PART I

STUDIES IN THE SYNTHESIS OF

CINNOLINES AND QUINOXALINES
CHAPTER I

A REVIEW ON THE SYNTHESIS OF
CINNOLINES AND QUINOXALINES
INTRODUCTION

DI-NITROGEN HETEROCYCLIC SYSTEMS

Six-membered heterocyclic compounds containing two nitrogen atoms in the ring are called diazines. Depending on the position of the two nitrogen atoms in the ring, they are named as 1,2-, 1,3- and 1,4-diazines or pyridazine (I), pyrimidine (II) and pyrazine (III) respectively. These three di-nitrogen heterocyclic ring systems and their numberings are illustrated below:

![Diazines](image)

Benzo derivatives of diazines are also known by their trivial names, such as, cinnolin (IV), phthalazine (V), quinazoline (VI) and quinoxaline (VII). The benzopyridazines having the benzo group attached to the 5,6 positions are called cinnolines. Benzopyrazines are called quinoxalines.
The benzodiazines and their numberings are shown below:

![Benzodiazines Diagram](image)

(IV)  (V)  (VI)  (VII)

The methods of synthesis of cinnolines and quinoxalines described so far in literature, with particular reference to the aryl substituted compounds, are briefly reviewed in this chapter.

SYNTHESIS OF CINNOLINES

No derivative of cinnoline has been found to occur in nature so far. Formation of the di-nitrogen heterocyclic system was first observed by von Richter in 1883 in the course of his unsuccessful attempts to prepare o-hydroxyacetophenone (IX) by heating the diazonium chloride of o-aminophenylpropionic acid (VIII) with water. The resulting hydroxy acid (X) on decarboxylation gave the compound (XI) which on subsequent heating with zinc dust gave the new heterocyclic compound (XII). The sequence of these reactions is shown in Fig. 1.

Although von Richter could not obtain the compound (XII) in a sufficiently pure condition for the determination of its physical properties and elemental analysis, he called this new heterocyclic system as cinnoline.
in analogy with quinoline (German: chinolin). Pure cinnolone was first obtained by Busch and Klett\(^2\) in 1894 by converting 4-hydroxyquinolone (\(\text{XI}\)), obtained by von Richter's method, to 4-chloroquinolone (\(\text{XIII}\)) with a mixture of phosphorus oxychloride and phosphorous pentachloride, followed by the reduction of the latter with iron and sulphuric acid. The resulting 1,2-dihydroquinolone (\(\text{XIV}\)) was finally oxidised to cinnolone (\(\text{XII}\)) with mercuric oxide (Fig. 1).

Three main approaches have been explored for the synthesis of cinnolines. The first approach makes use of the condensation between the \(\beta\)-nitrogen atom of a chain of two nitrogen atoms and the \(\beta\)-carbon atom of a chain of two or more carbon atoms, these chains being oriented in the ortho positions of a benzene ring (\(\text{XV}\)).

In the second approach, the chain of two nitrogen atoms is increased by one carbon atom which condenses with the \(\alpha\)-carbon of a second chain in the ortho position to build up the heterocyclic ring (\(\text{XVI}\)).

In the third approach, the \(\delta\)-carbon atom of a chain of two nitrogen and two carbon atoms reacts with the hydrogen in the ortho position of the aromatic ring to yield the cinnoline derivatives (\(\text{XVIII}\)).
BUSCH AND KLETT'S SYNTHESIS

$$\text{OH} \quad \text{POCl}_3 + \text{PCL}_5 \quad \text{Cl}$$

$$\text{(XI)} \quad \rightarrow \quad \text{(XIII)}$$

$$\text{HgCl}$$

$$\text{(XII)}$$

FIG. 1
These three approaches for the building up of the cinnoline structure have been shown in Fig. 2.

Plausible mechanisms for these three synthetic approaches to the cinnoline structure have been put forward by various workers\textsuperscript{3,4,5}, although not supported by experimental evidence. The first two approaches are believed to possess the common feature of electrophilic attack by the diazonium cation on the carbon-carbon centre of unsaturation (XVIII).

\[
\begin{align*}
\text{C} & \quad \text{C} \\
\text{N} & \quad \text{N:} \\
\text{N} & \quad \text{N:} \\
\end{align*}
\]

(XVIII)

[A] SYNTHETIC METHODS BASED ON THE FIRST APPROACH

In this approach, the heterocyclic ring is built up from an aniline having a carbon chain in the ortho position containing a suitably activated β-carbon atom. The additional nitrogen atom is introduced through the diazo reaction on the amino group. The methods described below are based on this approach.
MAIN APPROACHES FOR THE SYNTHESIS OF CINNOLINES

WIDMAN-STOERMER'S SYNTHESIS

\[
\begin{align*}
\text{C}=\text{CHR}'' & \overset{\text{HNO}_2}{\rightarrow} \text{C}=\text{CHR}'' \\
\text{NH}_2 & \quad \text{(HCl)} \\
\end{align*}
\]

MECHANISM OF WIDMAN-STOERMER'S SYNTHESIS

FIG. 2
1. **von Richter’s Synthesis**

This method has already been described earlier in connection with the synthesis of the parent compound. (Fig. 1).

2. **Widman-Stoermer’s Synthesis**

Widman\(^6,7\) observed that on keeping a diazotized solution of 3-amino-4-isopropenylbenzoic acid at the room temperature, a product was formed which was identified as 4-methylcinnoline-7-carboxylic acid. This method was later exhaustively studied by Stoermer\(^3,9\), who synthesised various cinnolines substituted in 3- and 4-positions, starting from suitable o-aminophenylethylenes. In general, this method can be represented by the sequence of reactions \(XIX \rightarrow XX \rightarrow X\)I (Fig. 2).

This reaction was further extended by Simpson et al.\(^3,4,10-16\) for the synthesis of various substituted cinnolines. Investigations on the scope of this reaction\(^11,13,16\) have shown that it proceeds successfully when \(R'\) is an aryl or a methyl group and \(R''\), an alkyl, aryl or aralkyl group, but that it fails if \(R'\) is a hydrogen or a carboxyl and \(R''\), an aryl or an \(\alpha\)-pyridyl group.

The reaction is usually very rapid and seemingly independent of the geometrical configuration of the groups around the ethylenic linkage. It was concluded from these results\(^13\) that the ring closure is, more or less, ionic in character, and that it is induced by polarisation of the diazonium salt (Fig. 2).
3. **Borsche's Synthesis**

Borsche et al.\textsuperscript{17} in 1941 observed that a solution of diazotized 2-amino-6-nitroacetophenone (XXII) when allowed to stand at the room temperature, slowly cyclised to yield 6-nitro-4-hydroxycinnolone (XXIII) (Fig. 3). This method has been found to be of general applicability for the synthesis of 4-hydroxycinnolines substituted at various positions starting from suitable o-aminoacetophenones. Cinnolone formation is considered to take place through acid catalysed enolisation of the carbonyl group of the acetophenone derivative. The cyclisation is facilitated by the electrophilic character of the diazonium group and is increased by electron attracting substituents. (Fig. 3)

The cyclization is slower than that in Widman-Stoermer's method, but is enhanced by electron attracting groups in the m-position to the acetyl group. Heating is avoided in this reaction to prevent the formation of phenol by the decomposition of the diazonium salt. The presence of strong hydrochloric acid assists ring closure, but can lead to the replacement of a nitro group by a chloro group\textsuperscript{18}.

These three methods based on the first approach have not found extensive application for the synthesis of cinnolines, since the starting materials are not easily accessible.
Borsche's Synthesis

\[
\begin{align*}
\text{NO}_2-CN\text{=N}^+\text{C}^\text{-CH}_3^+ & \rightarrow \text{NO}_2-\text{C}^\text{\textit{C}_2}\text{N}^\text{\textit{C}_2}\text{H}_\text{OH}^+ + \text{HCl} \\
(\text{XXII}) & \rightarrow (\text{XXIII})
\end{align*}
\]

Mechanism of Borsche's Synthesis

\[
\begin{align*}
\text{CO}_{\text{C}^\text{\textit{C}_2}\text{N}^\text{\textit{C}_2}\text{H}_3}^\text{+} & \xrightarrow{\text{H}^+} \text{CO}_{\text{C}^\text{\textit{C}_2}\text{N}^\text{\textit{C}_2}\text{H}_3}^- \\
& \xrightarrow{-\text{H}^+} \text{CO}_{\text{C}^\text{\textit{C}_2}\text{N}^\text{\textit{C}_2}\text{H}_3}^+ \\
\text{CO}_{\text{C}^\text{\textit{C}_2}\text{N}^\text{\textit{C}_2}\text{H}_3}^+ & \xrightarrow{\text{H}^+} \text{CO}_{\text{C}^\text{\textit{C}_2}\text{N}^\text{\textit{C}_2}\text{H}_3}^- \\
& \xrightarrow{-\text{H}^+} \text{CO}_{\text{C}^\text{\textit{C}_2}\text{N}^\text{\textit{C}_2}\text{H}_3}^+ \\
\text{CO}_{\text{C}^\text{\textit{C}_2}\text{N}^\text{\textit{C}_2}\text{H}_3}^+ & \xrightarrow{\text{H}^+} \text{CO}_{\text{C}^\text{\textit{C}_2}\text{N}^\text{\textit{C}_2}\text{H}_3}^- \\
& \xrightarrow{-\text{H}^+} \text{CO}_{\text{C}^\text{\textit{C}_2}\text{N}^\text{\textit{C}_2}\text{H}_3}^+ \\
\end{align*}
\]

\[
\begin{align*}
\text{CO}_{\text{C}^\text{\textit{C}_2}\text{N}^\text{\textit{C}_2}\text{H}_3}^+ & \xrightarrow{\text{H}^+} \text{CO}_{\text{C}^\text{\textit{C}_2}\text{N}^\text{\textit{C}_2}\text{H}_3}^- \\
& \xrightarrow{-\text{H}^+} \text{CO}_{\text{C}^\text{\textit{C}_2}\text{N}^\text{\textit{C}_2}\text{H}_3}^+ \\
\end{align*}
\]

\[
\begin{align*}
\text{CO}_{\text{C}^\text{\textit{C}_2}\text{N}^\text{\textit{C}_2}\text{H}_3}^+ & \xrightarrow{\text{H}^+} \text{CO}_{\text{C}^\text{\textit{C}_2}\text{N}^\text{\textit{C}_2}\text{H}_3}^- \\
& \xrightarrow{-\text{H}^+} \text{CO}_{\text{C}^\text{\textit{C}_2}\text{N}^\text{\textit{C}_2}\text{H}_3}^+ \\
\end{align*}
\]

FIG. 3
[6] **SYNTHETIC METHODS BASED ON THE SECOND APPROACH**

The second approach for building up of the cinnoline ring involves the condensation between the carbon atoms which become positions 3 and 4 respectively of the heterocyclic ring of the cinnoline formed (Fig. 2).

The methods described below are based on this approach.

1. **Stolle'-Becker's Synthesis:**

   In 1924, Stolle and Becker\(^1\) reported that N-substituted isatin derivatives (XXV), obtained through reaction between substituted benzaldehyde phenyl hydrazone (XXIV) and oxalyl chloride, give on treatment with alkali, 3-phenylcinnoline-4-carboxylic acid derivatives (XXVII). This on decarboxylation gives substituted 3-phenylcinnolines (XXVIII). The reaction evidently proceeds through opening up of the heterocyclic ring of the isatin derivative to the intermediate keto acid structure (XXVI) containing the structural requirements of the second approach for the synthesis of cinnolines. This reaction is depicted in Fig. 4.

   This method was studied in details later by Baumgarten and Furnas\(^2\) and modified recently by Lowrie\(^3\).

2. **Pfannstiel-Janecke's Synthesis:**

   Another synthesis of cinnolines based on the second approach was reported by Pfannstiel and Janecke\(^4\), in which the phenylhydrazone (XXX) prepared by condensing
STÖLLE - BECKER'S SYNTHESIS

R

$\text{Cl-C=O}$

$\text{Cl-}$

$\text{AlCl}_3$

$\text{XXV}$

$\text{N}=\text{CH}-$

$\text{COOH}$

$\text{N=CH-}$

$\text{XXVII}$

$\text{XXVIII}$

FIG. 4
benzaldehyde with 6-chloro-2-hydrazinobenzoic acid (XXIX) gave on heating two products, one of which was 5-chloro-3-phenyl-4-hydroxycinnoline (XXXI) and the other 4-chloroindazoline (XXXII). The sequence of this reaction has been shown in Fig. 5.

This method illustrates only an isolated case of synthesis of a cinnoline derivative and attempts to modify this method were unsuccessful.

3. **Baumgarten's Synthesis**

The only method of general applicability for the synthesis of cinnolines based on the second approach, was developed by Baumgarten et al in 1964. In this synthesis the required intermediate (XXXIV), obtained by the action of nitromethane on o-formylbenzene-diazonium chloride (XXXIII), undergoes cyclization with aqueous alkali or with a suspension of alumina in acetone to yield the corresponding 3-nitrocinnolines (XXXV) (Fig. 5).

This method was further successfully extended by Baumgarten in 1968, for the preparation of cinnolines having various other substituents in the 3-position, starting from intermediates obtained through the reaction between the o-substituted benzenediazonium chloride and acetoacetic acid or ethylhydrogen malonate.
PFANNSTIAEL-JANECKE'S SYNTHESIS

XXXIX

XXXI

XXXII

XXX

BAUMGARTEN'S SYNTHESIS

XXXIII

XXXIV

XXXV

FIG 5
SYNTHETIC METHODS BASED ON THE THIRD APPROACH

In the third approach, the heterocyclic ring of the cinnolone system is built up through the condensation of the $\delta$-carbon atom of a side chain containing two nitrogen and at least two carbon atoms at the ortho position of the benzene ring. The following methods are based on this approach.

1. Barber's Synthesis:

This synthetic approach to the cinnolone structure was first described by Barber et al in 1966 in a British Patent dealing with the preparation of intermediates useful for the production of compounds having therapeutic use. The details of this method were described in a subsequent publication. In this method, the appropriate intermediate (XXXVII) was obtained by condensation of suitably substituted benzenediazonium chlorides with diethyl malonate and hydrolysis of the resulting condensation product (XXXVI), followed by conversion to the acid chloride. On treatment with titanium tetrachloride the acid chloride (XXXVII) cyclised to the 4-hydroxycinnoline 3-carboxylic acid (XXXVIII), which could be thermally decarboxylated in Dowtherm at 205-215°C, to the corresponding 4-hydroxycinnolones (XXXIX). The sequence of this reaction is shown in Fig. 6.

A modification of this method for the synthesis of N-alkyl- and N-aryl-4-cinnolones has been described recently by Barber et al. In this method, N-substituted
anilines (XL) are first converted to their nitroso derivatives (XLI), which however failed to condense with diethyl malonate. These were, therefore, reduced to \( \alpha \)-substituted phenylhydrazines (XLII) and condensed with diethyl mesoxalate to obtain the diesters (XLIII). The monoester (XLIV) obtained by partial hydrolysis of the diester was converted then to the acid chloride and finally cyclised with titanium tetrachloride to yield the 4-cinnolone derivative (XLV) [Fig.6].

2. Moore’s Synthesis:

Moore\(^{30}\) synthesised 3,4-diphenylcinnoline (XLVII) in good yields by cyclising benzil monophenylhydrazone (XLVI) with sulphuric acid. A repetition of this procedure under slightly different conditions, however, gave low yields of the cinnoline (Fig. 7) and considerable quantities of a sulphonated product\(^{31}\).

3. Bhat and Bose’s Synthesis:

Allen and Van Allen\(^{31}\) in 1961 made attempts to cyclise phenylglyoxal-2-phenylhydrazones with concentrated sulphuric acid to obtain 4-phenylcinnolines by a procedure analogous to that of Moore’s synthesis\(^{30}\). The reaction, however, was unsuccessful and led to the formation of sulphonated products.

Bhat and Bose were, however, successful to bring about the cyclization of o-hydroxyphenylglyoxal-2-phenylhydrazone (XLIX) with molten aluminium chloride or a melt of aluminium and
MOORE'S SYNTHESIS

\[ \text{XLVI} \]

\[ \text{H}_2\text{SO}_4 \]

\[ (75-80\%) \]

\[ \text{XLVII} \]

BHAT AND BOSE'S SYNTHESIS

\[ \text{XLVIII} \]

\[ \text{XLIX} \]

\[ \text{L} \]

FIG 7
sodium chlorides\textsuperscript{32,33}. The resulting products were first considered to be 4-phenylcinnolones\textsuperscript{32} (Fig. 7). These structures were later revised to those of 4-(o-hydroxyphenyl)-cinnolines\textsuperscript{33}(L).

The intermediate o-hydroxyphenylglyoxal-2-phenylhydrazone (XLIX) were prepared by condensing 4-hydroxycoumarin with benzenediazonium chloride under slightly alkaline conditions and opening up of the lactone ring of the resulting triketochroman-3-phenylhydrazone (XLVIII) with simultaneous decarboxylation.

**SYNTHESIS OF QUINOXALINES**

The natural product lactoflavin or vitamin $B_2$ (LI) can be regarded to contain the elements of the quinoxaline structure.

\[
\begin{align*}
\text{CH}_3 & \quad \text{N} \quad \text{C} \\
\text{CH}_3 & \quad \text{N} \quad \text{C} \\
& \quad \text{CH}_2-(\text{CHOH})_3-\text{CH}_2\text{OH}
\end{align*}
\]

Lactoflavin (LI)
Quinoxaline was first obtained in 1884, almost simultaneously by Hinsberg and Körner, by condensing o-phenylenediamine with glyoxal:

\[
\begin{align*}
\text{NH}_2 & \quad + \quad \begin{array}{c}
\text{O} = \text{CH} \\
\text{O} = \text{CH}
\end{array} \\
\rightarrow & \\
\end{align*}
\]

The studies in quinoxaline have been stimulated recently by the finding that the N-oxides of quinoxalines undergo interesting rearrangement reactions and are biologically active.

Very few methods have been developed so far for the synthesis of this dinitrogen heterocyclic system. In all of these methods, the heterocyclic nitrogen atoms are provided by o-phenylenediamines or o-nitroanilines.

1. **Hinsberg's Synthesis**

This classical synthesis of quinoxalines, as already described for the parent compound, involves condensation between the amino groups of an o-phenylenediamine and the carbonyl groups of an \(-\text{dicarbonyl compound.}\)
The reaction is of general applicability and has been extensively employed also for detection and characterisation of o-phenylenediamines as well as of \( \alpha \)-dicarbonyl compounds.

In this reaction the mono-substituted o-phenylenediamines often give rise to two isomeric products:

\[
\begin{align*}
\text{R} & \quad \text{NH}_2 \\
& \quad \text{NH}_2 \\
\text{O} & \quad \text{C} \quad \text{R'} \\
\text{O} & \quad \text{C} \quad \text{H}
\end{align*}
\]

Alloxan (LIII) can also take part in this reaction as the \( \alpha \)-dicarbonyl compound to give a mixture of ureides (LIII) and (LIV) respectively containing the quinoxaline rings\(^\text{41}\) (Fig.8).

The sugar derivatives such as osones, osonehydrazones, and dehydro-L-ascorbic acid have also been used successfully as the dicarbonyl compounds in this reaction.\(^\text{42}\)

\( \alpha \)-Keto- and \( \alpha \)-aldehyde acids like mesoxalic\(^\text{43,44}\), pyruvic\(^\text{45}\) and glyoxylic\(^\text{46}\) acid derivatives can also take part in this reaction in the place of \( \alpha \)-dicarbonyl compounds. Some of these reactions are complicated and accompanied with by-products.

Ketomethylene compounds like \( \omega \)-nitroacetophenones can also take part in this reaction in the presence of sodium dithionate to yield 2-phenyl-quinoxalines.\(^\text{47}\)
α-Chloroketones as well as α-formyl- and α-keto alcohols have also been condensed with o-phenylenediamines to give dihydroquinoxalines which may get oxidised spontaneously to yield quinoxalines.48

2. Osdene and Timmis’ Synthesis:

Osdene and Timmis49 found that aromatic o-nitrosoamines condense with cyanoacetic acid or cyanoacetamide to yield quinoxaline derivatives. This method affords unambiguous syntheses of unsymmetrically substituted quinoxalines. Thus, o-nitroso-m-phenylenediamine reacts with cyanoacetic acid to yield only 3,6-diaminoquinoxaline (Fig. 8).

3. Horner, Schwenk and Junghans’ Synthesis:

In this method,50 the o-nitrophenyl derivative of an α-amino acid, prepared readily from the amino acid and an o-nitrohalogenobenzene, is subjected to reductive ring closure to yield a 1,2,3,4-tetrahydro-2-oxo-quinoxaline. This is then oxidised with alkaline permanganate to the corresponding quinoxalin-2-ones (Fig. 8).

This method has been extensively employed for unambiguous synthesis of quinoxalin-2-ones.51-53
REACTION BETWEEN o-PHENILENEDIAMINES AND ALLOXAN

OsdeNe and TimMIs' Synthesis

Horner, Schwenk and Junghann's Synthesis

FIG. 8
REFERENCES

1. V. Richter, Ber., 16, 677 (1883).
2. M. Busch and M. Klett, Ber., 25, 2847 (1892).
6. O. Widman, Ber., 12, 722-7 (1884).
7. O. Widman, Ber., 42, 4216-17 (1909).
33. V. V. Bhat and J. L. Bose, Chem. and Ind., 1685 (1965).
34. G. Hinsberg, Ber., 17, 318a (1884).
35. G. Körner, Ber., 17, 573 (1884).

Reviews:

**Stannolines:**

2. see ref. 3, pp. 3-66

**Quinoxalines:**

1. See ref. 3, pp. 203-367.

CHAPTER II

CYCLODEHYDRATION OF PHENYLGLYOXAL-2-ARYLHYDRAZONES

A NEW SYNTHESIS OF 2-ARYLQUINOXALINES
INTRODUCTION

2,3,4-Triketopyran-3-phenylhydrazones and their 5,6-cycloalkylene derivatives (I) have been found to yield the corresponding 1,4-dihydro-1-phenyl-4-oxo-3-pyridazine-carboxylic acids¹ and their 5,6-cycloalkylene derivatives² (III) respectively, by the action of alkali, evidently as a result of opening up of the <-pyrone ring of (I) and cyclization of the intermediate (II) in a different position. Attempts to extend this method further for the cyclization of 2,3,4-triketochroman-3-phenylhydrazone (IV) to yield the corresponding 1-phenyl-4-cinnolones, however, were unsuccessful. The principal products obtained in these reactions were α-hydroxyphenylglyoxal-2-phenylhydrazones (V) resulting from decarboxylation of the intermediate 2-carboxylic acids³.

In 1963, Bhat and Bose⁴ reported that α-hydroxyphenylglyoxal-2-phenylhydrazones (V) could be successfully cyclodehydrated by heating with molten aluminium chloride. They assigned 1-phenyl-4-cinnolone (VI) structures to these cyclized products, which were supported by analytical data and the presence of a weak carbonyl band at 1639 cm⁻¹ in the I.R. spectra.

In the same year Lunt and Threlfall⁵ reported an unambiguous synthesis of 1-phenyl-4-cinnolone (VI) through cyclization of the acid chloride (VII) by heating it with titanium tetrachloride in nitrobenzene medium at 100°C, followed by decarboxylation of the resulting carboxylic acid (VIII).
A direct comparison of Bhat and Bose's and Lunt and Threlfall's 1-phenyl-4-cinnolone established their non-identity. Their spectral characteristics were also quite different. A bathochromic shift with alkali was also observed in the U.V. spectrum of Bhat and Bose's compound, suggesting the presence of a phenolic hydroxyl group in it, although IR spectrum did not show any absorption in the hydroxyl region.

Re-examination of the compounds prepared by Bhat and Bose revealed that these contained an active hydrogen. Their tosyl and acetyl derivatives could be prepared by modified methods. The NMR spectrum of the parent compound gave two non-aromatic proton signals at 560 cps and 750 cps. The proton at 750 cps disappeared on exchange with trifluoroacetic acid and thus confirmed the presence of a phenolic hydroxyl group in the compound.

In view of these observations, these compounds were assigned the alternative 4-(α-hydroxyphenyl)-cinnolone structure (IX) which resulted from an alternative mode of cyclodehydration of α-hydroxyphenylglyoxal-2-phenylhydrazone (V).
The present investigations were undertaken with a view
to extend the possible scope of the method of synthesis of
4-(a-hydroxyphenyl)-cinnolines developed by Bhat and Bose
It was thought of interest to synthesise initially,
4-phenyl-cinnolines having no a-hydroxyl group in the
4-phenyl nucleus.

The intermediates for this synthesis, the
arylglyoxal-2-arylhydrazone are capable of existing as the
syn or anti geometrical isomers. Although Bhat and Bose
did not mention the geometric form of the intermediate
a-hydroxyphenylglyoxal-2-arylhydrazone used in their synthesis
of 4-(a-hydroxyphenyl)-cinnolines, these were evidently the
syn isomers (X) in view of hydrogen bonding of the N-H group
with the C=O. Moreover, only the syn isomers could easily
undergo cyclodehydration.
In view of lack of necessary information in literature on the isomeric forms of arylglyoxal-2-arylhydrazone, a detailed study on the subject was considered necessary before undertaking the work on the proposed synthesis of cinnolines from these intermediates.

The present chapter is, therefore, divided into the following three sections.

Section A: Studies in arylglyoxal-2-arylhydrazone

Section B: Cyclodehydration of phenylglyoxal-2-arylhydrazone with aluminium chloride

Section C: Synthesis and characterization of the N-oxides of arylcinnolines and arylquinoxalines.
SECTION A

STUDIES IN ARYLGYXAL-2-ARYLHYDRAZONES
PHENYLGLYOXAL-2-PHENYHYDRAZONES

The two geometric isomers of phenylglyoxal-2-phenylhydrazone were prepared according to the procedure described by Bodendorf and Wössner. Ethylbenzoyl acetate (XI) on coupling with benzene diazonium chloride gave ethyl phenylazo-benzoylacetate (XII), which on saponification and decarboxylation yielded phenylglyoxal-2-phenylhydrazone (XIII), m.p. 114°, in good yields. This compound which has been assigned a syn structure (XIIIa) gave on digestion with ethanol, for ~65 hr. at 50-60°, the isomer (XIIIb) m.p. 140° (Lit. m.p. 146°), which has been assigned the anti structure.

1. INFRARED SPECTRAL STUDIES:

Tanner reported that the carbonyl absorption frequencies of the syn and anti forms of phenylglyoxal-2-phenylhydrazone (in nujol) are almost the same (1641 and 1640 cm\(^{-1}\) respectively). The \(\geq N-H\) frequencies of these two isomers were reported as 3128 and 3166 cm\(^{-1}\) respectively.

We were led to suspect that these values were, perhaps incorrect, since the syn form (XIIIa) is expected to have hydrogen bonding between the \(\geq N-H\) and the \(\geq C=O\) groups, which would necessarily lower the absorption frequency of \(\geq C=O\). Such a lowering is well documented.
For example, it has been observed\textsuperscript{10} that pyruvamide phenylhydrazone shows $>\text{C}=\text{O}$ absorption frequencies at 1656 cm\textsuperscript{-1} and 1681 cm\textsuperscript{-1} for the \textit{syn} and \textit{anti} forms respectively.

The IR spectrum (in nujol) of the isomer, m.p. 140\textdegree, prepared by us showed the $>\text{C}=\text{O}$ and $>\text{N-H}$ absorptions at 1645 and 3200 cm\textsuperscript{-1} respectively, where as that of the isomer, m.p. 114\textdegree, showed no $>\text{N-H}$ absorption and a $>\text{C}=\text{O}$ absorption at a much lower frequency of 1600 cm\textsuperscript{-1}. These observations were, therefore, in agreement with the already assigned structures of the two isomeric phenylglyoxal 2-phenylhydrazones and established that it was possible to obtain conclusive evidence on the structures of the geometric isomers of arylglyoxal arylhydrazones from their IR spectra. Tanner’s\textsuperscript{3} observations on the IR spectra of these two isomers, therefore, appear to be erroneous.

These two isomers were, however, found to give identical IR spectra in carbon tetrachloride solution showing a strong $>\text{C}=\text{O}$ absorption at 1600 cm\textsuperscript{-1} and no $>\text{N-H}$ absorption. This could be explained by the fact that the \textit{anti} form was converted rapidly to the \textit{syn} form in carbon tetrachloride solution. This is supported by the observations of Bamberger and Schmidt\textsuperscript{11}, that the \textit{anti} forms are converted to \textit{syn} forms completely in carbon tetrachloride solution. These observations also confirm that the compound m.p. 114\textdegree is the \textit{syn} isomer.
In order to find out the standard IR absorption frequency of non-bonded C=O in this series, attempts were made to synthesise phenylglyoxal methylphenylhydrazone (XIV), in which hydrogen bonding is eliminated. Condensation of phenylglyoxal with α-phenyl-α-methylhydrazone, however, gave instead of the desired product (XIV), a crystalline compound, m.p. 147-48°C, which proved to be phenylglyoxal methylphenylhydrazone (found, N, 15.93; C_{26}H_{22}N_{4} required N, 16.36%).

The absorption frequency of the unbonded carbonyl in an analogous compound is, however, afforded by the work of Tanner, who reported that the C=O absorption frequency of pyruvaldehyde methylphenylhydrazone (XV) appeared at 1668 cm\(^{-1}\). In the present example, the unbonded carbonyl absorption is expected to be lowered by 10-15 cm\(^{-1}\) from this value due to the conjugation of the carbonyl group with the phenyl ring.
The $>\text{C}=\text{O}$ absorption for the anti form of phenylglyoxal-2-phenylhydrazone should, therefore, be in the range of 1644-1639 cm$^{-1}$. The actual value of 1646 cm$^{-1}$ observed by us for the isomer, m.p. 140°C, agrees with the anti structure and confirms the structure assigned earlier, to this isomer by Bamberger and Schmidt$^{11}$.

The difference between the carbonyl frequencies of the syn and anti forms of phenylglyoxal-2-phenylhydrazone is, however, much larger than that reported for syn and anti isomers of methylpyruvate and pyruvamide phenylhydrazones. Some of the absorption frequencies of these compounds are given in Table 1.
### Table 1

IR absorption bands of Phenylhydrazones.

\[ R = \text{N} \text{N} \text{H} \text{Ph}, \ R' = \text{N} \text{N} \text{N}(\text{CH}_3)\text{Ph}; \text{ Frequencies in cm}^{-1} \]

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Compound</th>
<th>Nujol ( \rangle \text{N-H} )</th>
<th>Mull ( \rangle \text{C=O} )</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>\text{Syn-CH}_3\text{C}R\text{C}OOCH}_3</td>
<td>3279</td>
<td>1675</td>
<td>10</td>
</tr>
<tr>
<td>2.</td>
<td>\text{Anti-CH}_3\text{C}R\text{C}OOCH}_3</td>
<td>3344</td>
<td>1698</td>
<td>10</td>
</tr>
<tr>
<td>3.</td>
<td>\text{Syn-CH}_3\text{C}R\text{CONH}_2</td>
<td>-</td>
<td>1656$^+$</td>
<td>10</td>
</tr>
<tr>
<td>4.</td>
<td>\text{Anti-CH}_3\text{C}R\text{CONH}_2</td>
<td>-</td>
<td>1681$^+$</td>
<td>10</td>
</tr>
<tr>
<td>5.</td>
<td>\text{CH}_3\text{COCH}_3R'</td>
<td>-</td>
<td>1694$\text{ w}^-$</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1668</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>\text{Syn-Ph.CO.CH}_3R\star</td>
<td>3128</td>
<td>1641</td>
<td>8</td>
</tr>
<tr>
<td>7.</td>
<td>\text{Anti-Ph.CO.CH}_3R\star</td>
<td>3166</td>
<td>1640</td>
<td>8</td>
</tr>
<tr>
<td>8.</td>
<td>\text{Syn-Ph.CO.CH}_3R, m.p. 114$^\circ$</td>
<td>-</td>
<td>1600</td>
<td>Fig. 1</td>
</tr>
<tr>
<td>9.</td>
<td>\text{Anti-Ph.CO.CH}_3R, m.p. 140$^\circ$</td>
<td>3200</td>
<td>1645</td>
<td>Fig. 2</td>
</tr>
</tbody>
</table>

$^+$ KCl disc

$\star$ The values reported by Tanner

$\star\star$ Present work.
FIG. 1 - IR SPECTRUM OF Syn-PHENYLGLYOXAL-2-PHENYLHYDRAZONE (XII a, m. p. 114°)
FIG 2 - IR SPECTRUM OF Anti-PHENYLGLYOXAL-2-PHENYLHYDRAZONE (XIII b, m.p. 140°)
The energy difference between the syn- (XIII\textsubscript a) and anti- (XIII\textsubscript b) forms of phenylglyoxal\textsubscript 2-phenylhydrazones is small. The syn-form is stabilized through the formation of an intramolecular hydrogen bond. It could, therefore, be expected that in those solvents which cannot form hydrogen bond, the syn- form would be more stable. It is due to this reason that the infrared spectra in carbon tetrachloride solution of the syn- and anti- forms were identical and corresponded to that of the syn-form as shown by the very low $\nu C=O$ frequency (1600 cm\textsuperscript{-1}) similar to that of the syn- form in nujol. This rationalization would explain the greater stability of the syn- form in petroleum ether, ligroin and carbon tetrachloride as observed by Bamberger and Schmidt\textsuperscript{11}. However, in ethanol, where the solvent molecule can form hydrogen bonds with the compound, the anti-form becomes more stable, than the syn-form through such solvation. In such a solvent, therefore, the anti-form would predominate. This rationalization by Bamberger and Schmidt\textsuperscript{11} explains the greater stability of the anti-form (XIII\textsubscript b) in ethanol and acetone. An extension of this would require that in dimethylsulphoxide also the anti-form should predominate. In keeping with this expectation the infrared spectra (in nujol) of the syn- and anti- forms after equilibration in DMSO at room temperature for 24 hr. were found to be identical and corresponded with that of the anti-form.
The NMR spectra of both forms were, therefore, examined in carbon tetrachloride and dimethyl sulphoxide solution. The spectra of the two isomers in carbon tetrachloride were found to be identical (Fig. 3) and revealed signals only in the low field portion (below 400 cps). The signal at the lowest field (876 cps) could conveniently be assigned to the N-H proton, which was enormously deshielded due to hydrogen bonding. The presence of only one N-H proton peak clearly indicated that there was complete transformation into one of the forms, which was necessarily the syn-form, as indicated by the infrared spectra of the two forms in carbon tetrachloride solution. The quartet at 480 cps corresponded to two protons. This quartet (J=3 and 8 cps) could be assigned to the protons on the aromatic nucleus \( < \text{to the} \) C=O group. These protons are deshielded because of the electron-withdrawing nature of \( \text{> C=O} \), as also of their location in the deshielding zone of the keto group. The aromatic signal at the highest field (425 cps, \( J = 3 \) and 8 cps) corresponded to two protons and from its quartet nature, could be attributed to the aromatic protons \( < \) to the N-H function. Such protons are usually shielded because of electron release by the nitrogen. The olefinic proton appeared as a singlet at 460 cps, due to its attachment to nitrogen. The low field four-proton triplet at 450 cps \( (J = 8 \) cps) represented the protons meta to the \( \text{> C=O} \) and \( \text{> N-H} \) groups. Two one-proton quartets appeared at 440 cps and 445 cps \( (J = 3 \) and 8 cps) and these could be assigned to the protons para to the \( \text{> N-H} \) and \( \text{> C=O} \) groups respectively.
FIG. 3 - NMR SPECTRUM OF PHENYLGLYOXAL-2-PHENYLHYDRAZONE (SYN.)
The NMR spectra of both the syn- and anti- forms in DMSO were identical and showed a one proton signal of N-H at 680 cps. Though this was considerably different from the location of this signal in carbon tetrachloride (876 cps), this in itself is not sufficient evidence to suggest that this may be the anti- form, because solvent induced shifts are well known\textsuperscript{16}, and the line position of the N-H proton depends on concentration, acidity and hydrogen bonding\textsuperscript{13}. In order, therefore, to confirm the infrared results, the NMR spectrum of a freshly prepared solution of the syn- form in DMSO was immediately examined. Significantly enough, under these conditions the syn- form showed absorption at 680 cps and 850 cps (Fig. 4A). As concentration and acidity effects of the solvent were equal in both cases, the signal at the lower field must correspond to the hydrogen bonded syn- form. Furthermore, when the freshly prepared solution in DMSO was allowed to age, the spectrum showed a characteristic peak at 680 cps and no signal at 850 cps. (Fig. 4B) A freshly prepared solution of the anti- form in DMSO under the same conditions, however, gave only the peak at 680 cps. (Fig. 5)

This evidence, therefore, fixed the direction of equilibration and also provided a NMR spectrum of the pure anti- form. (Fig. 6) The analysis of which is outlined in Table 2.
Figure 4 - Low field portion of the NMR spectrum of
\textit{Syn-Phenylglyoxal-2-phenylhydrazone (DMSO)}

Figure 5 - NMR spectrum of \textit{Anti-Phenylglyoxal-2-phenylhydrazone (DMSO)}
**TABLE 2**

Analysis of the NMR spectrum of anti-phenylglyoxal-2-phenylhydrazone (XIIIb)

<table>
<thead>
<tr>
<th>Position of signal (cps)</th>
<th>Nature</th>
<th>Number of protons</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>429</td>
<td>Quartet (J = 2 and 3 cps)</td>
<td>Two</td>
<td>Protons ortho to N-H</td>
</tr>
<tr>
<td>433</td>
<td>Triplet (J = 8 cps)</td>
<td>Two</td>
<td>Protons meta to N-H</td>
</tr>
<tr>
<td>438</td>
<td>Quartet (J = 2 and 8 cps)</td>
<td>One</td>
<td>Proton para to N-H</td>
</tr>
<tr>
<td>453</td>
<td>Quartet (J = 2 and 7 cps)</td>
<td>One</td>
<td>Proton para to C=O</td>
</tr>
<tr>
<td>455</td>
<td>Triplet (J = 7 cps)</td>
<td>Two</td>
<td>Protons meta to C=O</td>
</tr>
<tr>
<td>467</td>
<td>Singlet</td>
<td>One</td>
<td>Olefinic proton</td>
</tr>
<tr>
<td>480</td>
<td>Quartet (J = 2 and 7 cps)</td>
<td>Two</td>
<td>Protons ortho to C=O</td>
</tr>
<tr>
<td>680</td>
<td>Singlet</td>
<td>One</td>
<td>N-H proton</td>
</tr>
</tbody>
</table>
This hydrazone was required for the synthesis of 4-aryleinnolines having a p-tolyl group in the C4-position. Only one form of this hydrazone, m.p. 122-23°C, has been reported so far\textsuperscript{17}. It was, however, not assigned any geometric configuration. Following the same procedure\textsuperscript{7} and using the diazonium sulphate\textsuperscript{18} instead of the diazonium chloride, the required phenylhydrazone was obtained in good yields. It crystallised from ethanol to give a product, m.p. 122-23°C, which agrees with that reported in literature.\textsuperscript{17}

As this product was isolated from ethanolic solution, it, most probably, represented the anti- form (XVI\textsubscript{a}). When the crude product was crystallised from petroleum ether, a product m.p. 94-95°C was obtained. Our studies on the syn- and anti- forms of phenylglyoxal-2-phenylhydrazone described earlier, clearly indicated that this product was possibly the hitherto unreported syn- form of phenylglyoxal-2-p-tolylhydrazone (XVI\textsubscript{a}). This was confirmed by its conversion to a product, m.p. 122-23°C by digesting it in ethanol at 50-60°C for 8 days. This product was found to be identical (mixed m.p., IR) with the compound originally prepared.

The IR spectra of these two compounds clearly established the validity of these rationalizations. The positions of the C=O and N-H frequencies of these syn- and anti- forms were found to be similar to that of the
unsubstituted compounds (Table 3).

\[
\begin{align*}
\text{(XVIa)} & \\
\text{(XVIb)} & 
\end{align*}
\]

**TABLE 3**

IR Absorption bands of phenylhydrazones

\([ R = :N\text{NH}.\text{Ph}, R' = :N\text{NH}C_6H_4-\text{CH}_3(2) ]; \text{ Freqencys in cm}^{-1}\)

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Compound</th>
<th>Nujol mull</th>
<th>N-H</th>
<th>C=O</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Syn- PhCO.CH:R (XIIIa)</td>
<td>-</td>
<td>1600</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Anti- Ph.CO.CH:R (XIIIb)</td>
<td>3200</td>
<td>1645</td>
<td></td>
</tr>
</tbody>
</table>
| 3.      | Syn- PhCOCH:R' (XVIa) | - | 1605 | m.p. 94-95°
| 4.      | Anti- Ph.CO'CH:R' (XVIb) | 3195 | 1645 | m.p. 122-23° |
The NMR spectrum (Fig. 6) of the syn isomer (m.p. 94-96°C) revealed the presence of a characteristic AB quartet at 430 cps \( J_{AB} = 9 \text{ cps}; \delta_B - \delta_A = 6 \text{ cps} \) assignable to the four protons of the para substituted benzene ring. The quartet \( (J = 2 \text{ and } 7 \text{ cps}) \) at low field (478 cps) could be attributed to the protons ortho to the carbonyl group, while a two proton triplet at 452 cps \( (\delta = 7 \text{ cps}) \) could be assigned to the protons meta to the carbonyl. The remaining aromatic proton appeared as a quartet centred at 447 cps \( (J = 2 \text{ and } 7 \text{ cps}) \).

The olefinic proton adjacent to the nitrogen atom appeared as a singlet at 458 cps. The \( N-H \) proton appeared as a broad singlet at 880 cps. These line positions are very similar to those of the parent compound.

Unlike the parent, the NMR of a fresh solution of the syn form in DMSO did not give two peaks for \( N-H \) proton corresponding to syn and anti forms, in fact this position was the same as that of the anti form suggesting very rapid transformation, in this case, of the syn to anti isomer in DMSO.*

* Another possibility in which both syn and anti forms had identical chemical shifts of their \( N-H \) protons does not seem attractive, because the entire spectrum is identical with that of the anti isomer.
FIG. 6 - NMR SPECTRUM OF PHENYLGLYOXAL-2-p- TOLYLHYDRAZONE (SYN)
The NMR spectrum (Fig. 7) of the anti form was examined in DMSO as this compound equilibrates completely to the syn form in carbon tetrachloride solution. In this solvent the signal assignable to the N-H proton appeared at 675 cps and disappeared on deuterium exchange. The complete analysis of the spectrum is presented in Table 4.

### Table 4

Analysis of the NMR spectrum of anti phenylglyoxal-2-p-tolylhydrazone. (XVIb)

<table>
<thead>
<tr>
<th>Position of signal (cps)</th>
<th>Nature</th>
<th>Number of protons</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>423.5</td>
<td>AB quartet*</td>
<td>Two</td>
<td>Protons ortho to N-H</td>
</tr>
<tr>
<td>427.6</td>
<td>$J_{AB} = 8$ cps</td>
<td>Two</td>
<td>Ortho to $-\text{CH}_3$</td>
</tr>
<tr>
<td>455</td>
<td>Multiplet</td>
<td>Three</td>
<td>Protons meta and para to C=O</td>
</tr>
<tr>
<td>464</td>
<td>Singlet</td>
<td>One</td>
<td>Olefinic proton</td>
</tr>
<tr>
<td>483</td>
<td>Quartet</td>
<td>Two</td>
<td>Protons ortho to C=O</td>
</tr>
<tr>
<td>(J = 2 and 7 cps)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>675</td>
<td>Singlet</td>
<td>One</td>
<td>N-H proton</td>
</tr>
</tbody>
</table>

* In this quartet the middle lines are merged and the spectrum gave the appearance of a singlet, but two end lines of low intensity can be detected.
FIG. 7 - NMR SPECTRUM OF anti-PHENYLGLYOXAL-2-p-TOLYLHYDRAZONE (DMSO)
**PHENYLGLYOXAL-2-p-CHLOROPHENYLHYDRAZONE**

This hydrazone was required for the preparation of chloro substituted 4-arylcinnoline. In this case also only one form of the hydrazone m.p. 174-76° has been reported and no geometric configuration was assigned to it. This hydrazone, prepared by us using diazonium sulphate, crystallised from ethanol to give a product m.p. 174-76°, which agrees with the m.p. reported in literature.

This hydrazone showed a C=O absorption at 1640 cm\(^{-1}\) and N-H stretching at 3200 cm\(^{-1}\) in its IR spectrum. Therefore, it was considered to be the *anti* form of phenylglyoxal-2-p-chlorophenylhydrazone (XVII). Attempts to convert it to the *syn* form by the usual methods of equilibration were not successful. In view of its very sparing solubility in chloroform as well as carbon tetrachloride, the IR and NMR spectra of this compound could not be recorded in these solvents, to ascertain whether the *syn* form exists at least in the solution state in these solvents.

The NMR spectrum of this compound in dimethyl sulphoxide* agreed with the above assignment. The analysis of the spectrum (Fig. 3) is depicted in Table 5.

---

* The compound is insoluble in carbon tetrachloride and chloroform.
FIG. 8 - NMR SPECTRUM OF PHENYLGLYOXAL-2-p-CHLOROPHENYLHYDRAZONE (DMSO)


**TABLE 6**

Analysis of the NMR spectrum of phenylglyoxal-2-p-chlorophenylhydrazine (XVII)

<table>
<thead>
<tr>
<th>Position of signal (cps)</th>
<th>Nature</th>
<th>Number of protons</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>428</td>
<td>$AB$ quartet</td>
<td>Two</td>
<td>Protons ortho to N-H</td>
</tr>
<tr>
<td></td>
<td>($J_{AB} = 8.5$ cps)</td>
<td></td>
<td>Protons ortho to -Cl.</td>
</tr>
<tr>
<td>440</td>
<td>Triplet</td>
<td>Two</td>
<td>Protons meta to C=O</td>
</tr>
<tr>
<td></td>
<td>($J = 8$ cps)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>455</td>
<td>Quartet</td>
<td>One</td>
<td>Proton para to C = 0</td>
</tr>
<tr>
<td></td>
<td>($J = 2$ and 8 cps)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>457</td>
<td>Singlet</td>
<td>One</td>
<td>Olefinic proton</td>
</tr>
<tr>
<td>480</td>
<td>Quartet</td>
<td>Two</td>
<td>Protons ortho to C=O</td>
</tr>
<tr>
<td></td>
<td>($J = 2$ and 8 cps)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>692</td>
<td>Singlet</td>
<td>One</td>
<td>N-H proton</td>
</tr>
</tbody>
</table>

It may be pointed out that Bamberger and Schmidt\(^7\) have reported that phenylglyoxal-2-p-nitrophenylhydrazone (XVIII) also exists only as the anti form.
SECTION B

CYCLODHYDRATION OF PHENYLGLYOXAL-2-ARYLHYDRAZONES

WITH ALUMINIUM CHLORIDE
SECTION B: CYCLODEHYDRATION OF PHENYLGLYOXAL-2-ARYLHYDRAZONES WITH ALUMINIUM CHLORIDE

1. CYCLODEHYDRATION OF PHENYLGLYOXAL-2-PHENYLHYDRAZONE

It has already been stated in the introductory part of this chapter that Bhat and Bose\(^6\) assigned a 4-(\(\alpha\)-hydroxyphenyl)-cinnoline structure to the products obtained by the action of fused aluminium chloride on \(\alpha\)-hydroxyphenylglyoxal-2-arylhydrazones. They also report that condensing agents such as concentrated sulphuric acid, polyphosphoric acid, phosphorous oxychloride, and BF\(_3\) etherate could not bring about the desired cyclization.

In attempts to prepare 4-phenylcinnolines, without \(\alpha\)-hydroxyl group in the 4-phenyl nucleus, syn-phenylglyoxal-2-phenylhydrazone was heated with aluminium chloride-sodium chloride melt (1:1) at 150-60\(^o\) for 30 min. The TLC of the reaction product* showed two spots of almost equal intensity (R\(_f\) 0.61 and 0.36**).

Chromatography of the reaction product on a silica gel column afforded the two compounds (A) and (B) in the ratio 3:2 (R\(_f\) 0.61 and 0.36 respectively). The faster moving product (A) obtained in the benzene eluate, on further purification by preparative layer chromatography (PLC), furnished a product

---

* The only literature report of such cyclization is by Allen and Van Allan\(^20\), who attempted this cyclization using sulphuric acid, but obtained only a sulphonated product.

** Solvent system: benzene-ethyl acetate (4:1).
which crystallised from pet. ether in almost colourless needles m.p. 75.5-76.5°.

The benzene-ethyl acetate (85:15) eluate provided the slower moving product (B), which after further purification by PLC, crystallised from pet. ether in yellow needles, m.p. 65-66°.

**Compound B:** The compound B, m.p. 65-66°, analysed for C_{14}H_{10}N_{2}. This molecular formula was supported by its mass spectrum which showed a molecular ion peak at m/e 206. The absence of any oxygenic function indicated that it was a cyclized product. Its IR spectrum displayed the characteristics of an aromatic compound and clearly established the absence of any C=O or -OH frequency suggesting cyclization of the product. It had UV absorptions at 227 (ε, 35480), 298 (ε, 6166) and 325 μ (ε, 5496).

The NMR spectrum of compound B (Fig. 3) exhibited a singlet (1 H) at 550 cps, quartet centred at 514 cps (J = 2 and 7 cps) indicated an aromatic proton coupled with ortho and meta hydrogen. The aromatic proton region displayed a three proton multiplet at 467 cps and a five proton singlet at 450 cps. The presence of five equivalent protons in the aromatic region requires a phenyl ring to be so situated that it does not feel the influence of the other aromatic protons. Such an arrangement is consistent with 4-phenyl-cinnoline structure, in which the phenyl group at C₄ is held out of the plane in order to avoid interaction.
FIG. 9 - NMR SPECTRUM OF 4-PHENYL CINNOLINE
with the C₅ carbon and the hydrogen on it. In this structure the signal at the lowest field is obviously the C₃ proton, whereas the quartet at 614 cps can represent either C₅ or C₆ proton. We prefer to consider this proton as a C₈ proton as Black and Heffernan have reported that in cinnoline the C₈ proton appears as a broadened doublet at 610 cps. The three proton multiplet at 467 cps may, therefore, be assigned to the C₅, C₆ and C₇ protons.

\[
\text{(XIX)}
\]

In keeping with this interpretation the 4-phenylcinnoline prepared according to the method of Bruce was identical in every respect (m.p.; mix. m.p.; U.V.; I.R. NMR and TLC) with the compound B.

The formation of 4-phenylcinnoline in this reaction may easily be explained on the basis of the simple mechanism shown in Chart I.

---

* Similar NMR values for 4-phenylcinnoline has been reported though no interpretations are given.
 Charter - 1

XII a  R = H
XVI a  R = CH₃
XVII  R = Cl

XII a  R = H
XVI a  R = CH₃
XVII  R = Cl

XIII a  R = H
XXXII  R = CH₃
XLI    R = Cl

ALCl₃ Δ →

CHART - 1
Compound A: The compound A, m.p. 76.5-76.6°C, analysed for C_{14}H_{10}O_{2} and had molecular weight 206 (Mass spectrum) consistent with this formulation. Absence of an oxygen function in the molecule and the absence of a C=O or -OH groups in its IR spectrum indicated that it was a cyclized product. Its UV spectrum had absorptions at 262 (ε, 28,180) and 335 με (ε, 11,970).

Its NMR spectrum (Fig. 10) displayed a one proton singlet at 557 cps, a four proton multiplet at 437 cps and a five proton multiplet at 450 cps. To account for one heavily deshielded proton and four partly deshielded ones, it is necessary to consider a structure in which a phenyl group is so situated that two of its protons will be more deshielded than others. In the isoquinoline series it has been reported that 3-phenylisoquinoline showed a down field position for the two ortho protons of the phenyl substituent at C_3. In such compounds the five phenyl protons are non-equivalent, whereas in a 4-phenylisoquinoline, for example, these protons are equivalent. On the basis of this analogy a 2-phenylquinazoline structure looked an attractive possibility.*

* A 3-phenylcinnoline structure can be ruled out because the singlet observed at 557 cps cannot be explained.
FIG. 10 - NMR SPECTRUM OF 2-PHENYLQUINOLINE
In this structure the C₃ proton can be expected to resonate at very low field, while the C₅, C₆ protons and the ortho protons of the phenyl group could be expected to appear as a multiplet at 487 cps. A closer examination of this multiplet revealed that it is made up of two quartets, one centred at 491 cps and the other at 483 cps with J values of 3 and 8 cps, respectively. These J values are characteristic of ortho and meta coupling and are in agreement with the assignments given earlier.

In order to substantiate this hypothesis, an authentic sample of 2-phenylquinoxaline was prepared according to the procedure described by Hinsberg. This product proved to be identical with the compound A in all respects (m.p.; mix.m.p.; TLC; IR; UV and NMR).
MECHANISM OF FORMATION OF 2-PHENYLQUINOXALINE FROM
PHENYLGLYOXAL-2-PHENYLHYDRAZONE:

The formation of a 2-phenylquinoxaline structure (XX) by cyclodehydration of syn-phenylglyoxal-2-phenyl-
hydrazone (XIII$_a$) with aluminium chloride can be explained satisfactorily by a novel rearrangement
postulating a diazetine intermediate (XXI) as shown in Chart 2, the reaction occurring in a concerted fashion.*

The diazetine intermediate (XXI) may be changing to 2-phenylquinoxaline (XX) through the intermediate (XXII).
This diazetine intermediate (XXI) appears quite plausible on the basis of extended Hückel Molecular Orbital
calculations.**

The formation of 2-phenylquinoxaline (XX) from syn-phenylglyoxal-2-phenylhydrazone (XIII$_a$) can also be
explained by assuming the migration of N(β) to the ring in (XIII$_a$) as the first step (Chart 3) and following
the sequence (XXIII) → (XXIV) → (XXV) → (XX).†

whereas, such a scheme appears to be quite attractive, the driving force in this rearrangement is likely to be weak

* We are grateful to Prof. B. D. Tilak of this Laboratory for suggesting this mechanism.

** We are thankful to Dr. P. T. Narasiman of I.I.T., Kanpur for these calculations.

† This mechanism was proposed by the referee of our publication.26
since the N(α) atom is vinylogously conjugated with the carbonyl group in (XIIIa). The cation formed by the interaction of the carbonyl group with aluminium chloride will, therefore, be delocalized over the atoms linking the two aryl residues in (XIIIa), thus making the migration of the N(β) atom to the ring difficult. The mechanism suggested earlier through the diazetine intermediate (Chart 2) is, therefore, preferred.

The proposed mechanism can give only the 6-substituted-2-phenylquinoxalines by cyclodehydration of α-hydroxyphenylglyoxal-2-(p-substituted)-phenylhydrazones. This has helped to establish the structure of substituted quinoxalines obtained earlier by Hinsberg’s method25, to which two alternative possible structures were assigned. For example, the product which was earlier given the structure of 6(or 7)-methyl-2-phenylquinoxaline has now been established to be the 6-methyl derivative.

Similarly, the product which was earlier assigned a 6-(or 7-) chloro-2-phenylquinoxaline has now been found to be a mixture of 6- and 7-chloro derivatives. The individual products were isolated from the mixture in a pure state and each assigned the correct structure by directly comparing with the 6-chloro derivative obtained unambiguously by aluminium chloride cyclodehydration of phenylglyoxal-2-p-chloro-phenylhydrazone (XVII)

[For details see later].
CHART 2

XIII \( a \)  \( R = H \)

XVI \( a \)  \( R = CH_3 \)

XVII  \( R = Cl \)

XX  \( R = H \)

XXXIII  \( R = CH_3 \)

XLII  \( R = Cl \)
This mechanism also explains the formation of tetrahydroacridines (XXVI) instead of tetrahydrophenanthridines (XXVII) as the product of cyclodehydration of \( \text{g} \)-2-arylaminomethylene cyclohexanones (XVIII) by interaction with arylamine hydrochloride/fused zinc chloride in boiling ethanol\(^{27}\) (Chart 4). Similarly, the formation of 1,2,3,4-tetrahydro-10-thioxanthylum perchlorate (XXIX) instead of 1,2,3,4-tetrahydro-6-thiophenanthrylum perchlorate (XXX) by cyclodehydration of \( \text{g} \)-2-phenylmercapto-methylene cyclohexanone (XXXI) by treatment with 70% perchloric acid has also been explained by this mechanism: \(^{26}\) (Chart 5)

With a view to establish the general applicability of this reaction, substituted phenylhydrazones of phenylglyoxal were also subjected to cyclodehydration with aluminium chloride-sodium chloride melt. It was found that phenylglyoxal-2-\( p \)-methyl (or chloro)-phenylhydrazones gave the two isomeric products, namely 6-substituted-4-phenylcinnolines and 6-substituted-2-phenylquinoxalines respectively as expected according to the mechanism already suggested.
2. CYCLODEHYDRATION OF PHYNYLGLYXAL-2-P-TOLYLHYRAZONE

The reaction product obtained by cyclodehydration of sym-phenylglyoxal-2-p-tolylhydrazone with aluminium chloride-sodium chloride melt (1:1) also showed the presence of mainly two compounds on TLC (Rf 0.35 and 0.67).

Separation of these two products by silica gel column chromatography, followed by purification by PLC technique furnished the individual compounds in a pure crystalline state. These proved to be 6-methyl-4-phenylcinnoline (XXXII) and 6-methyl-2-phenylquinoxaline (XXXIII) respectively. (See Chart 1, 2 and 3).

\[
\begin{align*}
\text{(XXXII)} & \quad \text{(XXXIII)} \\
\end{align*}
\]

6-Methyl-2-phenylquinoxaline: The faster moving compound (Rf 0.67), \(C_{16}H_{12}N_2\), \((M^+ 220)\), m.p. 135-36° was predominant and an analogy with the relative Rf values and yields of the unsubstituted products described earlier, it was expected to be the quinoxaline isomer. It had UV absorption at 258 (ε, 27,080) and 340 μ (ε, 12,300) characteristic of a 2-phenylquinoxaline. Its NMR spectrum (Fig. 11) also established its structure. The analysis

\* Solvent system: benzene-ethylacetate (4:1)
FIG. II - NMR SPECTRUM OF 6-METHYL-2-PHENYLQUINOXALINE
of the spectrum is depicted in Table 6. These spectral data require the structure of this compound to be 6- or 7-methyl-2-phenylquinoxaline (XXXIII and XXXIV).

From the mode of its synthesis and on the basis of the mechanism already proposed for the formation of 2-phenylquinoxalines, however, it was assigned the structure of 6-methyl-2-phenylquinoxaline (XXXIII).

**TABLE 6**

Analysis of the N.M.R. spectrum of 6-methyl-2-phenylquinoxaline (XXXIII)

<table>
<thead>
<tr>
<th>Position of signal cps</th>
<th>Nature</th>
<th>No. of protons</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>156</td>
<td>Singlet</td>
<td>Three</td>
<td>Ar-CH₃</td>
</tr>
<tr>
<td>450</td>
<td>Complex multiplet</td>
<td>Four</td>
<td>C₇(or C₆'), C₅', C₃' and C₄'-H</td>
</tr>
<tr>
<td>468</td>
<td>Doublet</td>
<td>One</td>
<td>C₅(or C₈)-H</td>
</tr>
<tr>
<td></td>
<td>(J = 2 cps)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>477</td>
<td>Doublet</td>
<td>One</td>
<td>C₆ (or C₅)-H</td>
</tr>
<tr>
<td></td>
<td>(J = 8 cps)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>485</td>
<td>Quartet</td>
<td>Two</td>
<td>C₂( and C₆₁)-H</td>
</tr>
<tr>
<td></td>
<td>(J = 22 and 7 cps)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>657</td>
<td>Singlet</td>
<td>One</td>
<td>C₃-H</td>
</tr>
</tbody>
</table>

(XXXIV)
7-Methyl-2-phenylquinoxaline (XXXIV) has been prepared earlier by an unambiguous method\(^\text{28}\), and was reported to have a m.p. 79°. Hinsberg\(^\text{25}\) synthesized a product m.p. 135-36° by method which could give either or both of the 7- or 6-methyl-2-phenylquinoxalines, and assigned a 6-methyl-2-phenylquinoxaline (XXXIII) structure to it. The m.p. agreed with that of our product.

The identity of our product was finally confirmed by an actual synthesis of 6-methyl-2-phenylquinoxaline (XXXIII) according to the procedure described by Hinsberg.\(^\text{25}\)

In this synthesis, the commercially available 2-nitro-p-toluidine* (XXXV) was catalytically reduced in the presence of Raney nickel to 4-methyl-o-toluidine (XXXVI) which on condensation with α-bromoacetophenone (XXXVII) furnished the desired product. No other isomer was detected on TLC. The sequence of reactions is shown in Chart 6. This product proved to be identical in all respects with the product obtained by cyclodehydration of phenylglyoxal-2-p-tolylhydrazone (m.p., mix. m.p., TLC, UV, IR, NMR).

6-Methyl-4-phenylcinnoline: The more polar compound (Rf 0.35) m.p. 123-26° analysed for C\(_{16}\)H\(_{12}\)N\(_2\) (M\(^+\) 220) and was, therefore, isomeric with the quinoxaline derivative. Its U.V. spectrum showed absorptions at 233 (ε, 34,800), 306 (ε, 6,310) and a shoulder at 325 μm (ε, 5,170). The similarity of the pattern of this UV spectrum with that of 4-phenylcinnoline and by analogy

* Marketted by ACNA under the trade name Fast red 3RT Base, Echrotrol GLBase, C.I. 37110.
with the earlier experiment it could be anticipated that this compound was 6-methyl-4-phenylcinnoline. This substituted cinnoline has not been prepared so far. Attempts were, therefore, made to synthesise this compound by a known route. Of the two different known methods\textsuperscript{23,29} available for its synthesis we selected the one starting from 2-amino-6-methylbenzophenone\textsuperscript{30,31} (XXXVIII).

This was subjected to Grignard reaction with methyl magnesium iodide (Chart 7) to obtain the carbinol (XXXIX) which on dehydration with sulphuric acid gave the substituted ethylene (XL), characterised by its IR (absence of ketone 1650 cm\textsuperscript{-1} and bands at 3400 cm\textsuperscript{-1} (-\textit{NH}_2) and 310 cm\textsuperscript{-1}, unsymmetrically disubstituted ethylene.) and NMR spectrum [two mutually coupled doublets at 316 and 342 cps (\textit{J} = 2 cps) assignable to the olefinic protons].

Diazotization of this olefin resulted in cyclization to 6-methyl-4-phenylcinnoline, m.p. 124-25° (XXXII).

The resulting cinnoline was characterised by its UV absorption spectrum [233 \textit{m}u (6, 35,200), 305 \textit{m}u (6, 5,940), and a shoulder at 325 \textit{m}u (6, 5,060)] and its NMR spectrum (Fig. 12). The analysis of the spectrum is depicted in Table 7.

6-Methyl-4-phenylcinnoline synthesised in this manner proved to be identical with the cyclodehydration product (m.p. 123-25°) of phenyglyoxal-2-p-tolylhydrazone in all respects [m.p., mix. m.p., TLC and IR (Fig. 13)].

* Partiality of material prevented an examination of the chemical properties or the NMR spectrum.
### TABLE 7

Analysis of the N.M.R. spectrum of 6-Methyl-α-phenylcinnolone (XXXII)

<table>
<thead>
<tr>
<th>Position of Signal (cps)</th>
<th>Nature</th>
<th>No. of protons</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>Singlet</td>
<td>Three</td>
<td>Ar-CH$_3$</td>
</tr>
<tr>
<td>450</td>
<td>Singlet</td>
<td>Five</td>
<td>C$_2$, C$_3$, C$_4$, C$_5$, and C$_6$-H.</td>
</tr>
<tr>
<td>453 (J = 2 and 9 cps)</td>
<td>Quartet</td>
<td>One</td>
<td>C$_7$-H</td>
</tr>
<tr>
<td>457</td>
<td>Broad singlet</td>
<td>One</td>
<td>C$_6$-H</td>
</tr>
<tr>
<td>W$_H$ = 3 cps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>503 (J = 9 cps)</td>
<td>Doublet</td>
<td>One</td>
<td>C$_3$-H</td>
</tr>
<tr>
<td>542</td>
<td>Singlet</td>
<td>One</td>
<td>C$_3$-H</td>
</tr>
</tbody>
</table>
FIG. 12 - NMR SPECTRUM OF 6-METHYL-4-PHENYL-CINNOLINE
FIG. 13 - IR SPECTRA OF COMPOUND m.p. 123-125° AND 6-METHYL-4-PHENYL CINNOLINE
3. CYCLODEHYDRATION OF PHENYLGLYOXAL-2-P-CHLOROPHENYLHYDRAZONE

It has already been stated earlier that the syn form of phenylglyoxal-2-p-chlorophenylhydrazone has not been prepared so far and our attempts to prepare this form of the phenylhydrazone were unsuccessful. Thus, we were confronted with the problem of using the unfavoured isomer, namely, the anti-phenylglyoxal-2-p-chlorophenylhydrazone (XVII) for cyclodehydration with aluminium chloride to obtain the 6-chloro substituted quinoxaline and cinnoline.

It can be expected on the basis of the mechanism of formation of both cinnoline and quinoxaline, that the reaction would not proceed favourably with the anti isomer of phenylglyoxal-2-phenylhydrazone, since the concerned sites of reaction are far away from each other. It is possible, however, that under the more or less, drastic conditions of the cyclodehydration process, a part of the anti isomer may go over to the syn form and then cyclize to give a mixture of the corresponding cinnoline and quinoxaline.

To verify this, first anti-phenylglyoxal-2-phenylhydrazone (XIIIb) was cyclodehyrated with aluminium chloride-sodium chloride melt. Under these conditions, it was observed that most of the starting material was lost as a tarry material, but small quantities of cinnoline and quinoxaline could be isolated from the reaction mixture.
On the basis of these results, anti-phenylglyoxal-2-p-chlorophenylhydrazone (XVII) was also subjected to the cyclodehydration reaction with aluminium chloride-sodium chloride melt. The reaction product showed two spots on TLC (Rf 0.46 and 0.73)*. The two products were separated in the pure state through chromatography of the crude product on silica gel column and subsequent purification of the individual compound by PLC. The yield of the products were poor, as expected. They have been found to be 6-chloro-4-phenylcinnoline (XLII) and 6-chloro-2-phenylquinoxaline (XLIII) respectively.

![Chemical structures](XLI) (XLII)

6-Chloro-2-phenylquinoxaline: The faster moving product (Rf 0.73) crystallised from ethanol in colourless needles m.p. 147-48°. It analysed for C_{14}H_{9}N_{2}Cl (M⁺ 240) and its U.V. spectrum [254 μμ (ε, 21,380), 340 μμ (ε, 9,870)] was typical of a 2-arylquinoxaline. The analysis of the NMR spectrum (Fig. 14) outlined in Table 8 required this compound to have a substituent at 6- or 7-position. The mechanism proposed for the formation of this product can give only the 6-chloro substituted compound. Therefore, the product

* Solvent system: benzene-ethylacetate (4:1).
FIG. 14 - NMR SPECTRUM OF 6-CHLORO-2-PHEYLQUINOXALINE
was assigned the structure of 6-chloro-2-phenylquinoxaline (XLII).

**TABLE 8**

Analysis of the N.M.R. spectrum of
6-chloro-2-phenylquinoxaline (XLII)

<table>
<thead>
<tr>
<th>Position of signal (cps)</th>
<th>Nature</th>
<th>No. of protons</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>450</td>
<td>Complex multiplate</td>
<td>Three</td>
<td>C₃, C₄, C₅₁-H</td>
</tr>
<tr>
<td>458</td>
<td>Quartet</td>
<td>One</td>
<td>C₇ (or C₆)-H</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(J = 2.5 and 8 cps)</td>
</tr>
<tr>
<td>478</td>
<td>Broad singlet</td>
<td>One</td>
<td>C₅ (or C₈)-H</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Wₜ = 3 cps)</td>
</tr>
<tr>
<td>487</td>
<td>Doublet</td>
<td>One</td>
<td>C₈ (or C₅)-H</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(J = 9 cps)</td>
</tr>
<tr>
<td>492</td>
<td>Quartet</td>
<td>Two</td>
<td>C₂₁ and C₆₁-H</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(J = 3 and 8 cps)</td>
</tr>
<tr>
<td>558</td>
<td>Singlet</td>
<td>One</td>
<td>C₃-H</td>
</tr>
</tbody>
</table>

Drucy and Hüniken²² reported the synthesis of a compound m.p. 125-27⁰, which they described as 6- (or 7-) chloro-2-phenylquinoxaline. Following the procedure of Hinsberg²⁵ 4-chloro-o-phenylenediamine³³ (XLIII) obtained from p-chloroaniline (XLIV), was condensed with
\(-\text{bromoacetophenone (Chart 8). The crude reaction product crystallised from ethanol in colourless needles m.p. 123-126^\circ, a m.p. very near to that recorded by Drucey and H"{u}ni}\) for their product.

TLC of this material, however, showed that it was a mixture of two compounds \((\text{RF} 0.35 \text{ and } 0.45)\). They were separated by inverted dry column chromatography on silica gel. The compound having RF 0.45 crystallised from ethanol in colourless needles m.p. 143-49^\circ and analysed for \(\text{C}_{14}\text{H}_9\text{N}_2\text{Cl}\). It was found to be identical with 6-chloro-2-phenylquinoxaline \(^{\star\star}\) prepared by cyclodehydration process. (m.p., mix. m.p., TLC, IR and NMR).

7-Chloro-2-phenylquinoxaline: The product RF 0.35 also crystallised from ethanol in colourless needles, m.p. 130-31^\circ. It analysed for \(\text{C}_{14}\text{H}_9\text{N}_2\text{Cl}\).

Its NMR spectrum (Fig. 15 and Table 9) was typical of that of a 6- or 7-chloro-2-phenylquinoxaline.

\(^*\text{Solvent system: benzene-ethylacetate (95:5).}\)

\(^{\star\star}\text{The examination of the NMR spectrum of N-oxide of this compound (see Section C) clearly established it to be the 6-chloro-2-phenylquinoxaline.}\)
FIG. 15 - NMR SPECTRUM OF 7-CHLORO-2-PHENYLQUINOXALINE
### Table 9

Analysis of the N.M.R. spectrum of 7-chloro-2-phenylquinoxaline (XLV)

<table>
<thead>
<tr>
<th>Position of signal (cps)</th>
<th>Nature</th>
<th>No. of protons</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>450</td>
<td>Multiplet</td>
<td>Three</td>
<td>C₃, C₄', and C₆₁-H</td>
</tr>
<tr>
<td>466</td>
<td>Quartet</td>
<td>One</td>
<td>C₆ (or C₇)-H</td>
</tr>
<tr>
<td></td>
<td>(J = 2 and 8 cps)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>479</td>
<td>Doublet</td>
<td>One</td>
<td>C₅-(or C₆)-H</td>
</tr>
<tr>
<td></td>
<td>(J = 8 cps)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>485</td>
<td>Doublet</td>
<td>One</td>
<td>C₆ (or C₅)-H</td>
</tr>
<tr>
<td></td>
<td>(J = 2 cps)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>488</td>
<td>Quartet</td>
<td>Two</td>
<td>C₂, and C₆₁-H</td>
</tr>
<tr>
<td></td>
<td>(J = 3 and 8 cps)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>555</td>
<td>Singlet</td>
<td>One</td>
<td>C₃-H</td>
</tr>
</tbody>
</table>

Since the structure of the isomeric product m.p. 148-49° has already been established as 6-chloro-2-phenylquinoxaline (XLII) this isomer, m.p. 130-31°, was assigned the structure of 7-chloro-2-phenylquinoxaline (XLV).

Both these isomers gave molecular ion peak at m/e 240 in their mass spectra.

The compound described by Drucey and Hüni³² is, therefore, proved to be a mixture of 6- and 7-chloro-2-phenylquinoxaline.
6-Chloro-4-phenylecinnoline: The more polar component of the product of cyclodehydration of phenylglyoxal-p-chlorophenylhydrazone (XVII) was isolated in a pure form through preparative layer chromatography as a semisolid which could not be induced to crystallise. The UV spectrum had absorptions at 232 (ε, 33,000), 305 (ε, 7,800) and a shoulder at 320 mλ (ε, 7,200) indicating the probability of a 4-phenylecinnoline structure for the compound. The NMR spectrum of the compound showed it to be substituted at C6 or C7. The analysis of the NMR spectrum (Fig. 16) is recorded in Table 10.

<table>
<thead>
<tr>
<th>Position of signal (cps)</th>
<th>Nature</th>
<th>No. of protons</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>456</td>
<td>Singlet</td>
<td>Five</td>
<td>C2'H, C3'H, C4'H, C5'H, C6, H</td>
</tr>
<tr>
<td>465</td>
<td>Quartet</td>
<td>One</td>
<td>C7-H</td>
</tr>
<tr>
<td>(J = 2 and 9 cps)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>475</td>
<td>Doublet</td>
<td>One</td>
<td>C5-H</td>
</tr>
<tr>
<td>(J = 2 cps)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>512</td>
<td>Doublet</td>
<td>One</td>
<td>C8-H</td>
</tr>
<tr>
<td>(J = 9 cps)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>550</td>
<td>Singlet</td>
<td>One</td>
<td>C3-H</td>
</tr>
</tbody>
</table>

**Table 10**

Analysis of the N.M.R. spectrum of 6-chloro-4-phenylecinnoline (XLI)
FIG. 16 - NMR SPECTRUM OF 6-CHLORO-4-PHENYLCINNOLINE
As the $G_8$ proton appears as an ortho coupled doublet, the substituent cannot be at $C_7$ and, therefore, should be at $C_6$. As already stated the mode of formation of this compound can also lead only to a 6-substituted cinnoline. Therefore, the compound is 6-chloro-4-phenylcinnoline (XLI).

This cinnoline derivative has not been described in literature so far. For confirmation of the structure of this product, 6-chloro-4-phenylcinnoline was synthesised following the general procedure of Stoermer and Fincke. Reaction between p-chloroaniline (XLIV) and benzoyl chloride in the presence of zinc chloride gave a benzoylamino ketone which was hydrolysed in situ to furnish the required ketone (XLVI), m.p. 98-99° (Lit. 98° 35, 100° 36). Grignard reaction with this ketone followed by dehydration of the resulting carbinol with sulphuric acid (30%) provided the desired ethylene derivative (XLVIII) [Chart 9], which was characterised by its IR and NMR spectrum [absence of a $\text{C}=\text{O}$ and a band at 890 cm$^{-1}$ for unsymmetrically disubstituted ethylene; two mutually coupled doublets at 316 and 336 cps ($J = 2$ cps) assignable to the olefinic protons.]

Diazotization of this amine afforded the required 6-chloro-4-phenylcinnoline (XLI), m.p. 140-42°C. It was characterised by its UV [233 ($\epsilon$, 32,800), 305 ($\epsilon$, 7,750) and a shoulder at 320 m$\mu$ ($\epsilon$, 7,300)] and IR spectrum [absence of $-\text{NH}_2$ and $\text{C}=\text{CH}_2$].

This product (m.p. 140-42°) was identical in its TLC behaviour and IR spectrum (Fig. 17) with the semisolid product obtained by cyclodehydration.
FIG. 17-IR SPECTRA OF COMPOUND Rf 0.73 AND 6-CHLORO-4-PHENYL CINNOLINE
Concluding remarks:

These studies reopened the problem of identity of the compounds obtained earlier by Bhat and Bose$^6$ by cyclodehydration of $o$-hydroxyphenylglyoxal-$2$-phenylhydrazone with fused aluminium chloride. This reaction was, therefore, re-examined by us. Thin layer chromatography of the crude reaction product showed two spots in this case also. The slower $\rho$ moving spot (Rf 0.15)$^*$ was very faint indicating that the faster moving material (Rf 0.47)$^*$ which gave a very strong spot was the main product. The relative mobilities of the two spots indicated a possible $2$-($o$-hydroxyphenyl)-quinazoline structure (XLIX) for the major product. Repeated crystallisation of this material from alcohol gave the pure product m.p. 191-92$^\circ$ which was found to be identical with the product m.p. 188$^\circ$, reported earlier by Bhat and Bose$^6$ (mix. m.p., TLC mobility and IR spectrum).

\[
\begin{align*}
\text{(XLIX)}
\end{align*}
\]

* Solvent system: benzene-ethylacetate (4:1)
A comparison of the U.V. spectrum of this compound with those of cinnolines and quinoxalines prepared in the course of the present work also indicated a possible quinoxaline structure for Bhat and Bose's compounds.

The NMR spectra of these compounds also agree with the present structure assignment, as they do not show a low field signal corresponding to the C₈ proton of cinnolines.

Bhat and Bose⁶ were also unable to explain the absence of a hydroxy stretching absorption in the IR spectra of their compounds in KBr pellet. This anomaly can be easily explained in a quinoxaline structure (XLI) where an intramolecular hydrogen bonding is possible with the nitrogen atom in position 1. This would also explain the extreme downfield value of the hydroxy proton in the NMR spectra of these compounds.¹³

The 2-(α-hydroxyphenyl)-quinoxaline structure of Bhat and Bose's compounds were further supported by their Mass spectra. These compounds showed a (M-27) fragment (loss of HCN) similar to those shown by quinoxalines, whereas cinnolines were found to show a (M-28) fragment (loss of N₂). (See Chapter III).

* In 4-phenylcinnolines the five protons of the unsubstituted 4-phenyl ring are identical and appears as a singlet. However, when a substituent is present in this phenyl ring, this method of identification of cinnolines does not hold good.
The identity of Bhat and Bose's compound was finally established by a direct comparison (mixed m.p., TLC, IR and Mass spectra) of the product m.p. 192° with an authentic sample of 2-(α-hydroxyphenyl)-quinoxaline* synthesised by Howe et al.\textsuperscript{37} by a different route. Mass spectra and TLC mobility of the other compounds of this series prepared by Bhat and Bose also confirm that they have a quinoxaline structure. The structure of the compounds described earlier by Bhat and Bose\textsuperscript{6} as 4-(α-hydroxyphenyl)-cinnolines should, therefore, now be revised to 2-(α-hydroxyphenyl)-quinoxalines.

Details on the methods of distinction between cinnolines and quinoxalines, based on their N-oxides is described in section C of this chapter and those based on the mass spectral studies are discussed in Chapter III. These studies also confirm the above observations.

From these studies it may be concluded that cyclodehydration of arylglyoxal-2-arylhydrazones is more facile for the synthesis of 2-arylquinoxaline derivatives rather than the isomeric 4-arylcinnotlines.

---

* Our thanks are due to Dr. R. Howe for an authentic sample of this compound (m.p. 192°).
SECTION C
SYNTHESIS AND CHARACTERISATION OF THE N-OXIDES
OF ARYLCINHOLINES AND ARYLUINOXALINES
SECTION C: SYNTHESIS AND CHARACTERIZATION OF THE N-OXIDES OF ARYLCHINOLINES AND ARYLQUINOXALINES.

In the earlier section evidences have been put forward which conclusively support the cinnoline and quinoxalines structures of the compounds obtained by cyclodehydration of phenylglyoxal-2-phenylhydrazone.

The present section deals with the study of the interesting group of derivatives of these cinnolines and quinoxalines, namely, their N-oxides which offer further evidences in support of the structures already assigned to these compounds earlier. These N-oxides are also likely to be pharmacologically potent.

N-oxides of cinnolines\textsuperscript{38-45}, quinoxalines\textsuperscript{46-49}, quinazolines\textsuperscript{50} and phthalazines\textsuperscript{51} have been studied earlier. Recently, the N-oxides of 4-methylcinnolines have been exhaustively investigated.\textsuperscript{40,41,44} Spectral studies of the N-oxides of 3-phenylcinnolines have also been made.\textsuperscript{43}

Although, Atkinson and Simpson\textsuperscript{39} have prepared the N-oxides of 4-arylcinnolines, they have not determined the position of the oxygen atom. Studies have also been made on the position of oxygen in the N-oxides of 2-phenylquinoxalines on the basis of their chemical reactions.\textsuperscript{48}
N-OXIDES OF 4-PHENYLCINNOLINES

N-Oxides of 4-phenylcinnoline: Treatment of 4-phenylcinnoline with hydrogen peroxide (30%) in glacial acetic acid afforded a product which on TLC examination revealed the presence of two components (RF 0.38 and 0.27°). Separation by TLC provided both these compounds in pure form.

The compound RF 0.38, C_{14}H_{10}N_2O, (M^+ 222) crystallised from ether-pet. ether in pale yellow needles, m.p. 107-8° and displayed typical peaks at 1365, 1390 and 1420 cm\(^{-1}\) (N = O)\(^{44}\) in its IR spectrum. The most convenient method to establish the position of the oxygen atom is a study of the NMR spectrum. The C_8 proton appears at a lower field than the C_3 proton when the oxygen atom is at N_1\(^{41}\). Taking this into consideration, this N-oxide must be the 1-oxide (L), as revealed by its NMR spectrum (Fig. 18). The C_8 proton appears as a quartet at 528 cps (\(J = 2\) and 8 cps), while the C_3 proton is seen as a singlet at 502 cps. The remaining aromatic protons appear as two peaks, a singlet at 458 cps (5 H) and a multiplet at 475 cps (3 H). The singlet at 458 cps obviously represents the five equivalent protons of the phenyl group at C_4.

It has been observed by Ogata et al\(^{41}\) that cinnoline-1-oxides showed a strong UV absorption at 360 μ. The UV absorption bands of this compound at 229 (є, 46,030), 255 (є, 18,640), 326 (є, 12,170) and 366 μ (є, 22,450) support this observation.

* Solvent system: benzene-ethylacetate (4:1).
FIG. 18 - NMR SPECTRUM OF 4-PHENYLCHYNNOLINE -1- OXIDE (L)

FIG. 19 - NMR SPECTRUM OF 4-PHENYLCHYNNOLINE -2- OXIDE (LI)
The compound Rf 0.27 crystallised from ether-pet.ether in colourless plates, m.p. 148-49° and analysed for C\textsubscript{14}H\textsubscript{10}N\textsubscript{2}O (M\textsuperscript{+} 222) and had N-oxide peaks at 1360, 1405 and shoulder at 1395 cm\textsuperscript{-1} in its IR spectrum. Its NMR spectrum (Fig. 19) revealed the presence of a singlet at 494 cps. As this peak was the one at the lowest field, this compound must be the 2-oxide (LI). The remaining protons appeared as a multiplet around 465 cps. The strong signal at 459 cps must include the five equivalent aromatic protons of the phenyl group at C\textsubscript{4}.

The UV spectrum of the 2-oxides are characterised\textsuperscript{41} by a maximum absorption at 265 μ. In keeping with this, the UV spectrum of this compound had absorptions at 265 (ε, 40,920), 320 (ε, 9,806) and 365 μ (ε, 6,763).

The difference in the UV absorption of these two N-oxides is clearly shown in Fig. 20.
Fig. 20 - UV Absorption Spectra of 4-Phenylcinnoline 1-Oxide (L) and 2-Oxide (L1)
**N-Oxides of 6-methyl-4-phenylcinnoline:**

Two N-oxides could be obtained from 6-methyl-4-phenylcinnoline similarly by oxidation with hydrogen peroxide and separation of the individual compound by the PLC technique. Table II depicts the properties of these two N-oxides.

**Table II**

Properties of the two N-oxides of 6-methyl-4-phenylcinnoline

<table>
<thead>
<tr>
<th>Analysed for</th>
<th>M.P.</th>
<th>U.V. (μ)</th>
<th>I.R. (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(cm⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compound (LII)</td>
<td>C₁₅H₁₂N₂O</td>
<td>124-25°C</td>
<td>234 (ε, 27,400), 1435,</td>
</tr>
<tr>
<td>Rf 0.57</td>
<td>M⁺ 236</td>
<td>256 (ε, 12,140), 1380 (bro)</td>
<td></td>
</tr>
<tr>
<td>(1-Oxide)</td>
<td></td>
<td>365 (ε, 15,840). 1330</td>
<td></td>
</tr>
<tr>
<td>Compound (LIII)</td>
<td>C₁₆H₁₂N₂O</td>
<td>202-3°C</td>
<td>268 (ε, 40,000) 1435,</td>
</tr>
<tr>
<td>Rf 0.41*</td>
<td>M⁺ 236</td>
<td>320 (ε, 9,363) 1385,</td>
<td></td>
</tr>
<tr>
<td>(2-Oxide)</td>
<td></td>
<td>365 (ε, 7,235) 1370 (sh)</td>
<td></td>
</tr>
</tbody>
</table>

* Solvent system:  benzene-ethylacetate (85:15)
[Twice run].

![Diagram](LII)

![Diagram](LIII)
From the UV spectrum it is obvious that compound Rf 0.57, m.p. 124-25° represents the 1-oxide (LII) while the other represents the 2-oxide (LIII). These conclusions are clearly supported by their NMR spectra, which are presented in Table 12.

**TABLE 12**

Analysis of the NMR spectra of N-oxides of 6-methyl-4-phenylcinnoline

<table>
<thead>
<tr>
<th>Assignment</th>
<th>Compound (LII)</th>
<th>Compound (LIII)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C$_3^{-}$CH$_3$</td>
<td>161 cps, Singlet</td>
<td>148 cps, Singlet</td>
</tr>
<tr>
<td>Five protons of phenyl group at C$_4$</td>
<td>451 cps, Singlet</td>
<td>454 cps, Singlet</td>
</tr>
<tr>
<td>C$_7$-H</td>
<td>464 cps, Doublet*</td>
<td>465 cps, multiplet</td>
</tr>
<tr>
<td></td>
<td>(J = 8 cps)</td>
<td></td>
</tr>
<tr>
<td>C$_6$-H</td>
<td>458 cps, broad singlet*</td>
<td></td>
</tr>
<tr>
<td>C$_3$-H</td>
<td>492 cps, Singlet</td>
<td>488 cps, Singlet</td>
</tr>
<tr>
<td>C$_8$-H</td>
<td>617 cps, Doublet</td>
<td>Cannot be definitely assigned</td>
</tr>
<tr>
<td></td>
<td>(J = 8 cps)</td>
<td></td>
</tr>
</tbody>
</table>

*Signal at 458 cps, which forms the lower field half of the doublet of C$_7$ proton, has $W_H$ = 3 cps.
FIG. 21 - NMR SPECTRUM OF 6-METHYL-4-PHENYL-CINNOLINE-1-OXIDE (LII)

FIG. 22 - NMR SPECTRUM OF 6-METHYL-4-PHENYL-CINNOLINE-2-OXIDE (LIII)
N-Oxides of 6-chloro-4-phenylcinnoline:

Using PLC technique both of the N-oxides formed by the hydrogen peroxide oxidation of 6-chloro-4-phenylcinnoline could be isolated in pure form. From the UV spectra, these two compounds having Rf 0.37 and 0.24* could be assigned the structures (LIV) and (LV) respectively.

![Chemical Structures](LIV) and (LV)

Table 13 summarises the characteristics of these compounds.

**Table 13**

<table>
<thead>
<tr>
<th>Characteristics of the N-oxides 6-chloro-4-phenylcinnoline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Analysed for</strong></td>
</tr>
<tr>
<td><strong>(LIV)</strong></td>
</tr>
<tr>
<td>C&lt;sub&gt;14&lt;/sub&gt;H&lt;sub&gt;9&lt;/sub&gt;ClN&lt;sub&gt;2&lt;/sub&gt;O</td>
</tr>
<tr>
<td>M&lt;sup&gt;+&lt;/sup&gt; 256</td>
</tr>
<tr>
<td><strong>(1-oxide)</strong></td>
</tr>
<tr>
<td>C&lt;sub&gt;14&lt;/sub&gt;H&lt;sub&gt;9&lt;/sub&gt;ClN&lt;sub&gt;2&lt;/sub&gt;O</td>
</tr>
<tr>
<td>M&lt;sup&gt;+&lt;/sup&gt; 256</td>
</tr>
</tbody>
</table>

* Solvent system: benzene-ethylacetate (9:1).
An analysis of the NMR spectra of these two compounds, outlined in Table 14, confirms these structures.

**TABLE 14**

Analysis of the N.M.R. spectra of the N-oxides of 6-chloro-4-phenylcinoline

<table>
<thead>
<tr>
<th>Assignment</th>
<th>Compound (LIV) Fig. 23</th>
<th>Compound (LV) Fig. 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Five protons of phenyl group at C&lt;sub&gt;4&lt;/sub&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;7&lt;/sub&gt;-H</td>
<td>467 cps, Singlet</td>
<td>457 cps, Singlet</td>
</tr>
<tr>
<td>C&lt;sub&gt;7&lt;/sub&gt;-H (2 and 8 cps)</td>
<td>472 cps, Quartet (J = 2 and 8 cps)</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;6&lt;/sub&gt;-H</td>
<td>476 cps, Doublet (J = 2 cps)</td>
<td>Multiplet between 455 to 473 cps</td>
</tr>
<tr>
<td>C&lt;sub&gt;8&lt;/sub&gt;-H</td>
<td>526 cps, Doublet (J = 8 cps)</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;3&lt;/sub&gt;-H</td>
<td>500 cps, Singlet</td>
<td>492 cps, Singlet</td>
</tr>
</tbody>
</table>

The U.V. spectra of the 1-oxides are combined and depicted in fig. 25, while fig.26 shows the UV spectra of the 2-oxides.
FIG. 23 - NMR SPECTRUM OF 6-CHLORO-4-PHENYL CYNNOLINE-1-OXIDE (LIV)

FIG. 24 - NMR SPECTRUM OF 6-CHLORO-4-PHENYL CYNNOLINE-2-OXIDE (LV)
FIG. 25 - UV ABSORPTION SPECTRA OF 4-PHENYLCINNOLINE 1-OXIDES
**N-OXIDES OF 2-PHENYLQUINOXALINES**

N-Oxides of 2-phenylquinoxaline: Treatment of 2-phenylquinoxaline with peracetic acid afforded a product which was separated into its components by PLC technique. The faster moving compound, C\textsubscript{14}H\textsubscript{10}N\textsubscript{2}O, M\textsuperscript{*} 222 crystallised from ethanol in colourless needles, m.p. 138-39\(^\circ\) (lit.\textsuperscript{47} m.p. 137-38\(^\circ\) for the 4-oxide). The UV spectrum of this compound was also similar to that of 2-phenylquinoxaline 4-oxide\textsuperscript{49} (LVI). The structure of this compound had been established earlier\textsuperscript{48} on the basis of its chemical reactions. This has now been confirmed by an examination of its NMR spectrum (Fig. 27) the salient feature of which is the marked upfield shift of the C\textsubscript{3} proton as compared to that of the parent 2-phenylquinoxaline. Such a marked upfield shift is only possible for a proton on a carbon adjacent to the N-oxide group. Under these circumstances the proton on the carbon \(\beta\) to the N-oxide group is expected to show a small down field shift.\textsuperscript{40,41} This obviously means that the N-oxide has been formed at the 4-position rather than at the 1-position.

The other difference in the NMR spectrum of the N-oxide in contrast with the parent is the down field shift of a hydrogen peri to the N-oxide, which appears as a quartet at 513 cps \((J = 2\) and 8 cps).

![Diagram](image-url)
FIG. 27 - NMR SPECTRUM OF 2-PHENYLQUINOXALINE-4-OXIDE (LVI)
The slower moving compound m.p. 202° had properties (m.p. and UV) identical with that reported in literature\textsuperscript{47,49} for 2-phenylquinoxaline 1,4-dioxide (LVII). Its structure is based on its formation on further oxidation of the 4-oxide (LVI). Its Mass spectrum clearly showed that it was a dioxide (M\textsuperscript{+} 238) and had important peaks corresponding to M-16 and M-32 due to the loss of the two oxygen atoms which is typical of the N-oxides.\textsuperscript{52}

It is significant that the TLC of the oxidation product did not show the presence of a third component, which could be theoretically formed, namely, the 1-oxide. This is in keeping with the postulate that the presence of the phenyl group favours the oxidation at the 4-position because of steric hindrance at the 1-position.\textsuperscript{53}

**N-Oxides of 6-substituted-2-phenylquinoxalines**

A point of special interest in the studies of quinoxaline N-oxides is the report\textsuperscript{54} that 6-methyl and 6-chloroquinoxalines direct oxidation at the 1-position whereas in quinoxalines substituted at 2-position the oxidation takes place at the 4-position. It was of interest to see whether the electronic factors resulting in N-oxidation at 1-position could be more powerful than the steric factors, which would be expected to cause oxidation at the 4-position, in the case of 6-substituted 2-phenylquinoxalines.
6-Chloro derivative: Of the two products obtained by N-oxidation of 6-chloro-2-phenylquinoxaline, only one could be isolated by PLC, and the structure (LVIII) for this compound could be assigned on the basis of its spectral properties.*

![Chemical structure](LVIII)

This compound displayed UV characteristics typical of a 4-oxide** as it is very similar to that of the 4-oxide of 2-phenylquinoxaline. In agreement with this, the NMR spectrum of this compound showed an appreciable upfield shift (from 558 cps to 529 cps+) for the C3 proton. This, as mentioned earlier, is only possible for oxidation at the 4-position and not at the 1-position.

* Paucity of material prevented the use of chemical methods for establishing its structure; moreover, the spectral assignments leave no doubt as to the correct structure.

** The 1-oxide would be expected to have a different UV as the phenyl group would now be twisted slightly out of plane.53

+ Comparison is made between the oxide and the unoxidized starting material.
Furthermore if oxidation occurs at the 4-position, the signal for peri hydrogen should appear as a doublet (meta coupled), whereas, if oxidation occurs at 1-position, this peri hydrogen would appear as an ortho coupled doublet. As the spectrum of the oxide shows a meta coupled doublet at 514 cps (J = 2 cps), there is no doubt at all that oxidation has occurred at the 4-position (Fig. 28).

It is significant that apart from a peak at 514 cps, 6-chloro-2-phenylquinoxaline in its NMR spectrum (Section B) shows no peak beyond 500 cps. The C6 hydrogen appears at 478 cps.

6-Methyl derivative: In this case both of the compounds obtained on N-oxidation could be separated by PLC. The UV spectrum of the faster moving compound was similar to that of 2-phenylquinoxaline-4-oxide (LV) and 6-chloro-2-phenylquinoxaline 4-oxide (LVIII) (Fig. 29), which indicates that this compound is the 4-oxide* (LIX).

The second compound isolated was the 1,4-dioxide (LX) as it had typical UV absorption (Fig. 30) and had a molecular weight of 252 (Mass spectrum).

* The NMR spectrum of this product could not be examined due to paucity of material.
FIG. 28-NMR SPECTRUM OF 6-CHLORO-2-PHENYLQUINOXALINE-4-OXIDE (LVIII)
UV of 2-Phenylquinoxaline-4-oxide (Hayashi et al.)

Fig. 29 - UV spectra of LVI, LVIII and LIX
FIG. 30 - UV SPECTRA OF LVII AND LX

UV OF 2-PHENYLQUINOXALINE 1,4-DIOXIDE (HAYASHI et al.)

LOG ε

LVII
LX
The presence of the two N-oxide groups could be shown by the characteristic peaks M-16 and M-32 observed in its Mass spectrum.
EXPERIMENTAL

The melting and boiling points are uncorrected, the former being determined in a Gallenkamp melting point apparatus. The U.V. spectra were taken on a Perkin-Elmer spectrophotometer (Model 360) or Beckman DU spectrophotometer, in 95% spectroscopic ethanol. The IR spectra were recorded, as nujol mulls unless otherwise stated, on a Perkin-Elmer Infracord (Model 137E). The maxima are reported in cm$^{-1}$. The NMR spectra were recorded on a Varian A-60 spectrometer as 10% solution in carbon tetrachloride or deuterio-chloroform (especially for N-oxides) unless otherwise stated using tetramethyl silane (TMS) as the internal standard. The chemical shifts are reported in cps from TMS. The mass spectra were recorded in a CEC-21-110B double focussing mass spectrometer operating at 70 eV using direct inlet system at temperatures well below the melting points.

Thin layer chromatography (TLC) was carried out on silica gel (-200 mesh) mixed with plaster of paris (15%) as binder. The visualization of developed thin-layer chromatograms was achieved by exposure to iodine vapour. The preparative thin-layer chromatography (PLC) was carried out on the plates (20x20 cm), coated with silica gel (20 g) mixed with plaster of paris (15%) as a binder, and the layer thickness $\sim$ 1 to 2 mm.
The "Inverted dry column chromatography", (IDCC), on silica gel (-200 mesh) was carried out according to the method of Bhalla et al. 34

The silica gel for column chromatography (100-200 mesh) was washed with hot distilled water till sulphate-free, dried and activated at 125-130°/6-8 hr. to secure a product of activity I-IIA. The product was deactivated to the desired grade and the activities checked by the method of Hernandez 57 et al.

The neutral alumina used for column chromatography was prepared from commercial alumina (100-200 mesh) by the method of Evans and Shoppee 58 and the activities were tested by the Brockmann-Schodder procedure. 59

Pet. ether refers to the fraction having the b.p. range 60-80°. All solvent extracts were washed with brine and dried over anhydrous sodium sulphate before the solvent was stripped.
Phenylglyoxal-2-arylhydrazones:

Phenylglyoxal-2-arylhydrazones were prepared by reacting ethylbenzoyl acetate with the required benzene diazonium salt.

(i) Ethylphenylazo-benzoylacetae: To a solution of ethylbenzoylacetate (19.2 g.; 0.1 mol) in ethanol (380 ml), a solution of fused sodium acetate (30 g. in 100 ml water) was added. It was stirred mechanically and cooled in ice-salt mixture. To this cooled solution a solution of benzene diazonium chloride [prepared from aniline (9.3 g.; 0.1 mol)] was added dropwise, taking care that the reaction temperature remains below 20°. After the addition was complete, the reaction mixture was further stirred for 2 hr. maintaining the temperature below 20°. The organic phase was separated and the aqueous layer was extracted with ether. The combined organic layers were washed with water and dried. The residue obtained on removal of the solvent was a syrupy material and not the expected crystalline solid m.p. 66°. Attempts to obtain the material in a crystalline state were unsuccessful. Therefore, the syrupy material (TLC pure) was used for the next stage.

(ii) Phenylazo-benzoylacetic acid: A solution of the syrupy ester (4.94 g.) in alcoholic potassium hydroxide solution (0.6 N, 40 ml), was heated on a waterbath for \( \sim 15-20 \text{ min.} \) The potassium salt which separated out was filtered under suction and washed with ethanol and ether. The precipitate was dissolved in 150 ml of water and
acidified with hydrochloric acid. The yellow product obtained was filtered under suction, washed well with water and dried. The end material crystallised from ethanol in yellow needles, m.p. 145-46°. The p-methyl and p-chloro derivatives were prepared in a similar manner.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. X = H</td>
<td>85</td>
<td>145-46°</td>
<td>146°</td>
<td>7</td>
</tr>
<tr>
<td>2. X = p-CH₃</td>
<td>60</td>
<td>172-73°</td>
<td>169-70°</td>
<td>17</td>
</tr>
<tr>
<td>3. X = p-Cl</td>
<td>65</td>
<td>137-88°</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* Analysis:

Found: C, 58.96; H, 3.57; N, 9.61%

C₁₆H₁₁ClN₂O₃ requires: C, 59.51; H, 3.64; N, 9.26%

(iii) Decarboxylation of the acids to the required phenylglyoxal-α-phenylhydrazones:

The above acids were decarboxylated by heating in an oilbath well above their melting points for 1-2 hr. The solids obtained were crystallised from pet. ether or ethanol.

<table>
<thead>
<tr>
<th>C₆H₅CO.CH:N:NH.C₆H₄-X</th>
<th>Yield</th>
<th>m.p.</th>
<th>Lit. m.p.</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. X = p-CH₃</td>
<td>90</td>
<td>94-95° (pet. ether)</td>
<td>122-23° (ethanol)</td>
<td>17</td>
</tr>
<tr>
<td>3. X = p-Cl</td>
<td>96</td>
<td>170-72° (ethanol)</td>
<td>172-4° (ethanol)</td>
<td>19</td>
</tr>
</tbody>
</table>
Isomerisation of the phenylhydrazones:

Conversion of the syn-form to the anti-form:

Phenylglyoxal-2-phenylhydrazone (1.0 g.), m.p. 114-116° (pet. ether) was digested with ethanol (50 ml) at 50-55° for ~65 hr, then concentrated under reduced pressure (water pump) and finally crystallised from ethanol in yellow micro crystals, m.p. 139-40° (lit.11 145-6°). Yield 0.8 g.

Similarly, phenylglyoxal-2-p-tolylhydrazone (0.23 g.), m.p.92-94°, was digested with ethanol (20 ml) at 50-60° for 8 days, then concentrated under reduced pressure and crystallised from ethanol in orange platelets, m.p. 122-23° (lit.17 122-23°), Yield, 0.16 g.

Cyclodehydration of phenylglyoxal-2-phenylhydrazone:

**Syn-phenylglyoxal-2-phenylhydrazone,** m.p. 114-116°, (0.5 g) was intimately mixed with a powdered mixture of anhydrous aluminium chloride and sodium chloride (1:1, 10 g.). The mixture was heated under anhydrous conditions in an oilbath maintained at 150-60° for 30 min. A vigorous reaction took place with the evolution of gas and the molten reaction mixture became dark brown in colour. After cooling to room temperature, it was decomposed with crushed ice, and the resulting dark brown coloured solid was filtered, washed well with water and dried. It was then extracted repeatedly with ether (6x 50 ml). The orange coloured ether extract was decolourised with charcoal and dried over anhydrous sodium sulphate. The residue, on removal of the solvent, obtained had a gummy consistency. It showed two major spots on TLC
(Rf. 0.61 and 0.36; benzene-ethylacetate 4:1). It was chromatographed on a silica gel column (15 g.) and the compound having Rf 0.61 was obtained on elution with benzene in almost colourless needles, m.p. 72-74° (30 mg.). It was further purified by distillation, 230-40° (bath)/1.0 mm. and the distillate was crystallised from pet. ether to furnish the pure material in colourless needles, m.p. 75.5-76.5°.

Analysis:

Found: C, 81.64; H, 4.93; N, 13.42%

C_{14}H_{10}N_2 requires: C, 81.63; H, 4.89; N, 13.58%.

The other product (Rf 0.36) was obtained on elution with benzene-ethylacetate (85:15) in yellow needles, m.p. 65-66° (20 mg.).

Analysis:

Found: C, 81.65; H, 4.72; N, 13.50%

C_{14}H_{10}N_2 requires: C, 81.63; H, 4.89; N, 13.58%.

4-Phenylcinnoline (XIX):

4-Phenylcinnoline was synthesised as described by Bruce. 23

A. 0-Aminocacetophenone: This was prepared as described by Kiang et al. 55 starting from o-nitrobenzoic acid.
The amine was obtained as a light greenish-yellow liquid, b.p. 85-87°/1.0 mm. (Lit. b.p. 23 60°/0.01 mm.); yield, 75%.
A. 1-9-Aminophenyl-1-phenylethylene:

9-Aminoacetophenone (3.0 g.) dissolved in dry ether (30 ml) was added during 10-15 min. to a stirred solution of phenyl-lithium, [from bromobenzene (12 g.) and lithium wire (1.3 g.)], in dry ether (50 ml). Stirring was continued at the room temperature for 1 hr, and the mixture was then cooled in ice and decomposed with water (25 ml). The ether layer was separated, washed with water, dried and the solvent was removed. The residue was shaken with a mixture of concentrated sulphuric acid (15 ml) and water (50 ml) and the insoluble material was removed by extraction with pet. ether. The aqueous solution was then refluxed for 1 hr., cooled and diluted with water (~126 ml). An excess of concentrated ammonia was added and the resulting suspension was cooled to 10-15° under stirring until the oil solidified. The solid was collected, washed with water, and distilled under reduced pressure.

Crystallisation of the distillate, b.p. 160-66° (bath)/0.5 mm. (Lit.23 b.p.110-12°/0.02 mm) from pet. ether gave the olefin (3.4 g.; 80%) in colourless rods m.p. 77-78° (Lit.23 m.p. 77-77.6°).

Analysis:

<table>
<thead>
<tr>
<th>Found</th>
<th>N, 6.92%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requires:</td>
<td>C_{14}H_{13}N, N, 7.17%</td>
</tr>
</tbody>
</table>
4-Phenylcinnoline (XIX):

To an ice cooled solution of above olefin (1.3 g.) in hydrochloric acid (10%, 16 ml) was added a slight excess of aqueous sodium nitrite (7%, 26 ml) under stirring. Stirring and cooling was continued for 30 min., and the resulting suspension was then basified with concentrated ammonia keeping the temperature below 10°. The precipitate was collected, triturated with dilute ammonia and then with water and finally distilled under reduced pressure. The fraction b.p. 180-86° (bath)/0.5 mm (Lit. 23 b.p. 138-40°/0.02 mm), obtained as a yellow viscous liquid, which crystallised from pet. ether to give pure 4-phenylcinnoline in yellow needles, m.p. 64-66° (Lit. 23 m.p. 65.5-66°), Yield, 0.82 g. (60%).

Analysis:

Found: C, 81.80; H, 4.53; N, 13.68%

C_{14}H_{10}N_{2} requires: C, 81.53; H, 4.89; N, 13.58%.

2-Phenylquinoxaline\textsuperscript{25} (XX)

-&-Bromoacetophenone (6.4 g, 0.027 mol) and 2-phenylenediamine (2.9 g., 0.027 mol) were dissolved in ethanol (50 ml) and refluxed on a waterbath for 48 hr. The dark brown material obtained on addition of 10% sodium carbonate solution (75 ml) to the cooled concentrated reaction mixture (volume ~ 20 ml), was extracted with ether. The ether layer was washed with water and brine and dried over anhydrous sodium sulphate. The crude product (4 g, 72%) obtained on removal of the solvent was chromatographed on a silica gel column (160 g.). The fraction obtained from the
benzene eluate, was further purified by IDCC \textsuperscript{34} (benzene-ethylacetate, 4:1) and finally crystallised from ethanol in colourless needles, m.p. 77-78\textdegree (Lit. \textsuperscript{25} m.p. 78\textdegree C).

**Analysis**

Found: C, 81.68; H, 4.71; N, 13.73%

\( \text{C}_{14}\text{H}_{10}\text{N}_{2} \) requires: C, 81.53; H, 4.39; N, 13.68%.

Cyclodehydration of phenylglyoxal-2-p-tolylhydrazone:

**Syn-Phenylglyoxal-2-p-tolylhydrazone** (m.p. 34-35\textdegree, 0.6 g) was intimately mixed with a powdered mixture of anhydrous aluminium chloride and sodium chloride (1:1, 10 g.) and the reaction was carried out as described earlier.

Evaporation of the ether extract gave material which showed (TLC) the presence of two products (Rf. 0.36 and 0.67, benzene-ethylacetate, 4:1). The crude product was chromatographed on a silica gel column (15 g.). The residue obtained from the benzene eluate was further purified by PLC and finally crystallised from pet. ether to provide the pure material (Rf. 0.67) in colourless needles, m.p. 135-36\textdegree.

Yield, 28 mg.

**Analysis**

Found: C, 81.56; H, 5.62; N, 12.50%

\( \text{C}_{16}\text{H}_{12}\text{N}_{2} \) requires: C, 81.79; H, 5.49; N, 12.72%.

The second product (Rf 0.35) was obtained, by elution of the column with benzene-ethylacetate (85:15), followed by purification by PLC. Crystallisation of this material from pet. ether gave the pure product, m.p. 123-25\textdegree. Yield, 19 mg.
Analysis:

Found: C, 81.87; H, 5.43; N, 12.59%

C_{15}H_{12}N_2 requires: C, 81.79; H, 5.49; N, 12.72%.

6-Methyl-2-phenylquinazoline\textsuperscript{25} (XXXIII):

A solution of 3,4-diaminotoluene (0.61 g., 0.005 mol) and \(-\)-bromoacetophenone (0.996 g., 0.005 mol) in ethanol (25 ml) was refluxed on a waterbath for 4 hr. After concentration under reduced pressure the reaction mixture was cooled and poured over crushed ice. The resulting solid was filtered under suction and dried. It was purified by the IDCC\textsuperscript{34} technique and then crystallised from ethanol in pale yellow needles m.p. 135-36° (lit.\textsuperscript{25} m.p. 135°). Yield, 0.56 g (60%).

Analysis:

Found: C, 81.62; H, 5.71; N, 12.57%

C_{15}H_{12}N_2 requires: C, 81.76; H, 5.49; N, 12.72%.

6-Methyl-4-phenylcinnoline (XXXII):

This cinnoline was prepared according to the procedure described by Stoermer et al.\textsuperscript{29} and Simpson\textsuperscript{29} for the synthesis of 3-methyl-4-phenylcinnoline.
A. 2-Amino-5-methylbenzophenone (XXXVIII):

This ketone was prepared according to the method described by Sternbach et al.\textsuperscript{66} for 5-substituted-2-aminobenzophenones.

To the benzoyl chloride (0.34 mol, 47.25 g) heated at 120° was added p-toluidine (0.16 mol, 16.65 g.) in small portions under stirring. The mixture was then heated to 180-200° and anhydrous zinc chloride (0.192 mol, 25.8 g.) was added. The temperature was gradually increased to 200-205° and maintained at this temperature until the hydrogen chloride evolution had ceased (\sim 2 \text{ hr.}). After cooling to 120°, hydrochloric acid (3N, 150 ml) was added to the mixture cautiously under stirring followed by heating to reflux temperature. The hot acid layer was decanted off and this acid washing was repeated thrice to remove the benzoic acid formed.

The water insoluble portion was then dissolved in a mixture of equal volumes of concentrated hydrochloric acid and glacial acetic acid (105 ml each) and refluxed for \sim 15 \text{ hr.} to hydrolyze the crude condensation product. The mixture was concentrated in \textit{vacuo} (water pump) and the hot concentrated solution was poured over ice-water under stirring.

The organic material was extracted out with ether (4 \times 75 ml) and the ether layer was washed with hydrochloric acid (3N, 3 \times 100 ml) to remove unreacted
p-toluidine and sodium hydroxide (5N, 3x100 ml) to remove the remaining benzoic acid. The crude product obtained on removal of the solvent was distilled under reduced pressure and the fraction b.p. 180-85° (bath)/0.8 mm. was collected. This yellow viscous liquid crystallised from ethanol to give pure 2-amino-5-methylbenzophenone in yellow needles, m.p. 64-65° (lit. 30, 31 64-66°). Yield, 5 g.

B. 1-(2-Amino-5-methyl-phenyl-1-phenylethylene (XL):

2-Amino-5-methylbenzophenone (1.0 g.) was reacted with methyl iodide (6.0 g.) and magnesium (1.2 g.) in dry ether solution. Evaporation of ether furnished the crude carbinol (1.2 g.), which was subjected to dehydration by refluxing with sulphuric acid (30%, 25 ml.) for 2 hrs. The cooled reaction mixture was neutralised slowly by dropwise addition of concentrated ammonia under further cooling. The neutralised solution was then extracted with ether. and The ether extract was washed with water and brine/finally dried under anhydrous sodium sulphate. After removal of ether, the residue was distilled under reduced pressure and the required olefine was collected as a yellow oil (b.p. 170-75°(bath)/0.6 mm.). Yield, 0.83 g.

**Analysis:**

Found: C, 86.92; H, 7.43; N, 6.38%

C\textsubscript{16}H\textsubscript{16}N requires: C, 86.08; H, 7.22; N, 6.69%.
C. 6-Methyl-4-phenylcinnoline (XXXII):

A solution of the olefin (0.4 g.) in hydrochloric acid (10%, 20 ml) was treated under cooling and stirring with a solution of sodium nitrite (7%, 15 ml). The temperature of the reaction mixture was maintained at 0-5°. After stirring for a further period of 30 min., the mixture was neutralised with concentrated ammonia under cooling and then extracted with ether. The ether layer was separated and washed with water and brine and dried over anhydrous sodium sulphate. The crude product obtained after removal of the solvent was further purified by chromatography on neutral alumina (12 g.). The residue from the benzene eluate on crystallisation from pet. ether gave the required cinnoline in yellow needles, m.p. 124-25°. Yield, 0.3 g.

Analysis:

\[
\text{Found: C, 81.70; H, 5.62; N, 12.82}\%
\]

\[
\text{C}_{15}\text{H}_{12}\text{N}_{2} \text{requires: C, 81.70; H, 5.49; N, 12.72.}
\]

Cyclodehydration of phenylglyoxal-2-p-chlorophenylhydrazone:

Anti-phenylglyoxal-2-p-chlorophenylhydrazone, m.p. 170-72°, (0.6 g.) was thoroughly mixed with a powdered mixture of anhydrous aluminium chloride and sodium chloride (1:1, 10 g.) and the reaction was carried out as described earlier.

Evaporation of the dried ether extract gave a crude product, which showed the presence of two major products (Rf 0.46 and 0.73; solvent system: benzene-ethylacetate, 4:1)
on TLC. The crude material was chromatographed on a silica gel column (20 g.). The benzene eluate on evaporation of the solvent furnished a product (Rf 0.73), m.p. 142-43° which was further purified on PLC. Crystallisation from ethanol gave the pure product in colourless needles, m.p. 147-48°. Yield, 30 mg.

**Analysis:**

Found: C, 69.56; H, 3.27; N, 11.74%

C_{14}H_{9}ClN_{2} requires: C, 69.35; H, 3.74; N, 11.64%.

The second product (Rf 0.45) was obtained by elution with benzene-ethylacetate (4:1), as a yellow liquid (15 mg), which could not be induced to crystallise.

**Analysis:**

Found: N, 10.97%

C_{14}H_{9}ClN_{2} requires: N, 11.67%.

**6-Chloro and 7-chloro-2-phenylquinoxaline:**

4-Chloro-2-phenylenediamine^{33} (1.425 g.; 0.01 mol) and α-bromoacetophenone (1.99 g.; 0.01 mol) were dissolved in ethanol (50 ml) and refluxed on a waterbath for 4 hr. The reaction mixture was concentrated, cooled and then poured on crushed ice. The crude product was filtered, washed with water and dried. The crude material (1.1 g.) showed the presence of two components [Rf 0.35 and 0.45, solvent system: benzene-ethylacetate (95:5)] on TLC. They were separated by the IDCC technique.

Crystallisation of the residue obtained from the ether extract from ethanol gave the compound, Rf 0.35, in colourless needles, m.p. 130-31° (0.375 g.).
This compound was shown by its spectral properties to be 7-chloro-2-phenylquinoxaline (XLV).

**Analysis:**

Found: C, 69.37; H, 3.92; N, 11.31%

C\(_{14}H_9ClN_2\) requires: C, 69.85; H, 3.74; N, 11.64%

Crystallisation of the residue obtained from the ether eluate furnished the second product (Rf. 0.45) in colourless needles, m.p. 148-49\(^{0}\)C (0.85 g.), which was identified by spectral methods as 6-chloro-2-phenylquinoxaline (XLII).

**Analysis:**

Found: C, 69.74; H, 3.67; N, 11.51%

C\(_{14}H_9ClN_2\) requires: C, 69.85; H, 3.74; N, 11.64%

**6-Chloro-4-phenylcinnolone (XLII)**

The cinnolone was also prepared according to the procedure described by Stoermer et al.\(^{29}\) and Simpson.\(^{29}\)

A. **2-Amino-5-chlorobenzophenone (XLVI):**

This ketone was prepared according to the method of Sternbach et al.\(^{56}\) \(p\)-Chloroaniline (16 g.) was allowed to react with benzoyl chloride (47.25 g.) in the presence of anhydrous zinc chloride (25.8 g.) at ~ 200\(^{0}\). The reaction was carried out as described earlier for the preparation of 2-amino-5-methylbenzophenone. The crude product crystallised from a mixture of chloroform and pet. ether in yellow needles, m.p. 98-99\(^{0}\)C (Lit. m.p. 98\(^{0}\)\(^{25}\) \(\text{and} \) 100\(^{0}\)\(^{36}\)). The yield was 4.0 g.
Analysis:
Found: N, 5.91%.
C_{13}H_{10}ClNO requires: N, 6.05%.

C. 1-(5-Chloro-2-amino)phenyl-1-phenylethylene (XLVIII):

2-Amino-5-chlorobenzophenone (1.15 g.) was reacted with Grignard reagent prepared from methyl iodide (7.0 g.) and magnesium (1.2 g.) in dry ether as a solvent to get the corresponding carbinol (1.0 g.).

The crude carbinol obtained on removal of ether was dissolved in sulphuric acid (30%, 25 ml), refluxed for 2 hrs, cooled and neutralised with concentrated ammonia. The neutralised solution was extracted with ether and the ether layer was washed with water, brine and finally dried over anhydrous sodium sulphate. The residue obtained, after removal of the solvent, was purified by distillation under reduced pressure when the required olefin was obtained as a yellow liquid, b.p. 160-66° (bath)/0.5 mm. Yield, 0.9 g.

Analysis:
Found: N, 6.23%
C_{14}H_{12}ClN requires: N, 6.1%

D. 6-Chloro-4-phenyleinnoline (XLII):

A solution of the olefin (0.48 g.) in hydrochloric acid (10%, 50 ml) was diazotized at 0-5° with a solution of sodium nitrite (7%, 15 ml) under stirring. The diazotized solution was neutralised with concentrated ammonia after keeping it under stirring for a period of 30 min.
The neutralised solution was extracted with ether and the extract was dried over sodium sulphate. The crude product obtained on removal of the solvent crystallised from a mixture of ether and pet. ether to furnish pure 6-chloro-4-phenylcinnoline in pale yellow wooly needles, m.p. 140-42°. Yield, 0.205 g.

**Analysis:**

**Found:** C, 69.37; H, 3.89; N, 11.47%

**C₁₄H₉N₂Cl requires:** C, 69.86; H, 3.74; N, 11.64%

**4-Phenylcinnoline 1-oxide (I) and 2-oxide (II):**

A mixture of 4-phenylcinnoline (200 mg), glacial acetic acid (1.0 ml) and hydrogen peroxide (30%, 0.5 ml) was heated at 65-70° for 3 hrs. After this period a further quantity of hydrogen peroxide (30%, 0.5 ml) was added and the mixture was again heated at the same temperature for a further period of 3 hrs. Water (1.0 ml) was then added to the mixture and acetic acid was removed under reduced pressure. This procedure was repeated twice. After neutralisation with aqueous sodium carbonate, the solution was extracted with chloroform. The chloroform layer was washed with water and dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure. The residual reaction product showed two major spots on TLC. [Rf 0.38 and 0.27; solvent system: benzene-ethylacetate (4:1)].

These two compounds were separated on TLC. The chloroform extractive of the fraction (Rf 0.38) crystallised from ether-pet. ether mixture in pale yellow needles (I), m.p. 107-8°, yield 50 mg.
**Analysis:**

Found: C, 76.41; H, 4.70; N, 12.84%

C_{14}H_{10}N_{2}O requires: C, 76.61; H, 4.60; N, 12.61%

IR spectrum: (in CHCl_3), 1365, 1390 and 1420 cm⁻¹ (N = O).

The chloroform extractive of the fraction (Rf 0.27) crystallised from ether-pet. ether mixture in colourless plates (LI), m.p. 148-49°, yield 76 mg.

**Analysis:**

Found: C, 75.19; H, 4.98; N, 12.84%

C_{14}H_{10}N_{2}O requires: C, 76.61; H, 4.60; N, 12.61%

IR spectrum: (in CHCl_3), 1360, 1406 and 1396 (sh) cm⁻¹ (N = O).

6-Methyl-4-phenylcinnoline 1-oxide (LII) and 2-oxide (LIII):

A mixture of 6-methyl-4-phenylcinnoline (175 mg), glacial acetic acid (1.0 ml) and hydrogen peroxide (30%, 0.5 ml) was treated in the same way as described for 4-phenylcinnoline. The reaction product showed two major spots on TLC [Rf 0.57 and 0.41, solvent: benzene-ethylacetate (85:15), twice run]. The individual compounds were obtained in pure form by using the PLC technique.

The residue, from the fraction (Rf 0.57) extracted with chloroform, was crystallised from pet. ether to furnish pale yellow rods (LII), m.p. 124-25°, yield 53 mg.

**Analysis:**

Found: C, 76.11; H, 4.90; N, 11.43%

C_{16}H_{12}N_{2}O requires: C, 76.25; H, 5.12; N, 11.86%

IR spectrum: (in CHCl_3) 1330, 1380 and 1435 cm⁻¹ (N = O).
The chloroform extractive of the fraction (Rf 0.41) crystallised from benzene-pet. ether mixture in pale yellow needles (LIII), m.p. 202°-203°, yield 80 mg.

Analysis:

Found: C, 75.96; H, 5.23; N, 11.75%

C_{16}H_{12}N_{2}O requires: C, 76.25; H, 5.12; N, 11.86%.

IR spectrum: (in CHCl_3) 1330, 1370 (Sh), 1386 and 1435 cm^{-1} (N → O).

6-Chloro-4-phenylcinnoline 1-oxide (LIV) and 2-oxide (LV):

A mixture of 6-chloro-4-phenylcinnoline (225 mg), glacial acetic acid (1.0 ml) and hydrogen peroxide (30%, 0.5 ml) was treated in the same way as described earlier. The two products [Rf 0.37 and 0.24, solvent system: benzene-ethyl-acetate (9:1)] obtained were separated on PLC.

The residue, obtained from the chloroform extract of the fraction (Rf 0.37), was crystallised from benzene-pet. ether mixture to furnish yellow needles (LIV), m.p. 163-164°C, yield 86 mg.

Analysis:

Found: C, 65.64; H, 3.72; N, 11.03%

C_{14}H_{9}ClN_{2}O requires: C, 65.49; H, 3.80; N, 10.91%.

IR spectrum: (in CHCl_3) 1325, 1360, 1390 and 1420 cm^{-1} (N → O).
The chloroform extractive of fraction (Rf 0.24) crystallised from benzene-pet. ether mixture in pale yellow needles (LV), m.p. 195-96°, yield 125 mg.

Analysis:

Found: C, 65.32; H, 3.61; N, 10.78%

C_{16}H_{20}N_{2}O requires: C, 66.49; H, 3.50; N, 10.91%.

IR spectrum: (in CHCl₃) 1330, 1376, 1395 and 1430 cm⁻¹ (N = O).

2-Phenylquinoxaline 4-oxide (LVII) and 1,4-dioxide (LVII):

A mixture of 2-phenylquinoxaline (270 mg), glacial acetic acid (5 ml) and hydrogen peroxide (30%, 1.5 ml) was heated at ~55° for 16 hr, cooled and neutralised with aqueous sodium hydroxide solution (40%) and ice. The neutralised solution was extracted with chloroform and the chloroform extract was washed well with water and brine and was finally dried over anhydrous sodium sulphate. Removal of chloroform afforded a crude product, the TLC of which showed the presence of two products (Rf 0.07 and 0.31, solvent system: benzene-ethylacetate 4:1). These two products were separated and obtained in the pure state by using the PLC technique.

The chloroform extractive of the fraction (Rf 0.31) crystallised from ethanol in yellow needles (LVII), m.p. 138-39° (Lit. 47, 48 m.p. 137-38°). Yield 195 mg.

Analysis:

Found: C, 75.42; H, 4.91; N, 12.52%

C_{14}H_{10}N_{2}O requires: C, 75.61; H, 4.50; N, 12.61%

IR spectrum: 1230, 1245, 1355 cm⁻¹ (N = O).
The chloroform extractive of the fraction (RF 0.07) crystallised from ethanol in lemon yellow needles (LVII) m.p. 202° (lit. 47.48 m.p. 202-3°). Yield 20 mg.

**Analysis:**

Found: N, 11.60%

C₁₄H₁₀ClO₂N₂ requires: N, 11.8%.

6-Chloro-2-phenylquinoxaline 4-oxide (LVIII):

A mixture of 6-chloro-2-phenylquinoxaline (90 mg), glacial acetic acid (2 ml) and hydrogen peroxide (30%, 0.75 ml) were heated at ~55° for 17 hrs. The crude product obtained in the usual manner described earlier showed two spots on TLC [RF 0.04 and 0.36, solvent system: benzene-ethylacetate (4:1)]. Out of these two products, only one (RF 0.36) could be obtained in crystalline form after separation by TLC. It crystallised from ethanol in yellow needles (LVIII), m.p. 196-98°. Yield 30 mg.

**Analysis:**

Found: C, 66.34; H, 3.81; N, 10.83%

C₁₄H₉ClO₂N₂ requires: C, 66.49; H, 3.60; N, 10.91%.

IR spectrum; (in CHCl₃) 1225, 1245 and 1357 cm⁻¹ (N - O).

6-Methyl-2-phenylquinoxaline 4-oxide (LIX) and 1,4-dioxide (LX):

A mixture of 6-methyl-2-phenylquinoxaline (110 mg), glacial acetic acid (2.5 ml) and hydrogen peroxide (30%, 0.75 ml) were heated at ~55° for 16 hr, cooled and poured over crushed ice. The crude product obtained in the usual manner described earlier was found to be a mixture of two major products [RF 0.39 and 0.45, solvent system: benzene-ethylacetate (4:1)]. These two compounds were obtained in pure
form by using the PLC technique.

The residue from the fraction (Rf 0.45) extracted with chloroform, was crystallised from pet. ether in orange yellow needles (LIX), m.p. 125-27°, yield 20 mg.

**Analysis:**

Found: C, 76.15; H, 4.93; N, 11.67%

C₁₆H₁₂N₂O requires: C, 76.25; H, 5.12; N, 11.86%

IR spectrum: (in CHCl₃): 1225, 1260 and 1360 cm⁻¹ (N = O).

The chloroform extractive of the fraction (Rf 0.09) crystallised from ether-pet. ether mixture in yellow tiny needles (LX), m.p. 168-70°, yield 10 mg.

Mass spectrum showed a M⁺ 252 (di-N-oxide).

**Analysis:**

Found: N, 10.93%

C₁₆H₁₂N₂O₂ requires: N₂, 11.11%.
REFERENCES

12. Ref. 9, p. 132.
15. Ref. 13, p. 63.
17. R. Stierlin, Ber., 21, 2124 (1888).
25. O. Hinsberg, Ann., 237, 370 (1887); 222, 245 (1896).
33. F. Ullmann and F. Mauthner, Ber., 36, 4027 (1903).


42. I. Suzuki, T. Nakashima and T. Itai, Chem. Pharm. Bull (Tokyo), 11, 268 (1963);
I. Suzuki and T. Nakashima, Chem. Pharm. Bull (Tokyo), 12, 619 (1964);


46. H. McIlwain, J. Chem. Soc., 322 (1943);


51. E. Hayashi, T. Higashino, C. Iijima, Y. Kono and T. Doihara, Yakugaku Zasshi, 82, 584 (1962); [C.A. 58:3425c].


59. H. Brockmann and M. Schodder, Ber., 74, 73 (1941).
CHAPTER III

MASS SPECTRAL IDENTIFICATION OF
ARYLCINNOLINES AND ARYLQUINOXALINES.
Mass spectrometry has become especially valuable for structural investigations of heterocyclic compounds, mainly because, they give very characteristic fragmentation patterns. The mass spectra of heterocyclic compounds containing two nitrogen atoms such as imidazoles$^1$, pyrimidines$^{2-5}$, pyrazines$^6,7$, benzimidazoles$^8$, purines$^2,9$ and phenazines$^{10}$ have been reported. Imidazole$^1$ (I) on electron impact, undergoes fragmentation as outlined below. The major fragment (m/e 41) arises from the loss of HCN from the molecular ion.

\[
\begin{align*}
\text{I} & \quad \xrightarrow{-e} \quad \text{m/e 67} \\
\text{I} & \quad \xrightarrow{-e} \quad \text{m/e 41} \\
\text{[N=N]}^+ & \quad \xrightarrow{-H^+} \quad \text{m/e 40}
\end{align*}
\]
In the case of benzimidazoles also, the major fragments are due to the loss of HCN. The spectra of \( N\text{-d}_1 \) imidazole (II) and \( N\text{-d}_1 \) benzimidazole (III) show loss of both HCN and DCN from the molecular ion, which indicates that the initial loss of HCN is non-specific.

![Molecular structures](image)

The main features in the mass spectrum\(^2\) of pyrimidine (IV) itself are the loss of HCN, resulting in the fragment m/e 53 and the subsequent formation of ionized acetylene (m/e 26) by a further loss of HCN.

![Molecular Structure](image)

In the case of benzpyrimidines or quinazolines, the fragmentation modes follow closely those outlined for pyrimidine derivatives.
The spectra of several polyalkylated pyrazines have been discussed by Biemann\textsuperscript{6,7}. In such molecules (V) all side chains are necessarily attached to a carbon atom adjacent to nitrogen. Hence, \(\beta\)-fission is unfavourable.

\[
\begin{align*}
\text{(V)} \\
\begin{array}{c}
\text{R}_1 \\
\text{CH}_2 \\
\text{R}_2 \\
\text{R}_3 \\
\text{R}_4
\end{array}
\end{align*}
\]

For the same reason \(\beta\)-fission is not favoured in the case of tetramethylpyrazine\textsuperscript{11} (VI), and since there are also no \(C_3\)-alkyl chains to permit the rearrangement process, a novel, but well substantiated fragmentation of the aromatic ring is apparent. The main fission ruptures the ring system with successive losses of two molecules of acetonitrile leading to dimethylacetylene (m/e 54).

\[
\begin{align*}
\text{(VI)} & \quad \text{CH}_3\text{C}≡\text{N} & \quad \text{m/e 95} \\
\text{CH}_3\text{C}≡\text{C} & \quad \text{m/e 39} \\
\text{m/e 54}
\end{align*}
\]
The mass spectra of phenazine and a number of substituted phenazines have been examined\(^{10}\). The substituted phenazines generally fragment by initial loss of the substituents, and different effects were observed depending on the relative positions of the substituents in the same or different rings. Phenazine (VII) itself loses the central nitrogen atoms first as cyanide radicals or as hydrogen cyanide, but substituted phenazines only suffered similar losses after elimination of the substituents (Chart 1).

Recently, the mass spectra of heterocyclic compounds containing adjacent nitrogen atoms, such as, pyridazines\(^{12}\), phthalazines\(^{12}\), and benzo(g)cinnolines\(^{13}\) have been published.

The facile loss of nitrogen from the molecular ion is a generally feature of fragmentations of simple pyridazines\(^{12}\) (VIII). The energetically favoured loss of nitrogen from the molecular ions of simple pyridazines shows the presence of \(-\text{N}=\text{N}-\) group [cf. the loss of \(\text{HCN}\) from the molecular ions of imidazoles\(^{1}\)].

\[
\text{\begin{align*}
\text{N} & \to -\text{N}_2 \\
\text{N} & \ochrome{\to} -\text{N}_2 \\
\text{m/e} & \ochrome{52} \\
\text{m/e} & \ochrome{50}
\end{align*}}
\]
In the case of phthalazine\textsuperscript{12} (IX), the loss of $N_2$ from the molecular ion is a minor process, the main fragmentation scheme is $M$-$HCN$-$HCN$-$HC=CH$, to form the fragment m/e 50. This is indicative of bond fixation

\[
\begin{align*}
&\text{[Phthalazine]}^{+} \\
&\xrightarrow{-HCN-HCN-HC\equiv CH} [HC\equiv C-C\equiv CH]^{+} \\
&\text{m/e 50}
\end{align*}
\]

(IX) m/e 130

\[
\begin{align*}
&\xrightarrow{-N_2} [\text{Cyclic Compound}]^{+} \\
&\text{m/e 102 (50%)}
\end{align*}
\]

in the C=N form in the case of phthalazine.

Benzo(g)cinnoline\textsuperscript{13} (X) fragments by loss of nitrogen from the molecular ion (m/e 180) to produce the stable biphenylene radical ion [m/e 152, base peak].

\[
\begin{align*}
&\text{[Benzo(g)cinnoline]}^{+} \\
&\xrightarrow{-N_2} [\text{Biphenylene}]^{+} \\
&m/e 152
\end{align*}
\]

m/e 180 (X)
Loss of nitrogen from either molecular ion or a fragment ion is a feature of spectra of these compounds and is, therefore, indicative of the presence of the \(-N=\equiv-\) group. In the spectra of 1,2 or 3 substituted benzo(g)cinnolines, the \(N-N_2\) process precedes fragmentation through \(Me, Cl, NH_2, NMe_2\) or \(COOH\) substituents, but when the substituent is \(MeO, EtO, NEt_2, COOMe\) or \(COOEt\), fragmentation through the substituent occurs before the loss of nitrogen.

**Present Work**

In the course of our work on the synthesis of phenyl substituted cinnolines\(^14,15\), some isomeric products were obtained which have now been identified as quinoxaline derivatives (See Chapter II, Section 8). The N.M.R. spectrum provides a good method for identifying the cinnolines and quinoxalines. In several cases, however, only very small quantities of cinnolines (less than 20 mgs) were available from these syntheses and it was considered of interest to study the mass spectral characteristics of the isomeric cinnolines and quinoxalines as an alternative means of their identification. These studies revealed that the fragmentation patterns of cinnolines and quinoxalines were quite distinct and mass spectrometry, therefore, constituted an efficient alternative method to distinguish between these two classes of compounds. In addition, the position of the various substituents could be clearly located.
by this method. To our knowledge, the mass spectra of these compounds are not reported in the literature so far.

This chapter deals with the mass spectral fragmentation modes of some arylcinnolines (XI<sub>a</sub>-XI<sub>f</sub>, Fig. 1-6) and arylquinoxalines (XII<sub>a</sub>-XII<sub>e</sub>, Fig. 7-11) and their characterization.

![Chemical structures](image)

(XI)  

- a; R<sub>1</sub> = C<sub>6</sub>H<sub>5</sub>, R<sub>2</sub> = H, R<sub>3</sub> = H  
- b; R<sub>1</sub> = H, R<sub>2</sub> = C<sub>6</sub>H<sub>5</sub>, R<sub>3</sub> = H  
- c; R<sub>1</sub> = C<sub>6</sub>H<sub>5</sub>, R<sub>2</sub> = H, R<sub>3</sub> = 6-CH<sub>3</sub>  
- d; R<sub>1</sub> = CH<sub>3</sub>, R<sub>2</sub> = C<sub>6</sub>H<sub>5</sub>, R<sub>3</sub> = H  
- e; R<sub>1</sub> = H, R<sub>2</sub> = C<sub>6</sub>H<sub>5</sub>, R<sub>3</sub> = 6-CH<sub>3</sub>  
- f; R<sub>1</sub> = H, R<sub>2</sub> = C<sub>6</sub>H<sub>5</sub>, R<sub>3</sub> = 6-Cl

(XII)

- a; R<sub>1</sub> = C<sub>6</sub>H<sub>5</sub>, R<sub>2</sub> = H, R<sub>3</sub> = H  
- b; R<sub>1</sub> = CH<sub>3</sub>, R<sub>2</sub> = C<sub>6</sub>H<sub>5</sub>, R<sub>3</sub> = H  
- c; R<sub>1</sub> = C<sub>6</sub>H<sub>5</sub>, R<sub>2</sub> = H, R<sub>3</sub> = 6-CH<sub>3</sub>  
- d; R<sub>1</sub> = C<sub>6</sub>H<sub>5</sub>OH, R<sub>2</sub> = H, R<sub>3</sub> = H  
- e; R<sub>1</sub> = H, R<sub>2</sub> = C<sub>6</sub>H<sub>5</sub>, R<sub>3</sub> = 6-Cl  
- f; R<sub>1</sub> = H, R<sub>2</sub> = C<sub>6</sub>H<sub>5</sub>, R<sub>3</sub> = 6-Cl.

* We are thankful to Dr. H. S. Lowrie for a generous gift of these samples.
RESULTS AND DISCUSSION

A. Cinnolines: Except in the case of 3-methyl-4-phenylcinnoline (IXd), the molecular ion is the base peak in the spectra of cinnolines. In (IXd) (M-28) fragment corresponded to the base peak. As in the case of other nitrogen heterocyclic compounds, doubly charged parent ions are fairly abundant in all these compounds. There is no direct loss of the aryl moiety from the molecular ion. (See Fig. 1-6).

The most characteristic fragmentation mode in cinnolines is the extrusion of molecular nitrogen from the parent ion. The intensity of this peak varies from 10.5% in (IXd) to 100% in $\text{IX}_e$. A substituted benzocyclobutadienyl cation is probably formed as a result of this fragmentation mode (Scheme 1). The asterisk indicate the presence of an appropriate metastable ion in the mass spectrum.

![Scheme 1](image)
A similar loss of molecular nitrogen has been reported in the fragmentation of pyridazines\textsuperscript{12}, 1,2,4-triazines\textsuperscript{16}, pyrazoles\textsuperscript{17} and benzo(g)cinnolines\textsuperscript{13}. Azo compounds are also known to undergo skeletal rearrangement involving the expulsion of a molecule of nitrogen\textsuperscript{13,19,20}.

Though the (M-1) and (M-2) fragments are not observed to any appreciable extent, the (M-29) and (M-30) ions are seen in the spectra of all of these compounds. It is probable that they arise due to the successive loss of two hydrogen atoms from the (M-28) ion. A skeletal rearrangement leading to biphenylene derivatives was observed in all of these compounds. This may be accounted for by assuming a loss of acetylene or its derivative (as in XI\textsubscript{d}) from the (M-28) fragment ion. The biphenylene ion (m/e 152) is usually seen in the spectra of many aromatic compounds containing two suitably substituted benzene rings\textsuperscript{21}. The composition of the (m/e 152) ion (C\textsubscript{12}H\textsubscript{8})\textsuperscript{+} in XI\textsubscript{a}, XI\textsubscript{b} and (XI\textsubscript{d}) was established by high resolution mass spectrometry.\textsuperscript{*} The corresponding substituted biphenylene ions were observed in the spectra of (XI\textsubscript{e}), (XI\textsubscript{f}) and (XI\textsubscript{g}) [m/e 166 and m/e 186 (188)]. This rearrangement is shown in scheme 2.

\textsuperscript{*} We are grateful to Dr. D. H. Williams for high resolution data.
Apart from the peaks for substituted biphenylenes, compounds (XI\textsubscript{c}), (XI\textsubscript{e}) and (XI\textsubscript{f}) also showed peaks for the (C\textsubscript{12}H\textsubscript{8})\textsuperscript{+} ion (at m/e 152) indicating thereby that the compounds (XI\textsubscript{c}) and (XI\textsubscript{e}) lose CH\textsubscript{3}-C=C and compound (XI\textsubscript{f}) loses Cl-C=C fragments from (M-28) ion.

The formation of arylacetylenes directly from the molecular ion on electron impact can be readily explained by the simple cleavage shown in scheme 3. The resulting fragment further loses molecular nitrogen to yield ions for benzene and substituted benzenes.

\begin{align*}
\text{Scheme 2:} & \\
[ \begin{array}{c}
R_3 \\
\text{N} \\
\text{N} \\
\text{R}_1 \\
\text{R}_2 \\
\text{R}_3
\end{array} ]^{\text{+\textsuperscript{*}}} & \rightarrow & [ \begin{array}{c}
\text{R}_3 \\
\text{R}_2 \\
\text{R}_1
\end{array} ]^{\text{+\textsuperscript{*}}}
\end{align*}

\begin{align*}
\text{Scheme 3:} & \\
[ \begin{array}{c}
R_3 \\
\text{N} \\
\text{N} \\
\text{R}_1 \\
\text{R}_2 \\
\text{R}_3
\end{array} ]^{\text{+\textsuperscript{*}}} & \rightarrow & [ \begin{array}{c}
\text{R}_3 \\
\text{N} \\
\text{N}
\end{array} ]^{\text{+\textsuperscript{*}}} & \rightarrow & [ \begin{array}{c}
\text{R}_3
\end{array} ]
\end{align*}
Table 1 gives the characteristic fragmentation pattern and Table 2 gives the metastable peaks in the mass spectra of arylcinnolines.

The comparison of the spectra of (XIₐ), (XIₖ), (XIₖ) and (XIₖ) shows that it is possible to distinguish 4-phenylcinnolines from 3-phenylcinnolines. The relative intensities of most of the fragments in 4-phenylcinnolines (XIₖ, XIₖ, XIₖ and XIₖ) are more than that in 3-phenylcinnolines (XIₐ and XIₖ). It appears that the phenyl group at C₃ position stabilises the molecular ion to a greater extent than that at C₄ position. Another factor contributing to the stability of 3-phenylcinnolines is the less crowding of the phenyl rings in them.

A significant difference is in the fragmentation mode leading to the loss of a molecule of nitrogen (M-28). This reaction is more favoured in 3-phenylcinnolines than in 4-phenylcinnolines. This is evidenced by the fraction of the total ion current carried by these ions. In (XIₐ) it is \(\Sigma_{40} = 23.77\%\) as compared to \(\Sigma_{40} = 10.24\%\) in (XIₖ) and (XIₖ), it is \(\Sigma_{40} = 18.49\%\) as against \(\Sigma_{40} = 2.24\%\) in (XIₖ).

Comparison between 3-methyl-4-phenylcinnoline (XIₖ) with 6-methyl-4-phenylcinnoline (XIₖ) again showed a significant difference in the (M-28) fragment. In (XIₖ), (M-28) is actually the base peak (100%), whereas, in (XIₖ)
<table>
<thead>
<tr>
<th>No.</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
<th>e</th>
<th>f</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>M+</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>66</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>2.</td>
<td>(M-H)^+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5.3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3.</td>
<td>(M-N_2)</td>
<td>97</td>
<td>80</td>
<td>79.5</td>
<td>100</td>
<td>10.5</td>
<td>26.5</td>
</tr>
<tr>
<td>4.</td>
<td>(M-N_2-H)</td>
<td>12.9</td>
<td>30.0</td>
<td>41.0</td>
<td>17.6</td>
<td>33.6</td>
<td>0.5</td>
</tr>
<tr>
<td>5.</td>
<td>(M-N_2-H-H)</td>
<td>24.0</td>
<td>51.8</td>
<td>9.7</td>
<td>25.5</td>
<td>10.6</td>
<td>0.7</td>
</tr>
<tr>
<td>6.</td>
<td>(M-N_2-C_2H_2)</td>
<td>17.7</td>
<td>49.0</td>
<td>2.3</td>
<td>3.2</td>
<td>2.0</td>
<td>2.2</td>
</tr>
<tr>
<td>7.</td>
<td>m/e</td>
<td>6.3</td>
<td>16.5</td>
<td>3.5</td>
<td>1.5</td>
<td>6.3</td>
<td>3.2</td>
</tr>
</tbody>
</table>

Table 1
CHARACTERISTIC FRAGMENTATION PATTERN OF ARYLCINNOLINES

R_1C=CR_2
## Table 2

**Metastable Peaks in the Mass Spectra of Arylcinolines**

\( (XI_{a-f}) \)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Transition</th>
<th>Calculated</th>
<th>Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>XIₐ</td>
<td>-N₂ → 178</td>
<td>163.8</td>
<td>164.0</td>
</tr>
<tr>
<td></td>
<td>-H → 177</td>
<td>176.0</td>
<td>176.0</td>
</tr>
<tr>
<td></td>
<td>-H → 176</td>
<td>175.0</td>
<td>175.0</td>
</tr>
<tr>
<td></td>
<td>-C₂H₂ → 152</td>
<td>129.8</td>
<td>130.0</td>
</tr>
<tr>
<td>XIₐ</td>
<td>-N₂ → 178</td>
<td>153.8</td>
<td>154.0</td>
</tr>
<tr>
<td></td>
<td>-H → 177</td>
<td>176.0</td>
<td>176.0</td>
</tr>
<tr>
<td></td>
<td>-H → 176</td>
<td>175.0</td>
<td>175.0</td>
</tr>
<tr>
<td></td>
<td>-C₂H₂ → 152</td>
<td>129.8</td>
<td>130.0</td>
</tr>
<tr>
<td>XIₐ</td>
<td>-N₂ → 192</td>
<td>167.6</td>
<td>167.5</td>
</tr>
<tr>
<td></td>
<td>-C₂H₂ → 166</td>
<td>143.5</td>
<td>143.0</td>
</tr>
<tr>
<td>XIₐ</td>
<td>-CH₃ → 206</td>
<td>191.1</td>
<td>191.5</td>
</tr>
<tr>
<td></td>
<td>-N₂ → 192</td>
<td>167.6</td>
<td>168.0</td>
</tr>
<tr>
<td></td>
<td>-C₂H₂ → 166</td>
<td>143.5</td>
<td>143.5</td>
</tr>
<tr>
<td></td>
<td>-H → 219</td>
<td>218.0</td>
<td>218.5</td>
</tr>
<tr>
<td>XIₐ</td>
<td>-N₂ → 192</td>
<td>167.6</td>
<td>167.5</td>
</tr>
<tr>
<td></td>
<td>-C₂H₂ → 166</td>
<td>143.5</td>
<td>143.0</td>
</tr>
<tr>
<td>XIₐ</td>
<td>-N₂ → 212</td>
<td>187.3</td>
<td>187.5</td>
</tr>
<tr>
<td></td>
<td>-Cl → 205</td>
<td>175.5</td>
<td>176.5</td>
</tr>
<tr>
<td></td>
<td>-C₂H₂ → 186</td>
<td>163.2</td>
<td>163.0</td>
</tr>
</tbody>
</table>
it is only 10.6%. In terms of the total ion current, the difference is nearly tenfold in favour of (XI_d).
Secondly, phenylmethylacetylene is more predominantly lost in (XI_d) than in (XI_e).

The intensities of m/e 165 and m/e 152 are quite different in this set of compounds. The fragment at m/e 165, which arises by the loss of acetylene from (M-28-1) ion,
\[ \Sigma \text{m/e 165} \]
is more predominant in (XI_d) (\[ \Sigma \text{m/e 165} = 5.03\% \]) than in (XI_e) (\[ \Sigma \text{m/e 165} = 2.7\% \]) and also than in (XI_c) (\[ \Sigma \text{m/e 165} = 3.37\% \]),
but the loss of methylacetylene species (\( \text{CH}_3\text{-C}≡\text{CH} \)) from (M-28) fragment (leading to m/e 152) is more predominant in (XI_e and XI_c) (\[ \Sigma \text{m/e 152} = 1.1\% \]) than in (XI_d) (\[ \Sigma \text{m/e 152} = 0.77\% \]).

This probably indicates which of the rings contain the methyl group. In (XI_d), there is much less scope for the elimination of methylacetylene species than either in (XI_c) or (XI_e) and similarly, in (XI_d) there is more scope for the elimination of acetylene molecule than in (XI_e) and (XI_e).
Fig. 5

Fig. 6
B. Quinoxalines

As in arylcinnolines, the molecular ion is the base peak in arylquinoxalines except in (XII\textsubscript{b}), where (M-1) fragment corresponds to the base peak (Figs. 7-11). The molecular ion is 61.5\% of the base peak. A strong (M-1) ion is characteristic of the mass spectra of arylquinoxalines. The intensity of this peak varied from 3.2\% in [XII\textsubscript{e} - Cl\textsuperscript{35}] to 100\% in (XII\textsubscript{b}).

Quinoxalines lose a molecule of hydrogen cyanide or substituted hydrogen cyanide (as in the case of (XII\textsubscript{b}), where methyl cyanide is lost), very readily. The (M-1) fragment is also shown to lose this moiety significantly. These fragments further lose acetylene readily. But in other compounds this loss is not seen. On the contrary, the (M-1-27) fragment seems to lose acetylene. The M\textsuperscript{+} and (M-1)\textsuperscript{+} fragments also lose aryl cyanide moieties.

The (M-27) fragment [(M-41) in the case of XII\textsubscript{b}] loses another molecule of hydrogen cyanide and the resulting fragment undergoes skeletal rearrangement leading to biphenylene or its derivatives. This is depicted in scheme 4.
The spectra of these compounds also show the aryl cyanide species and M⁺⁺ peaks. Table 3 gives the characteristic fragmentation pattern in arylquinoxalines. The metastable peaks in the mass spectra of these compounds are recorded in Table 4.

A comparison of the spectra (Figs. 8 and 9) of 2-phenyl-3-methylquinoxaline (XII_b) with 2-phenyl-6-methylquinoxaline (XII_c) indicates that the position of the substituent can be pinpointed. The most striking feature of the spectrum of (XII_c) is the loss of HCN as against the loss of CH₂CN in (XII_b). This shows the ring position of the methyl substitution. Secondly, the loss of hydrogen atom from the molecular ion appears to be more facile in (XII_b) (Σ₄₀ = 33.36%) than in (XII_c) (Σ₄₀ = 2.39%). The probable site for losing hydrogen atom is the methyl substituent and the radical ion resulting from (XII_c), therefore, appears to be stabler than that from (XII_b). The second loss of HCN leading to the skeletal rearrangement after (XII_b)
### Table 3

REMARKS ON ARLQUINOXALINES

<table>
<thead>
<tr>
<th>No.</th>
<th>Compound</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
<th>e</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M⁺</td>
<td>100</td>
<td>61.5</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>(M-H)</td>
<td>4.5</td>
<td>100</td>
<td>5.4</td>
<td>59</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>(M-HCN)</td>
<td>44.5</td>
<td>22.1</td>
<td>17.1</td>
<td>7.4</td>
<td>4.6</td>
</tr>
<tr>
<td></td>
<td>(M-CH₂CN)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>(M-H-HCN)</td>
<td>7.3</td>
<td>12.3</td>
<td>4.8</td>
<td>29.5</td>
<td>17.3</td>
</tr>
<tr>
<td></td>
<td>(M-CH₃CN)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>(M-HCN-HCN)</td>
<td>4.0</td>
<td>6.6</td>
<td>0.9</td>
<td>7.7</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td>(M-CH₃CN-HCN)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>(M-C₆H₅CN)</td>
<td>12.7</td>
<td>9.3</td>
<td>1.4</td>
<td>5.1</td>
<td>2.0</td>
</tr>
<tr>
<td>7</td>
<td>C₆H₅CN⁺</td>
<td>12.7</td>
<td>1.7</td>
<td>2.8</td>
<td>4.8</td>
<td>1.9</td>
</tr>
<tr>
<td>8</td>
<td>M⁺⁺</td>
<td>12.7</td>
<td>9.3</td>
<td>5</td>
<td>7.2</td>
<td>6.6</td>
</tr>
<tr>
<td>Compound</td>
<td>Transition</td>
<td>Calculated</td>
<td>Observed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>------------</td>
<td>------------</td>
<td>----------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XII\textsubscript{a}</td>
<td>-H - 205</td>
<td>204.0</td>
<td>204.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-H - 179</td>
<td>165.5</td>
<td>165.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-H - 152</td>
<td>129.0</td>
<td>128.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XII\textsubscript{b}</td>
<td>-H - 219</td>
<td>218.0</td>
<td>218.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-CH\textsubscript{3}CN - 179</td>
<td>145.6</td>
<td>145.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-HCN - 152</td>
<td>129.0</td>
<td>128.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-CH\textsubscript{3} - 205</td>
<td>191.1</td>
<td>191.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XII\textsubscript{c}</td>
<td>-H - 219</td>
<td>218.0</td>
<td>218.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-CH\textsubscript{3} - 205</td>
<td>191.1</td>
<td>191.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-HCN - 193</td>
<td>169.3</td>
<td>169.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-HCN - 166</td>
<td>142.8</td>
<td>142.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XII\textsubscript{d}</td>
<td>+H - 221</td>
<td>220.0</td>
<td>220.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-CO - 194</td>
<td>169.5</td>
<td>169.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-HCN - 167</td>
<td>143.7</td>
<td>143.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-HCN - 140</td>
<td>117.3</td>
<td>117.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XII\textsubscript{e}</td>
<td>-H - 239</td>
<td>238.0</td>
<td>238.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-Cl - 205</td>
<td>175.2</td>
<td>175.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-HCN - 213</td>
<td>189.1</td>
<td>189.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-HCN - 186</td>
<td>162.4</td>
<td>162.5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
has lost CH$_3$CN and (XII$_c$) has lost HCN is unfavoured in (XII$_b$) as compared to that in (XII$_c$). On electron impact, compound (XII$_b$) loses the aryl group more readily than (XII$_c$). It is possible that the steric strain in (XII$_b$) is relieved by the loss of an aryl group but this situation is completely absent in (XII$_c$). The loss of aryl cyanide is also more facilitated in (XII$_b$) than in (XII$_c$).

In conclusion, the ring position of the substituents can be located from the mass spectra of aryl-quinoxalines.

C. Comparison of cinnolines and quinoxalines

Closer examination of the fragmentation behaviour of cinnolines and quinoxalines brings out the following differences:

1. The loss of hydrogen atom from the molecular ion is observed only in the quinoxalines.

2. The cinnolines lose 28 mass units (N$_2$) and quinoxalines R$_1$ CN from the parent ions.

3. The resulting fragments undergo skeletal rearrangement leading to substituted biphenylene derivatives. Obviously, the fragment from the quinoxaline loses HCN and the fragment from the cinnoline loses C$_2$H$_2$.

4. Peaks corresponding to phenyl acetylene and substituted aryl cyanides were observed in the spectra of the cinnolines and quinoxalines respectively.
EXPERIMENTAL

The compounds (XI_a) and (XI_c) were obtained from Dr. H. S. Lowrie\textsuperscript{22}. The compounds (XI_d)\textsuperscript{23} and (XII_b)\textsuperscript{24} were prepared according to the methods reported in the literature. The compounds (XI_p), (XI_e), (XI_f), (XII_a), (XII_c), (XII_d), and (XII_e) were prepared by the cyclodehydration of appropriate phenylglyoxal phenylhydrazone with aluminium chloride-sodium chloride melt\textsuperscript{15} (See Chapter II).

The mass spectra of these compounds were recorded in a CEC-21-110B double focussing mass spectrometer operating at 70 eV using direct inlet system at temperatures well below the melting points.
REFERENCES


13. J. H. Bowie, O. E. Lewis and J. A. Reiss, 

14. J. L. Bose and V. V. Bhat., 
Chem. and Ind., 1655 (1965).

15. B. D. Tilak, J. L. Bose, S. N. Bannore, V. N. Gogte,  

4, 224 (1967).


19. N. S. Vul'fson, V. A. Puchkov and V. S. Nekrasov,  
Izvestiya Akademii Nauk, U.S.S.R. (Seriya Khimicheskaya),  
2, 1881 (1967).


24. V. Auwers, Ber., 50, 1182 (1917).