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Alkaloids of *Corydalis incisa* Pers. V.[1] The Structures of Corydalispirone and Corydalisol

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Two new alkaloids, corydalispirone, $C_{20}H_{17}O_6N$, mp 196—198°, $[\alpha]_D$ 0°, and corydalisol, $C_{20}H_{21}O_5N$, mp 160—161°, $[\alpha]_D$ +21.4°, were isolated from *Corydalis incisa* Pers. (Papaveraceae). The structure of corydalispirone was established to be I by the spectroscopic examinations and chemical correlation with bicucullinediol and adlumidinediol, and the structure of corydalisol was determined as VIII by the conversion to *d*-tetrahydrocoptisine.

Corydalispirone and corydalisol are noted as a new series of isoquinoline-type alkaloids having one more carbon atom at the benzyl moiety, and probably are metabolites of coptisine.

In part I of this series[3] we reported the isolation of unknown alkaloids, TN-5 (named corydalispirone) and TN-14 (named corydalisol), from *Corydalis incisa* Pers. (Papaveraceae). In this paper we describe the structural elucidation of these alkaloids.

Corydalispirone (I) was obtained as colorless prisms, mp 196—198°, $[\alpha]_D$ 0° ($CHCl_3$), $C_{20}H_{17}O_6N$. The ultraviolet (UV) spectrum of I exhibits the absorption maxima at 240, 292 and 320 nm, which show bathochromic shifts to 247, 300, 343 and 382 (sh.) nm on addition of 1 N HCl. The nuclear magnetic resonance (NMR) spectrum of I confirms the presence of a N-methyl group (δ 2.39), two methylenedioxy groups (δ 5.85, 6.08) and four aromatic protons (δ 6.52—7.84). I depicts the absorption bands of aryl carbonyl (1690, 1630 cm^{-1}) and no hydroxyl absorption bands on the infrared (IR) spectrum.

I gave a pale brown perchlorate (II), mp 248—250° (decomp.), $C_{20}H_{18}O_{10}NCl$, which exhibited the perturbed bands indicative of highly conjugated carbonyl and double bonds (1670—1615 cm^{-1}) and a hydroxyl absorption band (3650 cm^{-1}) on the IR spectrum.

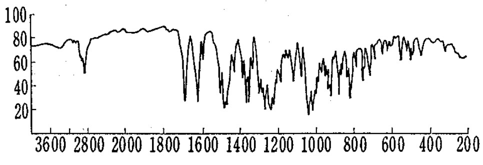

Fig. 1. IR (KBr) Spectrum of Corydalispirone (I)

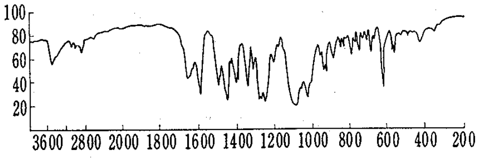

Fig. 2. IR (KBr) Spectrum of Corydalispirone Perchlorate (II)

These spectral data suggest that the aryl carbonyl group is conjugated with carbon-nitrogen double bond in II, and I contains a carbinol amine-like functional group whose properties are closely resemble to those of corynoloxine.[4]

On reduction with lithium aluminium hydride in tetrahydrofuran followed by chromatography over silica gel, I yielded an alcohol (III), mp 147—148° and a small amount of colorless oily alcohol (IV). III and IV show almost the same fragmentation patterns on the mass spectra, having a molecular peak at *m/e* 371 and a base peak at *m/e* 190. The molecular peak

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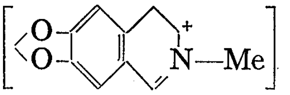
[1] Part IV: G. Nonaka and I. Nishioka, *Phytochemistry*, **13**, 2620 (1974).

[2] Location: *Katakasu, Higashi-ku, Fukuoka.*

[3] G. Nonaka, H. Okabe, I. Nishioka, and N. Takao, *Yakugaku Zasshi*, **93**, 87 (1973).

[4] N. Takao, *Chem. Pharm. Bull.* (Tokyo), **19**, 247 (1971).

indicates the uptake of 2 moles equivalent of hydrogen on the reduction, and the base peak at *m/e* 190 is ascribable to a fragment ion due to N-methyl dihydroisoquinoline residue  characterizing III and IV to be 1-benzyl-isoquinoline-type alkaloids. III depicts the signals due to a benzylic proton adjacent to the nitrogen atom and a methine proton bearing a hydroxyl group as a pair of doublets (δ 3.56, 4.69, respectively; $J=7.5$ Hz) on the NMR spectrum. Furthermore, it reveals the signals due to two benzyl methylene protons neighbouring an oxygen atom as an AB-type quartet (δ 4.47, 4.72; $J=12.0$ Hz). From these findings III and IV are speculated to be bicucullinediol[5] and adlumidinediol, the reduction products of phthalideisoquinoline-type alkaloids, respectively.

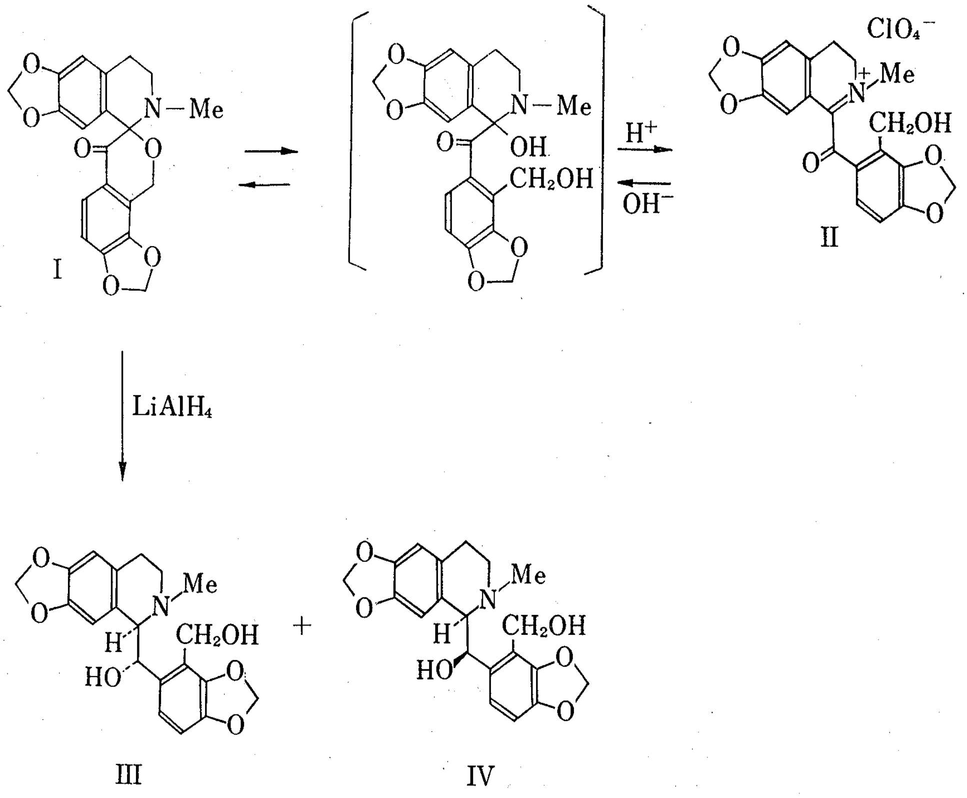


Chart 1

In order to clarify these structures the conversion of *l*-β-hydrastine (V) to III and IV was attempted. O-Demethylation of V with pyridine hydrochloride[6] followed by methylenation with methylene chloride and sodium hydroxide in dimethyl sulfoxide[6,7] afforded naturally occurring alkaloids, *l*-bicuculline (VI), mp 193.5—194.5°, $C_{20}H_{17}O_6N$. On reduction with lithium aluminium hydride in tetrahydrofuran, VI gave bicucullinediol, mp 149—150°, $[\alpha]_D$ +32° ($CHCl_3$), which was identified with III in terms of the direct comparison of thin-layer chromatography (TLC), IR, NMR and mass spectra. *l*-α-Hydrastine, mp 161—162°, $C_{21}H_{21}O_6N$, prepared by the epimerization of V with sodium hydroxide,[8,9] was treated in the similar ways as bicuculline to yield *l*-adlumidine (VII), mp 241—242°, $[\alpha]_D$ −116° ($CHCl_3$), $C_{20}H_{17}O_6N$.

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5) K. Blaha, J. Hrbek, J. Kovar, L. Pjevska, and F. Santavy, *Collect. Czech. Chem. Commun.*, **29**, 2328 (1964).
6) S. Teitel, J. O'Brien, and A. Brossi, *J. Org. Chem.*, **37**, 1879 (1972).
7) W. Bonthrone and J.W. Cornforth, *J. Chem. Soc.* (*C*), **1969**, 1202.
8) M.A. Marshall, F.L. Pyman, and R. Robinson, *J. Chem. Soc.*, **1934**, 1315.
9) M. Ohta, H. Tani, and S. Morozumi, *Chem. Pharm. Bull.* (Tokyo), **12**, 1072 (1964).

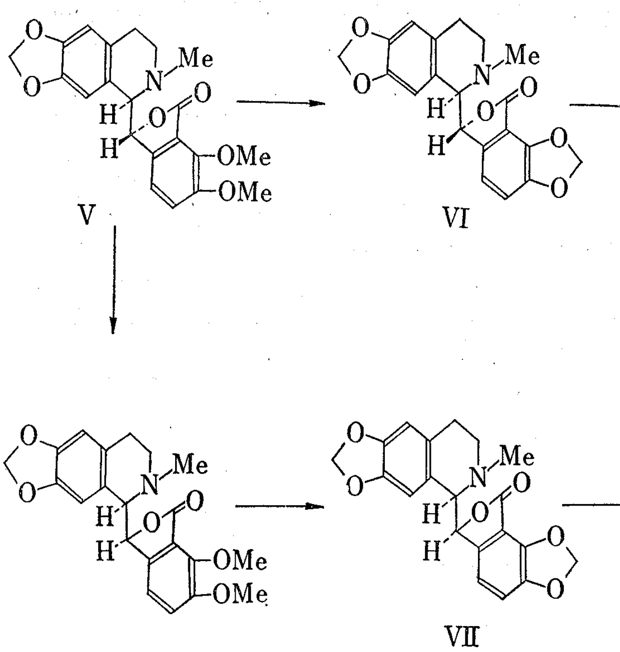

Chart 2

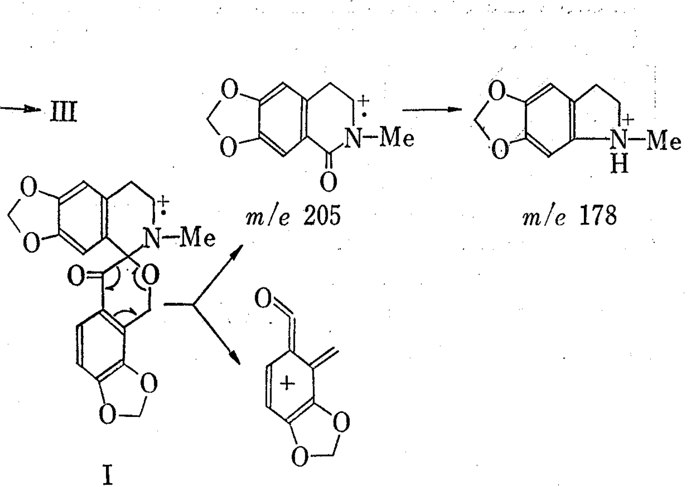

Chart 3. Fragmentation Pathway of Corydalispirone (I)

Lithium aluminium hydride reduction of VII gave the corresponding diol, a colorless oil, $[\alpha]_D$ +24° ($CHCl_3$), which was identified with IV by TLC, IR and mass spectral comparison.

From these results, III and IV are characterized to be bicucullinediol and adlumidinediol, respectively.

Since the absence of the signal due to a benzylic proton adjacent to the nitrogen atom of I is confirmed on the NMR spectrum and no hydroxyl absorption band is observed on the IR spectrum of I, the primary alcohol and the hydroxyl group of the carbinol amine in II should form an ether linkage.

Therefore, the structure of corydalispirone is represented as the formula I.

This conclusion is also supported by the examination of the mass spectrum of I. The base peak at *m/e* 162, as well as the higher peak at *m/e* 205 attributed to the isoquinoline moiety, can be explained to be formed by a retro-Diels-Alder type cleavage, and the loss of CO group from this isoquinolinium ion gives rise to a less abundunt ion peak at *m/e* 178 (Chart 3).

Corydalisol (VIII) was obtained as colorless needles, mp 160—161°, $[\alpha]_D$ +21.4° ($CHCl_3$), $C_{20}H_{21}O_5N$. The mass spectrum of VIII discloses a base peak at *m/e* 190, characteristic of 1-benzylisoquinoline-type alkaloids. The NMR spectrum of VIII exhibits the triplet signal due to a benzylic hydrogen adjacent to the nitrogen atom (δ 3.67, J=6.0 Hz), suggesting the presence of the 1-benzylisoquinoline skeleton. Furthermore, it reveals the benzylic protons as an AB-type quartet (δ 4.45, 4.68, J=12.0 Hz), protons due to two methylenedioxy groups (δ 5.94, 5.99) and four aromatic protons (δ 6.55—6.70). The IR spectrum of VIII exhibits the hydroxyl absorption band (3120 cm^{-1}). These spectral data suggest that VIII possesses the same skeleton as III and IV.

On treatment with thionyl chloride in benzene followed by neutralization with alkali, VIII afforded a quaternary base, which was further treated with *ortho*-dichlorobenzene to furnish *d*-tetrahydrocoptisine (IX), mp 198—200°, $[\alpha]_D$ +320° ($CHCl_3$).

Consequently, the structure of corydalisol is represented as the formula VIII.

Corydalispirone and corydalisol represent a new type of isoquinoline alkaloids having one more carbon atom at the benzyl moiety, and biogenetically, these alkaloids are possibly derived from coptisine by a cleavage of C-ring in protoberberine skeleton, being different from the usual benzylisoquinoline-type alkaloids. Therefore, these new alkaloids are very interesting from a biogenetic point of view.

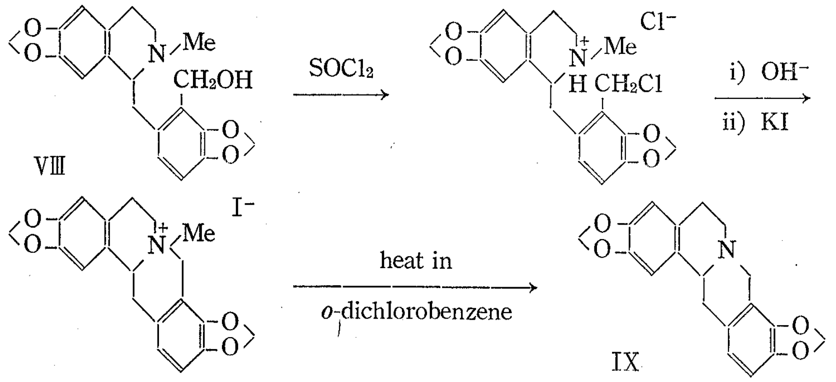

Chart 4

Experimental[10]

Corydalispirone (I)——Colorless prisms ($CHCl_3$–MeOH), mp 196—198°, $[\alpha]_D^{16}$ 0° ($c=0.22$, $CHCl_3$). *Anal.* Calcd. for $C_{20}H_{17}O_6N$: C, 65.39; H, 4.66; N, 3.81. Found: C, 65.19; H, 4.72; N, 3.88. Mass Spectrum: Calcd. for $[M^+]$, $C_{20}H_{17}O_6N$: 367.109. Found: 367.106. UV λ_{max}^{MeOH} nm (log ε): 240 (4.36), 292 (4.08), 320 (3.93). UV $\lambda_{max}^{MeOH+1NHCl}$ nm: 247, 300, 343, 382 (sh.). IR ν_{max}^{KBr} cm^{-1}: 1690, 1630 (Ar–CO–), 1596 (aromatic ring). NMR ($CDCl_3$): 2.39 (3H, s, $\rangle N-CH_3$), 2.50—3.60 (4H, m, $-CH_2CH_2-$), 4.24, 5.19 (2H, ABq, $J=15.8$ Hz, $Ar-CH_2-O-$), 5.85 (2H, s, $-OCH_2O-$), 6.08 (2H, s, $-OCH_2O-$), 6.52, 6.60 (each 1H, s, aromatic proton), 6.87 (1H, d, $J=8.5$ Hz, aromatic proton), 7.77 (1H, d, $J=8.5$ Hz, aromatic proton). Perchlorate (II): Pale brown needles (MeOH), mp 248—250° (decomp.). *Anal.* Calcd. for $C_{20}H_{18}O_{10}NCl$: C, 51.33; H, 3.88; N, 2.99. Found: C, 51.38; H, 3.84; N, 2.88. IR ν_{max}^{KBr} cm^{-1}: 3560 (OH), 1670—1615 (conjugated $\rangle C=O$ and $\rangle C=C\langle$), 1595 (aromatic ring).

Formation of III and IV from I——To a solution of I (80 mg) in dry tetrahydrofuran (THF) (3 ml) was added $LiAlH_4$ (30 mg in dry THF) and the solution was refluxed for 45 min. An excess of $LiAlH_4$ was decomposed by adding AcOEt, and then the reaction mixture was extracted with AcOEt. The combined AcOEt solution was washed with H_2O, dried (Na_2SO_4), and evaporated to give a colorless oil, which was chromatographed over silica gel. The $CHCl_3$–MeOH (96: 4) eluate was recrystallized from acetone–petroleum ether to afford colorless prisms (III); mp 147—148°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3620 (OH). NMR ($CDCl_3$): 2.06 (3H, s, $\rangle N-CH_3$), 3.56 (1H, d, $J=7.5$ Hz, $Ar-\dot{C}H-N\langle$), 4.69 (1H, d, $J=7.5$ Hz, $Ar-\dot{C}H-O-$), 4.47, 4.72 (2H, ABq, $J=12.0$ Hz, $Ar-CH_2-O-$), 5.93 (2H, s, $-OCH_2O-$), 6.00 (2H, q, $J=2.0$ Hz, $-OCH_2O-$), 6.65, 6.70 (each 1H, s, aromatic proton), 6.81, 7.12 (each 1H, d, $J=8.3$ Hz, aromatic proton). Subsequent elution with $CHCl_3$–MeOH (94: 6) gave a colorless oil (IV); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3610 (OH). Mass Spectrum *m/e*: 371 (M^+), 190 (base peak).

Formation of Bicucullinediol——A mixture of *l*-β-hydrastine (V) hydrochloride (1.34 g) and pyridine hydrochloride (7.0 g) was heated at 190° for 30 min in a N_2 atmosphere. The reaction mixture was partitioned between AcOEt and H_2O saturated with $NaHCO_3$. The combined AcOEt layer was dried (Na_2SO_4), and evaporated under reduced pressure. A brown crystalline residue (728 mg) was dissolved in CH_2Cl_2 (5 ml) and dimethylsulfoxide (10 ml), and then NaOH (0.4 g) was added. The mixture was refluxed at 110° for 1 hr in a N_2 atmosphere. The reaction mixture was acidified with 3N HCl and evaporated under reduced pressure. The residue was partitioned between $CHCl_3$ and H_2O saturated with Na_2CO_3. The $CHCl_3$ layer was washed with H_2O, dried (Na_2SO_4), and evaporated. The brown oily residue was chromatographed over silica gel (25 g, 2.5×14 cm) and benzene–AcOEt (3: 1) eluate gave *l*-bicuculline (VI) (102 mg); pale yellow prisms ($CHCl_3$–MeOH), mp 193.5—194.5°. *Anal.* Calcd. for $C_{20}H_{17}O_6N$: C, 65.39; H, 4.66; N, 3.81. Found: C, 65.20; H, 4.70; N, 3.58. UV λ_{max}^{MeOH} nm (log ε): 222 (4.43), 297 (3.71), 325 (3.66). IR ν_{max}^{KBr} cm^{-1}: 1740 (γ-lactone). NMR ($CDCl_3$): 2.57 (3H, s, $\rangle N-CH_3$), 4.07 (1H, d, $J=4.0$ Hz, $Ar-\dot{C}H-N\langle$), 5.59 (1H, d, $J=4.0$ Hz, $Ar-\dot{C}H-O-$), 5.93 (2H, s, $-OCH_2O-$), 6.16 (2H, s, $-OCH_2O-$), 6.22, 6.92 (each 1H, d, $J=8.0$ Hz, aromatic proton), 6.44, 6.58 (each 1H, s, aromatic proton). Subsequent elution with benzene–AcOEt (1: 1) gave O-monodemethylhydrastine (94 mg); colorless needles ($CHCl_3$–MeOH), mp 194—195°, *Anal.* Calcd. for $C_{20}H_{19}O_6N$: C, 65.03; H, 5.19; N, 3.79. Found: C, 64.82; H, 5.24; N, 3.74. IR ν_{max}^{KBr} cm^{-1}: 1760 (γ-lactone). NMR ($CDCl_3$): 2.57 (3H, s, OCH_3), 4.09 (1H, d, $J=4.0$ Hz, $Ar-\dot{C}H-N\langle$), 5.20—5.60 (1H, broad s, OH), 5.61 (1H, d, $J=4.0$ Hz, $Ar-CH-O-$), 5.93 (2H, s, $-OCH_2O-$), 6.31, 7.02 (each 1H, d, $J=8.0$ Hz, aromatic proton), 6.42, 6.58 (each 1H, s, aromatic proton).

To a solution of VI in dry THF (1 ml) was added $LiAlH_4$ (30 mg in dry THF) and the solution was refluxed for 30 min. An excess of $LiAlH_4$ was decomposed by AcOEt and a small amount of H_2O, and the reaction

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[10] Refer to Part II: G. Nonaka, Y. Kodera, and I. Nishioka, *Chem. Pharm. Bull.* (Tokyo), 21, 1020 (1973) for general methods.

mixture was extracted with AcOEt. The AcOEt solution was washed with H_2O, dried (Na_2SO_4), and evaporated. A colorless oily residue (44 mg) was crystallized from ether to afford bicucullinediol as colorless prisms, mp 149—151°, $[\alpha]_D^{27}$ +32° (c=0.25, $CHCl_3$), which was identified with III by the comparison on TLC, IR ($CHCl_3$), NMR and mass spectra.

Formation of Adlumidinediol——A solution of *l*-β-hydrastine (V) hydrochloride (910 mg) and KOH (1.10 g) in MeOH (20 ml) was refluxed for 90 hr. The reaction mixture was acidified with 6 N HCl, and evaporated. The residue was dissolved in H_2O saturated with $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried (Na_2SO_4), and evaporated. The reddish oily residue (814 mg) was chromatographed over silica gel (18 g, 2×15 cm). The benzene–AcOEt (19: 1) eluate gave *l*-α-hydrastine (532 mg), colorless prisms (EtOH), mp 161—162°. *Anal.* Calcd. for $C_{21}H_{21}O_6N$: C, 65.78; H, 5.52; N, 3.65. Found: C, 65.84; H, 5.55; N, 3.60. UV λ_{max}^{MeOH} nm (log ε): 297 (3.81). IR ν_{max}^{KBr} cm^{-1}: 1750 (γ-lactone). NMR ($CDCl_3$): 2.56 (3H, s, ⟩N–CH_3), 3.86 (3H, s, –OCH_3), 3.99 (3H, s, –OCH_3), 4.01 (1H, d, J=3.0 Hz, Ar–$\dot{C}$H–N⟨), 5.55 (1H, d, J=3.0 Hz, Ar–$\dot{C}$H–O–), 5.81 (4H, q, J=1.0 Hz, 2×–OCH_2O–), 6.37, 6.65 (each 1H, s, aromatic proton), 7.02, 7.31 (each 1H, d, J=7.5 Hz, aromatic proton). Subsequent elution using benzene–AcOEt (9: 1) afforded unreacted *l*-β-hydrastine (V) (276 mg).

A mixture of *l*-α-hydrastine (1.31 g) and pyridine hydrochloride (6.0 g) was heated at 190—200° for 45 min in a N_2 atmosphere. The reaction mixture was worked up by the procedure in the preceding example. A mixture of the resulting brown oily residue (564 mg) and NaOH (0.19 g) in CH_2Cl_2 (2 ml) and dimethyl sulfoxide (5 ml) was refluxed at 120° for 1 hr in a N_2 atmosphere, and worked up by the similar procedure above described. The brown oily residue was purified by silica gel column chromatography (35 g, 2.8×12 cm). Benzene–AcOEt (5: 1) eluate was crystallized from EtOH to give *l*-adlumidine (VII) (145 mg), pale yellow prisms ($CHCl_3$–EtOH), mp 241—242°, $[\alpha]_D^{20}$ −116° (c=1.65, $CHCl_3$). *Anal.* Calcd. for $C_{20}H_{17}O_6N$: C, 65.39; H, 4.66; N, 3.81. Found: C, 65.19; H, 4.65; N, 3.70. IR ν_{max}^{KBr} cm^{-1}: 1755 (γ-lactone). NMR ($CDCl_3$): 2.56 (3H, s, ⟩N–CH_3), 4.06 (1H, d, J=3.5 Hz, Ar–$\dot{C}$H–N⟨), 5.66 (1H, d, J=3.5 Hz, Ar–$\dot{C}$H–O–), 5.87 (2H, s, –OCH_2O–), 6.12 (2H, s, –OCH_2O–), 6.43, 6.69 (each 1H, s, aromatic proton), 6.97, 7.18 (each 1H, d, J=8.0 Hz, aromatic proton).

To a solution of *l*-adlumidine (VII) (100 mg) in dry THF (2 ml) was added $LiAlH_4$ (60 mg in 2 ml of dry THF), and refluxed for 30 min. Usual working up gave a crude product (100 mg), which was chromatographed over silica gel (5.0 g, 1.2×9 cm). The $CHCl_3$–MeOH (98: 2 to 95: 5) eluate afforded adlumidinediol as a colorless oil, $[\alpha]_D^{24}$ +24.0° (c=0.5, $CHCl_3$). NMR ($CDCl_3$): 2.59 (3H, s, ⟩N–CH_3), 5.84 (2H, q, J=1.5 Hz, –OCH_2O–), 5.73, 6.53 (each 1H, s, aromatic proton), 6.43, 6.63 (each 1H, d, J=8.0 Hz, aromatic proton). The IR ($CHCl_3$) and mass spectra were superimposable with those of IV.

Corydalisol (VIII)——Colorless prisms (MeOH), mp 160—161°, $[\alpha]_D^{21}$ +21.4° (c=0.28, $CHCl_3$). Mass Spectrum *m/e*: 355.1420 (M^+, Calcd. for $C_{20}H_{21}O_5N$: 355.1408), 190.0845 (base peak, $C_{11}H_{12}O_2N$: 190.0855), 175.0636 ($C_{10}H_9O_2N$: 175.0633), 165.0569 ($C_9H_9O_3$: 165.0552), 160.0773 ($C_{10}H_{10}ON$: 160.0762), 149.0635 ($C_9H_9O_2$: 149.0603), 132.0836 ($C_9H_{10}N$: 132.0813). UV λ_{max}^{MeOH} nm (log ε): 240 (3.75), 294 (3.83). IR $\nu_{max}^{CHCl_3}$: 3120 (OH, broad). NMR ($CDCl_3$): 2.26 (3H, s, ⟩N–CH_3), 3.63 (1H, t, J=6.0 Hz, Ar–$\dot{C}$H–N⟨), 4.45, 4.68 (2H, ABq, J=12.0 Hz, Ar–CH_2–O–), 5.94 (2H, s, –OCH_2O–), 5.97 (2H, q, J=1.0 Hz, –OCH_2O–), 6.55—6.70 (4H, m, aromatic proton).

Formation of *d*-Tetrahydrocoptisine (IX) from VIII——To an ice-cooled solution of VIII (24 mg) in dry benzene (2 ml) was added $SOCl_2$ (0.25 ml in dry benzene). The reaction mixture was allowed to stand at 0° for 30 min and then at room temperature for 2 hr. The solvent was evaporated off *in vacuo*. The residue was dissolved in a small amount of H_2O, and neutralized with 10% K_2CO_3. The resulting precipitate was removed by washing with ether. The alkaline layer was acidified with AcOH, and saturated KI solution was added. The deposited crystalline mass (7 mg) was filtered, washed with H_2O and dried. This iodide was suspended in *o*-dichlorobenzene (1.5 ml), and heated at 190° for 1.5 hr. The solvent was evaporated off *in vacuo* to give a reddish oily residue, which was chromatographed on silica gel. Recrystallization from $CHCl_3$–MeOH afforded colorless needles (3 mg), mp 198—200°, $[\alpha]_D^{18}$ +320° (c=0.067, $CHCl_3$), whose *Rf* value on TLC and IR ($CHCl_3$) spectrum were identical with those of *l*-tetrahydrocoptisine which was isolated from *Chelidonium majus*.[11]

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[11] J. Slavik, *Collection Czek. Chem. Commun.*, 20, 198 (1955).