peak is a doublet (J=1.2 c.p.s.). The two peaks in the 1390-1410 cm⁻¹ region of the infrared spectra of the cis dimers of aromatic nitroso compounds have been assigned to the $\cdot\hat{\text{N}(\hat{\text{O}})\cdot\hat{\text{N}(\hat{\text{O}})}}$ group. Benzo[c]cinnoline-5,6-dioxide is anomalous in that respect and has peaks at 1342 and 1399 cm⁻¹; this may be a result of the structure approximating to that of a biphenyl, with a bridging $\cdot\hat{\text{N}(\hat{\text{O}})\cdot\hat{\text{N}(\hat{\text{O}})}}$ group having little conjugation in the heterocyclic ring, since cis azomethane-1,2-dioxide and also some related compounds have vmax. 1342 and 1399 cm⁻¹. Either assignment may be applied to the present compound.

Under comparable conditions to those used in the preparation of 4-methylcinnoline-1,2-dioxide, 4-methylcinnoline-2-oxide is apparently unchanged; the corresponding 1-oxide is also largely unchanged but a very small amount of material which may be the 1,2-dioxide, is also formed.

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