PART II
SYNTHETIC EXPERIMENTS IN
PYRROLO-(2, 3-b)-QUINOLINE SYSTEM
Apart from our interest in the chemical investigation of the plants of the 'Rutaceae' (Part -I) available in this region, we were interested in evolving new methodologies for the synthesis of natural products such as furoquinoline alkaloids isolated from these plant species as well as 'aza' and other analogues. One such programme, we envisaged, was the synthesis of Pyrrolo(2,3-b)quinoline system (lb) which constitute the 'aza' analogue of the furo(2,3-b)quinoline (la) the parent ring feature of the dictamnine (Al) group of alkaloids of the Rutaceae.
INTRODUCTION

Several types of pyrroloquinoline system are theoretically possible. They can be broadly divided into i) those in which the pyrrole ring is fused to the pyridine half and ii) those in which it is fused to benzene half of the quinoline unit (Chart - I).

REVIEW OF LITERATURE

For the construction of pyrroloquinolines two principal approaches have been employed i) construction of the quinoline ring on the pyrrole nucleus through an annealation procedure and ii) transformation of functionalized quinoline into the corresponding pyrroloquinoline.

\text{\textit{\textbf{H-Pyrrolo[2,3-b]quinoline(1)}}}
CHART I

[2,3-b] [3,4-b] [3,2-b]

[2,3-c] [3,4-c] [3,2-c]

[2,3-f] [3,4-f] [3,2-f]

[2,3-g] [3,4-g] [3,2-g]

[2,3-h] [3,4-h] [3,2-h]
The synthetic methods hitherto known for this system will be presented at the end of this chapter for it would serve as a prelude to our present work on the pyrrolo[2,3-b]quinoline(1) system discussed in the subsequent chapter.

2H-Pyrrolo[3,4-b]quinoline(2)

This system forms part of the alkaloid Campothecin(3) isolated from the stemwood of *Campotheca acuminata*².
The various methods that are known for the synthesis of pyrrolo(3,4-b)quinoline system have recently been reviewed. They start from i) quinolines; ii) o-aminoaromatic aldehydes and ketones; β keto esters and iii) by miscellaneous methods.

From quinolines:

Appropriately 2,3-disubstituted quinolines were used for the synthesis of various 2H-pyrrolo(3,4-b)quinolines\textsuperscript{4,5,6(7a)}. The quinolinedicarboxylate acid 4 was converted into pyrroloquinoline as outlined below.
2,3-dihydro(2H)pyrrolo(3,4-b)quinoline-1-one(10a) was obtained by Tanaka et al. by way of ethyl 2-bromo-methylquinoline-3-carboxylate(9) which was reacted with ammonia to give the pyrroloquinoline 10a.

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Sugaswa et al. synthesized 10a by proceeding through the following sequence of reactions starting from the diester 11.

\[ \text{NH}_3 \rightarrow 10a \]

a) \( R = H \)

b) \( R = \text{CH}_2\text{Ph} \)

10a

Sugaswa et al. synthesized 10a by proceeding through the following sequence of reactions starting from the diester 11.

\[ 11 \xrightarrow{\text{COOMe NaNO}_2/\text{AcOH}} 12 \]

\[ 13 \xrightarrow{\text{Zn/AcOH}} \xrightarrow{\text{HCl/AcOH}} 10a \]
The same workers\textsuperscript{9} synthesised the isomeric pyrroloquinolone \textit{16} by the hydrolysis of the Reissert's complex \textit{15} derived from the acetamide \textit{14}.

Recently Corey and co-workers\textsuperscript{10} synthesised 1,3-dihydro-2H-pyrrolo(3,4-b)quinoline(\textit{18}) starting from 2,3-di-(hydroxymethyl)quinoline(\textit{17a}).
Starting from methyl 3-methylquinoline-2-carboxylate, Danishefsky and co-workers obtained 2-methyl derivative of 16 by proceeding through the following sequence of reactions.

\[ 17 \xrightarrow{\text{NH}_3/\text{EtOH}} 18 \]

\[ 19 \xrightarrow{\text{NBS}} 20 \]

\[ 20 \xrightarrow{\text{MeNH}_2/\text{MeOH}} 16 \]
From o-aminobenzaldehydes and o-amino ketones:

Condensation of ortho-amino benzaldehyde as well as ortho-aminoacetophenones with N-substituted pyrrolidine-3-one were reported\textsuperscript{12-19} to produce pyrrolo(3,4-b)quinolines (21a and b).

\[
\begin{align*}
& \text{a) } R = H  \\
& \text{b) } R = \text{CH}_3
\end{align*}
\]

\[
\begin{align*}
& \text{a) } R = H; R' = \text{Me}  \\
& \text{b) } R = R' = \text{Me}
\end{align*}
\]

Some Friedlander-Type condensation leading first to appropriately substituted quinolines of the type 22 were also carried out and pyrrolo(3,4-b)quinolones 16 were produced\textsuperscript{20} by a reductive cyclization.
An interesting variation of the above sequence resulting in a totally aromatic system was due to Haddadin et al.\textsuperscript{21}

\[ \text{CHO} + \text{CN} \xrightarrow{\text{COOEt}} \text{COOEt} \]

\[ \text{NH}_2 \]

22

\[ \text{NH} \]

16

An interesting variation of the above sequence resulting in a totally aromatic system was due to Haddadin et al.\textsuperscript{21}

\[ \text{CHO} + \text{Ph} \xrightarrow{\text{Piperidine}} \text{COPh} \]

\[ \text{NH}_2 \]

\[ \text{CH}_2\text{COPh} \]

23

\[ \text{CrO}_3/\text{Ac}_2\text{O} \]

\[ \text{MeNH}_2/\text{MeOH} \]

\[ \text{NaBH}_4 \]

24

25
Synthesis of pyrrolo(3,4-b)quinoline system has also been accomplished using appropriate ketoesters.7

Thus aniline was allowed to condense into 1,4-dicarbethoxypyrrolidin-5-one in ethanol containing hydrochloric acid and the resulting compound 26 was heated in boiling diphenyl ether to give 2-carbethoxy-9-hydroxy-2H-pyrrolo-
(3,4-b)quinoline 27. Tanaka et al\textsuperscript{7} used calcium sulphate in acetic acid in the condensation step.

Other Methods:

Price and Velzen\textsuperscript{22} obtained the pyrrolo(3,4-b)-quinoline 30 by proceeding through the following sequence of reactions.
Another synthesis\textsuperscript{23} of pyrrolo(3,4-b)quinoline system was via a Dields-Alder reaction of N-Phenyl maleimide with anthranil. It proceeds as follows.

![Chemical diagram showing the reaction process involving N-Phenyl maleimide and anthranil to form pyrrolo(3,4-b)quinoline system.]

Robinson and Co-workers\(^{26}\) synthesised pyrrolo(3,2-b)-quinoline from 3-amino-2-quinaldine\(^{41}\). The basic ring system\(^{36}\) was obtained by condensation of triethylorthoformate with \(^{41}\).

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{NH}_2 & \quad \text{CH}_3 \\
\text{N} & \quad \text{N}
\end{align*}
\]

[1] i. HC(OEt)_3  
[2] ii': HCl

Eiter and Nagy\(^{27}\) synthesised 1-methyl-derivative of 1H-pyrrolo(3,2-b)quinoline\(^{36a}\) starting from 3-hydroxy-quinaldine\(^{39}\).

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{Me} \\
\text{N} & \quad \text{Me}
\end{align*}
\]

[3] aq MeNH_2  
[4] \Delta

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

[5] ZnCl_2  
[6] \Delta

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

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]
A novel synthesis of pyrrolo(3,4-b)quinoline(35) was achieved through oxidation of β-carboline 34 derivatives in the presence of potassium t-butoxide.

\[ \text{O}_2 \xrightarrow{\text{t. BuOK in DMF}} \]

\[ \text{34} \rightarrow \text{35} \]

1H Pyrrolo(3,2-b)quinoline(36):

The various routes that were reported for the construction of this system have been reviewed recently.
Parrick and co-workers obtained Pyrrolo(3,2-b)quinoline-3-carboxyaldehyde (40), by reacting 3-amino-2-quinaldine (41) with POCl₃ and DMF.

\[
\text{41} \quad \text{POCl₃/DMF} \quad \text{40}
\]

It was found that the Pyrroloquinoline 43 was obtained when a 1,3-dicarbonyl compound was heated with a compound of the type 42.

\[
\text{42} \quad \text{MeCOCH₂COMe} \quad \text{43}
\]
The same workers synthesized 7-chloro-2-methyl-9-phenyl-1H-pyrrolo(3,2-b)quinoline 45 by treatment of 44 with \( \text{POCl}_3 \) and then with triethylamine.

\[ \text{3H-Pyrrolo(2,3-\( \delta \))quinoline (46):} \]

The methods reported for the synthesis of this system have been recently reviewed. During chemical
degradation of calycanthine, a base was isolated and it was shown to be 2-methyl derivative of 46. Eiter and Nagy synthesized 3H-pyrrol(2,3-c)quinoline(46) from 3-aminolepidine(48) by treating with formic acid and Phosphorous pentoxide.

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{NO}_2 & \quad \text{NH}_2 \\
\text{SnCl}_2 & \quad \text{P}_2\text{O}_5 \\
\end{align*}
\]

Fischer's Indolization method has also been adapted for the synthesis of 3H-pyrrolo(2,3-c)quinoline system(49).
Umio et al.\textsuperscript{33, 34} synthesised 3H-pyrrolo(2,3-c)quinolines (50) from 3(2'-nitro-3'-chlorophenyl)pyrrolo-2-carboxaldehydes (49a) by reductive cyclisation.

2H-Pyrrolo(3,4-c)quinoline (52a):

Fritz and Schenk\textsuperscript{35}, reported the synthesis of substituted 2H-pyrrolo(3,4-c)quinolines (52d) by heating the phenylhydrazones of 1,2,5-trisubstituted-pyrrolo-3-aldehydes with Hydrogen bromide in glacial acetic acid.
\[
\begin{align*}
&\text{a) } R = \text{CH}_3 \\
&\text{b) } R = \text{C}_2\text{H}_5 \\
&\text{c) } R = \text{C}_6\text{H}_5
\end{align*}
\]
Grundon and McCorkindale\textsuperscript{36a} synthesised 1-phenyl-1H-pyrrolo-(3,2-c)quinoline-4-one (53c) by heating the dianilide 53a followed by dehydrogenation of the product using 10\% palladium-charcoal in boiling diphenylether.

Grundon and McCorkindale\textsuperscript{36a} synthesised 1-phenyl-1H-pyrrolo-(3,2-c)quinoline-4-one (53c) by heating the dianilide 53a followed by dehydrogenation of the product using 10\% palladium-charcoal in boiling diphenylether.
In this laboratory Shanmugam et al. have developed a neat synthesis of 4-methoxy-2,3-dihydro-1H-pyrrolo(3,2-c)quinoline (54g) starting from 4-cyano-3-vinyl-2-chloroquinoline (122) as depicted below.

\[ 122 \xrightarrow{\text{HOFMANN}} 124 \]

\[ 123 \xrightarrow{\text{PPA}} 54g \]
Beveridge and Huppatz\textsuperscript{36b} during the course of their studies on pyrrolo compounds obtained a spiroindoline (53d) and treated with Hydrochloric acid when ethyl 3,4-dimethyl-1H-pyrrolo(3,2-c)quinolin-2-carboxylate (53e) was obtained.

Mc donald and Prochor\textsuperscript{36c} obtained 7-chloro-1-ethyl-2-methyl-1H-pyrrolo(3,2-c)quinoline (54b) from 7-chloro-\(\text{N}-(2\text{chloro-allyl})\text{ethylamino}\)quinoline (54a) by heating with PPA.

3-(2-chloroethyl)-2,4,7-trichloroquinoline when reacted with benzylamine was reported to give
1-benzyl-4-benzylamino-7-chloro-2,3-dihydro-1H-pyrrolo-(3,2-c)quinoline (55b). A similar reaction with ammonia

\[ R_1 = CH_2 Ph, R_2 = NHCH_2 Ph \]

(55c)

\[ R_1 = H, R_2 = Cl \]

gave 55c. Nagaoka\(^{37a}\) prepared 4-methyl-1-phenyl-1H-pyrrolo (3,2-c)quinoline (55f) from 4-chloro-3-vinyl-quinolines (55d) by the route outlined below.
Nagaoka$^{37b}$ synthesised 4-methyl-2,3-dihydro-1H-pyrrolo(3,2-c)quinoline(53) by heating a mixture of 4-chloro-3(2-chloroethyl)quinoline(51) and salicylamide at 180°C followed by hydrolysis of the product with 5% sodium hydroxide.

1H-Pyrrolo(2,3-f)quinoline(56) and 3H-Pyrrolo(3,2-f)quinoline(57)
Sergeeva et al. synthesized 1H-pyrrolo[3,2-h]quinoline 62 by acid-catalysed cyclisation of the hydrazone 63 followed by decarboxylation.
Grayaznov et al. synthesized 1H-pyrrolo(2,3-b)-quinoline (60) from 5-hydrazinoquinoline as outlined below.

Analogously they synthesized 3H-pyrrolo(3,2-f)-quinoline (61) starting from 6-hydrazinoquinoline.
Pyrrolo(2,3-b)quinoline:

Synthetic effort in the pyrrolo(2,3-b)quinoline system started in 1913 during the structural elucidation of harmine and harmaline alkaloids of harmala group. Perkin and Robinson reported the synthesis of 1H-2-chloropyrrolo(2,3-b)quinoline by the following sequence of reactions starting from 2-quinolone-3-acetic acid.
The process involved treatment of the amide 65 derived from the acid with phosphorylchloride to give 67. Tanaka et al. later showed this result to be erroneous and proved the product to be 2-chloro-3-cyanoethylquinoline 66 and not 67 as reported by Perkin and Robinson.

Tanaka et al. synthesized 1H-pyrrolo(2,3-b)quinolines by proceeding through 2,3,4,5-tetrahydrofuro(3,2-b)quinolines which were earlier recognized as precursors for the synthesis of furoquinoline alkaloids. They synthesised 2,3-dihydro-4-hydroxy-1H-pyrrolo(2,3-b)quinolines (72) from 4-chloro-2,3-dihydrofuro(3,2-c)quinoline (71) and 4-chloro-2,3-dihydro-1H-pyrrolo(2,3-b)quinolines (72a) from 2,3-dichloro-3(2'-chloroethylquinoline (74) by the action of ammonia and other primary amines.
The dihydrocompounds were dehydrogenated using chemical methods as illustrated below.

\[ \text{CH}_2\text{N}_2 \rightarrow \]

73

74

(Sealed tube)

72a

The dihydrocompounds were dehydrogenated using chemical methods as illustrated below.
They found that when 75 was reacted with sodium methoxide in dimethylsulfoxide it interestingly gave the parent pyrrolo(2,3-b)quinolines.

The formation of 75 was mechanistically interpreted as follows.
Subsequently Tanaka et al. achieved the synthesis of 7-chloro-4-methoxy-2,3-dihydro-1H-pyrrolo(2,3-b)-quinoline by an improved version of the same method as depicted below.

\[
\text{PhNH}_2 + \text{N-CH}_2\text{CH}_2\text{-CH(COEt)}_2 \rightarrow \text{1}
\]
i) CH$_2$N$_2$

ii) NH$_2$-NH$_2$ dioxan-MeOH

80

1) CH$_2$N$_2$

ii) NH$_2$-NH$_2$ dioxan-MeOH

81

82

83

84

POCl$_3$
Jen et al.\textsuperscript{42} obtained 2,3,4-tetrahydro-1H-pyrrolo-(2,3-b)quinoline\textsuperscript{86} by the following reaction sequence.

\[ \text{85} \rightarrow \text{86} \]

Zimmer et al.\textsuperscript{53} obtained 1-acetyl-2,3-dihydro-(1H)-pyrrolo(2,3-b)quinoline\textsuperscript{91} along with the corresponding carbonylitrils by the photolysis of 1-acetyl-trans-3(2-aminobenzylidene)pyrrolidine-2(1H)ones\textsuperscript{90}.
A method for the synthesis of 1-substituted 2,3-dihydropyrrolo(2,3-b)quinolines which appeared in patent reports involved cyclization of 3-(2'-diethylaminoethyl)quinoline-2(1H)-one (93) with phosphorous halides.
Another synthesis of Pyrrolo(2,3-b)quinoline system was due to Vogel et al.\textsuperscript{55}. It involved pyrolysis of an azepine derivative 94 to give 1-alkyl-2-oxo-4-phenyl-2,3,3a,4-tetrahydropyrrolo(2,3-b)quinoline(95).

\begin{equation}
\begin{array}{cc}
\text{94} & \text{95} \\
\end{array}
\end{equation}

Ritcher et al.\textsuperscript{56} obtained the dihydropyrrolo(2,3-b)quinoline 96 as one of the products when 1-methyl-2-pyrrolidinone was heated with phenylisocyanate.

\begin{equation}
\begin{array}{ccc}
\text{96} \\
\end{array}
\end{equation}
Zhidkova and co-workers synthesized 4-chloro-1-methyl-2,3-dihydropyrroloquinoline (100) through the following reaction sequence.
In this laboratory several new methodologies have been developed by Shanmugam et al.\textsuperscript{62,64,67} for the construction of the parent pyrrolo(2,3-b)quinoline as well as its derivatives. Two types of precursors were utilized as starting points.

They were:

1) 2-quinolone-3-acetic acids(63)

![Chemical structure of 2-quinolone-3-acetic acids](image)

2) 3-vinyl-2-quinolones(115)

![Chemical structure of 3-vinyl-2-quinolones](image)

The quinolone acetic acids were obtained in two ways. 

1) one\textsuperscript{59,60} proceeds via acylation of o-aminocarbonyl-benzenes with succinic anhydride followed by ring closure
of the resulting compound with aqueous alkali. The quinolone acid was recovered from alkaline solution by acidification.

\[
\begin{align*}
\text{CHO} & + \text{O} \rightarrow \text{CHO} \rightarrow 63 \\
101
\end{align*}
\]

The other one was by a novel technique involving rearrangement of N-arylaconanilides 63a in the presence of polyphosphoric acid.
The quinolone-3-acetic acids were then transformed into the alcohol\textsuperscript{58,59}(105) from which the pyrrolo(2,3-b)-quinolines(1) were synthesised as outlined below\textsuperscript{62}.

This method was extended to several derivatives of 1.
The alcohol 105 was also obtained by a photochemical route by Shanmugam et al. It involved the photolysis of the anilide of 4,5-dihydrofuroic acid.
It was also shown by Shanmugam et al.\textsuperscript{64} that 2-quinolone-3-acetanilides(111) when heated with phosphorylchloride afforded the compound 1-aryl-2-chloropyrrolo(2,3-b)quinoline(112).

For preparing the anilide 111 a simple technique had been developed\textsuperscript{64}. It involved heating the 2-quinolone-acetic acid(63) with \textgreek{Ac}$_2$O and then treating the resulting lactone 113 with aniline in boiling benzene containing traces of glacial acetic acid.
1-Aryl-2-chloro-pyrrolo(2,3-b)quinolines on hydrogenation with hydrogen using 5% Pd/C in ethanol afforded 1-aryl-pyrrolo(2,3-b)quinolines as well as 1-aryl-2,3-dihydro pyrrolo(2,3-b)quinolines.

Interestingly with the use of 10% palladium on charcoal the C^-substituted 2-chloropyrroloquinolines

Interestingly with the use of 10% palladium on charcoal the C^-substituted 2-chloropyrroloquinolines
gave only the corresponding dehydropyrroloquinolines where as C₄-unsubstituted chloropyrroloquinolines gave the dihydropyrrolo(2,3-b)quinolines(112d)

The vinyl quinolone precursors were obtained by reacting o-aminocarbonylbenzene with 3-butenoylchloride in the presence of pyridine and subjecting the resulting amide(114) to a Friedlander type ring closure with potassium hydroxide in ethanol.
The vinylquinolone 115 was treated with phosphoryl chloride to give 2-chloro-3-vinylquinoline (116) which was then fused with p-aminobenzene sulphonamide. The aminoquinoline 117 was treated with an ice cold solution of bromine in chloroform and the adduct was treated with triethylamine to give the pyrrolo(2,3-b)quinoline (118).

\[
\begin{align*}
\text{115} & \xrightarrow{\text{POCl}_3} \text{116} \\
\text{i) p-aminobenzene sulphonamide} & \xrightarrow{\text{ii) 10\% aq. sodium carbonate}} \text{117} \\
\text{i) Br}_2 & \xrightarrow{\text{ii) N(Et)}_3} \text{118}
\end{align*}
\]
As an alternative procedure, bromine was added to the vinylquinolone and the resulting adduct, the trihalocompound, was fused with p-aminobenzencesulphonamide. The resulting mass when hydrolysed with alkali readily furnished the pyrroloquinoline.

\[ \text{Vinylquinolone} \xrightarrow{\text{Br}_2} \text{Trihalocompound} \xrightarrow{\text{POCl}_3} \text{Pyroloquinoline} \]

1) p-aminobenzencesulphonamide
2) 5% alc. KOH
3) N(Et)_3