PART-I

SYNTHETIC STUDIES ON PROTOBERBERINE ALKALOIDS: ON THE STRUCTURES OF GLABRINE AND GLABRININE FROM STEPHANIA GLABRA
SECTION-A

THE PROTOBERBERINE ALKALOIDS

The protoberberines, among the important alkaloids, have broad spectrum of activities viz. antimicrobial, tranquilizing, hypotensive, antitubercular and many others. Several research workers isolated and characterised a number of naturally occurring protoberberines from the plant sources, synthesized them by different routes in order to settle their structure and stereochemistry, and also carried out a wide variety of interesting chemical reactions. The important syntheses, reactions and other characteristics of protoberberines reported till 1977 have been elegantly highlighted by M. Shammas.1,2,3

Protoberberine alkaloids, widely distributed in nature, are generally found in the form of tetrahydroderivatives, e.g. norcoraldehyde4 (A), quaternary salts e.g. palmatine5 (B), a few in

\[
\begin{align*}
A & \quad B \\
\text{H}_3\text{CO} & \quad \text{H}_3\text{CO} \\
\text{H}_3\text{CO} & \quad \text{H}_3\text{CO} \\
\text{OCH}_3 & \quad \text{OCH}_3 \\
\text{OCH}_3 & \quad \text{OCH}_3 \\
\end{align*}
\]

the form of quaternary N-methyltetrahydroprotoberberine (C) as well as N-oxides (D). In some cases hydroxyl or methoxyl groups may be present in some cases hydroxyl or methoxyl groups may be present. In some cases hydroxyl or methoxyl groups may be present at C-1 and in a few cases C-13 or C-5 may have alcoholic hydroxyl group. In a few cases a methyl group is also present at C-13 or C-3 position. Retroprotoberberines i.e., one additional carbon as a side chain bonded to ring D are also known.

Protoberberines having oxygen function at 2,3,9,10-positions are generally derived from the appropriate benzylisoquinoline either by the oxidative cyclisation of N-methyl function or by Mannich type condensation with formaldehyde. Some of the isoquinoline alkaloids

(for example aporphines leucoxine\textsuperscript{12}, ocopodine\textsuperscript{12,13} and dehydroocopodine\textsuperscript{14} etc.) are known to contain three oxygen functions in ring D. Recently two unusual protoberberine alkaloids which also contain three oxygen functions in ring D have been isolated by Dr. Patra and his co-workers\textsuperscript{15}. These unusually oxygenated aporphines as well as berbenoids may be formed in nature from normal isoquinolines as appropriate by a subsequent oxygenation. However, the isolation of polycarpine\textsuperscript{16} and the easy derivation of this and a related compound from the appropriate protoberberines\textsuperscript{17} revealed that the unusually oxygenated isoquinoline alkaloids (viz. aporphines, protoberberines etc.) containing three oxygen functions in ring D may also be derived from polycarpine type compounds as shown in Scheme 1.1.

The photocyclization of nonphenolic benzylisoquinoline enzmides and enurethans to aporphinoids is a well established transformation\textsuperscript{13} (Scheme 1.2). The natural aporphines with three oxygen functions in ring D may also be formed following a more or less similar route.

Thus polycarpinoids may serve as the precursor of all the aporphinoids and berbenoids with three oxygen functions in ring D.

In order to establish the structure of the unusually oxygenated protoberberoids glabrine and glabrinine isolated from Stephanie glabra the present investigator has undertaken the synthesis of penta-oxygenated

Scheme 1.1 Conversion of polycarpine into protoberberines.

\[ R = \text{CH}_3, \text{Polycarpine} \]

\[ R + R = \text{-CH}_2 -, \text{(-)-Ledecarine} \]

\[ \text{(Corydalis ledebouriana)} \]

Scheme 1.2
protoberberine alkaloids having three oxygen functions in different positions of ring D. Before proceeding to the syntheses of the protoberberines an up-to-date survey on the syntheses, and reactions of protoberberines were made.

In the recent years two new group of protoberberine alkaloids have been isolated. Solidaline\textsuperscript{19} (10), a modified protoberberine alkaloid was isolated from Corydalis solida. L-8-oxotetrahydropalmatine\textsuperscript{20} (11), a new oxoprotoberberine alkaloid, was isolated from Anamirta cocoulus. The chemistry and reactions of these two new alkaloids are also presented here.

![Solidaline](image1)

\textbf{10 (Solidaline)}

![L-8-Oxotetrahydropalmatine](image2)

\textbf{11 (L-8-Oxotetrahydropalmatine)}

**SOLIDALINE:**

Spectral analysis of solidaline, C\textsubscript{23}H\textsubscript{27}NO\textsubscript{6}, did not permit unequivocal assignment to any known group of isoquinoline alkaloids. The mass spectrum, however, indicated a protoberberine alkaloid: fragment ions at m/e 206 (C\textsubscript{12}H\textsubscript{14}O\textsubscript{3}) and 207 (C\textsubscript{11}H\textsubscript{13}NO\textsubscript{3}) which together


comprise the entire molecule, may readily arise from molecular ion at m/e 413 by a fragmentation characteristic of this class of alkaloid. Spectral data showed the presence of nonphenolic hydroxy, one tertiary C-methyl, four methoxy groups, and two tetrasubstituted aromatic rings. The $^1$H NMR data although suggestive of a protoberberine skeleton, were not uniquely interpretable, but a combination of $^1$H NMR data and $^{13}$C NMR data enabled Richard et al. to assign tentatively structure 10 to solidaline.

Structure 10 accounts for all the major fragment ions of the mass spectrum shown below. The fragmentation (Scheme 1.3) were parallel to the pattern observed for the protoberberine alkaloids. The failure of the ion at m/e 207 to lose hydrogen giving a full aromatic system (as observed with protoberberine alkaloids) may be attributed to the presence of oxygen at C-14.

Comparison of the $^{13}$C NMR spectra of 10 with that of corydalmine, mesocorydaline, ophiocarpine and hydrastine strengthened the proposed structure 10 for solidaline. The $^{13}$C NMR assignments of 10 are given below:

| $^{13}$C NMR SIGNALS OF SOLIDALINE (CDCl$_3$, $^5$) |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| C$_1$           | C$_2$           | C$_3$           | C$_4$           | C$_{4a}$        | C$_5$           | C$_6$           | C$_7$           | C$_{8a}$        |
| 113.0*          | 146.1*          | 147.9*          | 110.9*          | 130.0           | 30.7            | 46.3            | 60.9            | 126.9           |
| C$_9$           | C$_{10}$        | C$_{11}$        | C$_{12}$        | C$_{12a}$       | C$_{13}$        | C$_{14}$        | C$_{14a}$       | C$_{15}$        |
| 150.7           | 149.6*          | 111.7*          | 123.6           | 134.2           | 69.0            | 78.3            | 130.0           | 22.2            |
| C$_{16}$        | C$_2$-OMe       | C$_3$-OMe       | C$_9$-OMe       | C$_{10}$-OMe    |                 |                 |                 |                 |
| 68.7            | 55.9            | 56.0            | 60.9            | 55.9            |                 |                 |                 |                 |

*Tentative assignments
Scheme 1.3 Mass fragmentation pattern of solidalin.
The structure is also compatible with the irreversible change observed in the uv spectrum of solidaline on heating with acid. Addition of acid at room temperature caused a reversible change in the spectrum but on heating a further irreversible change occurred. This phenomena is interpreted as resulting from a reversible immonium ion-carbinolamine ether equilibrium followed by a dehydration as shown below under more vigorous acidic condition.

L-8-Oxotetrahydropalmatine

This tertiary alkaloid was isolated from the stem and roots of *Anamirta cocoulus*.*20* The structure of this new alkaloid was proved by means of UV, MS, \(^1\)H NMR and \(^{13}\)C NMR spectrometry and chemical conversion into 1-tetrahydropalmatine.

In the \(^1\)H-NMR, signals of four methoxy groups at \(\delta\) 4.023 and 3.893 (3 \times OCH\(_3\)) were observed. Furthermore, an AB doublet at \(\delta\) 6.397, 6.973, 6.987, 7.07 \((\text{H}_1, \text{H}_2)\) and a two proton singlet at \(\delta\) 6.684 \((\text{H}_3, \text{H}_4)\) were observed in the aromatic region. From these data it was concluded that the alkaloid was a protoberberine derivative, most likely a tetrahydropalmatine derivative. This was further confirmed by means of \(^{13}\)C NMR spectra. The \(^{13}\)C NMR signal assignments are given below:

\[\text{\(^{13}\)C NMR SIGNALS OF L-8-OXOTETRAHYDROPALMATINE (\(\delta\))}\]

<table>
<thead>
<tr>
<th>C(_1)</th>
<th>C(_2)</th>
<th>C(_3)</th>
<th>C(_4)</th>
<th>C(_{4a})</th>
<th>C(_5)</th>
<th>C(_6)</th>
<th>C(_7)</th>
<th>C(_8a)</th>
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<tr>
<td>109.0</td>
<td>147.8</td>
<td>147.3</td>
<td>111.3</td>
<td>127.6</td>
<td>29.4</td>
<td>39.2**</td>
<td>162.6</td>
<td>123.5*</td>
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</table>

<table>
<thead>
<tr>
<th>C(_9)</th>
<th>C(_{10})</th>
<th>C(_{11})</th>
<th>C(_{12})</th>
<th>C(_{12a})</th>
<th>C(_{13})</th>
<th>C(_{14})</th>
<th>C(_{14a})</th>
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<tr>
<td>153.0</td>
<td>152.9</td>
<td>115.1</td>
<td>121.9</td>
<td>127.4*</td>
<td>38.1**</td>
<td>54.9</td>
<td>130.3*</td>
</tr>
</tbody>
</table>

\(\text{C}_2-\text{OMe}\) \(\text{C}_3-\text{OMe}\) \(\text{C}_9-\text{OMe}\) \(\text{C}_{10}-\text{OMe}\)

| 56.5***| 56.5***| 61.5 | 55.9***|

*, ** and *** are interchangeable
The singlet at $\delta$ 162.6 ppm pointed to the presence of a lactam function, i.e., substitution on C$_6$ or C$_9$. The signal of C$_5$ was observed at $\delta$ 29.4, which was very similar to the shift of this carbon in tetrahydropalmatine (29.1 ppm) and canadine (29.5 ppm)\textsuperscript{22}. Therefore it was concluded that the substitution was in the C$_3$-position. This was confirmed by the 4.0 ppm downfield shift of C-$11$ (compared with benzamide where a 2.7 ppm downfield shift observed for the carbon para to the amide group\textsuperscript{24}).

The alkaloid on reduction with LAH yielded l-tetrahydropalmatine which was identified by means of UV, ms and tlc comparison with a reference compound.

[Chemical structure images]

Synthesis:

Several methods for the synthesis of protoberberine alkaloids are known. Some of them together with the recent developments in this field are discussed below:


A. **Bischler-Napieralski Cyclisation**

Bischler-Napieralski cyclisation is a well established method in the syntheses of protoberberine alkaloids. This involves the closure of either ring B or ring C. Using brominated tetrahydrobenzylisoquinoline formamide heilanthifoline\(^{25}\) and tetrahydrogroenlandicaine\(^{26}\) were synthesized recently. POCI\(_3\) was the cyclising agent in these syntheses. PBr\(_5\) and P\(_2\)O\(_5\) mixture\(^{27}\) or POBr\(_3\) has also been used as cyclising agent in the synthesis of dl-sinactine\(^{23}\), thalictrifoline\(^{27}\) (19) and dl-stylopine. Some of the syntheses were PBr\(_5\) and P\(_2\)O\(_5\) or POBr\(_3\) has been used as cyclising agent as given in Scheme 1.4.

B. From Aminoacids

Berbines were synthesized from \(\alpha\)- (tertiaryamino) acids in high yields through decarbonylation to regiospecific imminium salts followed by acid-catalyzed cyclisation reaction\(^{29}\). The reaction was carried out by brief heating in POCI\(_3\), subsequent addition of water followed by warming (Scheme 1.5).

Syntheses of the \(\alpha\)- (tertiaryamino) acids from various phenylalanines involved, as the key step, the alkylation of 1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid with a 2-phenylethylbromide (Scheme 1.6).

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Scheme 1.4 Synthesis of Thalictriofoline.

1. \( \text{PBr}_5 \) and \( \text{P}_2\text{O}_5 \)
2. \( \text{NaBH}_4 \)

13. \( X = \text{Br} \)
14. \( X = \text{H} \)
15. \( X = \text{H} \)
16. \( X = \text{Br} \)

17.\( \text{H}_3\text{CO} \)
18. Debromination

Thalictriofoline
<table>
<thead>
<tr>
<th></th>
<th>R$_3$</th>
<th>R$_6$</th>
<th>R$_7$</th>
<th>R$_8$</th>
<th>R$_{51}$</th>
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<tbody>
<tr>
<td>20</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>21</td>
<td>H</td>
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<td>OCH$_3$</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>22</td>
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<td>OCH$_3$</td>
<td>OCH$_3$</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>23</td>
<td>H</td>
<td>OCH$_3$</td>
<td>OCH$_3$</td>
<td>H</td>
<td>OCH$_3$</td>
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<tr>
<td>24</td>
<td>H</td>
<td>H</td>
<td>OCH$_3$</td>
<td>OCH$_3$</td>
<td>H</td>
</tr>
</tbody>
</table>

**Scheme 1.5 Synthesis from α-(tertiary amino) acids.**

![Chemical Structure](image1)

<table>
<thead>
<tr>
<th></th>
<th>R$_1$</th>
<th>R$_9$</th>
<th>R$_{10}$</th>
<th>R$_{11}$</th>
<th>R$_{13a}$</th>
</tr>
</thead>
<tbody>
<tr>
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<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>26</td>
<td>H</td>
<td>H</td>
<td>OCH$_3$</td>
<td>OCH$_3$</td>
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</tr>
<tr>
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<td>H</td>
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<td>OCH$_3$</td>
<td>CH$_3$</td>
</tr>
<tr>
<td>28</td>
<td>OCH$_3$</td>
<td>H</td>
<td>OCH$_3$</td>
<td>OCH$_{14}$</td>
<td>H</td>
</tr>
<tr>
<td>29</td>
<td>H</td>
<td>OCH$_3$</td>
<td>OCH$_3$</td>
<td>H</td>
<td>H</td>
</tr>
</tbody>
</table>

**Scheme 1.6 Synthesis of the α-(tertiary amino) acid.**

![Chemical Structure](image2)
The synthesis of isopropyl 1,2,3,4-tetrahydro-7,8-dimethoxy-3-isoquinoline carboxylate, obligatory to the synthesis of 9,10-dimethoxyberbines by the above method utilized a metalation reaction to align four contiguous substituents on the aromatic nucleus followed by a difficult selective reduction on an amide α-to an ester.

C. Photolytic Synthesis

Kametani et al. reported that the photolysis of 35 afforded 32 and 33. However, the photolysis of the hydrochloride of 1-(2'-bromo-5'-hydroxy-4'-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline gave the aporphine dl-laurotetanine, 12-bromoschefferine (34), dl-schefferine (33), dl-corytenchirine (32) and 1-(3'-hydroxy-4'-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (35). Formaldehyde required for the reaction was formed by a 'dark' reaction during photolysis (Scheme 1.7).

D. Thermolysis of Benzocyclobutenes

Conrotatory opening of benzocyclobutenes upon thermolysis is well known and was utilised in the synthesis of coreximine. More recently Kametani et al. applied this technique in the synthesis of corelydine (37) and O-methylocorytenchirine (33) employing the benzo-cyclobutene derivative (36) (Scheme 1.8).

Scheme 1.7 Photolytic Syntheses.

Scheme 1.8 Synthesis of corydalmine (37) and O-methyl corytenchinine (38).
E. From bromoester via Lactam

More recently Tiwari and Pandey reported the syntheses of several protoberberines e.g., (+)-scoulerine (39) and pseudoepitetratherberberines from bromoester derivative via corresponding lactams (Scheme 1.9).

Tiwari and Pandey also reported the synthesis of protoberberine (40) by use of palladium catalysed insertion of carbon monoxide (Scheme 1.10).

F. From homophthalic Anhydride

Recently discovered reaction of homophthalic anhydrides with 3,4-dihydropseudoisoquinolines has been employed by Cushman et al. in synthesizing (+)-corydalmine (43) in which condensation of 3,4-dihydro-6,7-dimethoxyisoquinoline (41) with 3,4-dimethoxyhomophthalic anhydride (42) was utilized (Scheme 1.11).

G. Biomimetic synthesis through N-oxide intermediate

Recently Kametani et al. reported the synthesis of (+)-coreximine (45) and (+)-scoulerine (46) from (+)-reticuline N-oxide (44) by treatment with FeSO₄ in MeOH. Similarly the conversion of orientatine N-oxide (47) to protoberberine was carried out by reaction with FeSO₄, but it required the acidic condition. These are the examples of the synthesis of protoberberines by redox reaction (Scheme 1.12).

Scheme 1.9 Synthesis of (±) - Scoulerine.

Scheme 1.9 Synthesis of (±) - Scoulerine.
Scheme 1.10 Synthesis of Protobserberine by palladium catalysed insertion of carbon monoxide.
Scheme 1.11 Synthesis of (+)-Corydalmine.
Scheme 1.12 Synthesis of protoberberines by redox reaction.
H. From Reissert Compound

A new multistep synthesis of (+)-mecambridine (52) has been achieved starting from 2-benzoyl-1-cyano-1,2-dihydro-3-methoxy-6,7-methylenedioxyisoquinoline (49), a Reissert compound, and 3-benzylxy-4-methoxybenzylchloride (50). 11-O-Demethylmecambridine (53) was also converted into (+)-orientalidine (54) by treatment with NaH/DMF in methylene chloride (Scheme 1.13).

I. By 1,3-asymmetric induction in Photolysis

Total synthesis of optically active xylopine (57) was achieved by irradiation of the enamide (56) as a key reaction. The enamide was synthesised from 55 first by treatment with Ac₂O in pyridine subsequent treatment with phosphoryl chloride followed by reaction of 55a with 3,4-dimethoxy benzoyl chloride (Scheme 1.14).

J. Electroreductive Annellation

Electroreductive annelation reaction of immonium salt (58) led to isomeric berbine type of compound in poor yield (Eq.1). However, controlled potential reduction of immonium salts in the presence of bromoesters such as O-bromomethylbenzoates has afforded annellated products in high yield without contamination with isomers.

Scheme 1.13 Synthesis of (±)-Mecambridine and (±)-Orientalidine.
Phosphoryl chloride in CH$_3$CN at 60°

3,4-dimethoxy benzoyl chloride

i) NaBH$_4$ in MeOH
ii) NaOH in EtOH

$\text{P}_2\text{O}_5$ & celite in Py

Scheme 1.14 Synthesis of (t)-Xylopine
Thus, electroreduction of mixtures of immonium salts 59 or 60 and methyl O-bromo-methylbenzoate (61), afforded cyclised amides 62 to 68 in high yield without contamination with isomers. These reactions probably proceed through reduction of immonium salts to anionic species followed by the attack of the anions on the bromomethyl group of the methyl O-bromomethyl esters and subsequent intramolecular aminolysis of amino esters (69) yielding ε-lactams as exemplified in equation 2.

Reactions

A. Carbon-Nitrogen Bond Cleavages

Various types of carbon-nitrogen bond cleavage are well known in protoberberine alkaloids viz. (i) N-7 to C-3 and N-7 to C-6 bond cleavage\(^{45,46}\) by Hofmann degradation of quaternary N-methyl tetrahydropseudoberberine, (ii) N-7 to C-3 bond cleavage\(^{47}\) by treatment with acetylation agents in presence of NaI, (iii) Nagata's cleavage of N-methyltetrahydropseudoberberine salts at the N-7 to C-14 bond by Birch reduction with Li/NH\(_3\) and through N-oxides formation\(^{48}\).

Very recently Shamma et al. reported an unusual carbon to nitrogen bond cleavage with acyl migration\(^{49}\) as shown in Scheme 1.16.

It is worth noting here the difference between the two key intermediates 70 and 71, both of which incorporate an \(\alpha\)-hydroperoxyketone moiety. The hydroxyl group at C-8 in species 70 furnishes the required source electrons for the rearrangement to take place. On the other hand 71 is a lactam which preferentially undergoes nucleophilic attack by methoxide anion with subsequent cleavage of C-13 to C-14 bond to give rise to methyl\(\alpha\)-hydroberberilate (72).

Ethylchloroformate was also found to be an effective reagent\(^{50}\) C\(_3\)-N bond cleavage takes place when tetrahydroprotoberberines incorporate a trans-quinolizidine conformation. On the other hand tetrahydroprotoberberines having a cis-conformation resulted in exclusive C\(_6\)-N bond cleavage on treatment with this reagent.

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47. Professor H.Ronsch, Private communication, unpublished result.
Scheme 1.15 Heteroatom bond cleavages.
**B. Oxidation**

Oxidation of tetrahydroprotoberberine to quaternary protoberberine by treatment with iodine, mercuric acetate, air, and that of dihydroprotoberberine by CH$_3$I, KMnO$_4$ to quaternary protoberberine together with some bridged derivative and amidoketone derivative are well established. Recently some protoberberines were treated with leadtetraacetate which resulted in some interesting product.

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Lead tetraacetate oxidation of (+)-2-(76) and (+)-10-(77) hydroxytetrahydroprotoberberines afforded the γ-quinolacetates (80) and (81), which on treatment with Ac₂O-conc. H₂SO₄ gave (+)-2,5β-(86), (+)-10,13α-(89) and (+)-10,13β-(90) diacetxytetrahydroprotoberberines respectively. Alkaline hydrolysis of the diacetate 85 produced the (+)-5α-(87) and (+)-5β-(88) methoxy compounds, whereas the similar treatment of the diacetates 89 and 90 produced the same (+)-13α-methoxy derivative 91 while oxidation of (+)-3-hydroxytetrahydroprotoberberine (78) gave directly the (+)-5α-(82) and (+)-5β-(83) acetoxy derivatives. Oxidation of the (+)-11-hydroxy-congener (79) produced the unexpected rearranged product, the (+)-12-acetoxy-9-hydroxy derivative (85), together with a small amount of (+)-13β-acetoxytetrahydroprotoberberine (84).

Shamma et al. also carried out pyridinium chlorochromate oxidation of oxyprotoberberines which on oxidation followed by methanol work-up, led to 3,13-dioxo-14-methoxyberberines as shown below.
Conversion of protoberberines to phthalideisoquinolines have been carried out by Kondo et al. The phthalideisoquinoline 94 was derived from 92 via 93 by dye-sensitized photooxygenation followed by treatment with sodium borohydride (Scheme 1.17).

Shamma et al. also succeeded in converting berberine (95) to a 1:2 mixture of (+)-α-hydrastine (97) and (+)-β-hydrastine (98) via a dimeric oxybisberberine and 3-methoxyberberinephenolbetaine (96). Ferricyanide oxidation of 95 yielded a dimer whose breakdown with methanolic HCl gave 3-methoxyberberinephenolbetaine (96). Hydration of 96 in wet ether furnished an enaminol (99), which was N-methylated to dehydrohydrastine methylester (99a), NaBH₄ reduction of which led to the final product. This was the first report of conversion of berberine to (+)-α-hydrastine (97) and (+)-β-hydrastine (98).

Scheme 1.17 Conversion of Protobberberine into Phthalideisoquinoline.
D. Conversion of Protoberberine into Aziridine derivatives

3-Methoxyberberinephenolbetaine derived from berberine, has been demonstrated to furnish a variety of ring systems such as the phthalideisoquinoline53-55, the 13-oxoberbine56, the spirobenzylisoquinoline57, methyl isoanhydroberberilate57,58, the 3,14-ethenoberbine59 and the 8H-isoquinol[2,1-b][2]benzazocine59. A further transformation60 of the berberinephenolbetaines (100) into the aziridine derivatives, 3,14-cyclo-berbines (101) by photochemical valence tautomerization and a synthesis of spirobenzylisoquinolines (102) by regioselective bond cleavage have now been reported. Irradiation of berberinephenolbetaines 100 afforded aziridine derivatives 101. Heating of 101a in benzene with ethylchloroformate provided regioselectively the amorphous spirobenzylisoquinoline (102). On similar treatment with ethyl chloroformate, the aziridines (101b and 101c) afforded the methylidene and ethylidene-spiro compounds 103 and 104 and the methyl iodide treatment of 101b and 101c in acetone effected both N-methylation and Hofmann elimination resulting 105 and 106 (Scheme 1.18).

E. Enamine Reactions of Dihydroberberines

Several derivatives of berberine (107) have been prepared from dihydroberberine (108a), 8-acetonyldihydroberberine (108b) and 8-benzyl-dihydroberberine (108c) by making use of their enamine character.

Scheme 1.18 Conversion of Protoberberine into Aziridine derivatives.
108  
\[ \text{a, } R_1 = R_2 = H \]
\[ \text{b, } R_1 = \text{Ph}, R_2 = \text{CH}_2 \text{Ph} \]
\[ \text{c, } R_1 = H, R_2 = \text{CH}_2 \text{Ph} \]

109  
\[ \text{a, } R_1 = \text{Ph} \]
\[ \text{b, } R_1 = R_2 = \text{CH}_2 \text{Ph} \]

110  
\[ \text{a, } R_1 = \text{Ph} \]
\[ \text{b, } R_1 = R_2 = \text{CH}_2 \text{Ph} \]

107  
\[ \text{a, } R_1 = \text{Ph} \]
\[ \text{b, } R_1 = R_2 = \text{CH}_2 \text{Ph} \]

111a  
\[ \text{a, } R_1 = \text{Ph} \]
\[ \text{b, } R_1 = R_2 = \text{CH}_2 \text{Ph} \]

111  
\[ \text{a, } R_1 = \text{Ph} \]
\[ \text{b, } R_1 = R_2 = \text{CH}_2 \text{Ph} \]

111b  
\[ \text{a, } R_1 = \text{Ph} \]
\[ \text{b, } R_1 = R_2 = \text{CH}_2 \text{Ph} \]

111c  
\[ \text{a, } R_1 = \text{Ph} \]
\[ \text{b, } R_1 = R_2 = \text{CH}_2 \text{Ph} \]
Alkylation of dihydroberberine (108a) with benzylbromide yielded 13-benzyldihydroberberinium bromide (109a) which was reduced with sodium borohydride to the tetrahydroderivative (110a). Similarly alkylation of 103b with benzylbromide yielded the salt 109b which on similar reduction afforded 8,13-dibenzyltetrahydroberberine (110b). Reaction of dihydroberberine (108a) with dimethylacetylenedicarboxylate resulted in cycloaddition followed by ring expansion of the adduct (111a) in a manner encountered in enamines62 to yield the diester 111.

Reaction of 103a with p-toluenesulphonyl azide and p-acetamido-benzenesulphonyl azide resulted in introduction of the arylsulphonamido residue at C-13 followed by oxidation at C7-C8 to yield the betaines (111b and 111c).

F. Conversion of Coptisine iodide to Peshwarine.

The conversion of coptisine (112), a quaternary protoberberine alkaloid to peshwarine (115), a new type of isoquinoline alkaloid, in the racemic form was recently carried out by Shamma et al.63. This conversion involved a novel approach to cyclic hemiacetals in which the key step was the transformation of the aldehyde (113) into hemiacetal (114) (Scheme 1.19).

G. The Photolysis of Berbine-N-oxides.

Recently Shamma et al. carried out the photolysis64 of transcyanadine N-oxide (116) which led to lactam (117) and formamide (118).

Scheme 1.19 Conversion of coptisine iodide to peshwarine (115).
Similarly, the photolysis of trans-xylopine N-oxide (119) produced lactam 120 and amide 121. Oxaziridine 122 was a probable intermediate in these transformations, so that the selective oxidation of the berbine nucleus at C-6 had been achieved, accompanied by fission of the N-7 to C-14 bond. LAH reduction of lactam 117 gave rise to dibenzazecine 123, while similar treatment of amide 118 generated dibenzazonine 113a. Alternatively, acid hydrolysis of 113 furnished dibenzazonine 113b.

H. 1,3-Dipolar Cycloaddition Reaction.

Cycloaddition of the berberinephenolbetaine 124 \( \text{R} = \text{OCH}_3 \) with acetylenes gave the cycloadducts 125 \( \text{R}^1 = \text{R}^2 = \text{COOCH}_3, \text{COPh}; \text{R}^1 = \text{CO}_2 \text{CH}_3, \text{CO.CH}_3, \text{R}^2 = \text{H}; \text{R}^1 = \text{H}, \text{R}^2 = \text{COOCH}_3, \text{COCH}_3 \) which underwent thermal isomerization to give the isoquinobenzazocines 126. 124 \( \text{R} = \text{H} \) and acetylenes similarly gave 126.

I. Transformation of tetrahydroberberine to retroprotoberberine.

In continuation of the research work (Vide reaction A) Imanishi et al. succeeded in synthesising a retroprotoberberine derivative. The retroprotoberberine was synthesised from tetrahydroberberine via the formation of urethane and amino alcohol.

ON THE STRUCTURES OF GLABRINE AND GLABRININE : SYNTHESIS OF PENTA-OXYGENATED PROTOBERBERINES AND OF NORCORALYDINE

The alkaloidal extract from the tubers of Stephanie glabra, a member of the family Menispermaceae, was recently the subject of chemical investigation in our laboratory\(^6\). This study has led to the isolation of several protoberberine alkaloids. Four of them were quaternary protoberberines, namely, palmatine\(^6,\)\(^69\) (1), palmatrubine\(^69\) (2), dehydrocorydalmine\(^6,69\) (3) and stepharanine\(^6,69\) (4), and the other three were tetrahydroprotoberberine alkaloids, namely, tetrahydropalmatine\(^6,70\) (5), corydalmine\(^6,70\) (6), stepholidine\(^6,70\) (7). This was probably the first isolation of palmatrubine from a plant source\(^69\). In addition two unusually oxygenated quaternary protoberberine alkaloids glabrine\(^71\) (8) and glabrinine\(^71\) (9) were also isolated. The oxygenation pattern in glabrine and glabrinine were tentatively assigned from their various spectral data as well as of their derivatives.

Glabrine (8) and glabrinine (9) were readily converted to tetrahydroderivatives viz. 10 and 11, when treated with \(\text{NaBH}_4\) in

---

1: $R = CH_3$

2: $R = H$

3: $R = CH_3$

4: $R = H$

5: $R_1 = R_2 = CH_3$

6: $R_1 = CH_3, R_2 = H$

7: $R_1 = R_2 = H$

8: $R_1 = R_2 = H$

9: $R_1 = CH_3, R_2 = H$

10: $R_1 = R_2 = H$

11: $R_1 = CH_3, R_2 = H$
methanol and the methyl ethers of 3 and 9 were identical. The UV spectrum of glabrine and glabrinine as well as of the tetrahydroderivatives were characteristics of quaternary protoberberines and tetrahydroprotoberberines, respectively, as appropriate. The PMR spectra of glabrinine, its tetrahydroderivative and its monomethylether suggested the presence of four methoxyl groups and a hydroxyl function in 9. Similarly glabrine (3) was found to have three methoxyl and two hydroxyl functions. The mass spectra of tetrahydroglabrine (10) and tetrahydroglabrinine (11) were typical of tetrahydroprotoberberines and showed the presence of an intense ion peak at m/e 192 indicative of the presence of two methoxyl functions in ring A in each of them. The PMR spectra showed the presence of two singlets integrating for one proton each at $\delta$ 6.72 and 6.81 in tetrahydroglabrine (10) and $\delta$ 6.72 and 6.60 in tetrahydroglabrinine (11). Similar signals were present in the PMR spectra of tetrahydropalmatine (69) (6.71 for $C_1$-H and 6.61 for $C_4$-H), corydalmine (69) (6.70 for $C_1$-H and 6.60 for $C_4$-H) and other related alkaloids with methoxyls at C-2 and C-3. Thus the two methoxyl groups in glabrine and glabrinine were at C-2 and C-3 positions. The mass spectrum showed also intense ion peaks at m/e 149 and 135 in 10 and at m/e 179, 164 and 149 in 11 which strongly suggested the presence of three oxygen functions in ring D i.e., two methoxyl and a hydroxyl for tetrahydroglabrinine whereas one methoxyl and two hydroxyl for tetrahydroglabrine. The easy loss of elements of hydrogen in the mass spectrum of the latter also suggested that the two hydroxyl should be either ortho or para oriented.
The three oxygen functions in ring D may be arranged in any one of the following ways:

Since all the protoberberines are invariably oxygenated either at C-9 and C-10 or C-10 and C-11 the oxygenation pattern as shown in formulation D is biogenetically unlikely. The pentaoxygenated protoberberine may be formed by further oxygenation of either 9,10 or 10,11-oxygenated berbenoids leading to formulation A. The recent isolation\(^{17}\) of polyar pine (12) and its derivation to berbenoids revealed the possibility of arrangement of oxygen functions as in B (palmatine or palmatrubine acting as precursor) and of the formulation C (norcoralydine acting as precursor).
The first objective of the investigator was to settle the oxygenation pattern in glabrine and glabrinine. The investigator was successful in synthesizing (±)-2,3,9,10,11-pentaoxygenated tetrahydroprotoberberine (13) and its quaternary salt (16), (±)-2,3,10,11,12-pentaoxygenated tetrahydroprotoberberine (14) and attempted the synthesis of (±)-2,3,9,10,12-pentaoxygenated tetrahydroprotoberberine (15). The synthesis of a retroprotoberberine ((±)-12-methoxy-2,3,9,10,11-pentamethoxytetrahydroprotoberberine (43) was achieved. A new and convenient synthesis of (±)-norcoralydine (40) was also achieved. 2,3,9,10,11-pentaoxygenated derivative (13) was identical with methyl ethers of glabrine and glabrinine. Various spectral data of 13, 14, 15 and also a comparative study of the PMR spectral data of the synthetic protoberberines as well as of the natural product given below also corroborated this view.

Thorough examination of the Table 1 revealed that 10 and 11 exhibited a one proton doublet at about $\delta$ 4.20-4.30 ($J = 16$ Hz) which is the characteristics for 9,10-oxygenated protoberberines72,73. The synthetic protoberberines 13 and 15 also showed the similar doublet at $\delta$4.10 ($J = 16$ Hz) and $\delta$ 4.21 ($J = 16$ Hz), respectively but 14 did not show similar doublet in this region. So the oxygenation pattern in glabrine (8) and glabrinine (9) should be similar to those in 13 or 15 but not like that of 14. In the spectrum of tetrahydroglabrine methyl ether $\equiv$ glabrinidimethyl ether (13), the

12: $\text{Ba} = \text{OCH}^\text{3}$

$\text{B_2} = \text{H}$

13: $\text{R}_2 - \text{OCH}_3$, $\text{R}_x = \text{H}$

14: $\text{R}_2 = \text{OCH}_3$, $R_1 = \text{H}$

15

16

17
ring D aromatic proton signal appeared at $\delta 6.48$ as singlet whereas in 15, H-11 appeared at $\delta 6.38$. Thus glabrine and glabrinine should have oxygen functions at C-9, C-10 and C-11. ($\pm$)-10-Hydroxy-2,3,9,11-tetramethoxytetrahydroprotoberberine (17) was also synthesised and its spectral properties were studied. 17 was shown to be not identical with tetrahydroglabrine.
Table 1

Comparison of the PMR spectrum of 10, 11, 13, 14 and 15 (\(\delta\), CDCl₃)

<table>
<thead>
<tr>
<th></th>
<th>10</th>
<th>11</th>
<th>13</th>
<th>14</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₁-H</td>
<td>6.72,s</td>
<td>6.72,s</td>
<td>6.71,s</td>
<td>6.73,s</td>
<td>6.73,s</td>
</tr>
<tr>
<td>C₄-H</td>
<td>6.60,s</td>
<td>6.61,s</td>
<td>6.61,s</td>
<td>6.61,s</td>
<td>6.59,s</td>
</tr>
<tr>
<td>C₉-H</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6.40,s</td>
<td>-</td>
</tr>
<tr>
<td>C₁₁-H</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6.33,s</td>
</tr>
<tr>
<td>C₁₂-H</td>
<td>6.72,s</td>
<td>6.72,s</td>
<td>6.43,s</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C₈-H</td>
<td>4.20,d ((\beta)-H)</td>
<td>4.20,d ((\beta)-H)</td>
<td>4.10,d ((\beta)-H)</td>
<td>3.96 ((\alpha)-H)</td>
<td>4.21 ((\alpha)-H)</td>
</tr>
<tr>
<td></td>
<td>J = 16Hz</td>
<td>J = 16Hz</td>
<td>J = 16Hz</td>
<td>J = 6.2Hz</td>
<td>J = 16Hz</td>
</tr>
<tr>
<td>OCH₃</td>
<td>3.83,s</td>
<td>3.83,s</td>
<td>3.91,s</td>
<td>3.38,s</td>
<td>3.38,s</td>
</tr>
<tr>
<td>OCH₂</td>
<td>3.80,s</td>
<td>3.82,s</td>
<td>3.89,s</td>
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<td>3.87,s</td>
<td>3.85,s</td>
<td>3.85,s</td>
</tr>
<tr>
<td>OCH₃</td>
<td>3.74,s</td>
<td>3.85,s</td>
<td>3.85,s</td>
<td>3.32,s</td>
<td>3.73,s</td>
</tr>
</tbody>
</table>
The present section describes the details of the synthetic work undertaken by the investigator.

SYNTHESIS OF 2,3,9,10,11-PENTAMETHOXYPROTOBERBERINIUM SALT AND ITS IDENTIFICATION WITH GLABRININE METHYL ETHER (≡ GLABRINE DIMETHYL ETHER)

The literature contains a large number of references relating to the synthesis of protoberberines. The protoberberines can be synthesised either by Bischler-Napieralski cyclisation to generate either ring B\textsuperscript{75} or the ring C\textsuperscript{76,77} of the protoberberine or the Mannich condensation to construct the ring C\textsuperscript{78,79}. The other methods of the synthesis include the use of isoquinoline-1-carboxaldehydes\textsuperscript{30-32}, protopines\textsuperscript{33}, phthalisoquinolines\textsuperscript{34}, spirobenzylisoquinolines\textsuperscript{35}, dihydroisoquinolines\textsuperscript{36-39}, methylvinylketone\textsuperscript{90}, enamido-photocyclisation\textsuperscript{91,92}, thermolysis of benzocyclobutenes\textsuperscript{93,94}, Pomeranz-Fritsch cyclisation\textsuperscript{95} and variants on the Bischler-Napieralski cyclisation\textsuperscript{96-98}. However, most of these methods are not satisfactory for large scale synthesis of protoberberines.

Pictet-Gaafs cyclisation\textsuperscript{99,100}, a common method by which these tetracyclic bases have been prepared in the past, is undoubtedly

\begin{itemize}
\item \textsuperscript{78} H.Pictet and A.Gams, \textit{Ber.}, 44, 2480 (1911).
\item \textsuperscript{80} C.K.Bradsher and J.H.Jones, \textit{J.Org.Chem.}, 23, 430 (1953).
\item \textsuperscript{81} C.K.Bradsher and N.L.Dutta, \textit{J.Am.Chem.Soc.}, 82, 1145 (1960).
\end{itemize}
the best method for the generation of these carbon skeleton. This route utilizes a tetrahydrobenzylisoquinoline which on treatment with formaldehyde undergoes Mannich condensation resulting in closure of the C ring. In general, the product is the 10,11-substituted tetrahydroprotoberberine. In most cases 9,10-isomer can be prepared by the use of bromine blocking group in the appropriate position on the benzyl moiety of the starting benzylisoquinoline derivative. But there is some disadvantage of the method because blocked bromine usually results in the reduced yields due to deactivation of the aromatic ring.

The required protoberberine alkaloid 16 (2,3,9,10,11-pentamethoxyprotoberberinum salt) has been synthesised by two separate routes. The first route was through the intermediacy of a N-formylbenzylisoquinoline and the second one was starting from an isochromanone derivative.

1st route

The required N-formylbenzylisoquinoline was obtained by the condensation between homoveratrylamine and 3,4,5-trimethoxyphenylacetyl chloride, subsequent cyclisation, reduction followed by formylation with formic acid.

The ultimate synthons for the synthesis was commercially available vanillin, which was converted to the corresponding \( \beta \)-phenylethylamine (homoveratrilyamine) (26). Gallic acid (18) was transformed into the required phenylacetic acid derivative (23) as shown in the Scheme 1.20.

Gallic acid (18) was converted to methylgallate-trimethyl-ether, in 80% yield, using dimethylsulphate and potassium carbonate in dry acetone. The product, m.p. 82° (lit. m.p. 80-80°), exhibited IR band at 1710 cm\(^{-1}\) indicating the formation of the ester derivative. The absence of peak in the region 3300-3500 cm\(^{-1}\) in the IR spectrum indicated the absence of free \(-\text{OH}\) group in the product. The PMR spectrum of the compound in CDCl\(_3\) confirmed the desired structure was 19 which exhibited the signals at 5.4 (2H, s) and 7.4 (2H, s). The structure was also confirmed by its \(^{13}\)C-NMR signals (vide Part II, Table 1).

![Scheme 1.20](image-url)
Ester 19 was cleanly reduced with lithium aluminium hydride in tetrahydrofuran to 3,4,5-trimethoxybenzylalcohol 20 in 70% yield as viscous liquid\(^{102}\), b.p. 172-6° at 2.5 mm. The presence of IR bands at 3500-3300 cm\(^{-1}\) (br) indicated the formation of an alcohol derivative. The PMR spectrum of the compound which exhibited the signals at \(\delta 3.35\) (3H, s, OCH\(_3\)), \(3.37\) (6H, s, 2 x OCH\(_3\)), \(4.75\) (2H, s, CH\(_2\)OH), 6.60 (2H, s, Ar-H) and the \(^{13}\)C-NMR signals (vide Part II, Table 1) of the compound confirmed the structure of the alcohol as 3,4,5-trimethoxybenzylalcohol (20).

Treatment of 20 with \(\text{PBr}_3\) in triethylamine and carbontetrachloride afforded the required 3,4,5-trimethoxybenzylbromide (21), (yield 30%), m.p. 72-4°, after chromatographic purification and repeated crystallisation from chloroform-petrol. It was found to be very unstable and darkened on standing at room temperature. Compound 21 exhibited PMR signals at \(\delta 3.82\) (2H, s, CH\(_2\)Br), 3.86 (3H, s, OCH\(_3\)), 3.88 (6H, s, 2 x OCH\(_3\)) and 6.61 (2H, s, Ar-H). \(^{13}\)C-NMR signals of the compound (vide Part II Table 1) were also in good agreement with the structure.

Bromide 21 was treated with sodium cyanide in dimethylsulfoxide under nitrogen atmosphere at room temperature. Usual work up and chromatography afforded (yield 75%) 3,4,5-trimethoxyphenylacetonitrile \( (\text{22}) \), m.p. 77-30° (lit. 79°). The presence of IR peak at 2240 cm\(^{-1}\) indicated the formation of nitrile, the structure of which was finally confirmed by PMR and \(^{13}\)C NMR spectra (vide \textit{footnote} II, Table 1). The PMR signals were at \(\delta 3.71 \text{ (2H, s, CH}_2\text{, s, CCH})\), \(\delta 3.36 \text{ (3H, s, OCH}_3\text{)}\), \(\delta 6.53 \text{ (2H, s, Ar-H)}\).

\(\text{22}\) was hydrolysed with 3N alcoholic potassium hydroxide to give rise to 92% yield of 3,4,5-trimethoxyphenylacetic acid, m.p. 121° (chloroform-petrol) (lit. 104 m.p. 122°, lit. 105 m.p. 120°). It exhibited IR bands at 1695 cm\(^{-1}\) which indicated the presence of carboxylic group. The compound displayed PMR signals at \(\delta 3.59 \text{ (2H, s, H}_2-1'\text{)}\), \(\delta 3.36 \text{ (9H, s, 3 x OCH}_3\text{)}\), \(\delta 6.51 \text{ (2H, s, Ar-H)}\) and \(^{13}\)C-NMR signals (vide \textit{footnote} II) at \(\delta 41.1 \text{ (C-1')}, 66.0 \text{ (C}_3\text{-OCH}_3\text{ and C}_5\text{-OCH}_3\text{)}\), \(60.7 \text{ (C}_4\text{-OCH}_3\text{)}\), \(106.5 \text{ (C-2 and C-6)}\), \(128.7 \text{ (C-1)}\), \(137.3 \text{ (C-4)}\), \(153.2 \text{ (C-3 and C-5)}\) and \(177.0 \text{ (CO)}\) which were in good agreement with its structure 23.

Veral-aldehyde, on the otherhand, was condensed with nitromethane to afford 3,4-dimethoxy-\(\beta\)-nitrostyrene, \(\text{25}\) in 80% yield. This material was reduced with lithium aluminium hydride in tetrahydrofuran to afford (vide Scheme 1.21) a 50% yield of homoveratrylamine (\(\text{26}\)) as a viscous liquid. \(^{13}\)C NMR spectrum of the compound recorded in CDCl\(_3\) and the signal assignments are given below. Detailed description of assignments are given in Chapter II.

![Scheme 1.21](image)


Phenylacetic acid derivative 23 was then treated with oxalyl chloride at room temperature in tetrahydrofuran to furnish the acid chloride which was then treated with homoveratrylamine under Schotten-Baumann conditions to afford the amide (27) in about 64% yield (Scheme 1.22). The presence of IR band at 3270 cm⁻¹ indicated the formation of amide functional group. The PMR spectrum of the compound recorded in CDCl₃ exhibited (Fig. 1.1) the following signals. The sharp signals at δ 3.32, 3.36, and 3.33 each integrating for three protons were due to five methoxyl groups. The peak at δ 6.30-6.55 (3H, complex) was due to three aromatic proton of ring A (from amine portion). The other two aromatic protons appeared at δ 6.37 as singlet. A broad signal at δ 5.45 which was exchangeable with D₂O was due to the NH proton. The ¹³C NMR spectrum of the compound was also recorded in CDCl₃ (vide infra II) which was shown to be in good agreement with its structure 27. 27 exhibited UV absorption maxima (EtOH) at 311 nm (log ε 4.0), 277(4.26), 230(4.67) and minima at 300 nm (3.95), 250(3.92) and 226 (4.66).

Cyclisation of N-β-(3',4'-dimethoxyphenyl)-3,4,5-trimethoxyphenylacetamide (27) with phosphorous oxychloride in refluxing acetonitrile resulted in ring closure to the 3,4-dihydrobenzylisoquinoline base which was immediately reduced with sodiumborohydride in methanol to furnish the required tetrahydrobenzylisoquinoline derivative 28, m.p. 102°, in 50% yield, the structure of which was shown to be in accordance with the expection as evidenced from its IR (Fig. 3.1), PMR (Fig. 3.2) and ¹³C-NMR (vide infra II) spectra. It exhibited PMR (CDCl₃) signals at δ 10.25-9.25 (15 H, br, NH₂), 6.55
Scheme 1.22 Synthesis of 2,3,9,10,11-pentamethoxyprotoberberinium salt (16). (1st route)
Fig. 11  $^1$H NMR SPECTRUM OF AMIDE

Fig. 21  $^1$H NMR SPECTRUM OF 31
Fig 3. IR SPECTRUM OF BENZYLISOQUINOLINE - 28
(1H, s, H-8), 6.44 (2H, s, H-2' and H-6'), 6.20 (1H, s, H-5), 4.75 (1H, m, H-1), 3.82, 3.79 (3H each, s, OCH₃), 3.75 (6H, s, 2xOCH₃), 3.60 (3H, s, OCH₃) and 3.55-3.20 (6H, br, H₂-3 and H₂-4 and H₂-5) and ¹³C NMR signals as shown below (details given in Chapter II).

**¹³C NMR SIGNALS OF BENZYLISOQUINOLINE (28 )**

![Diagram of ¹³C NMR signals of benzylisoquinoline](image)

*interchangeable

N-formylbenzylisoquinoline derivative 29 was synthesised from 6,7-dimethoxy-1-(3',4',5'-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (28) by gentle refluxing with formic acid and triethylamine at 150° for 1 hr. The formation of N-formyl derivative was indicated by the presence of IR band at 1660 cm⁻¹ (Fig. 4.1) and confirmed from PMR spectrum (Fig. 4.2) (Page 57e) which showed two signals at 8.13 and 7.79 (integrating for one proton). The two signals for N-CHO were probably due to the two possible orientation of the -CH₂Ar and N-CHO functions (cis and trans). The remaining aromatic protons appeared at 6.55 (H-8), 6.53 (H-5) and 6.30 (H-2' and H-6') as singlets and
Fig 4.1 IR SPECTRUM OF N-FORMYLBENZYLISOQUINOLINE
Other signals at δ 3.87, 3.83, 3.81, and 3.75 were due to the five methoxyl protons. Other signals were at δ 3.72 (2H, d, J = 6.0 Hz, H_2-C) and 3.50-2.95C4H_2, m, H_{4-2} and H_{3-4}).

2,3,9,10,11-pentamethoxyprotoberberinium salt (16) was finally synthesised from N-formyl benzylisoquinoline derivative (29) in about 70% yield, by cyclisation with POCl_3 in acetonitrile solvent under nitrogen atmosphere which was carried out by standing the reaction mixture just at refluxing temperature for one hour followed by usual work up (and subsequent oxidation with air during work up and chromatographic purification).

2nd route

16 was also synthesised by iodine oxidation of its tetrahydroderivative (13) which was synthesised from N-β-(3',4'-dimethoxyphenethyl)-2-hydroxymethyl-3,4,5-trimethoxyphenylacetamide (31) obtained from the interaction of isochromanone derivative (30) and homoveratrylamine (26).

3,4,5-Trimethoxyphenylacetic acid upon refluxing with conc. HCl and formalin afforded 6,7,8-trimethoxyisochroman-3-one (30), m.p. 140° (chloroform-petrol) in excellent yield (above 80%). The compound exhibiting IR absorption band at 1750 cm^{-1} (Fig. 4.1) was indicative of the presence of lactone functional group.
The PMR spectrum of isochromanone (Fig. 12) derivative (30) displayed signals at 3.65 (2H, s) for CH\textsubscript{2}-CO\textsubscript{-}, 3.70 (3H, s) and 3.90 (6H, s) for three methoxyls, 5.40 (2H, s, -CH\textsubscript{2}O-CO) and the aromatic proton appeared at 7.45 as singlet.

Condensation of homoveratrylamine (26) with 6,7,8-trimethoxyisochroman-3-one (30) in refluxing ethanol (Scheme 1.23) afforded a product which showed IR bands at 3330 and 1650 cm\textsuperscript{-1} indicating the formation of amide. Both the PMR spectrum (Fig. 2.1) and \textsuperscript{13}C-NMR spectrum (vide infra II) of the compound recorded in CDCl\textsubscript{3} showed the presence of signals in accordance with the structure 31 for the product.

Table 2
PMR signals of Amide - 31

<table>
<thead>
<tr>
<th>Chemical shift ( \delta )</th>
<th>Corresponding Proton Number</th>
<th>Multiplicity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.70</td>
<td>2</td>
<td>Triplet ( J=6.5\text{Hz} )</td>
<td>C\textsubscript{\beta} -H\textsubscript{2}</td>
</tr>
<tr>
<td>3.40-3.70</td>
<td>4</td>
<td>Multiplet</td>
<td>C\textsubscript{\alpha} -H\textsubscript{2} and C\textsubscript{\alpha'} -H\textsubscript{2}</td>
</tr>
<tr>
<td>3.75</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.80</td>
<td>15</td>
<td>Singlet(\dagger)</td>
<td>5 \times -OCH\textsubscript{3}</td>
</tr>
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<td>3.85</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>3.90</td>
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<tr>
<td>4.65</td>
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<td>Singlet</td>
<td>CH\textsubscript{2}OH</td>
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<tr>
<td>5.15</td>
<td>1</td>
<td>Singlet</td>
<td>-CONH</td>
</tr>
<tr>
<td>6.70-6.30</td>
<td>4</td>
<td>Complex</td>
<td>4 \times Ar-H</td>
</tr>
</tbody>
</table>
Scheme 1.23 Synthesis of (±)-2,3,9,10,11-pentamethoxyprotoberberinium salt (16) (2nd route).
Cyclisation of the above amide 31 with POCl₃ and subsequent reduction of the reaction product with sodiumborohydride afforded a compound, m.p. 77º, which exhibited UV absorption maxima (Fig. 5.4) at 283 (log ε 3.96), 310 (sh. 3.47), 346 nm (sh 3.71) indicative of tetrahydroprotoberberine skeleton. The PMR (Fig. 5.2) and mass spectrum (Fig. 5.3) of the compound was shown to be in accordance with the structure (13).

On refluxing with iodine in 90% ethanol under nitrogen atmosphere, 2,3,9,10,11-pentamethoxytetrahydroprotoberberine (13) afforded quaternary protoberberinium salt (16). The pentamethoxyquaternaryprotoberberinium salt (16), on the other hand, was shown to be smoothly reduced (80% yield) by refluxing with sodiumborohydride in methanol.

PMR spectra (Fig. 5.2) of the quaternary salt (16) and its tetrahydroderivative (Fig. 5.2) were studied in D₂O and CDCl₃, respectively. Signals with their assignments are given in table-3, and table 4, respectively.

<table>
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<th>Chemical Shift δ</th>
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<tr>
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<td>Singlet</td>
<td>C₁₃-H</td>
</tr>
<tr>
<td>6.32</td>
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<td>Singlet</td>
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<tr>
<td>6.79</td>
<td>1</td>
<td>Singlet</td>
<td>C₄-H</td>
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<tr>
<td>4.05</td>
<td>3</td>
<td>Singlet</td>
<td>OCH₃</td>
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</tbody>
</table>
(±) GLABRININE TETRAHYDRO-METHYLEThER (KBr)

IR SPECTRUM OF 13

TRANSMITTANCE (%)
Fig.-5.2 H NMR SPECTRUM OF ALKALOID 13

80 MHz
CDCl₃
FIG. 5.4 UV SPECTRUM OF 2,3,9,10,11-PENTAMETHOXYTETRAHYDRO-
PROTOBERBERINE.

$\lambda_{max} = 283(396)$
310 (Sh 347)
346 (Sh 371)
Table 3 (Contd.)

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<tr>
<td>2.91</td>
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<td>Broad</td>
<td>Ar-CH₂</td>
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Table 4

PMR signals of glabrinetetrahydromethylether (CDCl₃)

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<th>Assignments</th>
</tr>
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<td>Singlet</td>
<td>C₁-H</td>
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<tr>
<td>6.61</td>
<td>1</td>
<td>Singlet</td>
<td>C₄-H</td>
</tr>
<tr>
<td>6.48</td>
<td>1</td>
<td>Singlet</td>
<td>C₁₂-H</td>
</tr>
<tr>
<td>4.10</td>
<td>1</td>
<td>Doublet</td>
<td>C₃-H</td>
</tr>
<tr>
<td>3.91</td>
<td>3</td>
<td>Singlet</td>
<td>OCH₃</td>
</tr>
<tr>
<td>3.89</td>
<td>3</td>
<td>Singlet</td>
<td>OCH₃</td>
</tr>
<tr>
<td>3.87</td>
<td>3</td>
<td>Singlet</td>
<td>OCH₃</td>
</tr>
<tr>
<td>3.85</td>
<td>3</td>
<td>Singlet</td>
<td>OCH₃</td>
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<tr>
<td>3.85</td>
<td>3</td>
<td>Singlet</td>
<td>OCH₃</td>
</tr>
</tbody>
</table>

Thorough comparison of the PMR spectra of glabrine and

Thorough comparison of the PMR spectra of glabrine and glabriné with that of synthetic protoberberinium salt (16) along with those of their corresponding tetrahydroderivatives revealed that glabrine and glabriné should have similar oxygenation with that of synthetic compound. The presence of a doublet at 8 4.1 (J = 16 Hz) in synthetic tetrahydroderivative (13) (Table 4) is
Fig 6.1 IR SPECTRUM OF GLABRINEMETHYLETHER (KBr)
FIG. 6-3 UV SPECTRUM OF 2,3,9,10,11-PENTAMETHOXYPROTOBERBERIUM SALT.
similar to the doublets at $S\,^4\,J = 13\,\text{Hz}$ in both the tetrahydro-derivatives of glabrine and glabrinine (Table 1), which is very informative.

The mass spectrum of both synthetic quaternary salt (16) and tetrahydroderivative (13) were studied which also support the proposed structure for glabrine and glabrinine.

**Mass Spectral Fragmentation of Quaternary Salt (16):**

Besides the ion peak at m/e 382 (90%) (Fig. 7.3) for the parent cation, the mass spectrum showed an ion peak at m/e 367 (35%) originating from the loss of one $\text{CH}_3$ from the parent cation (Fig. 6.14). Loss of another $\text{CH}_3$ from m/e 367 gave rise the ion at m/e 352 (100%). M/e at 383 was due to $M^+ + 1$.

The mass spectrum of tetrahydroderivative (13) is given (Fig. 6.3). Some of the important fragmentations are given in Scheme 1.24. The significant fragmentation involved retro-Diels-Alder cleavage of ring C generating the ion at 194 (100%) and 179 (37%). The molecular ion peak at m/e 385 (53%) which corresponded to its molecular formula $C_{22}H_{27}O_5N$.

The UV spectrum of 2,3,9,10,11-pentamethoxy quaternary protoberinium salt (16) exhibited $\lambda_{\text{max}}$ at 242 ($\log e = 4.20$), 239 (4.53), 312 (sh 4.26), 343 (sh 4.14), 390 (4.37) and $\lambda_{\text{min}}$ at 254 (4.03). The UV (Fig. 6.3) and IR spectra (Fig. 6.1) of 16 were found to be superimposable with those of methyl ether of glabrine and glabrinine.
Fig. 6.1: Mass spectrum of 16.
Scheme-124. Mass fragmentation pattern of 2,3,9,10,11-pentamethoxy tetrahydroprotoberberine (13).
The tetrahydroderivative (13) was also obtained from the benzylisoquinoline 23 by refluxing with formalin in 50% yield.

Synthesis of 2,3,10,11,12-pentamethoxytetrahydroprotoberberine

(±)-2,3,10,11,12-pentamethoxytetrahydroprotoberberine (14) was synthesised from homoveratrylamine (26) and 2,3,4-trimethoxyphenylacetic acid (34). The acid was synthesized from 2,3,4-trimethoxybenzaldehyde (32) through the intermediacy of azalactone derivative 32a (Scheme 1.25). Treatment of aldehyde 32 with hippuric acid in presence of sodium acetate in acetic anhydride resulted in the formation of azalactone derivative (32a), m.p. 135°, as yellow crystalline solid. The azalactone 32a on hydrolysis with alkali and subsequent decomposition with hydrogen peroxide under alkaline condition afforded 2,3,4-trimethoxyphenylacetic acid (34) together with benzoic acid. Since the chromatographic separation of these two acids were not possible due to their close polarity, the mixture of the acids was converted to their corresponding methylester by refluxing with methanol in presence of few drops of conc. H₂SO₄. The two esters were separated by chromatographic resolution over silica gel.

Scheme 1.25 Synthesis of 2,3,4-trimethoxyphenylacetic acid (34)
Finally the acid 34, m.p. 101° was synthesised by alkaline hydrolysis of its corresponding methyl ester (33) followed by usual work-up and chromatography. The formation of the acid was confirmed from its IR, PMR and $^{13}$C-NMR spectra (vide p. 56 II).

Treatment of 2,3,4-trimethoxyphenylacetic acid with phosphorous pentachloride resulted the acid chloride which was dissolved in dry and cold chloroform and added to a well stirred cold solution of homoveratrylamine in chloroform and sodium carbonate in water under nitrogen atmosphere. Stirring continued for another one hour at room temperature which resulted after usual work up, N-β-(3',4'-dimethoxyphenylamino)-2,3,4-trimethoxyphenylacetamide (35).

The structure of the amide (35), m.p. 90°, was confirmed by IR, PMR (Fig. 7.1) and $^{13}$C-NMR spectra (vide p. 56 II). The IR spectrum (KBr) indicated the presence of an amide function (3230 and 1645 cm$^{-1}$) in addition to bands for aromatic ring and aromatic methoxyls. The PMR spectra, recorded in CDCl$_3$, is given in the following table (Table-5).

The amide on cyclisation with POCl$_3$ and subsequent reduction of the reaction product with sodiumborohydride (Scheme 1.26) in methanol afforded, after repeated chromatographic resolution over silica gel, the benzyltetrahydroisoquinoline derivative 36. This was then refluxed with formaldehyde and acetic acid for 30 min. to furnish a product as an amorphous material after chromatographic purification over silica gel. The compound was found to exhibit UV
Scheme 1.26 Synthesis of \[2,3,10,11,12\text{-pentamethoxytetrhydroprotoberberine}\](14).
Table 5

<table>
<thead>
<tr>
<th>Chemical Shift</th>
<th>Corresponding proton number</th>
<th>Multiplicity</th>
<th>Assignments</th>
</tr>
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<td>Multiplet</td>
<td>Ar-H</td>
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<tr>
<td>5.85-5.75</td>
<td>1</td>
<td>Broad</td>
<td>NH</td>
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<td>3.84</td>
<td>6</td>
<td>Singlet</td>
<td>2xOCH₃</td>
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<tr>
<td>3.82</td>
<td>9</td>
<td>Singlet</td>
<td>3xOCH₃</td>
</tr>
</tbody>
</table>
| 3.44           | 2                           | Double Triplet | J = 6.8,6.9Hz | C₁⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻ нарко-

absorption maxima at 282 nm (log ε 4.64) and minimum 255 nm (log ε 4.23), characteristics of tetrahydroprotoberberine derivatives.

The IR (Fig. 8.1), PMR (Fig. 8.2), ¹³C-NMR (Fig. 2.23) and Mass spectra of the tetrahydroprotoberberine derivative (14) were studied. The data were found to be in agreement with the structure 14 for the compound. The spectroscopic data are given below:
Fig 8.1 IR SPECTRUM OF ALKALOID 14
FIG. 6f. NMR SPECTRUM OF ALKALOID 1f.
Table 6
PMR signals of tetrahydroprotoberberine 14 in CDCl₃ (Fig. 8.2)

<table>
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<th>Corresponding Proton number</th>
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<th>Assignments</th>
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<td>6.61</td>
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<td>C₄-H</td>
</tr>
<tr>
<td>6.40</td>
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<td>C₉-H</td>
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<tr>
<td>3.96</td>
<td>1</td>
<td>Doublet, J = 6.2 Hz</td>
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<td>3.88</td>
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<td>OCH₃</td>
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<td>Singlet</td>
<td>3 x OCH₃</td>
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<tr>
<td>3.82</td>
<td>3</td>
<td>Singlet</td>
<td>OCH₃</td>
</tr>
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</table>

The ¹³C-NMR spectrum of the compound was recorded in CDCl₃. Carbon shift values are given by the side of corresponding carbon (details given in Part II).

PMR and ¹³C NMR spectra of the benzylisoquinoline 36 (Fig. 7.1 and 2.21 respectively) were recorded in CDCl₃.
Table 7

PMR signals of benzylisoquinoline 36 in CDCl₃

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<th>Chemical Shift</th>
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<td>5.00</td>
<td>1</td>
<td>broad Singlet</td>
<td>NH</td>
</tr>
<tr>
<td></td>
<td>(exchangeable with D₂O)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.80</td>
<td>9</td>
<td>Singlet</td>
<td>3 x OCH₃</td>
</tr>
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<td>3.75</td>
<td>6</td>
<td>Singlet</td>
<td>2 x OCH₃</td>
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<tr>
<td>3.20-2.80</td>
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¹³C-NMR Signals of Benzylisoquinoline derivative (36) (CDCl₃, δ)

![Carbon NMR Spectrum]

* Interchangeable
SYNTHESIS OF (+)-NORCORALYDINE

Though the synthesis of the naturally occurring tetraoxyge-nated protoberberine, (+)-norcoralydine, has been carried out by various routes a new and convenient synthesis has been developed employing the starting material homoveratrylamine and 6,7-dimethoxy-isochroman-3-one. The latter was prepared from 3,4-dimethoxyphenylacetic acid following Nagata's procedure. PMR (Fig. 3.1) and 13C-NMR spectra (vide part II) of the isochromanone was in good agreement with structure 33. Homoveratrylamine, as shown in Scheme 1.27 was condensed with isochromanone in ethanol to give N-β-(3',4'-dimethoxyphenylethyl)2-hydroxymethyl-4,5-dimethoxy phenylacetamide in 90% yield. The structure of the amide was confirmed from its IR 1H-NMR (Fig. 19.1), 13C-NMR (vide part II) and UV spectra. The presence of strong absorption peak at 3400-3240 (br) cm⁻¹ and 1645 cm⁻¹ indicate the formation of amide. It displayed PMR signals at δ 2.62 (3H, t, J = 6.8 Hz, H2-β), 3.46 (2H, dt, J = 6.8 Hz, H3-α), 3.50 (2H, s, H2-α'), 3.52, 3.53, 3.55 and 3.89 (3H each, s, 4xOCH3) 4.54 (3H, s, CH2OH), 6.0 (1H, br, CONH), 6.25-6.30 (4H, complex, Ar-H) and 6.37 (1H, s, Ar-H). Carbon-13 NMR signals of amide 39 at δ 34.3 (C-β'), 39.3(C-α'), 40.5(C-α'), 55.3(four OCH3), 62.5(C2H5OH),

Fig 9.1 ¹H NMR SPECTRUM OF ISOCHROMANONE 38
Fig. 10-1  $^1$H NMR SPECTRUM OF AMIDE

Fig. 11-1  $^1$H NMR SPECTRUM OF (z)-NORCOXALLYNE
Scheme 1.27 Synthesis of (1)-Norcoralydine (40)
110.9 (C-5'), 111.5 (C-2'), 112.9 and 113.0 (C-3 and C-6), 120.1 (C-6'), 125.9 (C-2), 130.8 (C-1'), 131.6 (C-1), 147.1 and 147.5 (C-4 and C-5), 148.1 and 148.4 (C-3' and C-4') and 171.5 ppm (C=O) were in conformity with its structure.

39 on treatment with POCl₃ followed by sodium borohydride reduction afforded after usual work-up a yellow solid which on crystallisation from acetone-petrol furnished (+)-norcoralydine (40) C₂₁H₂₅O₁N (M⁺ 355), m.p. 155-56° (lit. 103, m.p. 157-58°).

Like other tetrahydroprotoberberines it displayed UV absorption maxima (Fig. 11.4) at 286 (log ε 3.92) and minima at 254 (log ε 3.35) respectively.

The PMR spectrum (Fig. 11.4) recorded on a FT PMR spectrometer showed signals at δ3.30 (6H₂s) for C-2, C-3 methyls and at δ3.84 (6H₂s) C-10, C-11 methoxyls. Four aromatic protons appeared at δ6.74, 6.66, 6.62, 6.58 each as 1H₂S.

The other spectral properties IR (Fig. 11.2) and Mass (Fig. 11.3) of (+)-norcoralydine also conclusively established the structure. The IR absorption spectrum indicated the presence of the bands at 1605, 1505, 1455, 1440, 1320, 1250, 1195, 1135, 1095, 850, 830, 780 and 765 cm⁻¹.

The mass spectrum of (+)-norcoralydine (40) was in conformity with its structure. It exhibited the molecular ion peak at m/e 355 (100%). The significant fragmentation involved retro-Diels-Alder cleavage of ring C generating the ions at m/e 191 (41%) and 164 (100%). Other prominent peaks appeared at m/e 149 (100%) was
\( \lambda_{\text{max (EtOH)}} \) 286 nm \( \log \varepsilon \) 3.92

**FIG-11-4 UV SPECTRUM OF (±) NORCORALYDINE**
due to loss of one methyl group from the ion having m/e 164 (100%). The peak at m/e 340 (41%) originated from the molecular ion peak at m/e 355 by the loss of one methyl group. The fragmentation pattern is schematically given below:

\[
\text{m/e 355 (H\textsubscript{2}O)} \quad \text{m/e 340 (91\%)}
\]

\[
\text{m/e 190 (100)} \quad \text{m/e 191 (91)} \quad \text{m/e 164 (100)}
\]

\[
\text{m/e 164} \quad \text{m/e 159 (20)} \quad \text{m/e 149 (100)}
\]
SYNTHESIS OF (+) 12-HYDROXYMETHYL-2,3,9,10,11-PENTAMETHOXYTETRAHYDROPROTOBERBERINE

During the synthesis of 6,7,8-trimethoxy isochroman-3-one (isochromanone-1) it was observed that 3,4,5-trimethoxy phenylacetic acid produced 5-hydroxymethyl-6,7,8-trimethoxyisochroman-3-one (isochromanone-2) in major amount using excess formalin. The minor amount of isochromanone-1 produced in this operation was shown to be easily separable due to their large polarity difference. This isochromanone-2 was employed for the synthesis of (+)-12-hydroxymethyl-2,3,9,10,11-pentamethoxytetrahydroprotoberberine (43), a retro-protoberberine having very close structure with the naturally occurring retro-protoberberines.

Isochromanone derivative (41), m.p. 124° synthesised from 3,4,5-trimethoxyphenylacetic acid in 80% yield was characterised by its different spectral data. It exhibited IR bands at 3460(OH) and 1705 (lactone)cm⁻¹ and displayed PMR signals (CDCl₃) (Fig. 12.1) at δ 1.30 (1H, br, OH), 3.75(2H, s, CH₂CO), 3.89 (3H, s, OCH₃), 3.93 (6H, s, 2 × OCH₃), 4.70(2H, s, CH₂OH), 5.33 (2H, s, CH₂-O-CO). Carbon-13 NMR spectra (Vide supra-II) of the compound also support the structure 41 for it.

Condensation shown in Scheme 1.28 of isochromanone 41 with homoveratrylamine led to the formation of 42, C₂₃H₃₁O₃N, m.p. 140°, as fine colourless crystals.
Fig-12.1 \(^1\)H NMR SPECTRUM OF ISOCHROMANONE

Fig-13.1 \(^1\)H NMR SPECTRUM OF AMIDE
was smoothly converted to 43 by refluxing with POC(3) in CH3CN followed by subsequent treatment of the reaction product with NaBH4. The product was purified by chromatographic resolution over silica gel. It was found to exhibit UV absorption maxima at 280 (log ε 3.95) and 320 nm (sh 3.45) typical of tetrahydroprotoberberine skeleton. The structure 43 for (+)-12-hydroxy-methyl-2,3,9,10,11-pentamethoxytetrahydroprotoberberine was supported from its PMR spectrum. PMR signals are given in Table 8.
The structure of amide 42 was also confirmed from its IR, PMR (Fig. 13.1) and $^{13}$C-NMR spectra (vide infra—II). It showed IR bands at 3430 (OH, NH), 1630 (C=NH) and PMR signals (CDCl$_3$) at 2.68 (2H, t, $J = 6.8$ Hz, $3.43$ (2H, dt, $J = 5.1$, 6.8 Hz, $H_2$-$\alpha$), 3.70 (2H, s, $H_2$-$\alpha$), 3.32, 3.35, 3.82, 3.85, 3.30, 3.90, 3.90 (3H each, s, 5xOCH$_3$), 4.63 (4H, s, two CH$_2$OH), 6.55-6.80 (3H, complex, Ar-H) and 7.10 (1H, br, NHCO).

Synthesis of 10-hydroxy-2,3,9,11-tetramethoxytetrahydroprotoberberrine (17)

The synthesis of this alkaloid was carried out through the intermediacy of 6,7-dimethoxy-1-(4'-benzoyloxy-3',5'-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline following the same route for 14 (Scheme-1.28). 4-Benzoyloxy-3,5-dimethoxyphenylacetic acid (49) was synthesised from 3,4,5-trimethoxybenzylecyanide (22) (Scheme 1.27). Since borontribromide causes demethylation, treatment of 1 mole of the reagent 44 with 3,4,5-trimethoxybenzylecyanide should result the demethylation of only one methoxy group. Since the

### Table 8

<table>
<thead>
<tr>
<th>Chemical Shift</th>
<th>Corresponding proton number</th>
<th>Multiplicity</th>
<th>Assignments</th>
</tr>
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<td>C$_1$-H</td>
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<tr>
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<td>2</td>
<td>Singlet</td>
<td>CH$_2$OH</td>
</tr>
<tr>
<td>3.34</td>
<td>15</td>
<td>Singlet</td>
<td>5xOCH$_3$</td>
</tr>
<tr>
<td>3.45-2.50</td>
<td>8</td>
<td>Complex</td>
<td>C$_6$-H$_2$, C$_9$-H$_2$, C$<em>3$-H, C$</em>{13}$-H$<em>2$ and C$</em>{14}$-H</td>
</tr>
</tbody>
</table>
demethylation of the central methoxy should cause the release of maximum steric overcrowding of the molecule, the use of 1 mole of BBr₃ afforded the product 4-hydroxy-3,5-dimethoxybenzylcyanide (44).

The presence of IR band at 3390 cm⁻¹ indicated the appearance of a phenolic hydroxyl while the peak at 2240 cm⁻¹ was the indicative of CN group. That the central methoxyl was demethylated, was deduced from its ¹³C-NMR spectrum (vide supra-III). The product was a symmetrical molecule and the absence of carbon signal at 860.0 ppm was observed.
4-Hydroxy-3,5-dimethoxybenzyl cyanide (44) was then treated with benzyl chloride in acetone in presence of K₂CO₃ and catalytic amount of KI at the refluxing temperature to furnish a yellow solid, m.p. 53°C. The absence of peak in the hydroxyl region in IR spectrum suggested the formation of benzyl derivative (45), the structure of which was finally confirmed by ¹³C-NMR spectrum (vide Expt-II).

The desired acid, m.p. 121°C (46) obtained in 80% yield, was finally derived by alkaline (3N KOH) hydrolysis of the cyanide derivative in alcohol.

Acid 46 on treatment with phosphorus pentachloride in dry benzene afforded acid chloride which was immediately treated with homoveratrylamide under Schotten-Baumann condition to furnish 80% yield of amide 47. Bischer-Napieralski cyclisation of 47 with phosphorous oxychloride in refluxing toluene resulted in ring closure to the 3,4-dihydrobenzylisoquinoline. The base was reduced immediately after isolation with sodium borohydride in ethanol to provide the required tetrahydrobenzylisoquinoline 48 in 50% yield (vide Scheme 1.28).

When 48 was treated with formaldehyde cyclisation took place to the tetrahydroprotoberberine (47), m.p. 165°C, through the intermediacy of a Schiff base, which was purified by chromatographic purification over silica gel.
The structure of the tetrahydroprotoberberine (17) was in good agreement with its IR, PMR, $^{13}$C-NMR, UV and Mass spectra.

The significant fragmentation (Fig. 1) involved Retro-Diels-Alder cleavage of ring C generating the ion at m/e 190 (52%), 192 (6%) and 180 (5%). The base peak at m/e 149 originated from the ion peak at m/e 130 by the loss of one methyl group. The other very weak peaks, generated from the base peak, are at m/e 136 (5%),
134 (6%) and 135 (1%). The fragmentation pattern may be rationalised as in Scheme 1.29.

Scheme 1.29
The \( ^1H \) NMR spectrum of the compound indicated the presence of a doublet at \( \delta 4.15 \) (\( J = 16 \) Hz) for H-8 which is the indicative of presence of an oxygen function at C-9. The signals at \( \delta 3.92, 3.90 \) and 3.39 are due to the methoxyl functions at C-2, C-3, C-9 and C-11. The aromatic protons appeared at \( \delta 6.78 \) (1H) and 6.63 (2H).

It exhibited UV absorption maxima at 283 nm (\( \log \varepsilon 3.90 \)), 321 nm (br 4.21) and minima at 256 nm (\( \log \varepsilon 3.56 \)) similar to that of tetrahydroprotoberberine alkaloids. Bathochromic shift of the absorption maxima and minima took place on addition of alkali corroborating its phenolic character.

The IR absorption spectrum indicated the presence of a hydroxyl function (3340 cm\(^{-1}\)) in addition to bands for aromatic ring and aromatic methoxyls.

The monohydroxy compound was found to be different (II, PMR, \( ^{13}C \) NMR) from the NaBH\(_4\) reduction product of glabrinine. So the hydroxyl function in glabrinine was not at C-10.

\((\pm)-10\)-Hydroxy-2,3,9,11-pentamethoxytetrahydroprotoberberine \( (17) \) dissolved in dry acetone was refluxed with dimethyl sulphate in K\(_2\)CO\(_3\). The compound isolated after removal of solvent, usual work up and chromatographic resolution over silica gel found to be
identical with (±)-2,3,9,10,11-pentamethoxytetrahydroprotoberberine 13.
ATTEMPTED SYNTHESIS OF (+)-2,3,9,10,12-PENTAMETHOXYTETRAHYDROPROTOBERBERINE

An attempt to synthesise (+)-2,3,9,10,12-pentamethoxytetrahydroprotoberberine (15) through the intermediacy of 6,7-dimethoxy-1-(2,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (53) (Scheme 1.30) was unsuccessful due to the formation of some abnormal reaction product in predominant amount and with consequent failure in cyclisation of the benzylisoquinoline 53 to the desired compound 15.

Trans-asarone 49 was readily converted (yield 30%) to 50 by oxidation with potassium dichromate and conc. H_2SO_4. 50 was treated with hippuric acid in acetic anhydride and fused NaOAc to afford the azalactone derivative following earlier procedure (page 67). Reaction of azalactone with alkali followed by treatment with alkaline H_2O_2 furnished 2,4,5-trimethoxyphenylacetic acid (51). Conversion of the 51 to 52 which was carried out by converting 51 to its acid-chloride using PCl_3 followed by subsequent reaction with homoveratrylamine resulted in N-(3',4'-dimethoxyphenethyl)-2'-chloro-3',4',6-trimethoxyphenylacetamide (54) in major amount together with minor amount of desired amide 52.

PMR spectrum (Fig. 1.4.1) and ^{13}C-NMR spectrum (vide Part II) of the compounds suggested the major product was 54 and the minor one was desired amide 52. Another attempt to synthesise 52 by heating homoveratrylamine and 2,4,5-trimethoxyphenylacetate in an
Fig. 14-1  $^1$H NMR SPECTRUM OF AMIDE S$_4$
Scheme 1.30 - Synthesis of (+)-2,3,9,10,12-pentamethoxytetrahydroprotoberberine.
oil bath did not improve the yield. Finally the conversion of 53 to 15 also was not successful.

An alternative synthesis of (+)-2,3,9,10,12-pentamethoxytetrahydroprotoberberine (Scheme 1.31) which involved the photolytic conversion of 56 to 57 was recently carried out by Bunsuke Umezawa.52

The PMR spectral data for (+)-2,3,9,10,12-pentamethoxytetrahydroprotoberberine as reported by Bunsuke Umezawa was taken for comparative study with other pentaoxygenated protoberberine derivatives (vide Table-1).
EXPERIMENTAL

3,4,5-Trimethoxyphenylacetic acid

3,4,5-Trimethoxyphenylacetic acid was prepared from gallic acid through the following steps:

Methyl gallate trimethyl ether (19)

Gallic acid (13) (25.0 g, 0.1 mole) taken in dry acetone (250 ml) was stirred at room temperature with freshly washed dry MgSO\(_4\) (67 ml) and solid K\(_2\)CO\(_3\) (69 g) for 2 hr. The reaction mixture was then refluxed for 43 hr to complete the reaction. The excess of the solvent was removed, poured into water and extracted with ether (3 x 200 ml). The ether layer was collected, washed with saturated NaCl solution and dried over anhy. MgSO\(_4\). The solid mass from ether layer was purified by chromatographic resolution over silica gel to afford methyl gallate trimethyl ether (19) (26.6 g, 30%), m.p 32° (chloroform-petrol) (lit. 30-32°). IR: \(\nu\) max 2950, 1710, 1590, 1500, 1450, 1330, 1215, 1110, 990, 860 and 760 cm\(^{-1}\). Mass: 272 (M\(^+\)) (Found: C, 58.70; H, 5.93; C\(_{11}\)H\(_{14}\)O\(_5\) requires C, 58.40; H, 6.19%).

3,4,5-Trimethoxybenzylalcohol (20)

An ice cold solution of methylgallate trimethyl ether (19) (22.6 g, 0.1 mole) in dry tetrahydrofuran (100 ml) was added dropwise to a suspension of LAH (6 g) in tetrahydrofuran (100 ml) placed on an ice bath. After the addition was complete, the reaction mixture was refluxed slowly for 12 hr. Excess hydride was decomposed by cautious
addition of saturated Na₂SO₄ solution. The organic layer was collected by filtration, dried over Na₂SO₄, and evaporated to afford a colourless viscous liquid. Distillation under reduced pressure gave pure 3,4,5-trimethoxybenzylalcohol (20) (b.p. 172-6° at 2.5 mm) (16.3 g, 70%).

IR: max at 3500-3300 (br), 2940, 1530, 1495, 1445, 1410, 1320, 1225, 1110, 995, 950, 935, 815, 770 and 675 cm⁻¹.

3,4,5-Trimethoxybenzylbromide (21)

A mixture of 3,4,5-trimethoxybenzylalcohol (15g, 0.075 mol) in CCl₄ (20 ml) and triethylamine (7.5 ml) taken in a two necked round bottomed flask was ice cooled. To it PBr₃ (6 ml) in CCl₄ (17 ml) was added dropwise for 1 hr with well stirring at ice cold temperature. The mixture was then stirred for 1 hr in the cold and for another 3 hr at room temperature. The reaction mixture was then poured into ice water, extracted with large volume of ether (2 x 150 ml) and washed with water (3 x 50 ml) to remove acid. The ether layer was then dried over anhy. Na₂SO₄ and evaporated to dryness to furnish white crystals of pure 3,4,5-trimethoxybenzylbromide (15.6g, 30%), m.p. 72-4° (chloroform-petroleum ether) which darkened on standing at room temperature. IR: max at 2940, 1530, 1490, 1450, 1415, 1320, 1230, 1200, 1110, 985, 935, 825 and 655 cm⁻¹.

3,4,5-Trimethoxybenzylecyanide (22)

To a mixture of NaCN (7.5 g) and redistilled dry DMSO (30 ml) a solution of 3,4,5-trimethoxybenzylbromide (21) (15.0g, 0.057 mol) in dry DMSO (30 ml) was added with vigorous stirring for about 1 hr. The resulting mixture was stirred for another 10 hr under nitrogen
atmosphere. The reaction mixture was poured into water (100 ml), extracted with chloroform (2 x 100 ml). The organic layer was washed with water (2 x 50 ml), dried over Na₂SO₄ and evaporated to furnish a yellow solid which was purified by chromatographic resolution over silica gel. The benzene-chloroform (1:1) eluted fractions afforded pure 3,4,5-trimethoxybenzylcyanide (22) (9g, 75%) m.p. 77-78° (chloroform-petroleum ether) (lit.103 m.p. 78°). IR \( \gamma_{\text{max}} \) at 3630, 2240, 1610, 1510, 1450, 1400, 1030, 990, 940, 905, 805 and 800 cm\(^{-1}\). Mass : 207 (M⁺) (Found : C, 63.70; H, 6.30; N, 6.92; \( \text{C}_{11}\text{H}_{13}\text{O}_{3}\text{N} \) requires C, 63.76; H, 6.19%).

**3,4,5-Trimethoxyphenylacetic acid (23)**

8.0 g (0.038 mol) of 3,4,5-trimethoxybenzylcyanide in 50 mL 3N aqueous KOH was refluxed with stirring under nitrogen atmosphere for 12 hr. when all the solid passed into solution and hydrolysis was complete. The reaction mixture was cooled to room temperature and acidified with 1:1 H₂SO₄. 3,4,5-Trimethoxyphenylacetic acid separated out as fine crystals. It was filtered out and dried (9g, 92%), m.p. 121° (chloroform-petroleum ether) (lit.104 m.p. 122°; lit.105 m.p. 120°). It exhibited absorption bands at 1695, 1585, 1500, 1455, 1410, 1310, 1230, 1175, 1140, 1110, 990, 820, 770, 740, 710 and 630 cm\(^{-1}\). MS : 206 (M⁺); Found C, 53.72; H, 6.32. \( \text{C}_{11}\text{H}_{14}\text{O}_{5} \) requires C, 53.40; H, 6.19%.

**Veratraldehyde (24)**

It was prepared from vanillin following an earlier method.106
3,4-Dimethoxynitrostyrene (25)

Methylamine hydrochloride (2g, 0.03 mol), Na₂CO₃ (2g, 0.02 mol), and abs. ethanol (100 ml) were heated on a steam bath for 15 min, and then filtered hot into a solution of vanillin methyl ether (49.8g, 0.3 mol) and nitromethane (19 ml, 0.35 mol) in absolute ethanol (200 ml). The reaction mixture was kept overnight, then extracted thrice with chloroform. The combined chloroform layer after usual work up was removed to furnish a yellow solid which was the desired crude nitrostyrene derivative. The crude product was then recrystallised from ethanol to yield the fine needles of 3,4-dimethoxynitrostyrene (50.1g, 80%), m.p. 137° (chloroform-petroleum ether). IR: \( \nu_{\text{max}} \) at 3330, 1635, 1600, 1495, 1340, 1260, 1235, 1165, 1140, 1020, 980 and 810 cm⁻¹; MS: 209 (M⁺). Found C, 57.50; H, 5.21; N, 6.09. \( \text{C}_{10}\text{H}_{11}\text{O}_{4}\text{N} \) requires C, 57.41; H, 5.26; N, 6.69%.

Homoveratrylamine (26)

In a 250 ml flask equipped with a magnetic stirrer, an addition funnel and a drying tube, was placed dry THF (150 ml) and lithium aluminium hydride (10g, 0.26 mol). A solution of 3,4-dimethoxy-β-nitrostyrene (22.9g, 0.11 mol) in THF (500 ml) was then added at such a rate as to maintain reflux. After the addition, the reaction mixture was refluxed for another 6 hr. and then cooled to room temperature, diluted with THF (250 ml). The excess LAH was destroyed by dropwise addition of saturated Na₂SO₄ solution with thorough stirring. The solvent was then decanted. The residue was washed with THF & the combined solutions (THF) dried over dry Na₂SO₄. The solvent on removal afforded oily liquid shown to be identical in
all respect with homoveratrylamine (13.9 g, 50%). IR \( \gamma_{\text{max}} \) at 3600-3020 (br.), 2930, 1590, 1505, 1460, 1260, 1230, 1150, 1140, 1020, 300 and 760 cm\(^{-1}\).

**N-β-(3',4',5'-Trimethoxyphenylethyl)-3',4',5'-trimethoxyphenylacetamide (27)**

3,4,5-Trimethoxyphenylacetic acid (2.26 g; 0.01 mol.) dissolved in dry tetrahydrofuran (25 ml) was treated with oxalyl chloride (1.3 ml) and pyridine (0.05 ml). The mixture was stirred at room temperature for 16 hr. Removal of the solvent under reduced pressure afforded a residue which was dissolved in chloroform (25 ml). The cold chloroform solution was added slowly to a well-stirred cold mixture of homoveratrylamine (2.0 g) in chloroform (15 ml) and sodium carbonate (1.3 g) in water (12 ml). The mixture was then stirred at room temperature under nitrogen atmosphere for 1 hr. and the chloroform layer removed, washed twice with cold 10% aq. sodium hydroxide solution and then once with 5% hydrochloric acid. Usual work-up of the chloroform layer furnished a residue which was purified by column chromatography over silica gel. Residue from benzene-chloroform (1:1) eluates gave fine crystals (2.5 g, 64%) of 27 from ethylacetate-petrol, m.p. 95°. MS : 339(M\(^+\)); (Found : C, 64.39; H, 6.35; N, 3.67. \( \text{C}_{21}\text{H}_{27}\text{O}_{6}\text{N} \) requires C, 64.76; H, 6.98; N, 3.59%). IR : \( \gamma_{\text{max}} \) at 3270, 2910, 1620, 1530, 1500, 1440, 1320, 1220, 1140, 1110, 1012 and 332 cm\(^{-1}\).

**6,7-Dimethoxy-1-(3',4',5'-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (28)**

Phosphorous oxychloride (1.0 ml) was added to a solution of the amide (1.5 g; 0.005 mol) in dry acetonitrile (20 ml) and the
mixture stirred under nitrogen atmosphere at room temperature for 15 min, then at 30° for 3 hr. Excess solvent and POC13 was removed in vacuo, then 50 ml ice-cold chloroform was added to it. The chloroform layer was washed with saturated sodium bicarbonate solution followed by dilute ammonia and finally dried over anhydrous sodium sulphate. Removal of solvent afforded a solid mass which was dissolved in methanol and treated with sodium borohydride (1.0 g) in portions with stirring at room temperature. After about 4 hr, the solvent was removed and the residue decomposed with water and extracted with chloroform. The chloroform layer was washed with water, dried and evaporated to give a solid which was chromatographed over alumina. Residue from chloroform eluates afforded 28 (1.0 g) crystallising from chloroform-methanol, m.p. 102° (Found : C,67.30; H,7.15; N,3.68. C21H270,N requires : C,67.54; H,7.28; N,3.75%). IR : \γ max at 3430, 2940, 1590, 1505, 1450, 1420, 1375, 1323, 1250, 1222, 1185, 1115, 1010, 998, 355 and 330 cm⁻¹.

N-Formyl-6,7-dimethoxy-1-(3',4',5'-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (28)

The benzyltetrahydroisoquinoline 23 (0.5 g) was added to an ice-cold solution of 98% formic acid (0.75 g) in triethylamine (0.35 g) and the mixture refluxed at 145–150° for 2 hr. The cooled reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water (2 x 50 ml), dried, usual work up of the chloroform layer afforded 29 (230 mg), IR : \γ max at 2940, 1660, 1590, 1505, 1450, 1420, 1320, 1230, 1112 and 1000 cm⁻¹. The compound was utilised as such for the subsequent reaction as the material was somewhat less stable.
2,3,9,10,11-Pentamethoxyprotoberberinium Salt (16) = Glabrine dimethyl ether and Glabrinine methyl ether

The N-formyl-l-benzyltetrahydroisoquinoline 29 (100 mg) in acetonitrile (10 ml) was treated with phosphorous oxychloride (0.2 ml). The mixture was refluxed at 80-82° for 3 hr and poured into ice-cold chloroform. The chloroform layer was washed with aqueous sodium bicarbonate and then with diluted ammonium hydroxide solution and finally dried over sodium sulphate. The solid mass obtained after removal of chloroform was chromatographed over silica gel. The residue from chloroform-methanol (95:5) fraction was freed from gummy materials by washing with methylene chloride-petrol. Subsequent crystallisation from methanol-chloroform afforded yellow crystals (50 mg), m.p. 207-209°, identical (IR, UV, PMR, Co-TLC) with glabrine dimethyl ether. It exhibited IR bands at 2950, 1630, 1605, 1562, 1503, 1480, 1450, 1408, 1383, 1365, 1263, 1210, 1132, 1100 and 1010 cm⁻¹.

Reduction of 2,3,9,10,11-Pentamethoxyprotoberberinium salt

2,3,9,10,11-Pentamethoxyprotoberberinium salt (16) (25 mg) was dissolved in methanol (50 ml). To this methanolic solution sodium borohydride (50 mg) was added pinch by pinch for 15 min. with thorough shaking after each addition and keeping the mixture at about room temperature (occasional cooling was necessary). The reaction mixture was kept for 6 hr. at room temperature. Excess of the solvent was removed under vacuo. The reaction mixture was decomposed with ice water (50 ml), extracted with chloroform (2 x 100 ml). The chloroform layer was washed with water (3 x 100 ml)
to free the alkali and dried (Na₂SO₄). On removal of chloroform the solid so afforded was purified by chromatographic resolution over silica gel. The chloroform eluted fractions afforded (+)-2,3,9,10,11-pentamethoxytetrhydroprotoberberine (13) (25 mg), m.p. 77°. IR: ν max at 2920, 1490, 1450, 1350, 1245, 1110, 1100, 1020, 850 and 770 cm⁻¹.

6,7,8-Trimethoxyisochroman-3-one (30)

3,4,5-Trimethoxyphenylacetic acid (4 g) dissolved in hot glacial AcOH (10 ml) was treated with conc. HCl (3.5 ml) and formalin (3.5 ml). The resulting mixture was refluxed for 1 hr, poured into water, extracted with CHCl₃ and the organic layer was dried over anhydrous Na₂SO₄. Removal of the solvent afforded a solid which was chromatographed over silica gel. The benzene eluted fractions afforded 6,7,8-Trimethoxyisochroman-3-one as fine crystals, m.p. 140° (chloroform-petrol). IR: ν max at 2930, 1750, 1600, 1475, 1430, 1290, 1360, 1260, 1230, 1110, 1120, 1030, 985, 840 and 755 cm⁻¹. Found: C, 60.21; H, 5.33%. C₁₂H₁₄O₅ requires C, 60.50; H, 5.92%.

N-Φ-(3',4'-Dimethoxyphenethyl)-2-hydroxymethyl-3,4,5-trimethoxyphenylacetamide (31)

Lactone 30 (2.38 g, 0.01 mole) and homoveratrylamine (2.71 g, 0.015 mole) dissolved in absolute EtOH (75 ml) was refluxed for 12 hr with well stirring. Solvent was removed and the resulting residue was extracted with CHCl₃ (2 x 100 ml). Chloroform layer was washed twice with 2N HCl and once with water, dried over anhydrous Na₂SO₄. Removal of the solvent furnished the amide 31.
POCl₃ (4.5 ml, 0.05 mol) was added to a solution of N-β-(3',4'-dimethoxyphenethyl)-2-hydroxymethyl-3,4,5-trimethoxy phenyl acetamide (2.09 g, 0.005 mole) in acetonitrile (15 ml) and the resulting solution was refluxed for 4 hr. The solvent and the excess reagent was removed in vacuo. The residue was treated with water and then extracted with CHCl₃. The organic layer was washed with NaHCO₃ solution, dried over anhydrous Na₂SO₄. Removal of the solvent left an oily residue which was dissolved in MeOH (25 ml), cooled in an ice-bath and NaBH₄ (3.8 g) was added with well stirring. The reaction mixture was left overnight. Methanol was then removed under reduced pressure. The residue was poured into water, extracted with CHCl₃. The CHCl₃ layer was then separated, washed with water (2 x 50 ml), saturated NaCl solution and then excess of the solvent was removed. The solid on chromatographic resolution over silica gel furnished 2,3,9,10,11-pentamethoxytetrahydroprotoberberine from chloroform eluted fractions (1.35 g, 70%), m.p. 77°. IR: νmax at 2920, 1580, 1490, 1450, 1350, 1325, 1245, 1110, 1100, 1020, 850 and 770 cm⁻¹. Mass: m/e at 335 (53%), 336(13), 334(13), 194(100), 193(6), 190(5), 179(37); (Found: C, 68.35; H, 6.84; N, 3.70% \( \text{C}_{22} \text{H}_{27} \text{O}_5 \text{N} \) requires C, 68.55; H, 7.06; N, 3.63%).
2,3,9,10,11-Pentamethoxyprotoberberinium Salt (≡ glabrinine methyl ether) (16)

2,3,9,10,11-Pentamethoxytetrahydroprotoberberine (13) (0.92 g, 0.0025 mole) dissolved in alcohol (90%) was refluxed slowly with iodine (0.18 g) in alcohol (30 ml) under nitrogen atmosphere for 1 hr. The excess of the solvent was removed under vacuo. The residue was then worked up in the usual way and chromatographed over silica gel to afford (0.73 g, 30%), m.p. 203°, from chloroform : methanol (1:1) fractions. This compound was found to be identical in all respect (m.m.p., UV, IR, PMR, MS) with the compound prepared earlier from homoveratrylamine and 3,4,5-trimethoxyphenylacetic acid.

(+)-2,3,9,10,11-Pentamethoxytetrahydro protoberberine (13) from benzylisoquinoline 23

6,7-Dimethoxy-1-(3',4',5'-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (23) (0.25 g) 37% formalin (2.0 ml) and glacial acetic acid (2.0 ml) was mixed. The resulting mixture was then slowly refluxed under nitrogen atmosphere for 1 hr. Excess of solvent and reagent were removed under vacuo. Resulting gummy mass was cooled. The material was subjected to chromatographic resolution over silica gel. The chloroform eluted fractions furnished impure solid. This was finally purified by preparative thin layer chromatography on silica gel. The product was shown to be identical in all respect (UV, IR, PMR, MS) with the(+)-2,3,9,10,11-pentamethoxytetrahydroprotoberberine (13) prepared earlier (from 31 and 16).
2,3,4-Trimethoxyphenylacetic acid (34)

This was synthesised from 2,3,4-trimethoxybenzaldehyde through the azalactone intermediate.

In a round bottomed flask a mixture of 2,3,4-trimethoxybenzaldehyde (32) (8 g), dry hippuric acid (8 g), freshly fused powdered sodium acetate (3.3 g) and redistilled Ac₂O (12 ml) was heated first in a water bath for 15 min, then in an oil bath at 110° for 2 hr. After this period, the reaction mixture was cooled to room temperature and 20 c.c. alcohol was added to the mixture. The mixture was allowed to stand for overnight. The yellow crystalline product was then filtered and washed carefully with 25 c.c. ice-cold alcohol followed by 25 c.c. boiling water. The product was finally purified by crystallisation from hot benzene (yield 9.0 g), m.p. 135°; IR (KBr): $\nu$ max at 1610, 1510, 1290, 1215, 1125, 1025, 865 and 755 cm$^{-1}$ shown to be the azalactone derivative 32a.

The azalactone (32a) was then hydrolysed by refluxing with 10% NaOH for 24 hr. The reaction mixture was cooled to room temperature, 4.5 c.c. 40% NaOH solution was added, ice cooled and 5 c.c. 30% H₂O₂ diluted with 5 c.c. H₂O was added dropwise with thorough stirring. After standing overnight at room temperature, the reaction mixture was acidified with H₂SO₄ (1:1) and extracted with chloroform. The organic layer after usual work up was dried (Na₂SO₄). Removal of solvent afforded a solid which was found to be a mixture of acids having very close Rf values separation of which was not possible by usual chromatography over silica gel.
The solid was dissolved in dry methanol (50 ml) and refluxed for 6 hr with conc. H$_2$SO$_4$ (3 drops). Methanol was removed by simple distillation, residue diluted with water (50 ml) and extracted with chloroform (250 ml). The chloroform layer was washed twice with water, once with saturated NaCl solution. Removal of chloroform furnished a mixture of compounds which was easily separated by column chromatography over silica gel. The benzene : chloroform (1:1) eluted fractions afforded methyl 2,3,4-trimethoxy phenylacetate from which pure acid in amorphous state was prepared by refluxing with 10% NaOH solution for 2 hr. and following usual work-up (Yield 5.5g); IR (KBr) : $\nu$ max at 3600-2300(br.), 1710, 1600, 1495, 1460, 1415, 1290-1220(br.), 1090, 1040, 1005, 955, 900 and 790 cm$^{-1}$.

N-$^2$-(3',4'-Dimethoxyphenethyl)-2,3,4-trimethoxyphenylacetamide (35)

2,3,4-Trimethoxyphenylacetic acid (2.26g, 0.01 mol) was dissolved in dry benzene (50 ml). Phosphorous pentachloride (2.1g, 0.01 mol) was added to it and the reaction mixture was refluxed slowly with constant stirring for 1 hr. POCl$_3$ formed during reaction was removed by distillation under reduced pressure. Dry benzene (25 ml) was further added and the same operation was carried out thrice to remove the trace of POCl$_3$. The oily acid chloride so obtained was dissolved in dry chloroform (25 ml). This operation was carried out very quickly to avoid exposure to moist atmosphere. The chloroform solution was then cooled and added slowly to a well stirred and cold mixture of homoveratrylamine (1.3g, 0.01 mol) in chloroform (25 ml) and sodium carbonate (1.8 g) in water (12 ml) under
nitrogen atmosphere. The mixture was then stirred at room temperature for 1 hr. The chloroform layer was then removed, washed twice with cold 10% aqueous sodium hydroxide solution and once with 5% hydrochloric acid. Usual work up of the chloroform layer furnished a residue which on chromatographic resolution over silica gel afforded the amide (3.2g) from the benzene-chloroform (1:1) eluted fractions. The compound was finally crystallised from ethylacetate-petrol to afford pure 35 (3.1g, 80%), m.p. 90°. IR (KBr) : $\gamma_{max}$ at 3280, 2920, 1645, 1515, 1495, 1460, 1255, 1230, 1135, 1090, 1020, 955, 930, 850, 790 and 760 cm$^{-1}$. Found : C,64.20; H,6.70; N,3.70. C$_{21}$H$_{27}$O$_6$N requires : C,64.76; H,6.98; N,3.59%.

6,7-Dimethoxy-1-(2',3',4'-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (36)

A mixture of amide 35 (1.5g, 6.0 mmol) in dry acetonitrile (50 ml) and phosphorous oxychloride (3.0 ml) was stirred under nitrogen atmosphere first at room temperature for 30 min., then at the refluxing temperature for 3 hr. The reaction mixture was allowed to attend room temperature, then poured into ice cold water (100 ml) and extracted with chloroform (2 x 100 ml). The chloroform layer was washed with saturated sodium bicarbonate solution (2x50ml) followed by diluted ammonium hydroxide (1x50 ml) and finally with water (2 x 50 ml). The chloroform layer was dried (Na$_2$SO$_4$) and evaporated to furnish an oil (1.5 g). The oil was dissolved in methanol (50 ml). To the methanolic solution (50 ml) of the oil NaBH$_4$ (1.0g) was added pinch by pinch during 1 hr. After about 4 hr, the solvent was removed and the residue decomposed with water.
This was then extracted with chloroform (2 x 50 ml), the chloroform layer was washed with water (2 x 50 ml), dried (Na₂SO₄) and evaporated to furnish a solid which was purified by chromatography over alumina. Residue from chloroform-methanol (9:1) afforded 37 as a viscous liquid (1.0 g). IR: $\nu_{\text{max}}$ at 3600-3300 (br.), 2920, 1610, 1500, 1470, 1420, 1265, 1230, 1100 and 860 cm⁻¹.

(+)-2,3,10,11,12-Pentamethoxytetrahydroprotoberberine (14)

6,7-Dimethoxy-1-(2',3',4'-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (36) (0.25 g) was slowly refluxed with 37% formalin (2.0 ml) and acetic acid (2.0 ml) for 1 hr under nitrogen atmosphere. Excess of formalin was removed in vacuo. Resulting mixture was cooled to room temperature. The gummy material was then poured into water (50 ml), extracted with chloroform (2 x 50 ml). The chloroform layer was washed with water (2 x 50 ml) & saturated NaCl solution and finally dried (Na₂SO₄). The chloroform layer on evaporation furnished a gummy mass which was repeatedly chromatographed over silica gel. The chloroform eluted fractions afforded 14 as an amorphous solid (0.12 g). IR: $\nu_{\text{max}}$ at 2920, 1605, 1495, 1455, 1360, 1250, 1230, 1145, 1115, 1100, 1025, 855 and 790 cm⁻¹.

3,4-Dimethoxyphenylacetic acid (37)

This was synthesized from 3,4-dimethoxybenzaldehyde (veratryldehyde) through the azalactone intermediate.

A mixture of 3,4-dimethoxybenzaldehyde (3.5 g), dry hippuryc acid (3.0 g), freshly fused sodium acetate (3.3 g) and 12 c.c. high grade distilled Ac₂O in a round bottomed flask, was heated first in oil bath with constant stirring for 30 min, then in a water bath.
for two hours. After this period the reaction mixture was cooled and 20 c.c. alcohol was added to the mixture. The mixture was allowed to stand for overnight, the yellow crystalline product was then filtered and washed carefully with 24 c.c. ice-cold alcohol followed by 25 c.c. boiling water. The product was finally purified by crystallisation from hot benzene (yield 3.5g) shown to be azalactone derivative, m.p. 151°C; IR \( \tilde{\nu} \, 1800, 1775, 1660, 1575, 1525, 1435, 1335, 1275, 1160, 1145, 1020, 870 \) and 711 cm\(^{-1}\).

The azalactone was then hydrolysed by refluxing with 10% NaOH for 24 hr. The reaction mixture was then cooled and 15 c.c. 40% sodium hydroxide solution was added with stirring followed by dropwise addition of 20 c.c. 30% hydrogen peroxide diluted with 20 c.c. water. The reaction mixture was then kept overnight, acidified with conc. H\(_2\)SO\(_4\) and extracted with warm chloroform. The chloroform layer was separated, washed (NaCl solution), dried (Na\(_2\)SO\(_4\)). The removal of the solvent afforded a solid mass which was dissolved in dry methanol (100 ml) and refluxed with 3 drops of conc. sulphuric acid for twelve hour. The solvent (methanol) was then removed by simple distillation, poured into water (50 ml) and extracted with chloroform (2 x 250 ml). The resulting mass from chloroform layer was subjected to chromatographic resolution over silica gel. After removal of the methylbenzoate in the petrol-benzene (1:1) eluates, the methyl ester of the desired acid was collected from the benzene-chloroform (2:1) fractions. The methyl ester was then hydrolysed using 3N KOH by refluxing for 10 hr to furnish 3,4-dimethoxyphenylacetic acid (yield 6.0g), m.p. 96° (lit. \( 10^7 \) m.p. 96°-97°) (chloroform-petrol) after usual work-up.
6.7-Dimethoxyisochroman-3-one (38)

3,4-Dimethoxyphenylacetic acid (11.7 g) dissolved in hot glacial acetic acid (50 ml) was treated with conc. HCl (10 ml) and formalin (10 ml). The resulting mixture was refluxed for 1 hr, poured into water, extracted with CHCl₃, washed with 5% NaHCO₃, then with water and finally the organic layer was dried over anhydrous Na₂SO₄. Removal of the solvent furnished a solid (11 g) which was purified by crystallisation from chloroform-petrol to afford fine crystals of 38 (10.5 g, 84%), m.p. 103° (lit 101°, m.p. 102-3°) found to be spectroscopically identical with the previously synthesised compound.

N-6-(3',4'-Dimethoxyphenethyl)-4,5-dimethoxy-2-hydroxymethylphenylacetamide (39)

Lactone 20 (2.03 g, 0.01 mole) and homoveratrylamine (2.71 g, 0.015 mole) was refluxed slowly in absolute alcohol (50 ml) with occasional shaking for 12 hr. After 12 hr, when the spot of the lactone disappeared in TLC plate, alcohol was removed under reduced pressure. The resulting residue was extracted with CHCl₃ (100 ml). Chloroform layer was washed twice with 2N HCl and once with water, then with saturated NaCl solution, dried over anhydrous Na₂SO₄. Removal of solvent afforded a solid (4.70 g). It was purified by chromatography over silica gel. The chloroform-methanol (9:1) eluates afforded 39 (4.25 g, 85%), m.p. 118° (chloroform-petrol) (Found: C, 64.38; H, 6.86; N, 3.67. C₂₁H₂₇O₆N requires C, 64.75; H, 6.99; N, 3.5%). IR: 3400-3240, 2920, 1645, 1515, 1460, 1145, 1110, 1030, 865, 810 and 755 cm⁻¹.
(+)-Norcoralydine (40)

N-(3',4'-Dimethoxyphenethyl)-4,5-dimethoxy-2-hydroxy-methylphenylacetamide 39 (1.93g, 0.05 mole) in acetonitrile (50 ml) was refluxed with POCI$_3$ (4.5 ml, 0.05 mole) for 4 hr. The solvent and the excess reagent was removed in vacuo. The residue was dissolved in chloroform, the organic layer was washed with $\text{EtOH}$ solution and then dried over anhy. MgSO$_4$. Removal of the solvent and chromatographic purification of the residue over silica gel afforded (+)-norcoralydine, m.p. 155.3° (lit. m.p. 157-8°); IR (as a KBr pellet): 3550, 1765, 1700, 1605, 1400, 1290, 1250, 1195, 1135, 1105, 800, 780 and 765 cm$^{-1}$.

5-Hydroxymethyl-6,7,8-trimethoxyisochroman-3-one (41)

3,4,5-Trimethoxyphenylacetic acid (4 g) dissolved in hot glacial AcOH (10.0 ml) was treated with cone. HCl (7.0 ml) and for­
aline compound after chromatographic resolution over silica gel. The resulting mixture was refluxed for 1 hr, poured into water, extracted with chloroform and the organic layer was dried over anhy. MgSO$_4$. Removal of the solvent afforded a fine crystalline compound after chromatographic purification of the residue over silica gel eluted with benzene (4.21, 8%) from the benzene eluted fractions, m.p. 165° (benzene-petrol) (Found: C, 58.02; H, 5.80. Cl, 9.6%). Requires: C, 58.02; H, 5.80, Cl, 9.67. IR (as a KBr pellet): 3550, 1765, 1700, 1605, 1400, 1290, 1250, 1195, 1135, 1105, 800, 780 and 765 cm$^{-1}$.
It exhibited IR bands at 3460, 2940, 1705, 1590, 1460, 1380, 1345, 1245, 1100, 815 cm\(^{-1}\).

\textbf{N-\(\beta\)-(3',4'-Dimethoxyphenethyl)-2,6-dihydroxymethyl-3,4,5-trimethoxyphenylacetamide (42)}

5-Hydroxymethyl-6,7,8-trimethoxyisochroman-3-one (2.63g, 0.01 mole) and homoveratrylamine (2.71g, 0.015 mole) was refluxed in absolute alcohol (50 ml) for 12 hr with well stirring. The solvent was removed under reduced pressure and the resulting residue was extracted with CHCl\(_3\) (2 x 100 ml). Chloroform layer was washed twice with 2N HCl and once with water, dried over anhydrous Na\(_2\)SO\(_4\). Removal of solvent and chromatography over silica gel afforded pure 42 from chloroform eluates (3.6g, 80\%), m.p. 140° (chloroform-petrol) (Found: C, 61.08; H, 7.18; N, 3.15. C\(_{23}\)H\(_{31}\)O\(_3\)N requires C, 61.45; H, 6.95; N, 3.12%). It exhibited IR bands at 3430, 3230, 3070, 2930, 1630, 1585, 1515, 1470, 1420, 1340, 1235, 1205, 1150, 1110, 1030 and 820 cm\(^{-1}\).

\textbf{C\(_{12}\)-Hydroxymethyl-2,3,9,10,11-pentamethoxytetrahydroprotoberberine (43)}

POCl\(_3\) (4.5 ml, 0.05 mol) was added to a solution of \(N-\beta-(3',4'-\text{dimethoxyphenethyl})-2,6-\text{dihydroxymethyl-3,4,5-trimethoxyphenylacetamide (42)}\) (2.24g, 0.005 mol) in dry acetonitrile (50 ml) and the resulting solution refluxed at 80° for 4 hr. The solvent and the excess reagent was removed in vacuo. The residue was then dissolved in chloroform (50 ml), the chloroform layer washed with aqueous NaHCO\(_3\) and dried (Na\(_2\)SO\(_4\)). Removal of the solvent gave an oily residue which was dissolved in methanol (25 ml), cooled in an
ice-bath and then treated with NaBH₄ (3.3 g) pinch by pinch with stirring during 1 hr. The mixture was allowed to stand at room temperature overnight, the solvent removed in vacuo, the residue treated with water and then extracted with chloroform, the organic layer dried (Na₂SO₄). Removal of the solvent and chromatographic purification of the residue over silica gel afforded 43 (0.85 g, 40%) as amorphous solid, IR : ν max at 3500-3300 (Br.), 1590, 1515, 1460, 1345, 1260, 1105 and 755 cm⁻¹.

4-Hydroxy 3,5-dimethoxybenzylcyanide (44)

3.3 gm (0.04 mole) 3,4,5-trimethoxybenzylcyanide dissolved in 80 ml CH₂Cl₂ was taken in a two necked round bottom flask (250 ml) and it was cooled at ice temperature with stirring. To this an ice cold solution of 2 ml BBr₃ (0.03 mole) in 80 ml CH₂Cl₂ was added dropwise for 1 hr under nitrogen atmosphere. The reaction mixture was then stirred for another 3 hr. at room temperature after which the resultant mixture was poured into ice water (100 ml). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 50 ml). The resultant organic layer was washed with water (2 x 50 ml) and saturated NaCl (1 x 50 ml), dried over anhy. Na₂SO₄. The solvent was removed to yield a gummy mass which was chromatographed over silica gel. The benzene:chloroform (1:2) eluted fractions afforded 4-hydroxy-3,5-dimethoxybenzylcyanide as white solid (4.6 g, 60%), m.p. 70° (chloroform-petroleumether). IR : ν max at 3390, 2930, 2240, 1605, 1510, 1290, 1100 and 860 cm⁻¹. (Found : C, 62.25; N, 7.20; H, 5.75%. C₁₀H₁₁O₃N requires C, 62.17; N, 7.25; H, 5.69%).
3.86 gm (0.02 mole) 4-hydroxy-3,5-dimethoxybenzylcyanide dissolved in 50 ml alcohol (90%) was refluxed with 2.52g benzylchloride, 0.25 g K$_2$CO$_3$ and 0.1g KI for 15 hr. The alcohol was then removed under vacuum. The reaction mixture was then poured into water (100 ml), extracted with chloroform (2x50 ml). The chloroform layer was then washed with water (2 x 50 ml) & satd. NaCl solution (1 x 50 ml). The organic layer afforded yellowish solid which was purified by chromatographic resolution over silica gel. The benzene eluted fractions furnished 4-benzyloxy-3,5-dimethoxybenzylcyanide (yield 4.5g, 80%), m.p. 58°(benzene-chloroform). IR : $\nu_{\max}$ at 2940, 2240, 1600, 1510, 1290, 1010, 860 cm$^{-1}$. (Found : C, 85.30; H, 14.05; N, 11.70%. C$_{17}$H$_{17}$O$_3$N requires C, 85.71; H, 14.23; N, 11.76%).

4-Benzyloxy 3,5-dimethoxyphenylacetic acid (46)

4-Benzyloxy 3,5-dimethoxyphenylacetic acid (4.0g) was synthesised by the alkaline hydrolysis of 4-benzyloxy 3,5-dimethoxybenzylcyanide (4.5g) which was carried out by refluxing the cyanide with 3N KOH (250 ml) in 50 ml alcohol (90%) under nitrogen atmosphere for 12 hr. The reaction mixture was then cooled to ice temperature and acidified with (1:1) H$_2$SO$_4$ when 4-benzyloxy-3,5-dimethoxyphenylacetic acid separated out as fine crystals. It was filtered off and dried (yield 80%), m.p. 12° (chloroform-petrol), IR : $\nu_{\max}$ at 2240, 1630, 1510, 1280, 1005 and 860 cm$^{-1}$. 
N-β-(3',4'-Dimethoxyphenethyl)-4-benzyloxy-3,5-dimethoxyphenylacetamide (47)

2.08 g (0.01 mol) of phosphorouspentachloride was added to a solution of 4-benzyloxy-3,5-dimethoxyphenylacetic acid (3.73 g, 0.01 mol) in dry benzene (50 ml). The reaction mixture was ther. refluxed slowly for 1 hr. Excess benzene and the reagent was removed under reduced pressure by azeotropic separation. The solid acid chloride was then dissolved in cold chloroform (25 ml). The cold chloroform solution was added slowly to a well stirred cold mixture of homoveratrylamine (2.71 g, 0.015 mol) in chloroform (15 ml) and sodium carbonate (0.5 g) in water (10 ml). The mixture was then stirred at room temperature under nitrogen atmosphere for 1 hr and then the chloroform layer removed, washed twice with cold aqueous sodium hydroxide solution and then once with 5% hydrochloric acid. Usual work up of the chloroform layer furnished a gummy residue. Column chromatographic purification of the above residue over silica gel furnished 47 from the benzene-chloroform (1:1) fractions as viscous liquid (2.4 g). IR: ν<sub>max</sub> at 3390, 2940, 1550, 1600, 1510, 1460, 1330, 1270, 1110, 1030, 750 and 700 cm<sup>-1</sup>.

(+)-6,7-Dimethoxy-1-(4'-hydroxy-3',5'-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (48)

Phosphorous oxychloride (1.0 ml) was added to the amide 26 (1.90 g, 0.003 mol) dissolved in dry acetonitrile (25 ml). The resulting mixture was stirred at room temperature for 15 min under nitrogen atmosphere, then it was refluxed slowly for 3 hr. The resulting mixture after standing for 30 min at room temperature was poured into
ice cold chloroform (150 ml). The chloroform layer was washed with saturated sodium bicarbonate followed by dilute ammonia, finally with water to remove excess ammonia. The chloroform layer was then dried over anhydrous sodium sulphate. Removal of the solvent furnished an oily mass which was dissolved in methanol (50 ml) and treated pinch by pinch with sodium borohydride (1.0 g) at room temperature. The mixture after standing overnight was freed from solvent and decomposed with water and extracted with chloroform. The chloroform layer was washed with water (2 x 100 ml), dried (Na₂SO₄) and evaporated to afford a solid which was purified by chromatographic resolution over alumina. The chloroform eluted fractions afforded 43 as a viscous liquid (0.67 g, 60%). IR: νmax 2945, 1600, 1505, 1460, 1325, 1255, 1215, 1100 and 1020 cm⁻¹.

(±)-10-Hydroxy-2,3,9,11-tetramethoxytetrahydroprotoberberine (17)

A mixture of 0.25 g of 43, 37% formalin (2.0 ml) and acetic acid (2.0 ml) was slowly refluxed under nitrogen atmosphere for 1 hr. Excess of solvent and the reagent were removed under vacuo. Resulting gummy mass was freed from acid by repeated washing with water. The material was then dissolved in 90% alcohol (50 ml), mixed with conc. HCl (2.5 ml), refluxed for 6 hr. The reaction mixture was then kept overnight, solvent was removed by distillation. The gummy residue was poured into water (50 ml), extracted with chloroform. The chloroform layer dried (Na₂SO₄), then evaporated to afford 17, in impure state. The material was purified by chromatography over silica gel. The benzene-chloroform (1:2) fractions afforded 17 (yield 0.15 g), m.p. 165°C. IR: νmax at 3340, 2940, 1510, 1455, 1385, 1340, 1260, 1140, 1090, 1010, 845 and 785 cm⁻¹.
2,4,5-Trimethoxyphenylacetic acid

This acid was synthesised from 2,4,5-trimethoxybenzaldehyde through the following steps:

**Synthesis of Azalactone (59):**

A mixture of 2,4,5-trimethoxybenzaldehyde (9.3g), 0.05 mol powdered dry hippuric acid (10.0g), freshly fused NaOAc (4.1g) and freshly distilled ACO (14.5 ml) was heated in an oil bath with constant shaking. The mixture became almost solid and as the temperature rose it gradually liquefied and turned deep yellow. As soon as the material liquefied completely the flask was transferred to a steam bath and heated for two hours. During this time a part of the product separated as deep yellow crystals. At the end of the heating 20 c.c. of alcohol was added to the contents of the flask after cooling it to room temperature. The yellow crystalline product separated after standing overnight was filtered with suction and washed with ice cold alcohol (2x10 ml) and finally with boiling water (2x10 ml). The product after drying weighed 11.5g, and melted at 103°C. IR νmax at 1790-1760(br.), 1665, 1660, 1610, 1510, 1460, 1410, 1290, 1260, 1215, 1125, 1040, 1025, 895, 320 and 755 cm⁻¹.

**Reaction of Azalactone with alkali (NaOH):**

The above azalactone (10g) taken in a r.b. with 50 ml 10% NaOH was refluxed in an oil bath until the evolution of ammonia was complete. The resulting solution contained the Na-salt of trimethoxyphenylpyruvic acid and benzoic acid.

To the above aqueous solution 4.5 c.c. of 40% NaOH solution was added. To this H₂O₂ (4 ml) diluted with equal amount of water
(4 ml) was added with stirring at such a rate that the temperature did not rise above 15°. The resulting mixture after standing overnight was acidified by cautious addition of conc. HCl. The acid solution was then extracted with chloroform. The chloroform layer after usual work up was evaporated to afford a solid mass which was the mixture of desired acid and the benzoic acid. The mixture was refluxed for 10 hr with 50 c.c. methanol and 0.25 c.c. conc. H₂SO₄. The solvent after removal afforded a solid which was chromatographed over silica gel to separate the methyl ester of the desired acid from methyl benzoate. 2,4,5-trimethoxyphenylacetic acid (6.5g) was then finally obtained by alkaline hydrolysis of its ester and usual work up. IR : 3100-2200 (br), 1630, 1450, 1420, 1320, 1290, 1130, 1070, 925, 800 and 700 cm⁻¹.

N-2-(3,4-Dimethoxyphenethyl)-2'-chloro-3',4',6'-trimethoxyphenylacetamide (54)

2,4,5-trimethoxyphenylacetic acid (1.13g, 5.0 mmol) dissolved in dry benzene (25 ml) was treated with phosphorous pentachloride (1.05, 5.0 mmol). The resulting mixture was refluxed slowly with constant stirring for 1 hr. Removal of the solvent under reduced pressure afforded an oily residue which was dissolved in cold chloroform (25 ml). The cold chloroform solution was then added slowly to a well stirred cold mixture of homoveratrylamine (0.30g, 5.0 mmol) in chloroform (50 ml) and sodium carbonate (0.9g) in water (6 ml). The mixture, was then stirred at room temperature under nitrogen atmosphere for about 1 hr and the chloroform layer was removed, washed first with 10% cold sodium hydroxide solution (2 x 25 ml),
then with 5% HCl (1 x 25 ml). Usual work up of the chloroform layer afforded a mixture which was purified by chromatography over silica gel. The benzene-chloroform (1:1) eluted reactions was crystallised from ethylacetate-petrol to furnish fine crystals of 54 (1.69 g, 80%), m.p. 143°C, together with minor amount of 52 (0.20g). IR νmax at 3310, 2940, 1645, 1530, 1550, 1500, 1460, 1450, 1400, 1325, 1260, 1225, 1190, 1135, 1035, 840 and 815 cm⁻¹.