CHAPTER - 1

Introduction
INTRODUCTION

The major stream of investigation that encompasses biologically active compounds has led to the discovery and synthesis of excellent therapeutic agents. The spectacular achievement of man lies in the fact that, many of the deadly diseases which threatened the very existence of human race, right from the early civilization, have been nearly brought under control and some of them have been completely eradicated. He is now engaged in his pursuit to resolve the biological intricacies woven around the mysterious and unconquered diseases like cancer and AIDS which have eluded human wisdom. The scientific quest for a suitable drug to combat such diseases still remain unanswered. Though in certain areas of investigation he has not achieved remarkable success, his spirit has not dampened his restless and persistent efforts to find a solution to such problems and thereby create a better and healthy world to live in, continue unabated.

It is a matter of pride that, with rapid advancement in science and technology, medicinal chemistry has made profound progress in the last few decades. Literature survey reveals that, heterocyclic compounds have acquired importance not only in the medicinal world but also in the field of agrochemicals. So far as chemotherapy is concerned, they have unequivocally qualified as life saving drugs.

In view of the general observation that, the pharmacological activities are invariably associated with a large variety of heterocyclic compounds, during the present investigation, we focused our attention on certain class of heterocyclic compounds which have wide spectrum of biological activities.
Owing to the importance and established physiological activities of these compounds, we were encouraged to synthesise and investigate compounds of comparable structures. Thus, the basis of our research programme was centered around the fact that, certain structural units present in known biologically active compounds are also found in other naturally occurring compounds of similar properties. Further, by affecting structural variation, the relationship in respect of chemical structure and biological activity could be better explored. It is well established that slight alterations in the structure of certain compounds are able to bring about drastic changes in biological activity. Several physico-chemical parameters are said to be associated with this phenomenon. Both steric and electronic factors are claimed to be prime determinants in the variation of biological activity.

The close association of pyrimidine nucleus with biologically important compounds like nucleic acids, vitamins, coenzymes and a wide variety of drugs has drawn the attention of a number of workers. Condensed pyrimidine systems have been extensively investigated. Although much work has been done on condensed pyrimidine with furan, thiophene, oxazole, pyrazole, isothiazole, pyridine, pyrazine, indole, etc., there is only one report concerning cinnolinopyrimidine in which cinnoline heterocycle is fused to a pyrimidine ring. During the present investigation, we planned the synthetic sequence of reactions leading to the preparation of compounds wherein the cinnoline nucleus is fused with other heterocycles like pyrazoles, oxazines and mercaptopyrimidines with a view to evaluate them for biological activity.
THEORETICAL AND STRUCTURAL STUDIES OF CINNOLINES

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 (1), pyrimidine (2) and pyrazine (3) respectively. These three dinitrogen heterocyclic ring systems and their numberings are as follows:

1

2

3

When benzene ring is fused to the 5,6-positions of the above diazines, they are known as cinnoline(4), quinazoline(5) and quinoxaline(6) respectively.

4

5

6

BIOLOGICAL IMPORTANCE OF CINNOLINES

Though no cinnoline occurs in nature, it is observed that considerable chemotherapeutic activity is associated with cinnoline derivatives. Busch and Rast reported that, the parent compound cinnoline showed antimicrobial activity against E.coli.
Kenford et al.\textsuperscript{15} have prepared various quaternary salts of aminocinnolines in order to simplify the phenanthridinium quaternary salts and at the same time retaining their trypanocidal activity and screened them against \textit{Trypanosma} and \textit{Spirochete} infections in mice. It was found that bis-(4-amino-6-cinnolyl) guanidinedimethiodide(7) had a chemotherapeutic index of the same order of antrycide methylsulphate and compound 7 has been designated as “L528”.

\begin{center}
\begin{tikzpicture}
\node[draw,rectangle,inner sep=0pt] (1) at (0,0) {\textbf{7}};
\end{tikzpicture}
\end{center}

A number of pyridylcinnoline quaternary salts have been reported as trypanocidal agents.\textsuperscript{16-18} Castle and Onda\textsuperscript{19} have prepared a series of substituted esters, ethers and amides for pharmacological screening and tested them for stimulatory activity in rats. Amongst the ethers tested, 4-dimethylaminoethoxy cinnoline(8) showed slight CNS stimulatory activity in rats.

\begin{center}
\begin{tikzpicture}
\node[draw,rectangle,inner sep=0pt] (1) at (0,0) {\textbf{8}};
\end{tikzpicture}
\end{center}
Taylor et al. 20 have reported the preparation of poly-methylenedicinnolinium salts and these compounds have been described as antimicrobial and antiparasitic agents.

A variety of 4-dialkylaminoalkylcinnolines have been prepared by condensing an appropriate 4-phenoxy-cinnoline with an aliphatic amine at about 130° 21. These aminocinnolines have been tested for antimalarial activity against *Plasmodium gallinaceum* in chicks and these compounds showed better activity. Two of them were also tested against other malarial strains and the most effective compound was 7-chloro-4(4-diethylamino-1-methylethylamino)cinnoline (9) which is the cinnoline analogue of chloroquine 22.

Cinnoline carbonitriles have been synthesised 23 by the reactions of 4-methylsulphonylcinnoline or 4-cyanocinnoline with alkali metal cyanides. These compounds have been reported as bactericides.
Ansley \textsuperscript{24} prepared a number of 1-alkyl-6,7-methylenedioxy-4(1H)-oxocinnolin-3-carboxylic acids (10). Compounds of the type 10 and their salts were found to be active against \textit{Mycoplasma gallicepitum}, \textit{Escherichia coli}, \textit{Salmonella dublin}, \textit{Vibrio coli}, \textit{Eruvina amylovora} and \textit{Xanthomonas phaseoli}.

\[
\begin{align*}
\text{R} &= \text{CH}_3, \text{CH}_2\text{CH}_2\text{CH}_3, \text{CH} (\text{CH}_3)_2, \text{CH}_2\text{CH}_2\text{OH} \text{ and } \text{CH}_2\text{CH}=\text{CH}_2
\end{align*}
\]

A number of substituted cinnolylsulphones have been prepared by the oxidation of the corresponding sulphides with potassium permanganate. These compounds have been reported as useful bactericides \textsuperscript{25}.

Lowrie \textsuperscript{26-31} prepared a large number of 3-phenylcinnolines, such as dialkylaminoalkyl esters of 3-phenylcinnolin-4-carboxylic acids(11), 3-phenyl-4-dialkyminocoxycinnolines(12), dialkylaminoalkylaminoamides(13), 3-phenyl-4-
dialkylaminoalkylcinnolines (14), 3-phenyl-4-aminocinnolines (15) and piperazine amides of 3-phenylcinnolin-4-carboxylic acids (16) and subjected them for pharmacological screening.

\[
\text{NR}_2\text{QNRR}_1
\]
\[
\text{NHR}
\]

\[
X = \text{H, Cl}, \\
R = R_1 = \text{CH}_3 \\
R_2 = \text{H} \\
Q = (\text{CH}_2)_3
\]

\[
\text{R} = \text{CH}_2\text{C}_6\text{H}_5, \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5, \\
\text{CH}_2\text{CH}_2\text{OCH}_3 \text{ and CH}_2\text{OH}
\]

\[
\text{R} = \text{H, } \text{C}_2\text{H}_5, \text{CH}_2\text{CH}_2\text{OH and} \\
\text{CH}_2\text{CH}_2\text{OCH}_3 \text{ and CH}_2\text{OH} \\
\text{R}_1 = \text{H or OCH}_3
\]

Compounds 11 to 16 have been reported to possess hypotensive, antiulcer, antifungal, antiprotozoal, anti-inflammatory, central nervous system depressant and antibiotic activity against various organisms. They also inhibited the growth of Diplococcus pneumoniae, Tetrahymena geleii, Chlorella vulgaris, Candida albicans and the germination of seeds of Trifolium.
Theodor and associates \( ^{32} \) have reported the preparation of 1,2-malonyl-1,2-dihydrocinnolines (17).

![Structure of 17](image)

Compounds of the type 17 have been reported to possess anti-inflammatory, antipyretic and analgesic activities.

Castle \( ^{33} \) prepared a number of compounds containing pyridazinecinnoline and imidazopyridazine and tested them against tumor cells in-vivo and in-vitro. Among the several cinnolines prepared and tested, seven cinnolines showed remarkable activity against certain types of tumor cells. The 8-chloro-4-(2,4-dichlorobenzylthio)cinnoline(18) showed the highest activity against both SA-180 and CA-755 tumor cells in-vivo.

![Structure of 18](image)

The antileukaemic activity of 6-mercaptopurine prompted the synthesis of mercaptocinnolines and related compounds by Castle et al \( ^{34} \). They have prepared 4-mercaptopcinnoline, 6,7-dimethoxy-4-mercaptopcinnoline and a number of alkyl and heterocyclic derivatives, with a view to subject them for a antitumor activity.
Castle et al.³⁵,³⁶ have prepared α-(ω-dialkylaminoalkyl)-α-phenyl-4-
cinnolinacetonitriles and related compounds with a view to screen them for pharmacological activities.

Several 4-amino and 4-(substituted amino)-6-nitrocinnoline quaternary salts (19) were prepared by Barber et al.³⁷, and tested them for trypanocidal activity primarily against Trypanosoma congelense. None of the derivatives showed considerable activity although several compounds of the type 19 were active at near toxic doses.

\[
\begin{array}{c}
\text{NHR}_1 \\
\text{O}_2\text{N} \\
\text{N} \quad \text{(R\textsubscript{2})} \\
\text{R}_2\text{X}\textsuperscript{-} \\
\text{R}_1 = \text{H, CH}_3 \text{ and CH}_2\text{CH}_2\text{CH}_3 \\
\text{R}_2 = \text{CH}_3 \text{ and C}_2\text{H}_5 \\
\text{X} = \text{I}
\end{array}
\]

Lunt and coworkers³⁸ have prepared 4-substituted aminocinnoline analogues of chloroquine together with several substituted α, ω-di(cinnolin-4-yl-amino) alkanes and their diquaternary salts and subjected them for antiprotozoal activity. None of the compounds showed any useful level of activity.
A Japanese patent 39 has reported the synthesis of cinnoline derivatives of the type 19a and were found to be useful central nervous system agents, e.g. anxiolytics.

\[
R = \text{CONR}_1 \text{R}_2 \quad [\text{Except } (\text{R}_1 = \text{R}_2 = \text{H}), (\text{halo})\text{alkenyl, alkenyl, alkynyl, (un)substituted alkyl, aryI, and aralkyl, 4,5-dihydrothiazol-2-yl or -NR}_2 = \text{N-containing heterocyclyl}, \text{CO}_2 \text{R}_4, \text{COCR}_3 \text{R} (\text{R}_3, \text{R}_4 = \text{H, alkyl}),]
\]

\[
\text{R}_5 - \text{R}_8 = \text{H, halo, OH, NO}_2 \text{cyanoalkenyl, (un) substituted NH}_2 \text{, alkenyl (oxy), (un) substituted alkyl or alkyhalo, alkenyl, and}
\]

\[
\text{R}_9 = \text{(un) substituted NH}_2 \text{ or OH}
\]

Resch 40 prepared a number of substituted cinnolincarboxamides(19b) as sedatives and tranquilizers.

\[
\text{R}_3 = \text{aminocarbonyl, alkoxycarbonyl and acyl,}
\]

\[
\text{R}_4 = \text{amino, hydroxy, alkoxy and acyloxy,}
\]

\[
\text{R}_5 - \text{R}_8 = \text{H, alkyl, substituted alkyl, alkenyl, cycloalkyl, aryl, substituted aryl, alkoxy, alkenyloxy, hydroxy, nitro, cyano and amino.}
\]
Miyamoto et al. 41 have synthesised various substituted fluorocinnolines of the type 19c and tested them for antibacterial activity.

\[
\begin{align*}
\text{F} & \quad \text{COOR} \\
\text{R} & = \text{CH}_3, \text{C}_2\text{H}_5 \\
\text{R}_1 = \text{H}, \text{F}, \text{and } \text{R}_2 = \text{N(CH}_3)_2, \text{morpholino,} \text{1-piperazinyl and 1-pyrrolidinyll}
\end{align*}
\]

Antibacterial activities of these compounds were evaluated and compared with cinoxacin and norfloxacin. Some compounds showed better activity than cinoxacin but less than norfloxacin.

Abbady et al. 42 have synthesised cinnoline derivatives of the type 20 containing a sulphone group and were screened for antibacterial and antifungal activity. They observed that the introduction of sulphone group in the cinnoline ring enhances the bactericidal and decreases the fungicidal activities.

\[
\begin{align*}
\text{RO}_2\text{S} & \quad \text{OCOCH}_3 \\
\text{R} = \text{OH, NH}_2, \text{piperidino,} \\
& \quad \text{C}_6\text{H}_5\text{NH, 2-pyridylamino}
\end{align*}
\]

The foregoing data reveals that, cinnoline derivatives are known to possess varied biodynamic properties. When such a biodynamic molecule is fused to other heterocycle such as pyrimidine it is expected to yield a tricyclic heterocycle with enhanced pharmacological activity.
SYNTHESIS OF CINNOLINES

The different methods employed for the synthesis of cinnolines are briefly discussed below:

**Von Richter's Synthesis:**

Till now cinnoline derivatives have not been detected in nature. The formation of dinitrogen heterocyclic system was first observed by Richter in 1883, in the course of his unsuccessful attempts to prepare o-hydroxy acetophenone by heating the diazonium chloride of o-aminophenylpropionic acid with water. The resulting hydroxy acid, on decarboxylation yielded the compound which on subsequent heating with zinc dust gave the new heterocyclic compound cinnoline. The sequence of reactions are shown below:
Busch and Klett's Synthesis:

Although Von Richter could not obtain 4-hydroxycinnoline (23) in a sufficiently pure condition for the determination of its physical properties and elemental analysis, he called this new heterocyclic system cinnoline in analogy with quinoline. Pure cinnoline was first obtained by Busch and Klett \(^{44}\) in 1892 by converting 4-hydroxycinnoline (23) obtained by Von Richter's method to 4-chlorocinnoline (26) with a mixture of phosphorous oxychloride and phosphorous pentachloride, followed by the reduction of the latter with iron and sulfuric acid. The resulting 1,2-dihydrocinnoline (27) was finally oxidised to cinnoline (24) with mercuric oxide.

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 the benzene ring as shown in 28.

\[ \text{Cinnoline (24)} \]

In the second approach, the chain of two nitrogen atoms is increased by one carbon atom which condenses with the \( \alpha \)-carbon atom of a second chain in the ortho position as in 29 to build up the heterocyclic ring cinnoline(24).

\[ \text{Cinnoline (24)} \]

In the third approach, the \( \delta \)-carbon atom of a chain containing two nitrogen and two carbon atoms react with the hydrogen in the ortho position of the aromatic ring(30) to yield cinnoline(24).

\[ \text{Cinnoline (24)} \]
Possible mechanism of the three synthetic approaches to cinnoline have been put forth by various workers although not supported by experimental evidences. The first two approaches are believed to possess a common feature of the electrophilic attack of the β-nitrogen on the β-carbon of the carbon-carbon centre of unsaturation.

![Chemical structure](image)

**Synthetic method 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 of the amino group. The methods described below are based on this approach.

**Widman-Stoermer's synthesis:**

Widman observed that, on keeping a diazotised solution of 3-amino-4-isopropenylbenzoic acid at room temperature, a product was formed which was identified as 4-methylcinnolin-7-carboxylic acid.

![Chemical reaction](image)
This method was later exhaustively studied by Stoermer et al.\textsuperscript{50,51}, who have synthesised various cinnolines substituted at 4-position starting from a suitable o-aminophenylethylenes. In general, this method can be represented by the following reaction.

This reaction was further extended by Simpson et al.\textsuperscript{45,46,52-56} for the synthesis of various substituted cinnolines. Investigations on the scope of this reaction\textsuperscript{53,55,57} has shown that, it proceeds successfully when $R_1$ is aryl or methyl group and $R_2$ is alkyl, aryl or arylalkyl group, but it fails if $R_1$ is hydrogen or carboxyl and $R_2$ is pyridyl group.
The reaction is usually very rapid and seemingly independent of the geometrical configuration of the group around the ethylenic linkage. It was concluded from these results that the ring closure is more or less ionic in character and that it is induced by the polarisation of the diazonium salt.

**Borsche’s Synthesis:**

Borsche and Herbert in 1941 found that a solution of diazotised 2-amino-5-nitroacetophenone(38) when allowed to stand at room temperature, slowly cyclised to yield 6-nitro-4-hydroxycinnoline(39).

![Mechanism of Borsche's Synthesis](image)

**Mechanism of Borsche’s Synthesis:**
This method has been found to be of general applicability for the synthesis of 4-hydroxycinnoiines substituted at various positions, starting from a suitable o-aminoacetophenone. Cinnoline 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.

The cyclisation to form the cinnoline ring in this method is slower than that in Widman-Stoermer's method, but is facilitated by electron withdrawing groups in the m-position to the acetyl group. In this reaction heating is avoided to prevent the formation of phenol by the decomposition of the diazonium salt. The presence of hydrochloric acid assists ring closure but can lead to the replacement of nitro group by chlorine.

Synthetic methods based on the second approach:

As already mentioned, the second approach for building up the cinnoline ring involves the condensation between the carbon atom attached to the two nitrogen atoms and the α-carbon atom of a second chain in the ortho position. The methods described below are based on this approach:

Stolle-Becker's Synthesis:

Stolle and Becker in 1924 reported that, N-substituted isatin derivatives obtained through the reaction between substituted phenylhydrazones and oxalylchlorides, gave 3-phenylcinnolin-4-carboxylic acid on treatment with alkali. These on decarboxylation gave the corresponding 3-phenylcinnolines. The reaction evidently proceeds through the opening of the
heterocyclic ring of the isatin derivative to the intermediate keto acid containing the structural requirements of the second approach for the synthesis of cinnolines.

Later on, this method studied in detail by Baumgarten and Furnas was modified by Lowrie.

Pfannstiehl-Janecke's Synthesis:

Another method for the synthesis of cinnolines based on the second approach was reported by Pfannstiehl and Janecke in which, the phenylhydrazone prepared by condensing benzaldehyde with 6-chloro-2-hydrazino benzoic acid gave two products on heating, one of which was
5-chloro-3-phenyl-4-hydroxycinnoline(46) and the other was 4-chloroindazolone(47).
The sequence of reactions are as follows:

Diagram:

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

**Baumgarten's synthesis:**

This method is of general applicability for the synthesis of cinnolines based on the second approach developed by Baumgarten et al. in 1954. In this method, the required intermediate 49 obtained by the action of nitromethane on o-formylbenzene diazonium chloride(48), undergoes cyclisation in aqueous alkali or with a suspension of alumina in acetone to yield the corresponding 4-substituted-3-nitrocinnolines(50).

Diagram:

\( R = H, CH_3, OH \)
This method was successfully extended by Baumgarten 67 in 1958 for the preparation of cinnoline having various substituents in the 3rd position. It involves the intermediates obtained through the reaction between the o-substituted benzenediazonium chloride and acetoacetic acid or ethylhydrogenmalonate.

Synthetic methods based on the third approach:

In this approach, the heterocyclic ring of the cinnoline system is built up through the condensation of the carbon atom of a side chain containing two nitrogen atoms and at least two carbon atoms. The following methods are based on this approach:

Barber's Synthesis:

This synthetic approach to the cinnoline ring system was first described in a British patent by Barber et al 68 in the preparation of intermediates useful for the preparation of compounds having pharmacological properties. The details of this method were described in a subsequent publication by Barber et al 69. In this method, the appropriate intermediate 52 was obtained by the condensation of a suitable benzene diazonium chloride 51 with diethylmalonate and the subsequent hydrolysis of the resulting product, followed by conversion to the acid chloride 53. The acid chloride 53 on treatment with titaniumtetrachloride, underwent cyclisation to yield 4-hydroxycinnolin-3-carboxylic acids(54) which could thermally be decarboxylated at 205-215° to 4-hydroxycinnone(55).
The sequence of the reactions are as shown below:

\[ \text{COX} = \text{H}, \text{COOH} \]
\[ + \text{2 2 -S} \]
\[ \text{Boiling EtOH} \]
\[ \text{ISLCI} \]
\[ \text{CO}_2\text{C}_2\text{H}_5 \]
\[ \text{NaOH} \]
\[ \rightarrow \]
\[ \text{R} = 4-\text{OH}, 4-\text{OCH}_3\text{-C}_6\text{H}_5, 4-\text{OCH}_3, 4-\text{NHAc}, 4-\text{NHCOOC}_2\text{H}_5, 3-\text{Cl}, 4-\text{Br} \text{ and } 4-\text{NO}_2 \]
\[ \text{R}_1 = \text{H}, 3-\text{Cl}, 4-\text{Cl}, 5-\text{Cl} \text{ and } 4-\text{CH}_3 \]

A modification of this method for the synthesis of N-alkyl and N-aryl-4-
cinnolines have been described by Barber et al. In this method, N-substituted
anilines(56) were first converted to their nitrosoderivatives which however failed to
condense with diethylmalonate. These were then reduced to the corresponding
\( \alpha \)-substituted phenylhydrazines(58) and then condensed with diethylmalonate to
obtain the diesters(59). The monoesters(60) obtained by partial hydrolysis of
diesters were then converted to the acid chlorides and finally cyclised with titaniumtetrachloride to 4-cinnolinone derivatives (61).

Moore's Synthesis:

Moore 72 synthesised 3,4-diphenylcinnoline in good yields by cyclising benzilmonophenylhydrazone (62) with sulfuric acid. Repeatation of this procedure under slightly different conditions, however, gave low yields of cinnoline (63) and considerable quantities of a sulphonated product.
C. Allen and V. Allen in 1951 made attempts to cyclise phenylglyoxal-2-phenylhydrazones with concentrated sulfuric acid. The reaction, however, was unsuccessful and led to the formation of sulphonated products.

**Bhat and Bose's Synthesis:**

Bhat and Bose were however successful to bring about the cyclisation of o-hydroxyphenylglyoxal-2-phenylhydrazine (65) by the action of anhydrous aluminium chloride at elevated temperature. In the absence of any solvent, the resulting products were considered to be 1-phenylcinnolin-4-one (67), but later investigations showed them to be 4-(o-hydroxyphenyl)cinnoline (66).

The intermediate o-hydroxyphenylglyoxal-2-phenylhydrazone (65) was prepared by condensing 4-hydroxycoumarin with benzenediazonium chloride under slightly alkaline conditions and opening up of the lactone ring of the resulting diketochromon-3-phenylhydrazone (64) with simultaneous decarboxylation.
Baxter and Swan \textsuperscript{76} have reported the reduction of 2-\(\beta\)-dinitrostyrenes(68) (mainly with alkoxy or benzyloxy groups in the 4-and 5-positions) with lithium aluminium hydride in tetrahydrofuran to give a mixture of cinnolines(69) and indoles(70) as shown below:

\[
\begin{align*}
R=R=H, \text{CH}_3 \text{ and } \text{CH}_2\text{C}_6\text{H}_5 & \quad R=\text{CH}_3; R=H & \quad R=\text{CH}_3; R=\text{CH}_2\text{C}_6\text{H}_5 \\
66 & \quad 65 & \quad 67
\end{align*}
\]
Baumgarten et al. 77 have described a new synthetic route to the cinnoline nucleus by the oxidative rearrangement of 1-aminooxindole(71) with lead tetracetate to give 3-hydroxycinnoline(72) in 78% yield and of excellent purity.

Schmidt et al. 78 have synthesised various 4-(1H)-oxocinnoline-3-carboxylic acid derivatives as useful synthons for pharmaceuticals by cyclising phenylhydrazones(73) in presence of an organic carboxylic acid anhydride with a Friedel-Crafts catalyst. Phenylhydrazone(73) in acetic anhydride was treated with POCI$_3$ and the mixture was stirred and warmed at 85-90$^\circ$ and further stirring for 15 minutes at 100-105$^\circ$ gave 74 in 65% yield.

Nagarajan et. al. 79 have synthesised 4,6,7,8-tetrahydro-5-(1H)-cinnolone(76) by the reaction of substituted dimedones(75) with hydrazines.
Juglet and Schwerther have reported the preparation of 1,2,3,4-tetrahydrocinnoline by electrochemical synthesis. The electrochemical oxidation of \( 77 \) gave the diazonium ion(\( 78 \)) which underwent cycloaddition with styrene to give the cinnoline derivative \( 79 \).

Laduree et al. have prepared 4-amino(1)benzofuro(3,2-g)cinnolines(80) by cyclisation of the corresponding Z-isomers of cyanoaryhydrazones. The latter compounds have been synthesised by the interaction between the diazonium salt of 3-aminodibenzofuran and various active methylene compounds by the Japp-Klingemann reaction.

\[
\begin{align*}
R = H, CH_3; R_1 = CH_3, C_6H_5; \\
R_2 = H, CH_3; R_3 = H, (CH_2)_3N(CH_3)_2, C_6H_5
\end{align*}
\]
During the present investigation, we have used the elegant method described by Gewald et al. A useful intermediate phenylhydrazono(cyano)acetamide(II) was prepared by the interaction between diazonium salts of substituted anilines(I) and active methylene compounds such as cyanoacetamide through the Japp-Klingemann reaction.

Phenyldrazono(cyano)acetamide in the E-form undergoes an intramolecular reaction in chlorobenzene and in presence of anhydrous aluminium chloride to form 4-amino-3-cinnolincarboxamide(III).

4-amino-3-cinnolincarboxamide on hydrolysis with alcoholic KOH, yielded 4-amino-3-cinnolincarboxylic acid(IV).
The following scheme summarises the reactions that have been employed in the preparation of substituted 4-amino-3-cinnolinicarboxylic acids(IV).

SCHEME :

$\text{R} - \text{NH}_2 \xrightarrow{\text{NaNO}_2 / \text{HCl}} \text{R} - \text{NNCl} + \text{CH}_2\text{CONH}_2$

$\text{CH}_2\text{COONa} / \text{C}_3\text{H}_7\text{OH}$

$5-10^\circ$

$\text{R} - \text{NH}_2 \xrightarrow{\text{AlCl}_3 / \text{C}_6\text{H}_5\text{Cl}} \text{R} - \text{CONH}_2$

Reflux

$\text{R} - \text{NH}_2 \xrightarrow{\text{Alcoholic KOH}} \text{R} - \text{COOH}$

$\text{R}=\text{H, 6-CH}_3, 7-\text{CH}_3\text{ and 8-CH}_3$

R=H, 6-CH$_3$, 7-CH$_3$ and 8-CH$_3$
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