Studies on the Alkaloids of Papaveraceae Plants. XX. Alkaloids of Corydalis koidzumiana. II. Structure of Corydalidizine

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The structure of corydalidizine isolated from Corydalis koidzumiana Ohwi collected in Taiwan was established to be 2,9-dimethoxy-13β-methyl-13αβ-berbine-3,10-diol by the spectroscopic methods and synthesis of $d$-base.

We previously reported$^1$ the isolation of several known alkaloids belonging to tetrahydroprotoberberine, benzophenanthridine, protopine, morphinandienone and benzylisoquinoline types from Corydalis koidzumiana Ohwi collected in Taiwan.

This paper deals with the structure elucidation and synthesis of corydalidizine, a new tertiary diphenolic alkaloid isolated from the same plant.

Corydalidizine (I), $C_{20}H_{22}O_2N$, mp 209—210° (in vacuo),$^4$ $[\alpha]_D^2 +333^\circ$ ($c=0.4$, in MeOH), was isolated by the multi-buffered extraction method.$^1,5$ It shows ultraviolet (UV) spectrum absorptions at 211.5, 225 (sh.) and 283.5 nm and infrared (IR) band at 3475 cm$^{-1}$ (OH absorption).

While these spectral data suggest the tetrahydroprotoberberine type structure,$^6$ further confirmative evidence for this structure comes from the nuclear magnetic resonance (NMR) and mass spectra. The NMR spectrum of corydalidizine (100 MHz, in DMSO-$d_6$) shows signals of a secondary methyl group at $\delta$ 0.83 (d, $J=7$ Hz), two methoxy groups at $\delta$ 3.74 and 3.75, four aromatic protons at $\delta$ 6.51 (1H, s) and 6.71 (3H, s), respectively, and also those of two hydroxy groups at $\delta$ 8.65 (1H, s) and 8.94 (1H, s), which disappear on deuterium exchange. In addition to these signals there is an AB quartet at $\delta$ 3.37 and 4.03 ($J_{AB}=16$ Hz) characteristic of C-8 methylene protons of tetrahydroprotoberberines, indicating that the ring D of corydalidizine carries the oxygen substituents at C-9 and C-10.$^7$

This assignment was confirmed by methylation of corydalidizine with diazomethane, giving $d$-corydaline (II).$^8$ Accordingly, it was revealed that this base has oxygen functions at C-2, 3, 9 and 10 and a secondary methyl group of S-configuration at C-13 position.

The mass spectrum of this alkaloid (I) has its molecular ion at $m/e$ 341 (38)$^9$ and fragment ions at $m/e$ 326 (10), 178 (100), 176 (12), 164 (45), 163 (8) and 149 (25). This fragmentation pattern indicates$^7$ that both rings A and D have a set of one hydroxy and one methoxy group.

The sites of these substituents on the ring A of corydalidizine were revealed by measurements of the nuclear Overhauser effects in 100 MHz NMR spectrum. Irradiation of the signal at $\delta$ 2.50 which was assigned to one of the C-5 benzylic protons$^{10}$ increased the intensity.

3) Location: Mokayamahikamachi, Higashinada-ku, Kobe.
4) The melting point was measured in a vacuum capillary.
9) Intensities are given in parentheses.
of the aromatic proton signal at δ 6.51 by 10%, indicating this signal to be attributable to the C-4 aromatic proton. Irradiation of the hydroxy signal at δ 8.65 also caused the increase of the area of the signal at δ 6.51 by 11%, while that at δ 6.71 was unaffected. Thus, the hydroxy group whose signal appears at δ 8.65 must be located at C-3 and consequently the methoxy group at C-2 on the ring A.

Naruto, et al.\textsuperscript{11} inferred the location of the methoxy and hydroxy groups on the ring D of tetrahydroprotoberberine type alkaloids from the signal pattern of the aromatic proton region of the NMR spectrum measured in a dimethyl sulfoxide (DMSO) solution. They pointed out that tetrahydroprotoberberines whose ring D has a C-9 hydroxy and a C-10 methoxy group show the signals due to C-11 and C-12 protons as an AB quartet ($J_{AB}$=8.5 Hz), while tetrahydroprotoberberines having C-9, C-10 dimethoxy groups show the signal of C-11 and C-12 protons as a singlet of coincident chemical shift. They also reported\textsuperscript{11} that the ring D protons of capaurimine (III) (which has a C-9 methoxy and a C-10 hydroxy group) also appear as a singlet at δ 6.65.

![Diagram](chart1.png)

The aromatic protons of corydalidzine appeared as two singlets at δ 6.71 (3H) and 6.51 (1H) and no AB quartet was observed, suggesting that the ring D of this base could have a C-9 methoxy and a C-10 hydroxy group.

It has been reported by MacLean, et al.\textsuperscript{7} and Naruto, et al.\textsuperscript{11a} that the substitution pattern of the ring D of tetrahydroprotoberberines could also be inferred from the mass spectrum by comparing the intensities of the fragment ions (ion b and ion c) derived from a retro Diels-Alder fragmentation\textsuperscript{7,11b} of the ring C of the alkaloids. As the hydrogen or methyl radical is eliminated preferentially from the substitutents located at the position corresponding to C-10 of the parent molecule, ion (b-1) is more intense in the case of tetrahydroprotoberberines bearing a C-9 methoxy and a C-10 hydroxy group compared to the case of the C-10 methoxy alkaloids (Chart 2).

As shown in Fig. 1, in the mass spectrum of corydalidzine, the fragment peak at m/e 163 is weaker than that of ion b (m/e 164, R₂=R₃=CH₃, R₄=H). It was also revealed by the high resolution mass spectrum that the composition of the peak at m/e 163 was not C₁₀H₁₅O₂ (ion c, R₂=R₃=CH₃) but C₉H₁₄O₂N, that is, this fragment is formed from ion a (R₁=CH₃, R₂=H) through the elimination of a methyl radical.

In the mass spectrum of $dl$-3,10-dihydroxy-2,9-dimethoxytetrahydroprotoberberine (IV) lacking the C-13 methyl group, the intensity of ion c (m/e 149, R₂=R₃=CH₃, R₄=H, C₉H₁₄O₂) is 51% of that of ion b (m/e 150, R₂=CH₃, R₃=R₄=H, C₉H₁₄O₂). Thus the absence of the peak of ion c in corydalidzine could be due to the presence of the C-13 methyl group.

\textsuperscript{11} a) H. Kaneko and S. Naruto, \textit{Yakugaku Zasshi}, 91, 101 (1971); b) \textit{Ibid., ibid.}, 92, 1017 (1972).
Therefore, the substitution pattern of the ring D of corydalidzine could not be deduced from the mass spectral data.

Although the Gibbs' test is usually negative for compounds having substituents at ϕ-position to the phenolic hydroxy group,\textsuperscript{13} it has been reported by Inouye, \textit{et al.}\textsuperscript{14} that tetrahydroprotobererine alkaloids having a C-3 hydroxy group give a positive reaction. The present examination of the effect of C-13 methyl group in tetrahydroprotobererines to the Gibbs' reaction revealed that corypalmine (V) is positive as reported,\textsuperscript{14} while corybulbine (VI), having extra C-13 methyl group, is negative to this reaction.

On the other hand, it has been reported\textsuperscript{12b} that tetrahydroprotobererine (VII) having a C-9 hydroxy and a C-13 methyl group shows a positive reaction to this test. Thus it has been inferred that in the case of the Gibbs' reaction the C-13 methyl group in tetrahydroprotobererines does not affect the ring D, but the ring A. The negative Gibbs' reaction of corydalidzine suggests that the ring D of this base is substituted with a C-9 methoxy and a C-10 hydroxy group.

Accordingly, the NMR assignment of the substitution pattern of the ring D described above could be conceivable.

The B/C ring juncture of tetrahydroprotobererines bearing a C-13 methyl group has been discussed by taking into consideration the findings from the IR (Bohmann bands)\textsuperscript{8} and the NMR spectra (the chemical shift of the C-13 methyl group, coupling constant between C-13 and C-13a protons and the difference of chemical shifts between AB doublets due to C-8 methylene protons).\textsuperscript{10,11a,b}

<table>
<thead>
<tr>
<th>B/C ring juncture of tetrahydroprotobererines bearing a C-13 methyl group</th>
<th>Bohmann bands</th>
<th>Chemical shift of C-13 (δ)</th>
<th>Methyl group (δ)</th>
<th>J12-13a (Hz)</th>
<th>Difference of chemical shifts between C-8 methylene protons (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B/C trans bases\textsuperscript{10,11b}</td>
<td>medium</td>
<td>0.97—0.99\textsuperscript{a}</td>
<td>0.83\textsuperscript{b}</td>
<td>3.0</td>
<td>0.55—0.7\textsuperscript{a}</td>
</tr>
<tr>
<td>B/C cis bases\textsuperscript{8,11b}</td>
<td>—</td>
<td>1.48\textsuperscript{a}</td>
<td>1.35—1.37\textsuperscript{b}</td>
<td>7.5</td>
<td>0.13—0.16\textsuperscript{a}</td>
</tr>
<tr>
<td>Corydalidzine</td>
<td>weak</td>
<td>0.83\textsuperscript{b}</td>
<td>3.0</td>
<td>0.66\textsuperscript{b}</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}) in a CDCl\textsubscript{3} solution \textsuperscript{b}) in a DMSO-d\textsubscript{4} solution

As shown in Table I, in spite of the ambiguous Bohlmann bands, the NMR data of corydaldizine revealed that this alkaloid should assume a trans B/C ring juncture. This conclusion is in accord with the fact that d-corydaline (II) has been derived from corydalidzine.

We thus infer that the structure of corydalidizine would be represented as I.

This structure was finally confirmed by the synthesis of dl-corydalidzine as shown in Chart 3.

Tetrahydroprotoberberine alkaloids having a C-9 methoxy and a C-10 hydroxy group were prepared so far by the cyclization of the appropriate isoquinolines, but Kametani, et al. carried out the synthesis of dl-kikemanine (dl-corydaline) (VIII) through the Mannich reaction of 1-(4-benzoyloxy-3-hydroxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline. We also synthesized dl-corydalidzine by this method.

Chart 3. Synthesis of dl-Corydalidzine

Condensation of 3-benzyloxy-4-methoxyphenethylamine\textsuperscript{15} with 4-benzyloxy-3-hydroxyphenylacetic acid\textsuperscript{16} at 150° under nitrogen atmosphere gave the phenolic amide (IX), which was converted by ethoxycarbonylation into the non-phenolic amide (X). Bischler-Napieralski reaction of X with phosphoryl chloride in refluxing benzene gave the 3,4-dihydroisoquinoline derivative. Reduction of the crude compound with sodium borohydride gave the 1-benzyl-1,2,3,4-tetrahydroisoquinoline (XI). A solution of the hydrochloride of XI and 37% formalin was allowed to stand at pH 6.4 at room temperature overnight, giving three tetrahydroprotroberines, which were separated by frequent recrystallization and chromatography. The main product (XII) derivable into $d_l$-tetrahydropalmatine (XX) was the expected $o$-coupled base having a C-9 hydroxy and a C-10 benzylxoy group. The other products were the mono-debenzylated $o$-coupled base (XIII), which was characterised from NMR and mass spectra, and the 10,11-dioxygenated compound (XIV), whose structure was confirmed by its conversion into $d_l$-xylopinine (XV).

The main base (XII) was methylated with diazomethane to give the non-phenolic base (XVI). Oxidation of XVI with mercuric acetate gave the quaternary base (XVII, X=I) as yellow needles, which was converted into the chloride (XVII, X=Cl) by passing through a column of the ion exchange resin.

This base chloride was reacted with acetone in alkaline medium to give the acetone adduct (XVIII). Heating XVIII with methyl iodide in a sealed tube for 16 hours followed by reduction with sodium borohydride gave the C-13 methyl tetrahydroprotroberine (XIX), whose B/C ring juncture was found to be trans from the chemical shift of C-13 methyl group (d 0.95, d, J=7 Hz).\textsuperscript{10}

Debenzylation of XIX with ethanolic hydrochloric acid gave a diphenolic $d_l$-base (I), which was identical with natural corydalidine in thin-layer chromatography (TLC), UV, NMR and mass spectra.

This is the first example of natural 3,10-dihydroxytetrahydroprotroberine.

**Experimental**

The melting points were determined by a Büchi Melting Point Apparatus and were not corrected. Silica gel G acc. to Stahl (E. Merck) and alumina (neutral, Woelm) were used for the TLC and Silica gel PF\textsubscript{254} (E. Merck) for the preparative thick layer chromatography. The spots were detected by exposing the plates to iodine vapour and or by developing with Dragendorff's reagent.

Silica gel (Mallinkrodt, 100 mesh) and alumina (Wako) were used for the column chromatography. The solvent ratio was expressed in volume. The UV absorption spectra were measured with a Hitachi 124 spectrophotometer. The IR spectra were determined with a Hitachi EPI-G2 or a Hitachi 215 spectrometer. Unless otherwise noted, the NMR spectra were taken on a Varian A-60D spectrometer in CDCl\textsubscript{3} with TMS as an internal standard. The mass spectra were measured on a JEOL-01S instrument. Specific rotations were measured on a Rex NEP-2 photoelectric polarimeter.

**Isolation of Corydalidine (I)**——The phenolic tertiary base fractions of *Corydalis hoodzumiana OHWI* which were collected in the suburbs of Taipei, Taiwan, were separated by the multi-buffered extraction method into pH 6.0, 5.0, 4.0, 3.0, 2.6 and 2.0 fractions.\textsuperscript{11} Among them, the pH 5.0 and 4.0 fractions from which sinoacine, l-capaurine and l-scoulerine had been removed by alumina chromatography\textsuperscript{12} were chromatographed on a silica gel column (10 g, 1.3×14 cm; CHCl\textsubscript{3}) to give corydalidine (I), mp 209—210°C (in vacuo)\textsuperscript{10} (from MeOH), 35 mg. $[\alpha]_D^2 +333^0$ (c=0.4, MeOH). High resolution mass spectrum: $C_{29}H_{30}O_8N$ (M\textsuperscript{+}) m/z: 414.161993; Calcd. 414.16271. $C_{29}H_{30}O_8$ m/z: 414.085186; Calcd. 414.08373. $C_{29}H_{30}O_8$ m/z: 164.062096; Calcd. 164.06333. $C_5H_4O_2$ m/z: 149.062290; Calcd. 149.06028.

**Methylation of Corydalidine (I)**——To a solution of corydalidine (10 mg) in MeOH (5 ml) was added an ethereal solution of CH\textsubscript{3}N\textsubscript{2} generated from nitrosomethyurea (3 g) and allowed to stand at room temperature for 3 hr. After concentration of the reaction mixture, the residue was recrystallized from aq. MeOH to give colorless prisms, mp 122—125°C, 0.2 mg. $[\alpha]_D^2 +274^0$ (c=0.13, CHCl\textsubscript{3}), which were identified with an authentic sample of $d$-corydaline (II) by TLC (silica gel, CHCl\textsubscript{3}: MeOH 97.5:2.5; alumina, benzene: ether 50:50), the mixed melting point and comparisons of NMR and mass spectra.

**4-Benzzyloxy-N-(3-benzyloxy-4-methoxyphenethyl)-3-hydroxyphenylacetamide (IX)**——A mixture of 3-benzyloxy-4-methoxyphenethylamine\textsuperscript{15} (12.9 g) and 4-benzyloxy-3-hydroxyphenylacetic acid,\textsuperscript{16} mp 123—
124°,19) (4.5 g) was heated at 150° for 4 hr under nitrogen atmosphere. The reaction product was dissolved in CHCl₃, washed successively with 5% HCl, 2%aq. NaHCO₃ and H₂O and dried over anhyd. MgSO₄. After evaporation of the solvent in vacuo, the residue was recrystallized from MeOH to give 9 g of the phenolic acetamide (IX), mp 128—129°. Anal. Calcd. for C₅₄H₄₃NO: C, 74.83; H, 6.28; N, 2.82. Found: C, 75.15; H, 6.33; N, 2.82. IR νₒₛ₃₅₃ cm⁻¹: 3550, 3400, 1630. NMR (δ): 3.81 (3H, s, OCH₃).

4-Benzoxyl-3-ethoxy carbonyl-N-(3-benzoxyl-4-methoxypenthyethyl) acetamide (X)—To a stirred solution of the phenolic acetamide (IX) (19.1 g) and triethylamine (5.4 g) in abs. benzene (1.2 liter) was added dropwise ethylchloroformate (6.5 g) at 4—9°.

The mixture was stirred for 1.5 hr at room temperature. The benzene solution was washed successively with H₂O, 5% HCl and H₂O and dried over anhyd. MgSO₄. Evaporation of the solvent gave 18.4 g of X, mp 51—52° (from ether). Anal. Calcd. for C₄₄H₃₃NO: C, 71.69; H, 6.19; N, 2.46. Found: C, 71.22; H, 6.27; N, 2.25. IR νₒₛ₃₅₃ cm⁻¹: 3445, 1760, 1655. NMR (δ): 1.30 (3H, t, J = 7 Hz; COOCH₂CH₃), 3.83 (3H, s, OCH₃), 4.27 (2H, q, J = 7 Hz; COOCH₂CH₃).

1-(4-Benzoxyl-3-hydroxybenzyl)-1,2,3,4-tetrahydro-6-benzoxyl-7-methoxyisoquinoline (XI)—A solution of the amide (X) (5 g) and POCl₃ (20 ml) in abs. benzene (300 ml) was refluxed for 2.5 hr.

After addition of n-hexane (900 ml), the reaction mixture was allowed to stand at room temperature overnight and the supernatant was removed by decantation. The syrup residue washed three times with n-hexane was concentrated to dryness in vacuo. To a solution of the residue in MeOH (250 ml) was added NaBH₄ (6.3 g) at room temperature and the solution was refluxed for 2 hr. After removal of the solvent in vacuo, H₂O was added and the resulting precipitates were dissolved in CHCl₃. The CHCl₃ solution was washed with H₂O, dried over anhyd. MgSO₄ and evaporated to dryness and the residue was recrystallized from MeOH yielding 2.6 g of the 1,2,3,4-tetrahydroisoquinoline (XI), mp 137—139°. Anal. Calcd. for C₂₅H₂₃NO: C, 77.31; H, 6.49; N, 2.81. Found: C, 77.57; H, 6.58; N, 3.21. IR νₒₛ₃₅₃ cm⁻¹: 3310, 2870—2900. NMR (δ): 3.79 (3H, s, OCH₃), 5.05 (2H, s, OCH₂CH₃), 5.09 (2H, s, OCH₂CH₃).

Mannich Cyclisation of the 1,2,3,4-Tetrahydroisoquinoline (XI)—To a solution of the hydrochloride (0.7 g) of 1,2,3,4-tetrahydroisoquinoline (XI) in a mixture of MeOH (100 ml) and H₂O (60 ml), whose pH value was adjusted to 6.4 with 5%aq. NaHCO₃, was added dropwise 37% formalin (50 ml) with stirring and the pH was again adjusted to 6.4 with 5%aq. NaHCO₃ and allowed to stand at room temperature overnight. The resulting precipitates were collected by filtration, dissolved in CHCl₃, washed with 5%aq. NaHCO₃ and dried over anhyd. MgSO₄. After evaporation of the solvent in vacuo, the residue was recrystallized repeatedly from CHCl₃—MeOH to give 0.35 g of the 9-hydroxytetrahydroprotoberberine (XII), mp 87—90° (in vacuo).49 Anal. Calcd. for C₃₀H₂₇NO·H₂O·CH₃OH: C, 75.40; H, 6.71; N, 2.67. Found: C, 74.99; H, 6.74; N, 2.93. IR νₒₛ₃₅₃ cm⁻¹: 3540, 2840—2750, 1607. NMR (δ): 3.87 (3H, s, OCH₃), 4.25 (1H, AB doublet, Jₘₐₓ = 16 Hz, lower part of C-8 methylene protons), 5.07 (2H, s, OCH₂CH₃), 5.10 (2H, s, OCH₂CH₃). Mass spectrum m/z: 493 (M⁺), 403, 311, 268. The filtrate obtained after removal of XII was extracted with CHCl₃, washed successively with 5%aq. NaHCO₃ and H₂O and dried over anhyd. MgSO₄. Evaporation of the solvent gave 198 mg of a syrup, which was combined with the mother liquor of the recrystallization of XII. The mixture was chromatographed on silica gel (7 g, 1.3 x 11 cm) eluted with a solvent consisting of CHCl₃—MeOH 99:1. The combined fractions No. 1—23 (1 g each) were evaporated in vacuo and recrystallized from MeOH to give the 11-hydroxy base (XIV), mp 111—113°, and 109.5—170.5° (dimorphism), 35 mg. Anal. Calcd. for C₂₅H₂₃NO·H₂O·CH₃OH: C, 77.86; H, 6.33; N, 2.84. Found: C, 77.68; H, 6.19; N, 3.05. IR νₒₛ₃₅₃ cm⁻¹: 3530, 2830—2750. NMR (δ): 3.38 (3H, s, OCH₃), 5.04 (2H, s, OCH₂CH₃), 5.10 (2H, s, OCH₂CH₃). Mass Spectrum m/z: 493 (M⁺), 149. The combined fractions No. 24—61 were evaporated in vacuo and recrystallized from MeOH to give the mono-benzylated base (XIII), mp 111—114° (decomp., in vacuo), 6.7 mg. Anal. Calcd. for C₂₅H₂₃NO·H₂O·CH₃OH: C, 71.70; H, 6.67; N, 3.22. Found: C, 72.02; H, 6.88; N, 3.67. NMR (δ): 3.87 (3H, s, OCH₃), 4.23 (1H, AB doublet, Jₘₐₓ = 16 Hz, lower part of C-8 methylene protons), 5.08 (2H, s, OCH₂CH₃). Mass Spectrum m/z: 403 (M⁺), 312, 178.

3,10-Dibenzyloxy-2,9-dimethoxytetrahydroprotoberberine (XVI)—To a solution of the phenolic base (XII) (2.6 g) in MeOH (700 ml) was added an ethereal solution of CH₃Na prepared from nitroso- methylurea (20 g) and allowed to stand at room temperature for 1 hr. After the reaction solvent and excess reagent, the resulting powder was recrystallized from MeOH to give the dimethoxy base (XVI) as colorless needles, mp 146.5—148.5°, 1.7 g. Anal. Calcd. for C₃₀H₂₇NO·H₂O·2CH₃OH: C, 78.08; H, 6.55; N, 2.77. Found: C, 77.99; H, 6.50; N, 2.71. NMR (δ): 3.87 (3H, s, OCH₃), 3.88 (3H, s, OCH₃), 5.12 (4H, s, 2 x OCH₂CH₃). Mass Spectrum m/z: 507 (M⁺), 416, 149.

3,10-Dibenzyloxy-2,9-dimethoxyprotoberberinum Salt (XVII)—To a solution of the tertiary base (XVI) (1.84 g) in 20%aq. acetic acid (400 ml) was added portionwise mercuric oxide (yellow, 2.46 g) and this solution was warmed on a steam bath for 2.5 hr. The resulting precipitates were removed by filtration and H₂S was introduced into the filtrate. After filtration, a 20%aq. KI solution was added to the filtrate and the resulting

18) The melting point of this acid is different from the value in the literature18 (mp 99—100°), but that of the methoxymethyl ester of the hydroxy acid (mp 66—67°) is identical with the reported value19 (mp 66—69.5°).

yellow precipitates were recrystallized from MeOH to give the quaternary base iodide (XVII, X = I), mp 222° (decomp.), 640 mg. *Anal.* Calcd. for C₉₆H₉₂O₅N: C, 62.76; H, 4.79; 2.22. Found: C, 62.48; H, 4.91; N, 2.47. A solution of the quaternary base iodide (XVII, X = I) (500 mg) in 50% aq. acetone (800 ml) was passed through the ion exchange resin (Amberlite IRA-410, Cl form). Then, the eluate was condensed and the residue was recrystallized from aq. MeOH to give the quaternary base chloride (XVII, X = Cl), mp 210° (decomp.), 330 mg.

3.10-Dibenzoxy-2,9-dimethoxy-13-methyltetrahydroprotoberine (XIX)—A suspension of the quaternary base chloride (XVII, X = Cl) (250 mg) in acetone (20 ml) and H₂O (5 ml) was vigorously shaken with 30% aq. NaOH (5 ml) in a separatory funnel. After removal of the acetone layer, the aq. layer was shaken again with acetone (20 ml) and the acetone layer was separated, the acetone solutions were combined and condensed *in vacuo* to give the acetone adduct (XVIII). A solution of the crude compound (XVIII) in acetone (20 ml) and CH₂Cl₂ (3 ml) was heated at 55° in a sealed tube for 16 hr giving rise to precipitates. A solution of the precipitates in MeOH (100 ml) was added NaN₃ (200 mg) and after refluxing for 30 min, the mixture was worked up in the usual way. The crude product was purified by preparative thick layer chromatography on silica gel (benzene: ether: toluene: 70: 30: 10) to give the 13-methyltetrahydroprotoberine base (XIX), mp 155—156° (from CHCl₃—MeOH), 113 mg. *Anal.* Calcd. for C₉₆H₉₂O₅N: C, 78.28; H, 6.76. Found: C, 78.46; H, 6.76. NMR (δ): 0.95 (3H, d, J = 7 Hz, CH₂CH₃), 3.86 (3H, s, OCH₃), 3.90 (3H, s, OCH₃), 5.12 (4H, s, 2 × OCH₂CH₃). Mass Spectrum *m/z*: 521 (M⁺), 430, 163.

dl-Corydalizine—A solution of the dibenzyl derivative (XIX) (100 mg) in EtOH (10 ml) and conc. HCl (5 ml) was refluxed for 4 hr. After removal of the solvent *in vacuo*, H₂O was added to the residue and the solution was made alkaline with 5% aq. NH₄OH, extracted with CH₂Cl₂, washed with H₂O and dried over anhyd. MgSO₄. After evaporation of the solvent, the residue was recrystallized from aq. MeOH to give dl-corydalizine (I), mp 156—157.5° (in vacuo), 26 mg, which was identified with natural corydalizidine by TLC (both solvent systems, CHCl₃: MeOH 90: 10 and benzene: ether 50: 50 were employed for silica gel and alumina), NMR (DMSO-d₆, UV and mass spectra. *Anal.* Calcd. for C₉₆H₉₂O₅N·2H₂O: C, 63.64; H, 7.21; N, 3.71. Found: C, 64.12; H, 7.00; N, 3.85. High resolution mass spectrum mass spectrometry: C₉₆H₉₂O₅N·2H₂O *m/z*: 541.163597; Calcd. 541.163271.

3.10-Dihydroxy-2,9-dimethoxytetrahydroprotoberine (IV)—A solution of the dibenzyl base (XVI) (100 mg) in EtOH (10 ml) and conc. HCl (5 ml) was refluxed for 5 hr. After removal of the solvent *in vacuo*, the residue was suspended in H₂O, made alkaline with 5% aq. NH₄OH, extracted with ether, washed with H₂O and dried over anhyd. MgSO₄ and evaporated to dryness. The residue was recrystallized from aq. MeOH giving the 3,10-dihydroxy base (IV), mp 215° (decomp.), 23 mg. *Anal.* Calcd. for C₉₆H₉₂O₅N: C, 69.70; H, 6.47; N, 4.28. Found: C, 69.97; H, 6.68; N, 4.58. IR νmax cm⁻¹: 3375. NMR (δ, DMSO-d₆): 3.74 (3H, s, OCH₃), 3.77 (3H, s, OCH₃), 6.53 (1H, s, aromatic proton), 6.73 (2H, s, aromatic protons), 6.85 (1H, s, aromatic proton). Mass Spectrum *m/z*: 327 (M⁺), 178, 176, 150, 150. High resolution mass spectrum: C₉₆H₉₂O₅N *m/z*: 150.068257; Calcd. 150.06808. C₉₆H₉₂O₅N *m/z*: 149.056824; Calcd. 149.060206.

dl-Tetrahydropalmatine (XX)—To a solution of the diphenyl base (IV) (44 mg) in MeOH (6 ml) was added an ethereal solution of CH₂N₂ prepared from 3 g of nitrosomethylurea and allowed to stand at room temperature for 3 hr. After condensation of the reaction mixture to dryness, the resulting powder was recrystallized from MeOH to give colorless plates, mp 149.5—150°, 17 mg, which were identified as an authentic sample of dl-tetrahydropalmatine (XX) by TLC (silica gel, benzene: ether 50: 50), IR (CHCl₃) and their mixed melting point. *Anal.* Calcd. for C₉₆H₉₂O₅N: C, 70.96; H, 7.09; N, 3.94. Found: C, 71.24; H, 6.93; N, 4.10.

3.10-Dibenzoxy-2,11-dimethoxytetrahydroprotoberine (XXI)—To a solution of the monophenolic base (XIV) (30 mg) in MeOH (5 ml) was added an ethereal solution of CH₂N₂ prepared from 3 g of nitrosomethylurea and allowed to stand at room temperature for 3 hr. After concentration to dryness, the resulting powder was recrystallized from MeOH to give the non-phenolic base (XXI) as colorless plates, mp 136—137°, 26.1 mg. *Anal.* Calcd. for C₉₆H₉₂O₅N: C, 78.08; H, 6.55; N, 2.77. Found: C, 78.13; H, 6.54; N, 3.11.

dl-Xylopinine (XV)—A solution of the dibenzoxyl base (XXI) (26.1 mg) in EtOH (30 ml) and conc. HCl (5 ml) was refluxed for 5 hr. After removal of the solvent *in vacuo*, the residue was dissolved in 2% aq. NaOH (20 ml) and washed with CH₂Cl₂. The alkaline solution was saturated with NH₄Cl, extracted with CH₂Cl₂, dried over anhyd. MgSO₄ and concentrated to dryness. To a solution of the residue in MeOH (20 ml) was added an ethereal solution of CH₂N₂ generated from 3 g of nitrosomethylurea and allowed to stand at room temperature for 3 hr. The methylated product was purified by preparative thick layer chromatography on silica gel (CHCl₃:MeOH 97.5: 2.5) to give colorless crystals, mp 148—149° (from MeOH—ether), 22.4 mg, which were identified as an authentic sample of dl-xylopinine (XV) by their mixed melting point, and comparisons of NMR and IR (CHCl₃) spectra. *Anal.* Calcd. for C₉₆H₉₂O₅N: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.89; H, 7.02; N, 4.03.

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