CHAPTER 1

RECENT DEVELOPMENTS IN BERBINE ALKALOIDS
RECENT DEVELOPMENTS IN BERBINE ALKALOIDS

1. Introduction

Protoberberines form an interesting group of alkaloids containing isoquinoline moiety\(^1\). These alkaloids commonly occur in plants belonging to the Papaveraceae, Berberidaceae, Ranunculaceae, Menispermaceae, Rutaceae and Annonaceae families\(^1\). These alkaloids are known since last 150 years. The first alkaloid of this series, berberine, was isolated from *Berberis vulgaris*, in 1837\(^2\). Since then more than 100 alkaloids belonging to this class, have been isolated. These alkaloids occur in nature mainly in two forms, the quaternary protoberberinium salt of type \(1\) and the tertiary base of type \(2\).

\[
\begin{align*}
1 & \quad \begin{array}{c}
\text{R}_1 \quad \text{N}^+ \\
\text{R}_2
\end{array} \\
\begin{array}{c}
\text{R}_1 \quad \text{N}^+ \\
\text{R}_2
\end{array}
\end{align*}
\]

\[
\begin{align*}
2 & \quad \begin{array}{c}
\text{R}_1 \\
\text{R}_2
\end{array} \\
\begin{array}{c}
\text{R}_1 \\
\text{R}_2
\end{array}
\end{align*}
\]
The systematic name for the fundamental nucleus of this ring system is $5,8,13,13a$-tetrahydro-$6H$-dibenzo[a,g]quinolizine or alternately $5,6,13,13a$-tetrahydro-$8H$-dibenzo[a,g]quinolizine. Recently, the much less cumbersome name berbine is being used to represent this nucleus. This name is preferable to the two other widely used terms, tetrahydroberberine and tetrahydroprotoberberine.

2. **Isolation**

Several protoberberine alkaloids have been isolated from natural sources. These occur in nature mainly as the quaternary salts of type 1 and tertiary bases of type 2. However, in the last few years a number of quaternary N-methylberbine salts as well as N-oxides have been isolated. Some alkaloids are reported to possess a keto group either at C$_8$ or C$_{13}$ position. Very few alkaloids contain two keto groups one at C$_8$ and the other at C$_{13}$. Recently some berbine alkaloids have been isolated from natural sources which contain novel structures. Some alkaloids contain a methyl group either at C$_8$ or C$_{13}$ position, which are described in Chapters 3 and 4. Some berbine alkaloids having hydroxyl group at C$_{13}$ position have also been isolated. Most of the berbine alkaloids are tetraoxygenated and have two oxygen functions each in ring A and ring D, as represented by structures 3-6.
There are a few berbine alkaloids which are penta-oxygenated. These alkaloids have either structure 7 or 8.

The isolation, structure determination, synthesis, chemistry, pharmacology and biogenesis of these alkaloids have been extensively reviewed in literature. Some of the recently isolated berbine alkaloids are depicted below.
## I. Simple berbines

![Structure of Simple Berbines](image)

<table>
<thead>
<tr>
<th>Ref.</th>
<th>R</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>R₅</th>
<th>R₆</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>H</td>
<td>OMe</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>OMe</td>
<td>Me</td>
<td>H</td>
<td>OH</td>
<td>OMe</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>OH</td>
<td>H</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td></td>
</tr>
<tr>
<td>7a</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>OH</td>
<td>OH</td>
<td>OMe</td>
<td>H</td>
</tr>
<tr>
<td>7b</td>
<td>OH</td>
<td>OMe</td>
<td>Me</td>
<td>H</td>
<td>OMe</td>
<td>OMe</td>
<td>H</td>
</tr>
<tr>
<td>7b</td>
<td>OMe</td>
<td>OMe</td>
<td>Me</td>
<td>H</td>
<td>OMe</td>
<td>OMe</td>
<td>H</td>
</tr>
<tr>
<td>7c</td>
<td>H</td>
<td>OMe</td>
<td>Me</td>
<td>OH</td>
<td>H</td>
<td>OMe</td>
<td>OMe</td>
</tr>
<tr>
<td>7c</td>
<td>H</td>
<td>OMe</td>
<td>Me</td>
<td>OH</td>
<td>H</td>
<td>OMe</td>
<td>OH</td>
</tr>
</tbody>
</table>

## II. N-Methylberbine salt

![Structure of N-Methylberbine Salt](image)
III. Protoberberine salts

\[
\begin{array}{cccccccc}
\text{Ref.} & R_1 & R_2 & R_3 & R_4 & R_5 & R_6 \\
a & H & Me & H & OMe & H & H & 9 \\
b & H & H & H & OMe & Me & H & 10 \\
c & H & Me & H & H & Me & OMe & 11 \\
d & H & Me & H & H & \text{—CH}_2\text{O—} & 11 \\
e & Me & H & H & H & \text{—CH}_2\text{O—} & 12 \\
f & Me & H & H & H & Me & OMe & 12 \\
g & \text{—CH}_2— & H & H & Me & OMe & 12 \\
h & \text{—CH}_2— & H & H & \text{—CH}_2\text{O—} & 12 \\
i & Me & Me & OH & H & Me & OMe & 7c \\
\end{array}
\]

IV. Berbine N-oxides$^{7c, 13}$

12a

12b
V. 8-Keto\textsuperscript{14}, 13-Keto\textsuperscript{15}, and 8,13-diketo\textsuperscript{16} berbines.

\begin{align*}
&\text{a) } R = H, \quad \text{b) } R = \text{OMe} \\
&\text{13} \\
&\text{14}
\end{align*}

VI. Unusual berbine alkaloids\textsuperscript{17-19}

\begin{align*}
&\text{16} \\
&\text{17} \\
&\text{18}
\end{align*}
Some alkaloids, structurally similar to berbines, have a second nitrogen atom at $C_{10}$ position. These are called as 10-azaberines. Some examples of these alkaloids are shown below.

![Chemical structures of 10-azaberines]

3. Chemical transformations of berbines

Numerous successful transformations of berbines and related alkaloids have been reported in literature. These involve cleavage and formation of bonds and some rearrangements. Some of the typical examples are depicted below:
Chemical transformations of berbines
4. **Biological activities**

Berberine group of alkaloids are reported to possess a variety of biological activities\(^{1a-c,1f}\). Thus, the alkaloid berberine is known for its sedative, hypotensive, antiinflammatory, uterine-stimulant, antibacterial, antiamoebic, anticholera, antidiarrhoeal and antigiardial activities\(^{25}\). Both berberine and palmatine are effective against experimental tumors\(^{26}\). Berberine protects dogs from developing ventricular arrhythmia\(^{27}\). Tetrahydro-palmatine is known to possess CNS-depressant activity\(^{25}\), while xylopinine is known for its antitussive activity\(^{28}\). Berberine hydrochloride inhibits glucose utilisation and interacts with nucleic acids\(^{29}\). 2,3,9,10-Tetrasubstituted berbines usually possess sedative activity\(^{30}\). Some berbines are found to be useful in the treatment of cardiovascular diseases\(^{31}\). These are also tested for their antihypertensive and peripheral vasodilating activities\(^{31}\). Some berbine alkaloids are known for their antitumor and antimicrobial\(^{32}\) activities. \(-\)Stepholidine possesses analgesic, sedative and antispastic\(^{33}\) activities. Palmatine showed analgesic effects in rats\(^{34}\).
5. **Biosynthesis**

According to classical theory\textsuperscript{35} protoberberine alkaloids could be derived in nature from suitably substituted 1-benzyl tetrahydroisoquinoline precursors, by condensation with one carbon unit. Spenser and coworkers\textsuperscript{36} have shown that tyrosine is a very efficient precursor for berberine and is incorporated into both the top and bottom parts of the alkaloid. However, if labelled dopamine is fed, only one molecule of this species is incorporated into the alkaloid.

\[\text{labelled tyrosine} \xrightarrow{H. \text{canadensis}} \text{protoberberine}\]

It has also been reported\textsuperscript{1b} in literature that the C\textsubscript{8}-carbon of these alkaloids can be derived from N-methyl group of 1-benzyltetrahydroisoquinoline precursors. Barton\textsuperscript{37}
and Battersby\textsuperscript{38} have independently demonstrated that N-methyl-1-benzyltetrahydroisoquinoline is converted to protoberberine by oxidative cyclisation of N-methyl function rather than by Mannich type condensation with formaldehyde. N-Methyl-1-benzylisoquinoline, reticuline, is an important intermediate in protoberberine biosynthesis\textsuperscript{39}. Labelled reticuline gave rise to radioactive berberine, a transformation which also shows that the methylenedioxy group, in nature, is derived from ortho-methoxyphenol\textsuperscript{37}. (+) Reticuline is incorporated much more efficiently than the levoenantiomer\textsuperscript{37}.

\[ \text{labelled (+) reticuline} \]

\[ \text{labelled berberine} \]
(+++) Norlaudanosoline and reticuline, but not
(+)+ laudanosine were found to be efficient precursors for
tetrahydropalmatine and palmatine\(^{40a}\). The following
sequence was shown for this transformation.

\[\text{tyrosine} \underset{C. laurifolius}{\longrightarrow} \text{norlaudanosoline} \]

\[\text{(+)+ reticuline} \longrightarrow \text{tetrahydropalmatine} \]

\[\text{palmatine} \]
Incorporation of norreticuline, reticuline and nororientaline into sinactine, in C. laurifolius has shown the following sequence for the biosynthesis of (+) sinactine⁴⁰⁷b.
6. **Synthesis of berbine alkaloids**

Careful look at the berbine skeleton (1), reveals that it contains two isoquinoline nuclei \(21\) and \(22\) consisting of AB and CD rings respectively.

![Chemical structure of berbine scaffold](image)

Almost all the reported methods utilize the preformed A and D rings. The B and C rings are then constructed in later steps. Recently a few methods have been reported in literature, in which ring D has been constructed in the synthetic sequence. The synthetic approaches for berbine skeleton involve either formation of AB or CD isoquinolizine ring part first, followed by construction of quinolizine or berbine skeleton. Thus, the final step involves formation of the remaining AB or CD isoquinoline ring, which makes use of any of the routes known for isoquinoline synthesis. Bischler-Napieralski\(^{4,1a}\), Pomeranz-Fritsch\(^{4,1c}\), Pictet-Spengler\(^{4,1b}\) and their modifications are among the well known routes for isoquinoline synthesis. Some methods construct AB
isoquinoline ring first and then cyclisation occurs to form ring C, while the other methods utilize CD isoquinoline ring and then construct B ring. Depending upon such mode of formation, the reported methods for the formation of berbine skeleton can be classified under six different types (Chart I).
Methods involving type I

Approaches of this type involve formation of C-C bond between C₈ and ring D. Among the classical methods of this type are the Bischler-Napieralski cyclisation and intramolecular Mannich condensation of 1-benzylisoquinolines. These methods mainly provide products possessing the 2,3,10,11-oxygenation pattern. When the benzylisoquinoline contains 3'-hydroxy group, Mannich cyclisation gives a mixture of 2,3,9,10- and 2,3,10,11-tetraoxygenated berbines. The ratio of the products depends on the nature of pH of the reaction mixture (Chart IIa). The use of bromine as a protecting group to promote formation of 2,3,9,10-oxygenated berbines in the Mannich condensation is illustrated in the synthesis of capaurine (Chart IIb).

The method involving Bischler-Napieralski cyclisation is presented in Chart IIc. This method also provides 2,3,10,11-oxygenated berbines. To achieve the synthesis of 2,3,9,10-oxygenated berbines by this method, cyclisations were carried out on brominated tetrahydrobenzylisoquinoline formamides as shown in Chart IIId.

N-Methyl-1-benzylisoquinoline-N-oxides on reaction with FeSO₄ provide 2,3,10,11-oxygenated berbines. Recently
a. Method involving Mannich cyclisation

1. Method involving Mannich cyclisation using bromine as a blocking group

<table>
<thead>
<tr>
<th>pH</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2</td>
<td>1:1</td>
<td></td>
</tr>
<tr>
<td>7.8</td>
<td>3.8:1</td>
<td></td>
</tr>
</tbody>
</table>

b. Method involving Mannich cyclisation using bromine as a blocking group

1. LiAlH$_4$
2. CH$_2$N$_2$
3. HCl, EtOH

(Chart II contd)
c. Method involving Bischler-Napieralski cyclisation

\[
\begin{align*}
\text{MeO} & \quad \text{CHO} \\
\text{MeO} & \quad \text{PNA} \\
\text{MeO} & \quad \text{MeO}
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{CHO} & \quad \text{PPA} \\
\text{MeO} & \quad \text{OMe}
\end{align*}
\]

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

\[
\begin{align*}
\text{d. Method involving Bischler-Napieralski cyclisation using bromine as a blocking group}
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{CHO} \\
\text{BnO} & \quad \text{1. POCl}_3 \\
\text{Br} & \quad \text{2. NaBH}_4
\end{align*}
\]

\[
\begin{align*}
\text{1. HCl / EtOH} \\
\text{2. LiAlH}_4
\end{align*}
\]

\[
\begin{align*}
\text{e. Method involving N-methyl-1-benzylisoquinoline-N-oxides}
\end{align*}
\]

\[
\begin{align*}
\text{FeSO}_4 & \quad \text{or} \\
\text{[Fe(dipy)_3]Cl}_2
\end{align*}
\]

\[
\begin{align*}
\text{R}_1 & \quad \text{R}_2 & \quad \text{R}_3 & \quad \text{R}_4 \\
\text{Me} & \quad \text{H} & \quad \text{Me} & \quad \text{H} \\
\text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} \\
\text{etc.}
\end{align*}
\]

Chart II
[Fe(dipy)$_3$]Cl$_2$ complex has been used$^{43}$ for such cyclisation (Chart IIe).

**Methods involving type II**

These methods involve formation of C-C bond between C$_{13}$ and ring D. The aroylation of 1-methyl-3,4-dihydroisoquinolines produces enamides which readily undergo photocyclisation to give oxoberbine derivatives$^{1c}$ which on LAH reduction provide berbines (Chart IIIa).

Bradsher and coworkers have also reported$^{44}$ a method which involves formation of C-C bond between C$_{13}$ and ring D. It utilises formylisoquinoline and benzylbromide derivatives. The steps involved are presented in Chart IIIb.

**Methods involving type III**

There are several methods falling into this category which involve formation of C$_8$-N bond. All these methods are presented in Chart IV.

The method reported$^{45}$ by Kametani and coworkers involves thermolysis of benzocyclobutenes (Chart IVa). By using this approach they have synthesised variously substituted berbines. Irie and coworkers$^{46}$ have synthesised xylopinine in excellent yield by a photochemical route which
a. Method involving photochemical cyclisation\textsuperscript{1c}

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

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

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

1. h\gamma
2. LiAlH\textsubscript{4}

b. Method due to Bradsher and Dutta\textsuperscript{44}

\[
\begin{align*}
\text{R} & = \text{CHO} \\
& = \text{CH} = \text{N} = \text{OH}
\end{align*}
\]

1. HCl, 100\degree
2. H\textsubscript{2}/PtO\textsubscript{2}

Chart III
utilises spirobenzylisoquinolines (Chart IVb). Cushman and coworkers have extensively used \(^{14}\) homophthalic anhydrides for the synthesis of berbines having both 2,3,10,11- and 2,3,9,10-oxygenated patterns (Chart IVc).

The method utilising phthalide isoquinolines for berbine synthesis also involves the formation of Cg-N bond. By using this approach Govindachari and coworkers have synthesised \(^{14}\) berbines from phthalides via phthalide isoquinolines. Recently Narasimhan and coworkers \(^{49a}\) and MacLean and coworkers \(^{49b}\) have used phthalide anion approach for the synthesis of phthalide isoquinolines. In MacLean's procedure the phthalide isoquinolines have not been isolated and are directly converted \(^{49b}\) to 13-hydroxyberbines (Chart IVd). Narasimhan and coworkers have developed \(^{50}\) a novel method for the synthesis of 2,3,9,10-oxygenated berbines. The key step in this approach involves heteroatom directed lithiation reaction (Chart IVe). Shono and coworkers have developed \(^{51}\) novel methods for the synthesis of variously substituted berbines. These methods make use of bromoesters and 3,4-dihydroisoquinolinium salts and involve electrochemical reductive annelation or zinc promoted reductive couplings (Chart IVf). Kessar and coworkers have reported \(^{52}\) a photochemical method which also involves
a. Method due to Kametani et al.\textsuperscript{45}

\[
\begin{array}{c}
\text{MeO} \\
\text{MeO} \\
\text{H} \\
\text{MeO} \\
\text{MeO}
\end{array}
\xrightarrow{1. \Delta}
\begin{array}{c}
\text{MeO} \\
\text{MeO} \\
\text{MeO} \\
\text{OMe} \\
\text{OMe}
\end{array}
\xrightarrow{2. \text{Reduction}}
\begin{array}{c}
\text{MeO} \\
\text{MeO} \\
\text{MeO} \\
\text{MeO} \\
\text{OMe}
\end{array}
\]

b. Method due to Irie et al.\textsuperscript{46}

\[
\begin{array}{c}
\text{HO} \\
\text{MeO} \\
\text{MeO} \\
\text{MeO}
\end{array}
+ \\
\begin{array}{c}
\text{HO} \\
\text{MeO} \\
\text{MeO} \\
\text{MeO}
\end{array}
\xrightarrow{1. \text{Pictet-Spengler}}
\begin{array}{c}
\text{MeO} \\
\text{MeO} \\
\text{MeO} \\
\text{OMe}
\end{array}
\xrightarrow{2. \text{CH}_2\text{N}_2}
\begin{array}{c}
\text{MeO} \\
\text{MeO} \\
\text{MeO} \\
\text{OMe}
\end{array}
\]

c. Method due to Cushman et al.\textsuperscript{47}

\[
\begin{array}{c}
\text{MeO} \\
\text{MeO} \\
\text{MeO} \\
\text{MeO}
\end{array}
\xrightarrow{\text{h} \nu \text{THF}}
\begin{array}{c}
\text{MeO} \\
\text{MeO} \\
\text{MeO} \\
\text{OMe}
\end{array}
\xrightarrow{\text{NaBH}_4}
\begin{array}{c}
\text{MeO} \\
\text{MeO} \\
\text{MeO} \\
\text{OMe}
\end{array}
\]

xylopinine

(Chart IV contd.)
1. Pb\((\text{OAc})_4\)/Cu\((\text{OAc})_2\)  
   \[\text{AcOH/DMF/r.t.}\]

2. \(100^\circ\)

\[\text{LiAlH}_4, \text{AlCl}_3, \text{Et}_2\text{O/rt.}\]

---

Method due to Marsden and MacLean\(^{49b}\)

\[\text{LDA, THF/-70°}\]

\[\text{THF, } \Delta\]

\[\text{Chart IV contd.}\]
Method due to Narasimhan et al.

1. nBuLi
2. (HCHO)$_n$
3. MeSO$_2$Cl
4. KI
5. $\Delta$

Method due to Shono et al.

(i)

$\text{RO} \quad \text{MeO}^+ \quad \text{OMe} \quad \text{H} \quad \text{RO}$

$\text{R}_2 \quad \text{CH}_2\text{Br}$

(ii)

$\text{R}_1\text{O} \quad \text{Br}^- \quad \text{R}_2\text{O}$

$\text{CH}_2\text{Ph}$

$\text{R}_3 \quad \text{COOMe}$

1. HCl
2. H$_2$/10% Pd-C
3. NEt$_3$

$\text{R}_1 \quad \text{R}_2 \quad \text{R}_3 \quad \text{R}_4$

$\text{Me} \quad \text{Me} \quad \text{OMe} \quad \text{OMe}$

$\text{-CH}_2^- \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{etc.}$

(Chart IV contd.)
formation of C8-N bond (Chart IVg). Isochroman-3-ones have also been used as synthons for the synthesis of berbines. Initially this method was used for the synthesis of 10,11-oxygenated berbines. Recently it has been extensively used for the synthesis of 9,10-oxygenated berbines (Chart IVh).

**Method involving type IV**

This approach involves formation of bond between C13 and C13a. Shono and coworkers have done lot of work on electrochemical cyclisations. By using this approach they have synthesised several heterocyclic compounds. Their approach for the synthesis of berbines is depicted in Chart Va. Takano et al have reported a method in which the C13-C13a bond is formed by nucleophilic addition of a carbanion, generated from an organosilicon compound to C=N. The steps involved are presented in Chart Vb. 3,4-Dihydroisoquinoline on reaction with ortho-chloromethylbenzoyl chloride gives the Reissert compound, which on reaction with NaH in DMF provides berbine derivatives. The steps involved are presented in Chart Vc.

**Methods involving type V**

This approach involves formation of C-C bond between C13a and ring A. The routes involving such bond formation
g. Method due to Kessar et al.$^{52}$

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

1. POCI$_3$
2. O$_2$-MeOH

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

1. MeOH, UV
2. HCl

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

h. Method due to Narasimhan et al.$^{54}$

\[
\begin{align*}
R & \quad R \\
R & \quad R \\
\end{align*}
\]

+ \[
\begin{align*}
R_1 & \quad \text{R1} \\
R_1 & \quad \text{R1} \\
\end{align*}
\]

NH$_2$

EtOH, $\Delta$

\[
\begin{align*}
R & \quad R \\
R & \quad R \\
\end{align*}
\]

1. PCl$_5$
2. NaBH$_4$

\[
\begin{align*}
R & \quad R \\
R & \quad R \\
\end{align*}
\]

Chart IV
a. Method due to Shono et al.\(^{55}\)

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

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

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

b. Method due to Takano et al.\(^{56}\)

\[ \begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{MeO} & \quad \text{SiMe}_3 \\
\text{MeO} & \quad \text{Br}_2, \text{CH}_2\text{Cl}_2 \\
\text{MeO} & \quad \text{aq. NaHCO}_3 \text{Me}_3 \text{SiMe}_3 \\
\text{MeO} & \quad \text{MeO} \\
\text{MeO} & \quad \text{Br} \\
\text{MeO} & \quad \text{Br}
\end{align*} \]

\[ \begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{MeO} & \quad \text{SiMe}_3 \\
\text{MeO} & \quad \text{NH}_2 \\
\text{MeO} & \quad \text{OMe} \\
\text{MeO} & \quad \text{MeCOOCHO}
\end{align*} \]

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

(Chart V contd.)
c. Methods involving Reissert compounds\textsuperscript{57}

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

\[
\begin{align*}
\text{CH}_2\text{Cl} & \quad \text{CH}_2\text{Cl} \\
\text{CH}_2\text{Cl} & \quad \text{CH}_2\text{Cl} \\
\text{CH}_2\text{Cl} & \quad \text{CH}_2\text{Cl} \\
\end{align*}
\]

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

\[
\begin{align*}
\text{Me}_3\text{SiCN} & \quad \text{Me}_3\text{SiCN} \\
\text{AlCl}_3 & \quad \text{AlCl}_3 \\
\text{AlCl}_3 & \quad \text{AlCl}_3 \\
\end{align*}
\]

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

\[
\begin{align*}
\text{LAH} & \quad \text{LAH} \\
\text{NaBH}_4 & \quad \text{NaBH}_4 \\
\text{NaBH}_4 & \quad \text{NaBH}_4 \\
\end{align*}
\]

\[
\begin{align*}
\text{R} & \quad \text{R} \\
\text{OMe} & \quad \text{OMe} \\
\text{OCH}_2\text{O} & \quad \text{OCH}_2\text{O} \\
\end{align*}
\]

\textbf{Chart V}
are presented in Chart VI.

Rapoport and coworkers have developed a method, which involves iminium salts, for the formation of berbines. By making use of this approach they have synthesised both 2,3,10,11- and 2,3,9,10-oxygenated berbines (Chart VIa).

Pandey and Tiwari have reported two approaches which involve C-C bond formation between C13a and ring A. These methods are depicted in Charts VIb and c.

Battersby and coworkers have also reported such bond formation approaches for the synthesis of both 2,3,9,10- and 2,3,10,11-oxygenated berbines (Charts VIId and e).

Methods involving type VI

Formation of bond between C5 and ring A is visualised in this type of approaches. Dyke and coworkers have successfully used Bobbit modifications of Pomeranz-Fritsch cyclisation in the synthesis of berbines. The steps involved are presented in Chart VII.

Recently reported miscellaneous methods

Recently Hillard and coworkers have developed a totally new approach for the synthesis of berbines, which involves construction of ring D also. This method starts
a. Method due to Dean and Rapoport\textsuperscript{3}

\[
\begin{aligned}
R_1 & \text{CH}_2\text{OH}, H^+ \xrightarrow{\Delta} & R_1 & \text{5 steps} & R_2 & N\text{Me}_2 \\
& R_2 & \xrightarrow{ROH, H_2SO_4, \Delta} & R_3 & \xrightarrow{benzene/DMF} & R_3 \\
& R_3 & \xrightarrow{K_2CO_3} & \xrightarrow{MeO} & & \\
R & = \text{iPr} & & = \text{Et} & & \\
\end{aligned}
\]

b. Method due to Pandey and Tiwari\textsuperscript{58a}

\[
\begin{aligned}
\text{MeO} & \text{MeO} & \xrightarrow{K_2CO_3, KI} & \text{abs. EtOH, } \Delta & & \\
& \text{MeO} & & \text{MeO} & & \\
& \text{MeO} & & \text{MeO} & & \\
\end{aligned}
\]

(Chart VI contd.)
c. Method due to Pandey and Tiwari \textsuperscript{58b}

\[
\begin{align*}
\text{MeO} & \quad \text{BnO} \\
\text{NH}_2 & \\
\text{MeO} & \quad \text{BnO} \\
\text{EtOOC} & \\
\Delta & \\
\text{EtOH} & \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{BnO} \\
\text{O} & \\
\text{O} & \\
\text{O} & \\
\text{OMe} & \\
\text{POCl}_3 & \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{BnO} \\
\text{O} & \\
\text{O} & \\
\text{O} & \\
\text{OMe} & \\
\text{NaBH}_4 & \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{BnO} \\
\text{O} & \\
\text{O} & \\
\text{O} & \\
\text{OMe} & \\
\text{EtOH} & \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{BnO} \\
\text{O} & \\
\text{O} & \\
\text{O} & \\
\text{OMe} & \\
\text{HCl} & \\
\end{align*}
\]

---

d. Method due to Battersby et al. \textsuperscript{59a}

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{NH}_2 & \\
\text{MeO} & \quad \text{O} \\
\text{CHO} & \\
\Delta & \\
\text{EtOH} & \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{O} & \\
\text{O} & \\
\text{O} & \\
\text{O} & \\
\text{NaBH}_4 & \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{O} & \\
\text{O} & \\
\text{O} & \\
\text{O} & \\
\text{H}_2\text{SO}_4 & \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{BnO} \\
\text{O} & \\
\text{O} & \\
\text{O} & \\
\text{O} & \\
\text{NaBH}_4 & \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{BnO} \\
\text{O} & \\
\text{O} & \\
\text{O} & \\
\text{O} & \\
\text{HCl} & \\
\end{align*}
\]

(Chart VI contd.)
Method due to Battersby et al.

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

\[
\text{MeOH} \quad \Delta \quad \text{MeO} \quad \text{Bn} \\
\text{Bn} \\
\]

\[
\text{LiAlH}_4 \\
\]

\[
\text{H}_3\text{PO}_4/\text{HCOOH} \quad \Delta \\
\]

Chart VI

Method due to Dyke et al.

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

\[
\text{HCl} \\
\text{MeO} \quad \text{MeO} \\
\text{NBS} \\
\]

\[
\begin{align*}
1. \quad \text{aq. EtOH-HCl} \\
2. \quad \text{MeO} \quad \text{MeO} \\
\end{align*}
\]

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

\[
\begin{align*}
1. \quad \text{LiAlH}_4 \\
2. \quad \text{HCl} \\
\end{align*}
\]

Chart VII
with ring A substrate. The rings B \rightarrow C and D are then constructed during the synthetic sequence (Chart VIIIa). Pandey and Tiwari have developed\(^\text{62}\) an approach, which involves palladium catalysed insertion of carbon monoxide. The C\(_8\) carbon comes from carbon monoxide. The formation of C\(_8\)-N and C\(_8\)-ring D bonds occurs during this process (Chart VIIIb). Stambach and Jung have used COCl\(_2\)/ZnCl\(_2\) as the reagent for such insertion\(^\text{63}\). The steps involved are presented in Chart VIIIc. The method reported\(^\text{64}\) by Ognyanov et al utilises homophthalic anhydride and 1-chloroisoquinolinones. Their approach for the synthesis of 1,2,10,11-oxygenated berbines is presented in Chart VIIIId. Recently\(^\text{65}\) Meyer and coworkers have developed an approach for the synthesis of optically pure berbines. The steps involved are presented in Chart VIIIe. Very recently\(^\text{66}\) Napolitano and coworkers have developed a route for the synthesis of berbines which involves rearrangement of isoindolo-[1,2-b][3] benzazepinium salts. This route is described in Chart VIIIif.
a. Method due to Hillard et al.\textsuperscript{61}

\[
\begin{align*}
\text{MeO} & \quad \text{NH}_2 \\
\text{MeO} & \quad \text{MeO} \\
\end{align*}
\]

\[
\begin{align*}
& \xrightarrow{\text{HCOOMe, MeOH}} \\
& \quad \xrightarrow{\text{POCl}_3} \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad (\text{Me})_3\text{Si} - \equiv \text{CH}_2\text{MgBr, THF} \\
\text{MeO} & \quad \text{H} - \equiv \text{CH Br, HMPA, THF} \\
\end{align*}
\]

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

\[
\begin{align*}
& \xrightarrow{\text{KOH, EtOH}} \\
& \quad \xrightarrow{\text{CpCo(CO)}_2} \\
\end{align*}
\]

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

\[
\begin{align*}
& \xrightarrow{\text{HBr/CH}_2\text{Br or CF}_3\text{COOH, CCl}_4} \\
\end{align*}
\]

\[
\begin{align*}
R_1 & \quad R_2 \\
\text{a} & \quad \text{SiMe}_3 \quad \text{SiMe}_3 \\
\text{b} & \quad \text{OMe} \quad \text{SiMe}_3 \\
\text{c} & \quad \text{SiMe}_3 \quad \text{OMe} \\
\end{align*}
\]

b. Method due to Pandey and Tiwari\textsuperscript{62}

\[
\begin{align*}
\text{MeO} & \quad \text{NH}_2 \\
\text{MeO} & \quad \text{MeO} \\
\end{align*}
\]

\[
\begin{align*}
& \xrightarrow{\text{CO, Pd (OAc)}_2} \\
& \quad \xrightarrow{\text{PPh}_3, \text{Bu}_3\text{N}} \\
\end{align*}
\]

(Chart VIII contd.)
c. Method due to Stambach and Jung

\[
\begin{align*}
R & \quad R_1 & \quad R_2 \\
\text{COC}_2 \quad \text{ZnCl}_2 & \xrightarrow{} & \text{LiAlH}_4 \\
\end{align*}
\]

\[
\begin{align*}
R & \quad R_1 & \quad R_2 \\
H & \quad H & \quad H \\
\text{OMe} & \quad \text{OMe} & \quad \text{OMe} \\
\text{OMe} & \quad H & \quad H \\
\end{align*}
\]

d. Method due to Ognyanov et al.

\[
\begin{align*}
\text{MeO} \quad \text{MeO} & \quad + & \quad \text{MeO} \\
\text{MeO} \quad \text{MeO} & \quad \text{OBe} & \quad \text{Ac}_2 \quad \text{O} & \quad \text{OBe} & \quad \text{MeO} \\
\text{MeO} \quad \text{MeO} & \quad \text{OBe} & \quad \text{MeO} \\
\text{2 Steps} & \quad \rightarrow & \quad \text{MeO} \quad \text{MeO} \\
\end{align*}
\]

e. Method due to Meyers et al.

\[
\begin{align*}
\text{MeO} \quad \text{MeO} & \quad + & \quad \text{MeO} \quad \text{MeO} \\
\text{MeO} \quad \text{MeO} & \quad \text{OBe} & \quad \text{Ac}_2 \quad \text{O} & \quad \text{OBe} & \quad \text{MeO} \\
\text{MeO} \quad \text{MeO} & \quad \text{OBe} & \quad \text{MeO} \\
\text{2 Steps} & \quad \rightarrow & \quad \text{MeO} \quad \text{MeO} \\
\end{align*}
\]

(Chart VIII contd.)
1. t-BuLi, THF -78°
2. 3,4-(OMe) \_2 C_6H_3CH_2Br
3. NH_2NH_2, aq. EtOH, AcOH.

f. Method due to Napolitano et al. 66

10% Pd-C/H_2
1 atm

(Chart VIII contd.)
1. LiAlH₄
2. MeI

KOH

AgOAc

C₆H₅CH₃
Acetonitrile
Δ sealed tube
2. Borane, THF, Δ

Chart VIII
7. **Present work**

In the present work, heteroatom directed lithiation reaction has been used for the synthesis of various berbines including some berbine alkaloids. The synthesis of recently isolated, unique protoberberine alkaloid, (+) bharatamine, having unoxygenated D ring has been achieved. (+) Isobharatamine has also been synthesised by making use of isochroman-3-one. A method has been developed for the synthesis of 1-methyl- and 1-aryl-7,8-dimethoxyisochroman-3-ones which could be used for the synthesis of 8-substituted berbines and some lignans. 8-Methyl- and 8-phenyl-2,3,9,10-tetramethoxy berbines have been synthesised by making use of the corresponding 1-methyl- and 1-phenyl-7,9-dimethoxyisochroman-3-ones. The stereochemistry of these compounds has also been established. 4'-Methylisochroman-3-ones have been synthesised by two different methods. These isochromanones have been used for the synthesis of 13-methylberbines.
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