[Chem. Pharm. Bull. 31(8)2685—2690(1983)]

Chemical Transformation of Protoberberines. IV.[1] A Novel, Simple Synthesis of (±)-Canadaline and a Retroprotoberberine from Tetrahydroberberine[2]

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(Received February 4, 1983)

Heating of tetrahydroberberine (**1**) in ethyl chloroformate preferentially afforded the C_8–N bond cleavage (**4**) with small amounts of the C_6–N and C_{14}–N bond cleavage products (**5** and **6**, respectively). The urethane (**4**) was effectively converted to (±)-canadaline (**2**), a secoberbine alkaloid, and a retroprotoberberine (**3**).

Keywords——ethyl chloroformate; regioselective C–N bond cleavage; biomimetic conversion; protoberberine alkaloid; secoberbine alkaloid; retroprotoberberine alkaloid; tetrahydroberberine; canadaline

Regioselective C_8–N bond cleavage of protoberberine alkaloids might be a key step for their transformation to related alkaloids such as secoberbine, retroprotoberberine, phthalideisoquinoline, spirobenzylisoquinoline, benzindenoazepine, and rhoeadine alkaloids (Chart 1).[3] Although several methods for C_6–N and C_{14}–N bond cleavage of tetrahydroprotoberberines have so far been reported,[4] little is known concerning general and selective C_8–N bond cleavage, except for some special examples.[5] In this paper we describe an efficient C_8–N bond cleavage of tetrahydroberberine (**1**) using ethyl chloroformate and its application to a simple, novel synthesis of (±)-canadaline (**2**) and a retroprotoberberine (**3**).

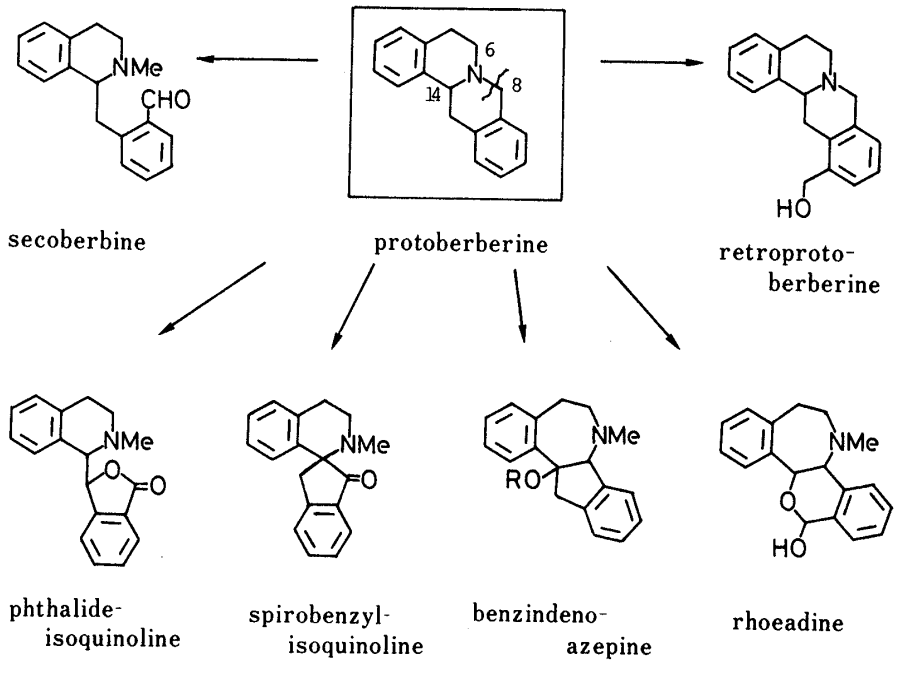
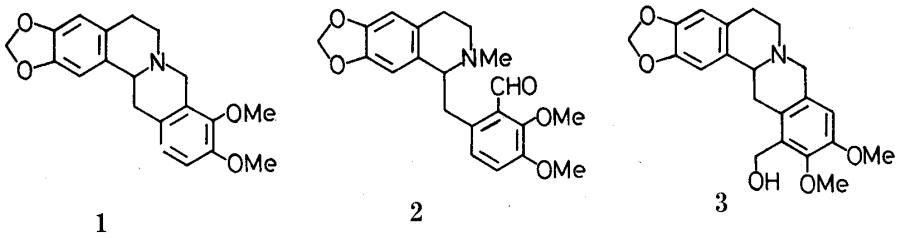


Chart 1[3]



1 2 3

Fig. 1

Knabe *et al.* have extensively studied C–N bond cleavage reactions of tertiary amines and alkaloids with ethyl chloroformate and found that tetrahydroberberine was inert to this reagent under Schotten–Baumann-like conditions.[6] We therefore investigated the reaction of **1** with ethyl chloroformate under different conditions.

On treatment with excess ethyl chloroformate in benzene or toluene, tetrahydroberberine (**1**) was recovered unchanged. However, heating of **1** in ethyl chloroformate at 85 °C for 9 h without solvent afforded three products, **4**, **5**, and **6** in 41 (59),[7] 10 (14), and 8.5% (12%) yields, respectively, in addition to the starting material **1** (29.5%), after careful chromatographic separation on silica gel.[8] The structures of these products were elucidated by analysis of their spectral data (see Experimental). The C_8–N bond cleavage product **4**, *m/e*: 449, 447 (M^+, 1 : 3), showed a rather complicated proton nuclear magnetic resonance (PMR) spectrum at 25 °C due to slow interconversion of urethane rotamers, whereas the regioisomeric C_6–N bond cleavage product **5**, *m/e*: 449, 447 (M^+, 1 : 3), showed a sharp PMR spectrum. The structure of **4** was further confirmed by its conversion to the amine **7** (97% yield) by lithium aluminum hydride reduction. The PMR spectrum of **7** exhibited two singlets at 2.46 and 2.02 ppm due to the *N*- and *C*-methyls, respectively. The third product **6** was derived through C_{14}–N bond cleavage followed by elimination of hydrogen chloride. *E*-Configuration of **6** was established from the 200 MHz PMR spectrum, which showed the olefinic proton signals as an AB-quartet ($J = 16.5$ Hz) at 6.66 and 6.63 ppm, though they appeared as a singlet at 100 MHz. This stereochemistry was further supported by photochemical isomerization[9] of **6** to the *Z*-isomer (**8**), the PMR spectrum of which exhibited an AB-quartet ($J = 12$ Hz) at 6.73 and 6.71 ppm due to the *cis* olefinic protons.

Thus, the C_8–N bond cleavage product (**4**) was obtained readily and directly from tetrahydroberberine (**1**). Next, we investigated a synthesis of (±)-canadaline and a retroprotoberberine starting from **4**.

Canadaline,[10] isolated from *Hydrastis canadensis* L. is a representative secoberbine alkaloid[11] and its racemate has been synthesized[11] from 8-benzyltetrahydroberberine *via* the Hofmann degradation.[5a]

Treatment of **4** with silver nitrate in aqueous acetone at room temperature gave the alcohol (**9**) in 66% yield. Alternatively, the same product **9** was readily obtained in 92% yield, upon stirring of **4** with alumina in dichloromethane at room temperature. More conveniently, **9** was directly synthesized from **1**, namely, the crude products derived from **1** with ethyl chloroformate were chromatographed on alumina to give **9** in 46% (64.5%)[7] yield along with **5**, **6**, and **1** in 9 (13), 11 (15.5), and 28.5% yields, respectively. Reduction of **9** with lithium aluminum hydride in ether afforded the *N*-methyl alcohol (**11**), mp 107—108 °C, *m/e*: 371 (M^+), in 80% yield. It was also derived in 31% yield from **4** *via* **10** on treatment with sodium acetate in acetic acid followed by lithium aluminum hydride. Oxidation of **11** with pyridinium chlorochromate[12] in dichloromethane in the presence of sodium acetate provided (±)-canadaline (**2**), mp 143—143.5 °C (lit.[11] mp 139—140 °C), in 68% yield. The synthetic (±)-canadaline was shown to be identical with natural canadaline in PMR spectral comparison. Independently, Rönsch has recently synthesized (±)-canadaline *via* a reaction sequence

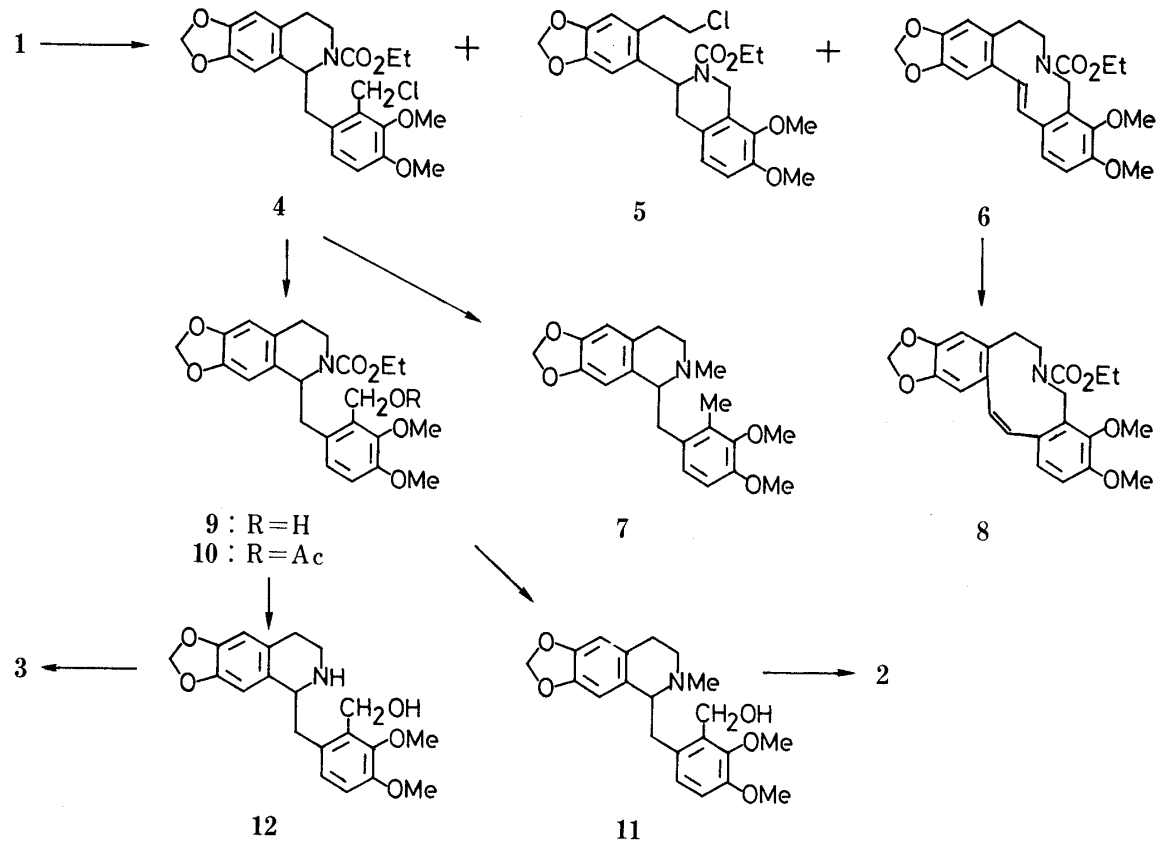


Chart 2

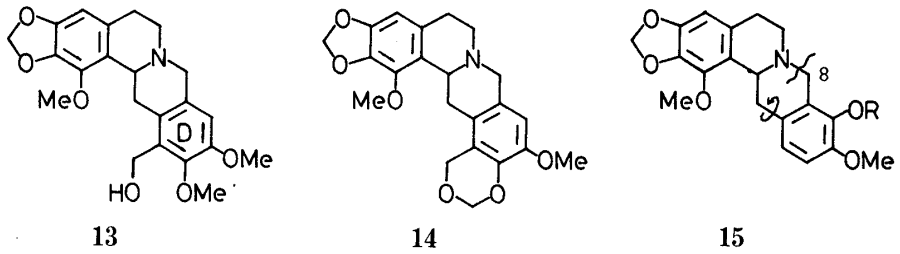


Fig. 2

similar to ours using ethyl chloroformate–sodium iodide in a key step.[13]

On the other hand, retroprotoberberine alkaloids,[14,15] *e.g.* mecambridine (**13**) and orientalidine (**14**), characterized by the presence of one extra carbon on ring D, have been proposed to be biosynthesized from the corresponding protoberberine (**15**) through C_8–N bond cleavage.[5b,16] Therefore, the extra carbon should originate from C_8 of the precursor protoberberine. On this biogenetic assumption, we tried to convert **1** to the retroprotoberberine (**3**).

Hydrolysis of the urethane (**9**) with potassium hydroxide in aqueous ethanol in a sealed tube at 140—145 °C afforded the amino-alcohol (**12**), mp 157—158 °C, in 67% yield accompanied with the starting material **9** (22% yield). The Mannich reaction of **12** with 37% aqueous formaldehyde in acetic acid furnished the retroprotoberberine (**3**), mp 195—196 °C, *m/e*: 369 (M^+), in 90% yield. This simple biogenetic-type conversion of tetrahydroberberine to **3** represents a new general method for the synthesis of the retroprotoberberine alkaloids.

The present efficient C_8–N bond cleavage reaction using ethyl chloroformate seems promising for the transformation of protoberberine alkaloids to the related alkaloids shown

in Chart 1. Studies on the scope and limitations of this reaction are in progress.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. All organic extracts were dried over anhydrous Na_2SO_4. Column chromatography was carried out with silica gel (Kieselgel 60, 70—230 or 230—400 mesh, Merck) and alumina (Aluminiumoxid 90, Aktivitätsstufe II-III, 70—230 mesh, Merck). Preparative thin-layer chromatography (PTLC) was performed on alumina (Aluminiumoxid GF_{254} Typ 60/E, Merck). Infrared (IR) spectra were measured with a JASCO A-102 spectrometer, mass spectra (MS) with a Hitachi M-80 mass spectrometer, ultraviolet (UV) spectra with a Hitachi 323 spectrometer, and PMR spectra with JEOL FX-100 and Varian XL-200 spectrometers in $CDCl_3$ using tetramethylsilane as an internal standard at 25 °C unless otherwise stated.

Reaction of Tetrahydroberberine (1) with Ethyl Chloroformate——A solution of tetrahydroberberine (**1**, 594 mg) in ethyl chloroformate (50 ml) was heated at 85 °C for 9 h with stirring. The excess ethyl chloroformate was removed *in vacuo* and the residue was taken up in $CHCl_3$. The organic layer was washed with aqueous K_2CO_3 and brine, dried, and concentrated *in vacuo* to leave an oily residue, which was chromatographed on SiO_2 with CH_2Cl_2. The first fraction afforded ethyl 3-[2-(2-chloroethyl)-4,5-methylenedioxyphenyl]-1,2,3,4-tetrahydro-7,8-dimethoxyisoquinoline-2-carboxylate [**5**, 78.6 mg, 10% (14% based on the consumed starting material)] as a pale brown oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680 (CO). MS *m/e*: 449, 447 (M^+, 1:3), 164 (base peak). High resolution MS *m/e*: Calcd for $C_{23}H_{26}ClNO_6$: 449.142, 447.145. Found: 449.146, 447.146. PMR δ: 6.83, 6.82 (2H, AB q, J=8.5 Hz, C_5- and C_6-H), 6.66, 6.48 (each 1H, s, $C_{3'}$- and $C_{6'}$-H), 5.85 (2H, s, OCH_2O), 5.39 (1H, t, J=5 Hz, C_3-H), 5.09, 4.18 (2H, AB q, J=17 Hz, C_1-H), 4.13 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 3.86 (6H, s, $OCH_3 \times 2$), 3.68 (2H, t, J=7 Hz, CH_2Cl), 3.20, 2.84 (2H, AB qd, J=16; 5 Hz, C_4-H), 3.11 (2H, t, J=7 Hz, $C\underline{H}_2CH_2Cl$), 1.22 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$). The second fraction afforded ethyl 1-(2-chloromethyl-3,4-dimethoxyphenylmethyl)-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline-2-carboxylate [**4**, 324.4 mg, 41% (59% based on consumed starting material)] as a pale brown oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680 (CO). MS *m/e*: 449, 447 (M^+, 1:3), 248 (base peak). High resolution MS *m/e*: Calcd for $C_{23}H_{26}ClNO_6$: 447.145. Found: 447.144. PMR δ: 6.78 (2H, t-like, $C_{5'}$- and $C_{6'}$-H), 6.60 (1H, s, C_5-H), 6.41, 5.95 (1H, each s, C_8-H), 5.89 (2H, br s, OCH_2O), *ca.* 5.2 (1H, m, C_1-H), 4.8—4.6 (2H, CH_2Cl), 4.2—4.0 (2H, $OC\underline{H}_2CH_3$), 3.93, 3.90 (3H, each s, OCH_3), 3.84 (3H, s, OCH_3), 1.26, 1.05 (3H, each t, J=7 Hz, $OCH_2C\underline{H}_3$). δ (80 °C): 6.76, 6.72 (2H, AB q, J=8 Hz, $C_{5'}$-H and $C_{6'}$-H), 6.57 (1H, s, C_5-H), 6.20 (1H, br s, C_8-H), 5.85 (2H, s, OCH_2O), 5.20 (1H, t, J=7 Hz, C_1-H), 4.8—4.4 (2H, CH_2Cl), 4.2—4.0 (2H, $OC\underline{H}_2CH_3$), 3.90, 3.83 (each 3H, s, $OCH_3 \times 2$), 1.14 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$). The third fraction afforded ethyl (*E*)-5,6,7,8-tetrahydro-3,4-dimethoxy-10,11-methylenedioxydibenzo[*c*, *g*]azecine-6-carboxylate [**6**, 61.4 mg, 8.5% (12% based on consumed starting material)] as colorless crystals. Recrystallization from MeOH afforded colorless needles, mp 186—187 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1685 (CO). MS *m/e*: 411 (M^+, base peak). PMR δ: 6.99, 6.87 (2H, AB q, J=8.5 Hz, C_1- and C_2-H), 6.75, 6.67 (each 1H, s, C_9- and C_{12}-H), 6.65 (2H, s, C_{13}- and C_{14}-H), 5.93 (2H, s, OCH_2O), 4.56 (2H, s, C_5-H), 3.85 (6H, s, $OCH_3 \times 2$), 4.1—3.8 (2H, $OC\underline{H}_2CH_3$), 1.3—0.9 (3H, $OCH_2C\underline{H}_3$). δ (70 °C): 6.96, 6.84 (2H, AB q, J=8.5 Hz, C_1- and C_2-H), 6.73, 6.65 (each 1H, s, C_9- and C_{12}-H), 6.64 (2H, s, C_{13}- and C_{14}-H), 5.90 (2H, s, OCH_2O), 4.54 (2H, s, C_5-H), 4.01 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 3.91, 3.86 (each 3H, s, $OCH_3 \times 2$), 3.61 (2H, t, J=5.5 Hz, C_7-H), 3.01 (2H, t, J=5.5 Hz, C_8-H), 1.01 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$). δ (200 MHz): 7.01, 6.84 (2H, AB q, J=8.5 Hz, C_1- and C_2-H), 6.74, 6.66 (each 1H, s, C_9- and C_{12}-H), 6.66, 6.63 (2H, AB q, J=16.5 Hz, C_{13}- and C_{14}-H), 5.92 (2H, s, OCH_2O), 4.55 (2H, s, C_5-H), 3.99 (2H, br s, $OC\underline{H}_2CH_3$), 3.87 (6H, s, $OCH_3 \times 2$), 3.7—3.6 (2H, br, C_7-H), 3.1—2.9 (2H, br, C_8-H), 1.21, 1.02 (3H, each t-like, $OCH_2C\underline{H}_3$). *Anal.* Calcd for $C_{23}H_{25}NO_6$: C, 67.14; H, 6.12; N, 3.40. Found: C, 67.22; H, 6.13; N, 3.48. The fourth fraction afforded the unchanged starting material (**1**, 175.5 mg, 29.5%).

1,2,3,4-Tetrahydro-1-(3,4-dimethoxy-2-methylphenylmethyl)-2-methyl-6,7-methylenedioxyisoquinoline (7)——A mixture of **4** (30 mg) and $LiAlH_4$ (10 mg) in anhyd. Et_2O (10 ml) was heated under reflux for 4.5 h with stirring. Work-up as usual gave the amine (**7**, 23 mg, 97%) as a colorless oil. PMR δ: 6.67 (2H, s, $C_{5'}$- and $C_{6'}$-H), 6.47 (1H, s, C_5-H), 5.83 (1H, s, C_8-H), 5.76 (2H, s, OCH_2O), 3.82, 3.72 (each 3H, s, $OCH_3 \times 2$), 2.46 (3H, s, NCH_3), 2.02 (3H, s, Ar-CH_3).

Picrate: Recrystallization from EtOH gave yellow plates, mp 175—176 °C. *Anal.* Calcd for $C_{21}H_{25}NO_4 \cdot C_6H_3N_3O_7$: C, 55.78; H, 4.83; N, 9.59. Found: C, 55.70; H, 4.71; N, 9.54.

Ethyl (*Z*)-5,6,7,8-Tetrahydro-3,4-dimethoxy-10,11-methylenedioxydibenzo[*c*, *g*]azecine-6-carboxylate (8)——A mixture of the *E*-azecine (**6**, 54.2 mg) in benzene (150 ml) and rose bengal (10 mg) in MeOH (20 ml) was irradiated with a 250 W high-pressure mercury lamp with a Pyrex filter in an N_2 atmosphere for 2 h at room temperature. The organic solvents were evaporated off *in vacuo* and the residue was purified by PTLC (Al_2O_3, $CHCl_3$) to give the *Z*-azecine (**8**, 17 mg, 32%) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680 (CO). MS *m/e*: 411 (M^+, base peak). High resolution MS *m/e*: Calcd for $C_{23}H_{25}NO_6$: 411.168. Found: 411.168. PMR δ: 6.73 (2H, br s, C_{13}- and C_{14}-H), 6.71 (2H, s, C_1- and C_2-H), 6.6—6.4 (2H, C_9- and C_{12}-H), 5.86 (2H, s, OCH_2O), 4.53, 4.44 (2H, each s, C_5-H), 4.3—4.0 (2H, $OC\underline{H}_2CH_3$), 3.79 (3H, s, OCH_3), 3.70, 3.67 (3H, each s, OCH_3), 1.4—1.1 (3H, $OCH_2C\underline{H}_3$). δ (70 °C): 6.73, 6.71 (2H, AB q, J=12 Hz, C_{13}- and C_{14}-H), 6.69, 6.68 (2H, AB q, J=8.5 Hz, C_1- and C_2-H), 6.50, 6.45 (each 1H, s, C_9- and C_{12}-

H), 5.82 (2H, s, OCH_2O), 4.49 (2H, s, C_5-H), 4.15 (2H, q, $J=7$ Hz, $OC\underline{H}_2CH_3$), 3.77, 3.68 (each 3H, s, $OCH_3\times2$), 3.1—2.9 (2H, C_7-H), 2.75 (2H, t, $J=6$ Hz, C_8-H), 1.23 (3H, t, $J=7$ Hz, $OCH_2C\underline{H}_3$).

Ethyl 1,2,3,4-Tetrahydro-1-(2-hydroxymethyl-3,4-dimethoxyphenylmethyl)-6,7-methylenedioxyisoquinoline-2-carboxylate (9)——1) A solution of $AgNO_3$ (300 mg) in water (10 ml) was added to a stirred solution of **4** (300 mg) in Me_2CO (10 ml) and stirring was continued for 40 h at room temperature. The organic solvent was evaporated off *in vacuo* and water was added to the residue. The aqueous layer was extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated *in vacuo*. The residue was purified by column chromatography (Al_2O_3, $CHCl_3$) to afford **9** (191 mg, 66%) as a pale brown oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1670 (CO). MS *m/e*: 429 (M^+), 248 (base peak). High resolution MS *m/e*: Calcd for $C_{23}H_{27}NO_7$: 429.179. Found: 429.179. PMR δ: 6.65 (2H, s, $C_{5'}$- and $C_{6'}$-H), 6.51 (1H, s, C_5-H), *ca.* 6.3 (1H, m, C_8-H), 5.82 (2H, s, OCH_2O), *ca.* 5.1 (1H, m, C_1-H), 4.57 (2H, br s, $C\underline{H}_2OH$), 3.84, 3.79 (each 3H, s, $OCH_3\times2$), 3.03 (2H, d, $J=7$ Hz, C_1-CH_2), 1.3—0.9 (3H, $OCH_2C\underline{H}_3$). δ (80 °C): 6.73, 6.70 (2H, AB q, $J=8.5$ Hz, $C_{5'}$- and $C_{6'}$-H), 6.57 (1H, s, C_5-H), 6.31 (1H, s, C_8-H), 5.85 (2H, s, OCH_2O), 5.21 (1H, t, $J=7$ Hz, C_1-H), 4.68 (2H, s, $C\underline{H}_2OH$), 3.95, 3.87 (each 3H, s, $OCH_3\times2$), 3.07 (2H, d, $J=7$ Hz, C_1-CH_2), 1.13 (3H, t, $J=7$ Hz, $OCH_2C\underline{H}_3$).

2) A solution of **4** (137.7 mg) in CH_2Cl_2 (10 ml) was stirred with Al_2O_3 (Aluminiumoxid 90 Aktivitätsstufe II-III, Merck, 10 g) for 48 h at room temperature. Al_2O_3 was filtered off and washed thoroughly with $CHCl_3$–MeOH (95 : 5). The filtrate and washings were concentrated *in vacuo* to leave **9** (121 mg, 92%) as a pale brown oil, which was identical with an authentic specimen obtained in 1).

3) A solution of tetrahydroberberine (**1**, 547 mg) in ethyl chloroformate (50 ml) was treated as described above to give an oily residue, which was chromatographed on Al_2O_3 with CH_2Cl_2. The first fraction gave a mixture which was further separated by PTLC to afford **5** [65.9 mg, 9.1% (12.7% based on consumed starting material)] as an upper fraction and **6** [73.3 mg, 11% (15.5% based on consumed starting material)] as a lower fraction. The second fraction afforded unchanged tetrahydroberberine **1** (155.8 mg, 28.5%). The third fraction, eluted with CH_2Cl_2–MeOH (98 : 2), afforded **9** [320.8 mg, 46% (64.5% based on consumed starting material)], which was identical with an authentic specimen.

1,2,3,4-Tetrahydro-1-(2-hydroxymethyl-3,4-dimethoxyphenylmethyl)-2-methyl-6,7-methylenedioxyisoquinoline (11)——1) A mixture of the urethane (**9**, 137 mg) and $LiAlH_4$ (53 mg) in anhyd. Et_2O (20 ml) was heated under reflux for 8 h with stirring. Work-up as usual gave **11** (94.5 mg, 80%) as an oil, which soon solidified. Recrystallization from MeOH gave colorless plates, mp 107—108 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350 (OH). MS *m/e*: 371 (M^+), 190 (base peak). PMR δ: 6.83 (2H, s, $C_{5'}$- and $C_{6'}$-H), 6.69, 6.54 (each 1H, s, C_5- and C_8-H), 5.92 (2H, s, OCH_2O), 4.76, 4.48 (2H, AB q, $J=11.5$ Hz, $C\underline{H}_2OH$), 3.89, 3.85 (each 3H, s, $OCH_3\times2$), 2.20 (3H, s, NCH_3). *Anal.* Calcd for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77. Found: C, 68.18; H, 6.97; N, 3.94.

2) A mixture of **4** (70 mg) and AcONa (30 mg) in AcOH (10 ml) was heated under reflux for 40 h. The organic solvent was evaporated off *in vacuo* and water was added to the residue. The aqueous layer was extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated to leave crude **10** [54 mg, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725 (OAc), 1675 (NCO)], which was used for the next step without further purification. A mixture of **10** (54 mg) and $LiAlH_4$ (20 mg) in anhyd. tetrahydrofuran (THF) (5 ml) was heated under reflux for 5.5 h with stirring. Work-up as usual followed by column chromatography (Al_2O_3, $CHCl_3$) gave **7** (18 mg, 31% from **4**), which was identical with an authentic specimen.

(±)-Canadaline (2)——PCC (193 mg) and NaOAc (73 mg) were added to a stirred solution of the alcohol **11** (221 mg) in CH_2Cl_2 (10 ml) and stirring was continued for 7.5 h at room temperature. PCC (60 mg) and NaOAc (24 mg) were again added to the reaction mixture and stirring was continued for another 2 h. The reaction mixture was passed through a short column packed with Florisil and the column was thoroughly washed with CH_2Cl_2. The eluate was concentrated *in vacuo* to leave (±)-canadaline (**2**, 150 mg, 68%). Recrystallization from MeOH afforded colorless prisms, mp 143—143.5 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680 (CO). MS *m/e*: 369 (M^+). PMR: 10.20 (1H, s, CHO), 6.86, 6.68 (2H, AB q, $J=8$ Hz, $C_{5'}$- and $C_{6'}$-H), 6.40 (2H, s, C_5- and C_8-H), 5.76 (2H, s, OCH_2O), 3.86, 3.82 (each 3H, s, $OCH_3\times2$), 2.32 (3H, s, NCH_3). UV λ_{max}^{MeOH} nm (log ε): 232 (4.13), 288 (3.85). *Anal.* Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 67.99; H, 6.24; N, 4.07.

1,2,3,4-Tetrahydro-1-(2-hydroxymethyl-3,4-dimethoxyphenylmethyl)-6,7-methylenedioxyisoquinoline (12)——A solution of **9** (116 mg) and 10% aqueous KOH (5 ml) in EtOH (2 ml) was heated in a sealed tube at 140 °C for 46 h in N_2 atmosphere. The organic solvent was evaporated off *in vacuo* and the residue was extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 with $CHCl_3$–MeOH (97 : 3). The first fraction afforded the unchanged starting material **9** (25.3 mg 22%). The second fraction afforded the amine **12** [64.9 mg, 67% (86% based on consumed starting material)] as colorless prisms, mp 157—158 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300, 3125 (NH and OH). MS *m/e*: 357 (M^+). PMR δ: 7.01, 6.86 (2H, AB q, $J=8.5$ Hz, $C_{5'}$- and $C_{6'}$-H), 6.80 (1H, s, C_8-H), 6.56 (1H, s, C_5-H), 5.93 (2H, s, OCH_2O), 4.84, 4.47 (2H, AB q, $J=11.5$ Hz, $C\underline{H}_2OH$), 3.90, 3.87 (each 3H, s, $OCH_3\times2$). *Anal.* Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 66.93; H, 6.52; N, 3.88.

5,8,13,13a-Tetrahydro-12-hydroxymethyl-10,11-dimethoxy-2,3-methylenedioxy-6*H*-dibenzo[*a*, *g*]quinolizine (3)——Aqueous formaldehyde (37%, 2 ml) was added to a solution of the amine **12** (27 mg) in AcOH (1 ml) and the

mixture was heated at 100 °C for 3.5 h. The solvent was evaporated off *in vacuo* and the residue was taken up in $CHCl_3$. The organic layer was washed with aqueous K_2CO_3 and brine, and then dried. Evaporation of the solvent left the crude product, which was purified by column chromatography [Al_2O_3, $CHCl_3$–MeOH (98:2)] to afford **3** (25.2 mg, 90%) as colorless needles, mp 195—196 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350 (OH). MS *m/e*: 369 (M^+). PMR δ: 6.78, 6.60, 6.58 (each 1H, s, C_1-, C_4-, and C_9-H), 5.92 (2H, s, OCH_2O), 4.73 (2H, br s, CH_2OH), 3.86, 3.85 (each 3H, s, $OCH_3 \times 2$). *Anal.* Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 67.98; H, 6.31; N, 3.86.

Acknowledgement The authors are grateful to Prof. E. Stanislas, U.E.R. des Sciences Pharmaceutiques, for providing the PMR spectrum of natural canadaline, to Prof. M. Ito, Kobe Women's College of Pharmacy, for a 200 MHz PMR spectral measurement, and to Mr. Y. Itatani and Misses Y. Arano and K. Ohata of this Faculty for elemental analyses and mass spectral measurements. Financial support from the Ministry of Education, Science, and Culture of Japan in the form of a Grant-in-Aid for Scientific Research is also gratefully acknowledged.

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