[Chem. Pharm. Bull. 31(3) 947—952 (1983)]

Chemical Transformation of Protoberberines. III.[1] Convenient Synthesis of 8-Methoxyberberinephenolbetaine by Photooxygenation of Berberine. A Novel Conversion of Berberine into (±)-Ophiocarpine, (±)-Epiophiocarpine, (±)-α-Hydrastine, and (±)-β-Hydrastine[2]

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(Received September 9, 1982)

Photooxygenation of berberine (**5**) in methanol in the presence of sodium methoxide and rose bengal afforded the 8,14-dimethoxy-13-oxoberbine (**12**), which, on being heated in methanol, readily yielded 8-methoxyberberinephenolbetaine (**6**), a key intermediate to phthalideisoquinoline alkaloids, (±)-α- and (±)-β-hydrastine (**7** and **8**). Reduction of **6** with sodium borohydride furnished mostly (±)-ophiocarpine (**9**) and a little (±)-epiophiocarpine (**10**).

Keywords——photooxygenation; singlet oxygen; biomimetic conversion; 8-methoxyberberinephenolbetaine; berberine; phthalideisoquinoline alkaloid; α-hydrastine; β-hydrastine; 13-oxyberbine alkaloid; ophiocarpine; epiophiocarpine

In the previous paper[3] we reported that photooxygenation of tetrahydroberberine (**1**) and dihydroberberine (**2**) afforded noroxyhydrastinine (**3**), an isoquinolone alkaloid, by ready cleavage of the C_{13}–C_{14} bond of **1** and **2**. In order to convert protoberberine alkaloids into biogenetically related alkaloids, it is essential to avoid the C_{13}–C_{14} bond fission in the photooxygenation of protoberberines. As one solution to this problem, we developed a one-step synthesis of allocryptopine (**4**) by photooxygenation using the methiodide of **1** as a starting material.[1] This paper describes another successful photooxygenation of berberine (**5**) without fission of the C_{13}–C_{14} bond to provide 8-methoxyberberinephenolbetaine (**6**), the key inter-

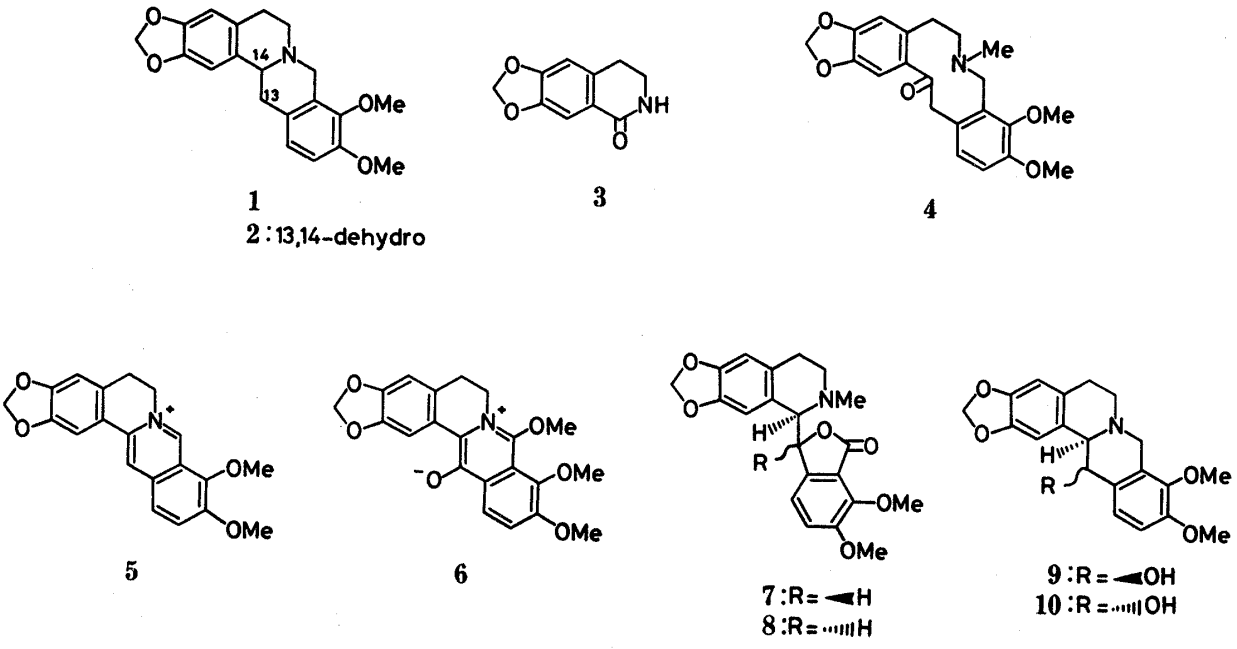

Fig. 1

mediate for (±)-α- and β-hydrastine (**7** and **8**), and also reports further transformation of **6** into (±)-ophiocarpine (**9**) and (±)-epiophiocarpine (**10**).

Generally an enamine reacts with singlet oxygen to give a dioxetane intermediate, which usually undergoes thermal degradation to yield two carbonyl fragments (Chart 1, path a).[4] This was exactly the case in our previous work[3] on **1** and **2**. However, two other degradation pathways exist for a dioxetane, namely elimination (path b) and substitution (path c) resulting in, for example, an α-hydroxy- or α-alkoxy-ketone without C–C bond fission.[5] These latter pathways should proceed preferentially if the photooxygenation is carried out in the presence of a strong base or nucleophile.

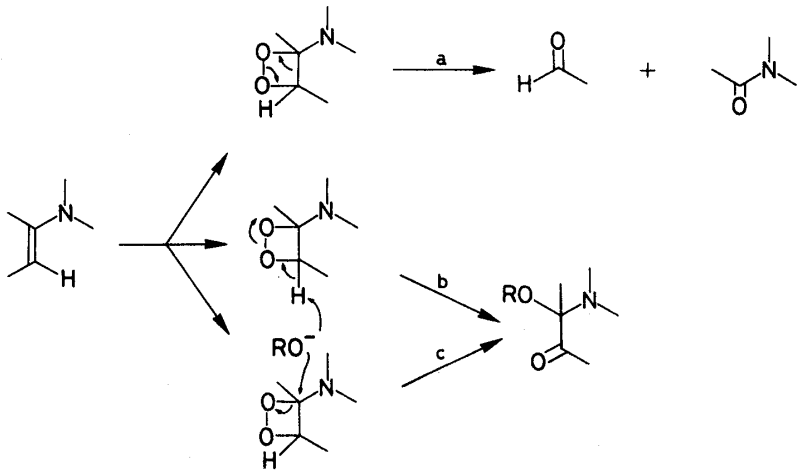

Chart 1

On the above assumption, we investigated the photooxygenation in the presence of sodium methoxide in methanol using berberine (**5**) as the substrate, because **5** is expected to be converted to the 8-oxygenated enamine, 8-methoxydihydroberberine (**11**) by addition of methoxide to the imminium moiety[6] in **5** before irradiation.

A solution of **5** in methanol containing 5 eq sodium methoxide was irradiated with a high-pressure mercury lamp (400W, with a Pyrex filter) in the presence of rose bengal in a stream of oxygen for 45 min at room temperature to give the labile 13-oxo compound (**12**) as a pale yellow precipitate in 59% yield. On being refluxed in methanol, **12** quantitatively afforded orange-colored 8-methoxyberberinephenolbetaine (**6**, mp 176—178°C). The structure of **6** was assigned by analysis of its spectral data, especially the characteristic lower field signals at 8.80 and 8.42 ppm due to H-1 and H-12, respectively, in the proton magnetic resonance (PMR) spectrum. Further support for this structure was obtained by hydrogenolysis of **6**; on hydrogenation in ethyl acetate over platinum oxide, **6** produced berberinephenolbetaine (**13**)[7] and (±)-ophiocarpine (**9**)[7] in 28 and 15% yields, respectively. Finally the structure of **6** was unambiguously confirmed by comparison with an authentic sample, which has been synthesized by Shamma *et al.*[8,9] from **5** by oxidation with potassium ferricyanide followed by treatment of a structurally unknown dimeric product with 10% methanolic hydrogen chloride.

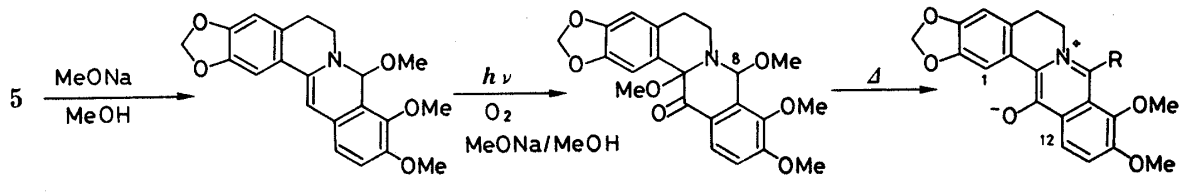

Chart 2

The structure of **12** was deduced on the basis of the following facts: 1) **12** is very unstable to heat and acid and easily transformed into the betaine (**6**), *e.g.* mass and PMR (in $CDCl_3$) spectra of **12** were the same as those of **6** (this phenomenon in the PMR is probably due to the presence of traces of acid in deuterochloroform), and 2) **12** showed a band at 1690 cm^{-1} due to a conjugated ketone in the infrared (IR) spectrum and gave a one-proton singlet at 5.41 ppm attributable to C_8–H and two additional aliphatic methoxyl signals (3.18 and 3.64 ppm) besides two aromatic methoxyl signals in the PMR spectrum in d_6-DMSO.

A possible mechanism for the above photooxygenation is shown in Chart 3. First, sodium methoxide adds to **5** to give 8-methoxydihydroberberine (**11**), the enamine part of which reacts with singlet oxygen to form the dioxetane (**14**), since the photo-reaction does not proceed in the absence of either the sensitizer or the base. Abstraction of the proton at C_{13} of **14** followed by displacement with methoxide (path i) or nucleophilic substitution by sodium methoxide and subsequent dehydration of the resultant peroxide (path ii) leads to **12**. Then elimination of methanol from **12** provides the betaine (**6**).

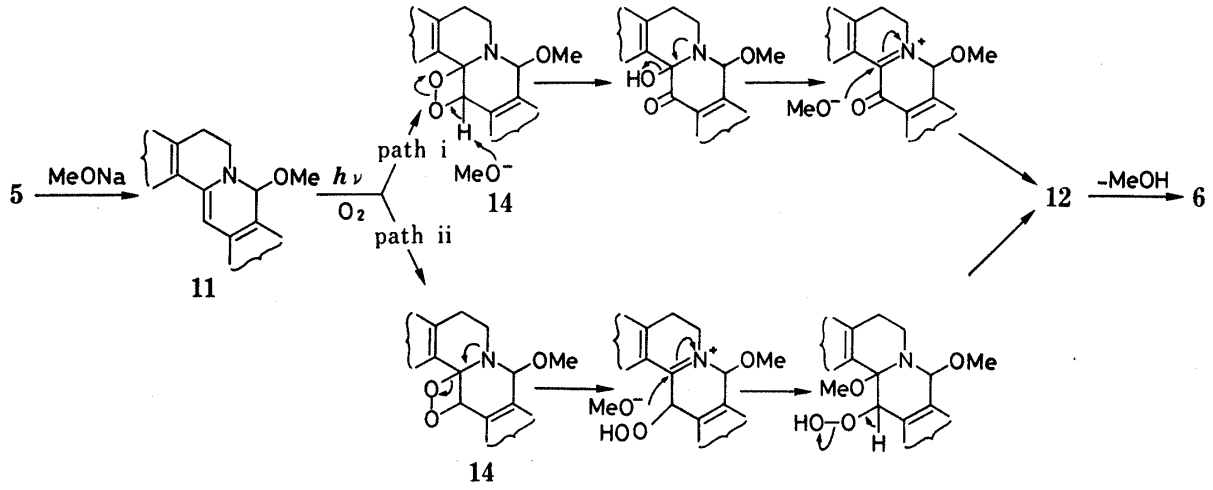

Chart 3

The betaine (**6**) has a masked carboxylic acid at C-8 and the requisite oxygenated function at C-13 in its molecule and has been elegantly converted to the phthalideisoquinoline alkaloids, (±)-α and (±)-β-hydrastine (**7** and **8**).[8,9] The present convenient synthesis of **6** from berberine (**5**), therefore, constitutes a formal synthesis of these phthalideisoquinoline alkaloids.

Some reactions of **6** with electrophiles were investigated. Treatment of **6** with methyl iodide in refluxing chloroform and with acetic anhydride in pyridine at room temperature afforded 13-methoxy- and 13-acetoxy-oxyberberine (**15** and **16**) in 62 and 92% yields, respectively. Heating of the latter with aqueous ammonia in methanol at 45°C furnished methyl anhydroberberilate (**17**) in 88% yield. The physical data for these products are in good agreement with those of the products obtained independently by Shamma *et al.*[9,10] after similar treatments.

Sodium borohydride reduction of **6** in methanol, followed by acetylation[11] with acetic anhydride in pyridine gave (±)-*O*-acetylophiocarpine (**18**, mp 178.5—179.5°C (lit.[12] mp 172—174°C)) and (±)-*O*-acetylepiophiocarpine (**19**, mp 187—188°C (lit.[12] mp 186°C)) in 87 and 6% yields, respectively. On treatment with 5% aqueous sodium hydroxide in methanol, **18** and **19** produced (±)-ophiocarpine (**9**, mp 248—251°C (lit.[12] mp 252°C)) and (±)-13-epiophiocarpine (**10**, mp 185—187°C (lit.[12] mp 176°C)) in quantitative and 91% yields, respectively. These products were proved to be identical with the corresponding authentic specimens[13] by mixed melting point determination, thin-layer chromatography (TLC), and IR spectral comparison.[15]

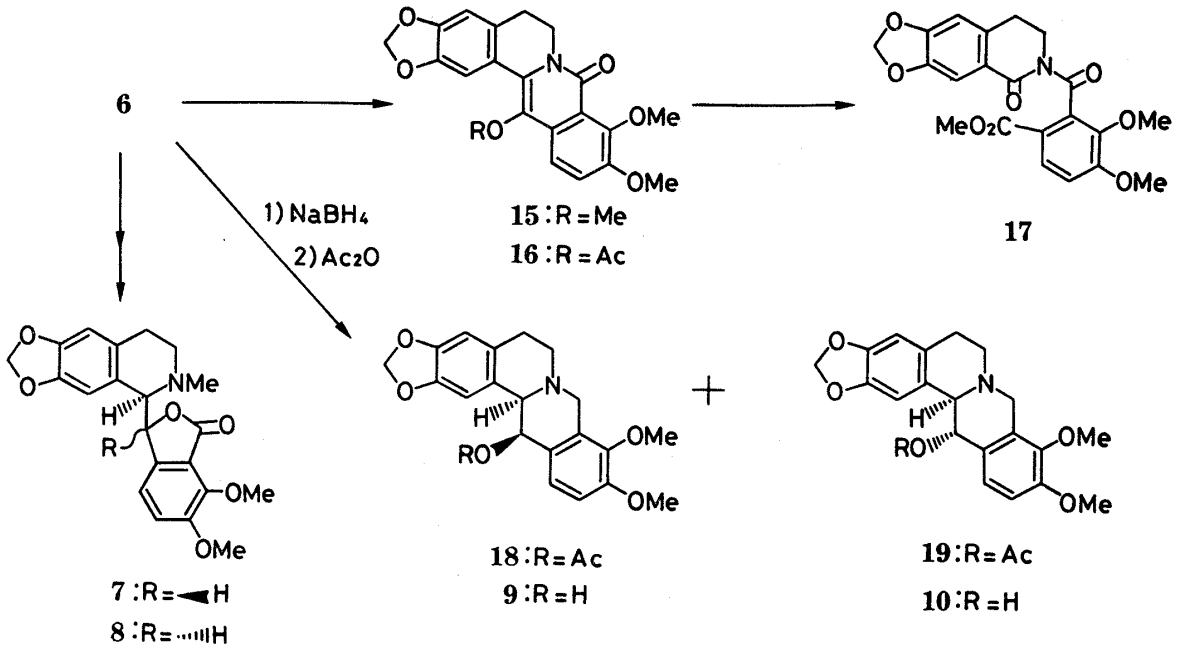

Chart 4

Thus, the above novel and efficient synthesis of 8-methoxyberberinephenolbetaine (**6**) provides a simple and general method for the synthesis of phthalideisoquinoline and 13-oxyberbine alkaloids from protoberberine alkaloids.

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Alumina (Brokmann grade II—III, Merck) was used for column chromatography. Extracts were dried over anhyd. Na_2SO_4. Unless otherwise stated, PMR spectra were measured in $CDCl_3$ with a JEOL PS 100 machine using tetramethylsilane as an internal standard, IR spectra with a JASCO IR G spectrophotometer, mass spectra (MS) with a JEOL JMS 01SG mass spectrometer, and ultraviolet (UV) spectra with a Hitachi Model 323 machine. Irradiation was carried out with a 400W high pressure mercury lamp (Riko Kagaku Co.) with a Pyrex filter.

Photooxygenation of Berberine (5)——A solution of berberine (**5**, 5.0 g, 12 mmol) and sodium methoxide (3.3 g, 61 mmol) in MeOH (450 ml) was irradiated in a stream of oxygen for 45 min at room temperature in the presence of rose bengal (250 mg). A pale yellow precipitate was collected by filtration and dried to give 8,9,10,14-tetramethoxy-2,3-methylenedioxy-13-oxoberbine (**12**, 3.0 g, 59%), mp 126—130°C. IR ν_{max}^{KBr} cm^{-1}: 1690 (ketone). PMR (DMSO-d_6) δ: 3.00—3.78 (4H, m, $-CH_2CH_2-$), 3.18, 3.64, 3.84, 3.91 (each 3H, each s, OMe×4), 5.41 (1H, s, C_8-H), 6.02 (2H, s, $-OCH_2O-$), 6.70 (1H, s, C_4-H), 6.85 (1H, s, C_1-H), 7.18, 7.52 (2H, AB-q, J=8.5 Hz, C_{11}-H and C_{12}-H). UV λ_{max}^{EtOH} nm (log ε): 230 (4.16), 291 (4.12).

8-Methoxyberberinephenolbetaine (6)——A solution of **12** (100 mg, 0.24 mmol) in MeOH (50 ml) was heated under reflux for 1 h and concentrated to give 8-methoxyberberinephenolbetaine (**6**, 91 mg, 99%) as orange prisms, mp 176—178°C (MeOH) (lit.[8] mp 175—176°C). PMR δ: 2.90 (2H, t, J=6 Hz, $-NCH_2C\underline{H}_2-$), 3.90 (3H, s, OMe), 4.02 (6H, s, OMe×2), 4.58 (2H, t, J=6 Hz, $-NC\underline{H}_2CH_2-$), 5.91 (2H, s, $-OCH_2O-$), 6.58 (1H, s, C_4-H), 7.40 (1H, d, J=9 Hz, C_{11}-H), 8.42 (1H, d, J=9 Hz, C_{12}-H), 8.80 (1H, s, C_1-H). MS *m/e*: 381 (M^+). UV λ_{max}^{EtOH} nm (log ε): 235 (4.22), 262 (4.15), 317 (4.13), 362 (3.92), 377 (4.12), 464 (4.13). *Anal.* Calcd for $C_{21}H_{19}NO_6 \cdot 1/2MeOH$: C, 64.98; H, 5.33; N, 3.52. Found: C, 64.90; H, 5.22; N, 3.54. The product was shown to be identical with an authentic specimen by IR spectral comparison and TLC.

Hydrogenation of 8-Methoxyberberinephenolbetaine (6)——A solution of **6** (500 mg, 1.3 mmol) in AcOEt (200 ml) was hydrogenated over PtO_2 (100 mg) under atmospheric pressure and at room temperature. After removal of the catalyst by filtration, the filtrate was concentrated and the residue was chromatographed on alumina with $CHCl_3$ to afford berberinephenolbetaine (**13**, 129 mg, 28%) as orange needles together with (±)-ophiocarpine (**9**, 70 mg, 15%). **13**: mp 260—264°C (MeOH) (lit.[7] mp 263°C). PMR δ: 3.03 (2H, t, J=6 Hz, $-NCH_2C\underline{H}_2-$), 4.02, 4.05 (each 3H, each s, OMe×2), 4.38 (2H, t, J=6 Hz, $-NC\underline{H}_2CH_2-$), 5.97 (2H, s, $-OCH_2O-$), 6.65 (1H, s, C_4-H), 7.39 (1H, d, J=9 Hz, C_{11}-H), 7.76 (1H, s, C_8-H), 8.37 (1H, d, J=9 Hz,

C_{12}-H), 9.01 (1H, s, C_1-H). MS *m/e*: 351 (M^+). *Anal.* Calcd for $C_{20}H_{17}NO_5 \cdot H_2O$: C 65.03; H, 5.19; N, 3.79. Found: C, 64.94; H, 5.39; N, 3.79. The synthetic **13** was found to be identical with an authentic specimen synthesized according to the literature[7] by IR spectral comparison and TLC.

13-Methoxyoxyberberine (15)——A solution of **6** (300 mg, 0.79 mmol) and methyl iodide (2 ml) in $CHCl_3$ (10 ml) was refluxed for 1.5 h. After evaporation of the solvent, the residue was recrystallized from MeOH to give 13-methoxyoxyberberine (**15**, 187 mg, 62%) as yellow plates, mp 211—212°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1639 (lactam). PMR δ: 2.83 (2H, t, J=6 Hz, $-NCH_2C\underline{H}_2-$), 3.61, 3.97, 4.01 (each 3H, each s, OMe×3), 4.24 (2H, t, J=6 Hz, $-NC\underline{H}_2CH_2-$), 6.00 (2H, s, $-OCH_2O-$), 6.70 (1H, s, C_4-H), 7.38, 7.64 (2H, AB-q, J=9 Hz, C_{11}-H and C_{12}-H), 7.96 (1H, s, C_1-H). MS *m/e*: 381 (M^+). UV λ_{max}^{MeOH} nm (log ε): 228.5 (4.68), 335 (4.40), 345.5 (4.42). *Anal.* Calcd for $C_{21}H_{19}NO_6$: C, 66.13; H, 5.02; N, 3.67. Found: C, 66.36; H, 5.01; N, 3.94.

13-Acetoxyoxyberberine (16)——Ac_2O (5 ml) was added to a solution of **6** (200 mg, 0.53 mmol) in pyridine (5 ml) and the mixture was allowed to stand at room temperature overnight. The solvent was evaporated off under reduced pressure, and the residue was taken up in $CHCl_3$. The solution was washed with saturated $NaHCO_3$ solution. The organic layer was dried and concentrated to give yellow crystals which were recrystallized from AcOEt to afford 13-acetoxyoxyberberine (**16**, 198 mg, 92%) as pale yellow needles, mp 241—242°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1768 (ester), 1645 (lactam). PMR δ: 2.38 (3H, s, CH_3CO), 2.72—3.00 (2H, m, $-NCH_2C\underline{H}_2-$), 3.96, 4.02 (each 3H, each s, OMe×2), 4.92—5.32 (2H, m, $-NC\underline{H}_2CH_2-$), 6.00 (2H, s, $-OCH_2O-$), 6.73 (1H, s, C_4-H), 7.20, 7.36 (2H, AB-q, J=9 Hz, C_{11}-H and C_{12}-H), 7.48 (1H, s, C_1-H). MS *m/e*: 409 (M^+). UV λ_{max}^{MeOH} nm (log ε): 229.5 (4.65), 343.5 (4.43). *Anal.* Calcd for $C_{22}H_{19}NO_7$: C, 64.54; H, 4.68; N, 3.42. Found: C, 64.31; H, 4.60; N, 3.33.

Methyl Anhydroberberilate (17)——A solution of **16** (300 mg, 0.73 mmol) in MeOH (80 ml) containing 28% aqueous NH_3 solution (20 ml) was heated at 45°C for 1 h, then the MeOH was evaporated off, and the residue was extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated to give crystals which were recrystallized from EtOH to afford methyl anhydroberberilate (**17**, 268 mg, 88%) as colorless plates, mp 186—187°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (ester), 1684 (imide). PMR δ: 3.03 (2H, t, J=6 Hz, $-NCH_2C\underline{H}_2-$), 3.80 (6H, s, OMe×2), 3.92 (3H, s, OMe), 4.16—4.60 (2H, m, $-NC\underline{H}_2'H_2-$), 5.99 (2H, s, $-OCH_2O-$), 6.68 (1H, s, C_5-H), 6.92, 7.80 (2H, AB-q, J=9 Hz, C_4'-H and C_5'-H), 7.39 (1H, s, C_8-H). MS *m/e*: 413 (M^+). UV λ_{max}^{MeOH} nm (log ε): 227.5 (4.25), 265.5 (4.24), 320 (4.05). *Anal.* Calcd for $C_{21}H_{19}NO_8$ C, 61.01; H, 4.63; N, 3.39. Found: C, 61.04; H, 4.65; N, 3.48.

(±)-*O*-Acetylophiocarpine (18) and (±)-*O*-Acetylepiophiocarpine (19)——$NaBH_4$ (145 mg, 3.8 mmol) was added portionwise to a stirred solution of **6** (300 mg, 0.79 mmol) in MeOH (20 ml) at room temperature. The mixture was stirred for 2 h, then MeOH was evaporated off and the residue was taken in $CHCl_3$. The $CHCl_3$ solution was washed with water, dried, and concentrated. The residue was dissolved in pyridine (30 ml) and Ac_2O (30 ml) was added to the solution. The reaction mixture was allowed to stand overnight at room temperature. The solvent was evaporated off under reduced pressure, and the residue was made alkaline with aqueous $NaHCO_3$ solution then extracted with $CHCl_3$. The extract was dried and concentrated, then the residue was chromatographed on alumina with $CHCl_3$/hexane (1/1). The first fraction gave (±)-*O*-acetylophiocarpine (**18**, 272 mg, 87%) as colorless prisms, mp 178.5—179.5°C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1728 (ester). PMR δ: 1.80 (3H, s, CH_3CO), 2.44—3.42 (4H, m, $-NCH_2CH_2-$), 3.52, 4.38 (2H, AB-q, J=16 Hz, C_8-H), 3.78 (1H, br s, C_{14}-H), 3.90 (6H, s, OMe×2), 5.90, 5.92 (2H, AB-q, J=1.5 Hz, $-OCH_2O-$), 6.46 (1H, d, J=3 Hz, C_{13}-H), 6.60 (1H, s, C_4-H), 6.72 (1H, s, C_1-H), 6.84, 7.28 (2H AB-q, J=8.5 Hz, C_{11}-H and C_{12}-H). MS *m/e*: 397 (M^+). UV λ_{max}^{MeOH} nm (log ε): 232.5 (4.25), 283 (3.73), 291.5 (3.78). *Anal.* Calcd for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.55; H, 5.79; N, 3.73. The second fraction afforded (±)-*O*-acetylepiophiocarpine (**19**, 18 mg, 6%) as colorless needles, mp 187—188°C (iso-Pr_2O). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1732 (ester). PMR δ: 2.21 (3H, s, CH_3CO), 2.58—3.26 (4H, m, $-NCH_2CH_2-$), 3.88, 4.16 (2H, AB-q, J=16 Hz, C_8-H), 3.88 (6H, s, OMe×2), 4.06 (1H, d, J=8 Hz, C_{14}-H), 5.92 (2H, s, $-OCH_2O-$), 6.10 (1H, d, J=8 Hz, C_{13}-H), 6.61 (1H, s, C_4-H), 6.72 (1H, s, C_1-H), 6.84, 7.00 (2H, AB-q, J=8.5 Hz, C_{11}-H and C_{12}-H). MS *m/e*: 397 (M^+). UV λ_{max}^{MeOH} nm (log ε): 232.5 (4.11), 283.5 (3.65), 291 (3.80). *Anal.* Calcd for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.68; H, 5.87; N, 3.79.

(±)-Ophiocarpine (9)——A solution of **18** (380 mg, 0.96 mmol) in MeOH (5 ml) was refluxed with 5% NaOH solution (5 ml) for 1h, then cooled. Precipitated crystals were collected by filtration and the filtrate was extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated to give colorless crystals. The combined crystals were recrystallized from $CHCl_3$ to afford (±)-ophiocarpine (**9**, 340 mg, 100%) as colorless needles, mp 248—251°C. MS *m/e*: 355 (M^+). *Anal.* Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.57; H, 5.77; N, 4.10. The synthetic (±)-ophiocarpine was shown to be identical with an authentic specimen by mixed melting point determination, IR spectral comparison, and TLC.

(±)-13-Epiophiocarpine (10)——A solution of **19** (44 mg, 0.11 mmol) in MeOH (5 ml) was refluxed with 5% NaOH solution (5 ml) for 1 h, then cooled. MeOH was evaporated off and the residue was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water, dried, and concentrated to give colorless crystals, which were recrystallized from MeOH to afford (±)-13-epiophiocarpine (**10**, 36 mg, 91%) as colorless needles, mp 185—187°C. MS *m/e*: 355 (M^+). *Anal.* Calcd for $C_{20}H_{21}NO_5$: C, 67.59: H, 5.96; N, 3.94. Found: C,

67.49; H, 5.92; N, 4.23. The product was shown to be identical with an authentic specimen by mixed melting point determination, IR spectral comparison, and TLC.

Acknowledgement The authors are grateful to Prof. M. Shamma, The Pennsylvania State University, for providing an authentic sample of 8-methoxyberberine-phenolbetaine, and to Mr. Y. Itatani, Misses Y. Arano, and K. Ohata of this Faculty for elemental analyses, PMR, and mass spectral measurements.

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