Studies on the Alkaloids of Papaveraceous Plants. XX.[1] Alkaloids of Corydalis koidzumiana. II.[1] Structure of Corydalidzine[2]

Chiaki Tani, Naotaka Nagakura, and Shin Hattori

Kobe Women's College of Pharmacy[3]

The structure of corydalidzine isolated from Corydalis koidzumiana Ohwi collected in Taiwan was established to be 2,9-dimethoxy-13α-methyl-13aβ-berbine-3,10-diol by the spectroscopic methods and synthesis of dl-base.

We previously reported[1] the isolation of several known alkaloids belonging to tetra-hydroprotoberberine, benzophenanthridine, protopine, morphinandienone and benzyliso-quinoline types from Corydalis koidzumiana Ohwi collected in Taiwan.

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

Corydalidzine (I), $C_{20}H_{23}O_4N$, mp 209—210° (in vacuo),[4] $[\alpha]_D^{23}$ +333° (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 corydalidzine (100 MHz, in DMSO-d_6) shows signals of a secondary methyl group at δ 0.83 (d, J=7 Hz), two methoxy groups at δ 3.74 and 3.75, four aromatic protons at δ 6.51 (1H, s) and 6.71 (3H, s), respectively, and also those of two hydroxy groups at δ 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 δ 3.37 and 4.03 (J_{AB}=16 Hz) characteristic of C-8 methylene protons of tetrahydroprotoberberines, indicating that the ring D of corydalidzine carries the oxygen substituents at C-9 and C-10.[7]

This assignment was confirmed by methylation of corydalidzine 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 corydalidzine were revealed by measure-ments of the nuclear Overhauser effects in 100 MHz NMR spectrum. Irradiation of the signal at δ 2.50 which was assigned to one of the C-5 benzylic protons[10] increased the intensity

1) Part XIX: C. Tani, N. Nagakura, and S. Hattori, Yakugaku Zasshi, 94, 844 (1974).
2) Preliminary communication, C. Tani, N. Nagakura, and S. Hattori, Tetrahedron Letters, 1973, 803.
3) Location: Motoyamakitamachi, Higashinada-ku, Kobe.
4) The melting point was measured in a vacuum capillary.
5) Y. Watanabe, M. Uchiyama, and K. Yasuda, Yakugaku Zasshi, 77, 807 (1957); E. Fujita, K. Bessho, Y. Saeki, M. Ochiai, and K. Fuji, Lloydia, 34, 306 (1971).
6) A.W. Sangster and K.L. Stuart, Chem. Rev., 65, 69 (1965).
7) C.-Y. Chen and D.B. MacLean, Can. J. Chem., 46, 2501 (1968).
8) P.W. Jeffs, Experientia, 21, 690 (1965).
9) Intensities are given in parentheses.
10) C.K. Yu, D.B. MacLean, R.G.A. Rodrigo, and R.H.F. Manske, Can. J. Chem., 48, 3673 (1970).

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.[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[11a] 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.
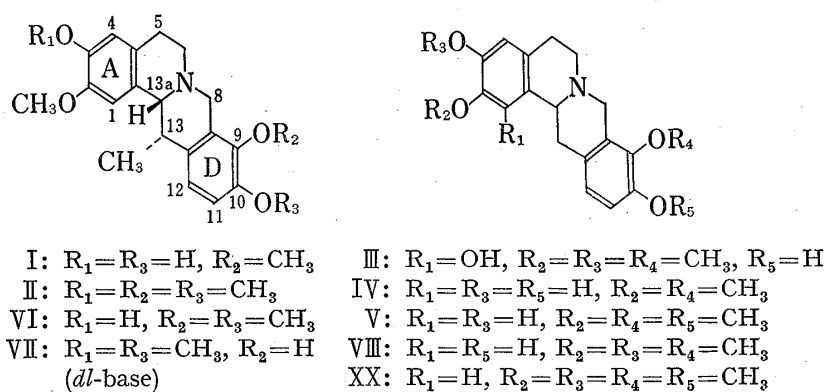

I: $R_1=R_3=H$, $R_2=CH_3$ III: $R_1=OH$, $R_2=R_3=R_4=CH_3$, $R_5=H$
II: $R_1=R_2=R_3=CH_3$ IV: $R_1=R_3=R_5=H$, $R_2=R_4=CH_3$
VI: $R_1=H$, $R_2=R_3=CH_3$ V: $R_1=R_3=H$, $R_2=R_4=R_5=CH_3$
VII: $R_1=R_3=CH_3$, $R_2=H$ VIII: $R_1=R_5=H$, $R_2=R_3=R_4=CH_3$
     (dl-base)   XX: $R_1=H$, $R_2=R_3=R_4=R_5=CH_3$

Chart 1

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.[7] and Naruto, et al.[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[7,12] of the ring C of the alkaloids. As the hydrogen or methyl radical is eliminated preferentially from the substituents 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, $R_3=R_5=CH_3$, $R_4=H$). It was also revealed by the high resolution mass spectrum that the composition of the peak at m/e 163 was not $C_{10}H_{11}O_2$ (ion c, $R_3=R_5=CH_3$) but $C_9H_9O_2N$, that is, this fragment is formed from ion a ($R_1=CH_3$, $R_2=H$) 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, $R_3=CH_3$, $R_5=H$, $C_9H_9O_2$) is 51% of that of ion b (m/e 150, $R_3=CH_3$, $R_4=R_5=H$, $C_9H_{10}O_2$). Thus the absence of the peak of ion c in corydalidzine could be due to the presence of the C-13 methyl group.

11) a) H. Kaneko and S. Naruto, Yakugaku Zasshi, 91, 101 (1971); b) Idem, ibid., 92, 1017 (1972).
12) M. Ohashi, J.M. Wilson, H. Budzikiewicz, M. Shamma, W.A. Slusachyk, and C. Djerassi, J. Am. Chem. Soc., 85, 2807 (1963).
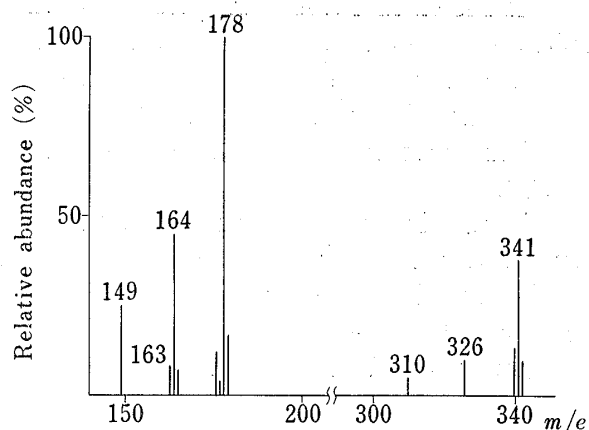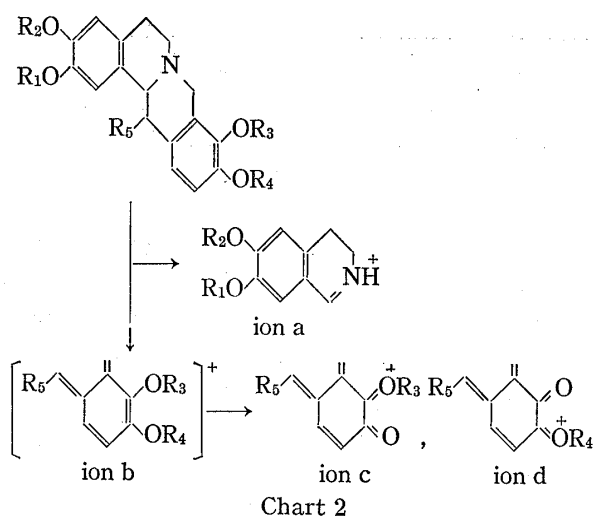
Chart 2

Fig. 1. Mass Spectrum of Corydalidzine

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 p-position to the phenolic hydroxy group,[13] it has been reported by Inouye, et al.[14] that tetrahydroprotoberberine alkaloids having a C-3 hydroxy group give a positive reaction. The present examination of the effect of C-13 methyl group in tetrahydroprotoberberines to the Gibbs' reaction revealed that corypalmine (V) is positive as reported,[14] while corybulbine (VI), having extra C-13 methyl group, is negative to this reaction.

On the other hand, it has been reported[11b] that tetrahydroprotoberberine (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 tetrahydroprotoberberines 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 tetrahydroprotoberberines bearing a C-13 methyl group has been discussed by taking into consideration the findings from the IR (Bohlmann bands)[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).[10,11b]

TABLE I.   Data for 13-Methyltetrahydroprotoberberines

	B/C trans bases[10,11b]	B/C cis bases[10,11b]	Corydalidzine
Bohlmann bands	medium	—	weak
Chemical shift of C-13 Methyl group (δ)	0.97—0.99[a] 0.83[b]	1.48[a] 1.35—1.37[b]	0.83[b]
J_{13-13a} (Hz)	3.0	7.5	3.0
Difference of chemical shifts between C-8 methylene protons (ppm)	0.55—0.7[a]	0.13—0.16[a]	0.66[b]

a) in a $CDCl_3$ solution   b) in a DMSO-d_6 solution

13) H.D. Gibbs, J. Biol. Chem., 72, 649 (1927).
14) H. Inouye, Y. Kanaya, and Y. Murata, Chem. Pharm. Bull. (Tokyo), 7, 573 (1959).

As shown in Table I, in spite of the ambiguous Bohlmann bands, the NMR data of cory-dalidzine 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 corydalidzine 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,[15] but Kametani, *et al.*[16] carried out the synthesis of *dl*-kikemanine (*dl*-corydalmine) (VIII) through the Mannich reaction of 1-(4-benzyloxy-3-hydroxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline. We also synthesized *dl*-corydalidzine by this method.

IX : R=H
X : R=COOC₂H₅

XII : $R_1=C_7H_7$, $R_2=H$
XIII : $R_1=R_2=H$
XVI : $R_1=C_7H_7$, $R_2=CH_3$

XIV : $R_1=R_2=C_7H_7$, $R_3=H$
XV : $R_1=R_2=R_3=CH_3$

XVII

XVIII
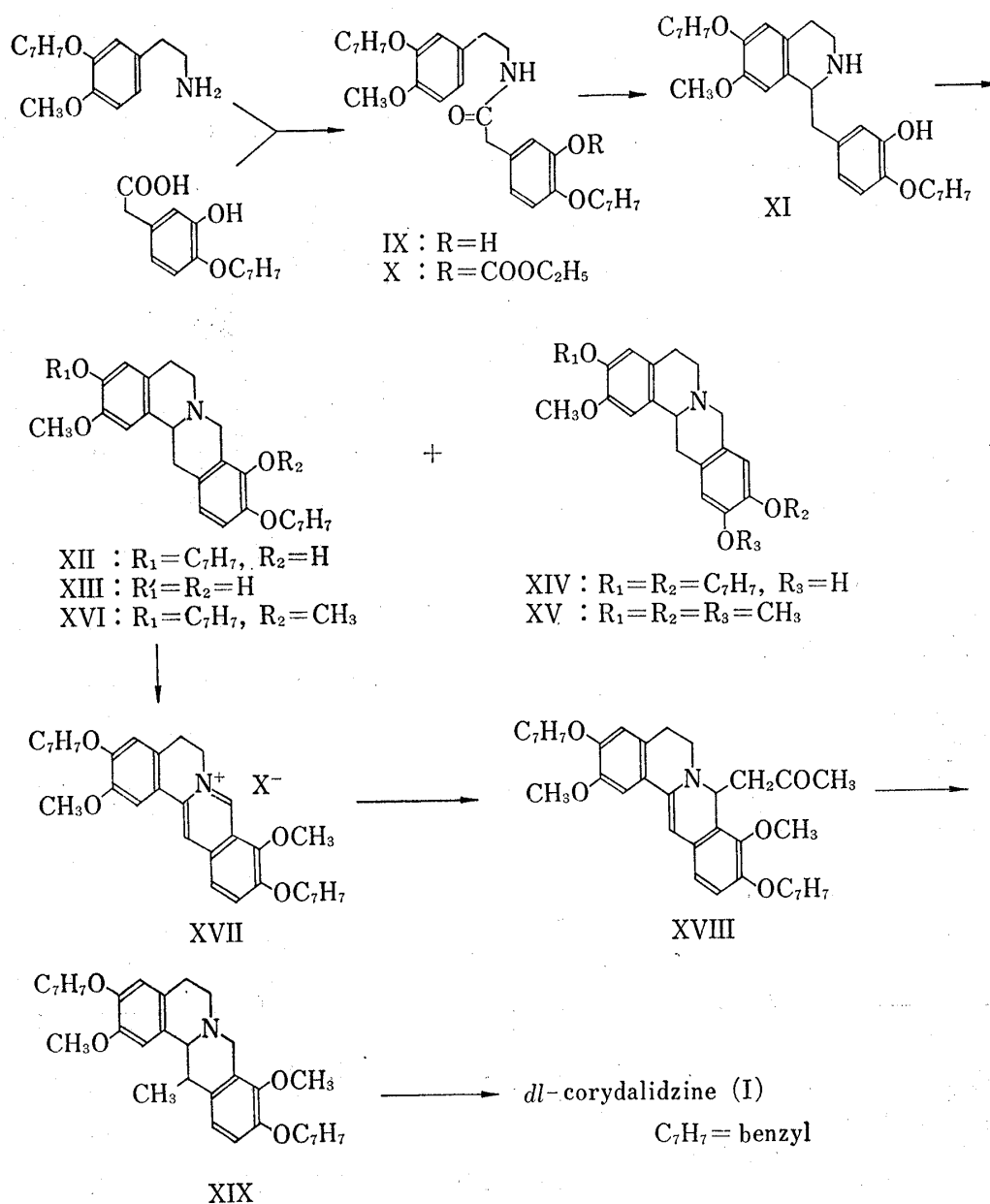
XIX

dl-corydalidzine (I)

C_7H_7 = benzyl

Chart 3. Synthesis of *dl*-Corydalidzine

15) S.A. Telang and C.K. Bradsher, *J. Org. Chem.*, **30**, 752 (1965).
16) T. Kametani, T. Honda, and M. Ihara, *J. Chem. Soc.* (*C*), 1971, 3318.
17) M. Tomita and H. Yamaguchi, *J. Pharm. Soc. Japan*, **72**, 1219 (1952).

Condensation of 3-benzyloxy-4-methoxyphenethylamine[17] with 4-benzyloxy-3-hydroxy-phenylacetic acid[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 tetrahydroproto-berberines, which were separated by frequent recrystallization and chromatography. The main product (XII) derivable into dl-tetrahydropalmatine (XX) was the expected o-coupled base having a C-9 hydroxy and a C-10 benzyloxy 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 dl-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 tetrahydroprotoberberine (XIX), whose B/C ring juncture was found to be *trans* from the chemical shift of C-13 methyl group (δ 0.95, d, $J=7$ Hz).[10]

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

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

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_{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 (Mallinckrodt, 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 spectro-meter. Unless otherwise noted, the NMR spectra were taken on a Varian A-60D spectrometer in $CDCl_3$ 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 Corydalidzine (I)——The phenolic tertiary base fractions of *Corydalis koidzumiana* 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.[1] Among them, the pH 5.0 and 4.0 fractions from which sinoacutine, l-capaurine and l-scoulerine had been removed by alumina chromatography[1] were chro-matographed on a silica gel column (10 g, 1.3×14 cm; $CHCl_3$) to give corydalidzine (I), mp 209—210° (*in vacuo*)[4] (from MeOH), 35 mg. $[\alpha]_D^{23}$ +333° (c=0.4, MeOH). High resolution mass spectrum: $C_{20}H_{23}O_4N$ (M+) m/e: 341.161993; Calcd. 341.16271. $C_{10}H_{12}O_2$ m/e: 164.085186; Calcd. 164.08373. $C_9H_9O_2N$ m/e: 163.062096; Calcd. 163.06333. $C_9H_9O_2$ m/e: 149.062220; Calcd. 149.06026.

Methylation of Corydalidzine (I)——To a solution of corydalidzine (10 mg) in MeOH (5 ml) was added an ethereal solution of CH_2N_2 generated from nitrosomethylurea (3 g) and allowed to stand at room tem-perature for 3 hr. After concentration of the reaction mixture, the residue was recrystallized from aq. MeOH to give colorless prisms, mp 122—125°, 9.2 mg, $[\alpha]_D^{23}$ +274° (c=0.13, $CHCl_3$), which were identified with an authentic sample of d-corydaline (II), by TLC (silica gel, $CHCl_3$: MeOH 97.5: 2.5; alumina, benzene: ether 50: 50), the mixed melting point and comparisons of NMR and mass spectra.

4-Benzyloxy-N-(3-benzyloxy-4-methoxyphenethyl)-3-hydroxyphenylacetamide (IX)——A mixture of 3-benzyloxy-4-methoxyphenethylamine[17] (12.9 g) and 4-benzyloxy-3-hydroxyphenylacetic acid,[16] mp 123—

124°,[18] (4.5 g) was heated at 150° for 4 hr under nitrogen atmosphere. The reaction product was dissolved in $CHCl_3$, washed successively with 5% HCl, 2% aq. $NaHCO_3$ and H_2O and dried over anhyd. $MgSO_4$. 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 $C_{31}H_{31}O_5N$: C, 74.83; H, 6.28; N, 2.82. Found: C, 75.15; H, 6.33; N, 2.87. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550, 3400, 1630. NMR (δ): 3.81 (3H, s, OCH_3).

4-Benzyloxy-3-ethoxycarbonyl-N-(3-benzyloxy-4-methoxyphenethyl)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 H_2O, 5% HCl and H_2O and dried over anhyd. $MgSO_4$. Evaporation of the solvent gave 18.4 g of X, mp 51—52° (from ether). *Anal.* Calcd. for $C_{34}H_{35}O_7N$: C, 71.69; H, 6.19; N, 2.46. Found: C, 71.22; H, 6.27; N, 2.25. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3445, 1760, 1655. NMR (δ): 1.30 (3H, t, $J=7$ Hz; $COOCH_2C\underline{H}_3$), 3.83 (3H, s, OCH_3), 4.27 (2H, q, $J=7$ Hz; $COOC\underline{H}_2CH_3$).

1-(4-Benzyloxy-3-hydroxybenzyl)-1,2,3,4-tetrahydro-6-benzyloxy-7-methoxyisoquinoline (XI)——A solution of the amide (X) (5 g) and $POCl_3$ (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 syrupy 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 $NaBH_4$ (6.3 g) at room temperature and the solution was refluxed for 2 hr. After removal of the solvent *in vacuo*, H_2O was added and the resulting precipitates were dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried over anhyd. $MgSO_4$ 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 $C_{31}H_{31}O_4N$: C, 77.31; H, 6.49; N, 2.91. Found: C, 77.57; H, 6.56; N, 3.21. IR ν_{max}^{Nujol} cm^{-1}: 3310, 2670—2300. NMR (δ): 3.79 (3H, s, OCH_3), 5.05 (2H, s, $OC\underline{H}_2C_6H_5$), 5.09 (2H, s, $OC\underline{H}_2C_6H_5$).

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 H_2O (60 ml), whose pH value was adjusted to 6.4 with 5% aq. $NaHCO_3$, was added dropwise 37% formalin (30 ml) with stirring and the pH was again adjusted to 6.4 with 5% aq. $NaHCO_3$ and allowed to stand at room temperature overnight. The resulting precipitates were collected by filtration, dissolved in $CHCl_3$, washed with 5% aq. $NaHCO_3$ and dried over anhyd. $MgSO_4$. After evaporation of the solvent *in vacuo*, the residue was recrystallized repeatedly from $CHCl_3$–MeOH to give 0.35 g of the 9-hydroxytetrahydroprotoberberine (XII), mp 87—90° (*in vacuo*).[4] *Anal.* Calcd. for $C_{32}H_{31}O_4N \cdot CH_3OH$: C, 75.40; H, 6.71; N, 2.67. Found: C, 74.99; H, 6.74; N, 2.93. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3540, 2840—2750, 1607. NMR (δ): 3.87 (3H, s, OCH_3), 4.25 (1H, AB doublet, $J_{AB}=16$ Hz, lower part of C-8 methylene protons), 5.07 (2H, s, $OC\underline{H}_2C_6H_5$), 5.10 (2H, s, $OC\underline{H}_2C_6H_5$). Mass spectrum m/e: 493 (M$^+$), 402, 311, 268. The filtrate obtained after removal of XII was extracted with $CHCl_3$, washed successively with 5% aq. $NaHCO_3$ and H_2O and dried over anhyd. $MgSO_4$. 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 × 11 cm) eluted with a solvent consisting of $CHCl_3$: 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 169.5—170.5° (dimorphism), 35 mg. *Anal.* Calcd. for $C_{32}H_{31}O_4N$: C, 77.86; H, 6.33; N, 2.84. Found: C, 77.68; H, 6.19; N, 3.05. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3530, 2830—2750. NMR (δ): 3.88 (3H, s, OCH_3), 5.04 (2H, s, $OCH_2C_6H_5$), 5.10 (2H, s, $OC\underline{H}_2C_6H_5$). Mass Spectrum m/e: 493 (M$^+$), 149. The combined fractions No. 24—61 were evaporated *in vacuo* and recrystallized from aq. MeOH to give the mono-benzylated base (XIII), mp 111—114° (decomp., *in vacuo*[4]), 6.7 mg. *Anal.* Calcd. for $C_{25}H_{25}O_4N \cdot CH_3OH$: C, 71.70; H, 6.71; N, 3.22. Found: C, 72.02; H, 6.88; N, 3.67. NMR (δ): 3.87 (3H, s, OCH_3), 4.28 (1H, AB doublet, $J_{AB}=16$ Hz, lower part of C-8 methylene protons), 5.08 (2H, s, $OC\underline{H}_2C_6H_5$). Mass Spectrum m/e: 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 CH_2N_2 prepared from nitroso-methylurea (20 g) and allowed to stand at room temperature for 1 hr. After evaporation of the 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 $C_{33}H_{33}O_4N$: 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, OCH_3), 3.88 (3H, s, OCH_3), 5.12 (4H, s, 2 × $OC\underline{H}_2C_6H_5$). Mass Spectrum m/e: 507 (M$^+$), 416, 149.

3,10-Dibenzyloxy-2,9-dimethoxyprotoberberinium Salt (XVII)——To a solution of the tertiary base (XVI) (1.34 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 H_2S was introduced into the filtrate. After filtration, a 20% aq. KI solution was added to the filtrate and the resulting

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18) The melting point of this acid is different from the value in the literature[16] (mp 99—100°), but that of the methoxy methyl ester of the hydroxy acid (mp 66—67°) is identical with the reported value[19] (mp 66—69.5°).

19) T. Kametani and M. Satoh, *Yakugaku Zasshi*, **87**, 179 (1967).

yellow precipitates were recrystallized from MeOH to give the quaternary base iodide (XVII, X=1), mp 222° (decomp.), 640 mg. *Anal.* Calcd. for $C_{33}H_{30}O_4NI$: 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-Dibenzyloxy-2,9-dimethoxy-13-methyltetrahydroprotoberberine (XIX)——A suspension of the quaternary base chloride (XVII, X=Cl) (250 mg) in acetone (20 ml) and H_2O (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 CH_3I (3 ml) was heated at 55° in a sealed tube for 16 hr giving rise to precipitates. To a solution of the precipitates in MeOH (100 ml) was added $NaBH_4$ (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 70: 30) to give the 13-methyltetrahydroprotoberberine base (XIX), mp 155—156° (from $CHCl_3$–MeOH), 113 mg. *Anal.* Calcd. for $C_{34}H_{35}O_4N$: C, 78.28; H, 6.76. Found: C, 78.46; H, 6.76. NMR (δ): 0.95 (3H, d, $J=7$ Hz, $CHCH_3$), 3.86 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 5.12 (4H, s, $2 \times OCH_2C_6H_5$). Mass Spectrum m/e: 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*, H_2O was added to the residue and the solution was made alkaline with 5% aq. NH_4OH, extracted with $CHCl_3$, washed with H_2O and dried over anhyd. $MgSO_4$. After evaporation of the solvent, the residue was recrystallized from aq. MeOH to give *dl*-corydalidzine (I), mp 156—157.5° (*in vacuo*),[4] 26 mg, which was identified with natural corydalidzine by TLC (both solvent systems, $CHCl_3$: MeOH 90: 10 and benzene: ether 50: 50 were employed for silica gel and alumina), NMR (DMSO-d_6), UV and mass spectra. *Anal.* Calcd. for $C_{20}H_{23}O_4N \cdot 2H_2O$: C, 63.64; H, 7.21; N, 3.71. Found: C, 64.12; H, 7.00; N, 3.85. High resolution mass spectrum: $C_{20}H_{23}O_4N$ m/e: 341.163507; Calcd. 341.16271.

3,10-Dihydroxy-2,9-dimethoxytetrahydroprotoberberine (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 H_2O, made alkaline with 5% aq. NH_4OH, extracted with ether, washed with H_2O, dried over anhyd. $MgSO_4$ 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 $C_{19}H_{21}O_4N$: C, 69.70; H, 6.47; N, 4.28. Found: C, 69.97; H, 6.68; N, 4.58. IR ν_{max}^{Nujol} cm^{-1}: 3375. NMR (δ, DMSO-d_6): 3.74 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 6.53 (1H, s, aromatic proton), 6.73 (2H, s, aromatic protons), 6.83 (1H, s, aromatic proton). Mass Spectrum m/e: 327 (M+), 178, 176, 150, 149. High resolution mass spectrum: $C_9H_{10}O_2$ m/e: 150.068257; Calcd. 150.06808. $C_9H_9O_2$ m/e: 149.056824; Calcd. 149.06026.

dl-**Tetrahydropalmatine (XX)**——To a solution of the diphenolic base (IV) (44 mg) in MeOH (6 ml) was added an ethereal solution of CH_2N_2 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 ($CHCl_3$) and their mixed melting point. *Anal.* Calcd. for $C_{21}H_{25}O_4N$: C, 70.96; H, 7.09; N, 3.94. Found: C, 71.24; H, 6.93; N, 4.10.

3,10-Dibenzyloxy-2,11-dimethoxytetrahydroprotoberberine (XXI)——To a solution of the monophenolic base (XIV) (30 mg) in MeOH (5 ml) was added an ethereal solution of CH_2N_2 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 $C_{33}H_{33}O_4N$: 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 dibenzyloxy 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 $CHCl_3$. The alkaline solution was saturated with NH_4Cl, extracted with $CHCl_3$, dried over anhyd. $MgSO_4$ and concentrated to dryness. To a solution of the residue in MeOH (20 ml) was added an ethereal solution of CH_2N_2 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 ($CHCl_3$: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 ($CHCl_3$) spectra. *Anal.* Calcd. for $C_{21}H_{25}O_4N$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.89; H, 7.02; N, 4.03.