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Chemical Transformation of Protoberberines. I. Conversion of Tetrahydroberberine and Dihydroberberine into Noroxyhydrastinine by Photooxygenation[1]

Miyoji Hanaoka,* Chisato Mukai, Itsuko Hamanaka, Kazue Seki, and Yoshio Arata

Faculty of Pharmaceutical Sciences, Kanazawa University
Takara-machi, Kanazawa, 920, Japan

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Simple and biomimetic conversions of tetrahydroberberine (**1**) and dihydroberberine (**6**) into noroxyhydrastinine (**3**), an isoquinolone alkaloid, are described. Photooxygenation of **1** afforded berberal (**2**), **3**, and *O*-methylpseudopianic acid (**4**). The same products were obtained more efficiently by photooxygenation of **6**.

Keywords——photooxygenation; singlet oxygen; biomimetic conversion; protoberberine alkaloid; tetrahydroberberine; dihydroberberine; isoquinolone alkaloid; noroxyhydrastinine

Protoberberine alkaloids have been shown to be the biogenetic precursors of related alkaloids such as 13-oxyberbine,[2] phthalideisoquinoline,[3] spirobenzylisoquinoline,[4] rhoeadine,[5,6] benzophenanthridine,[3] and protopine[3,7,8] alkaloids. As these related alkaloids have oxygenated skeletons, as shown in Chart 1,[9] oxygenation would be a crucial step in the biotransformation and should take place principally at the α-carbons with respect to the nitrogen of the starting protoberberines, namely C_6, C_8, and C_{14}.

On the above biogenetic assumption, we investigated the biomimetic transformation of protoberberines to related alkaloids by photooxygenation, which was expected to oxygenate

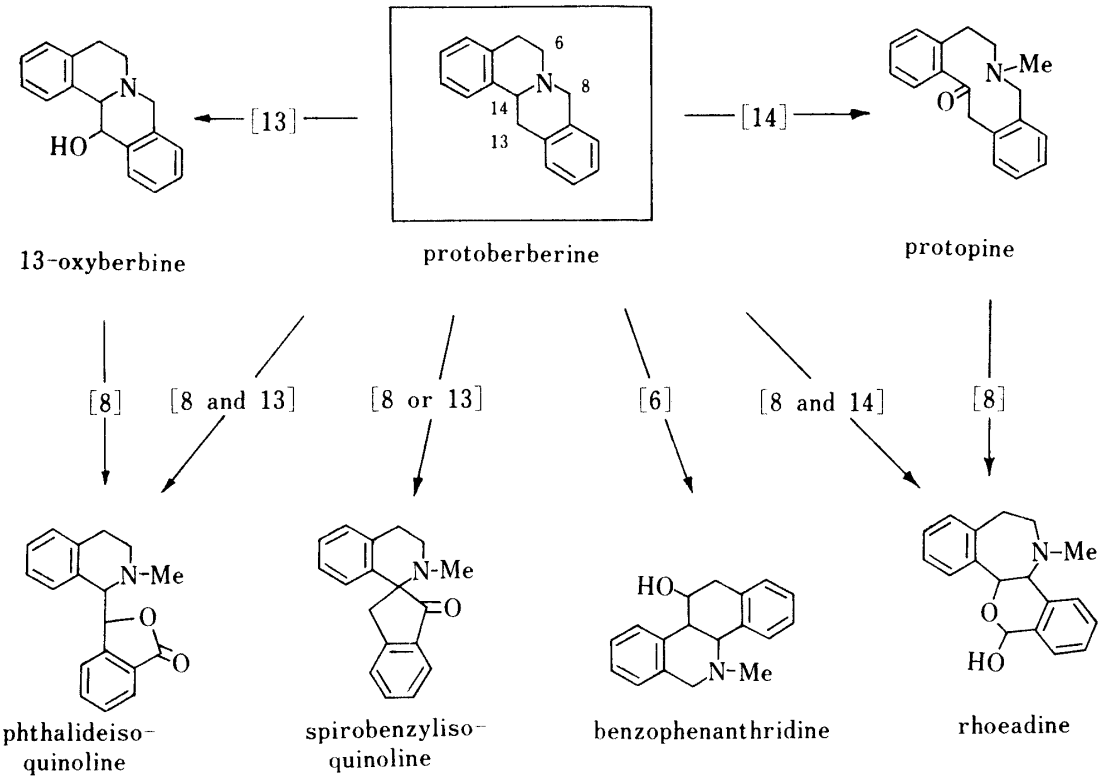

Chart 1[9]

carbons α to the tertiary nitrogen.[10] This paper describes the easy oxidative cleavage of the C_{13}–C_{14} bond of tetrahydroberberine and dihydroberberine by photooxygenation to yield noroxyhydrastinine,[11] a representative isoquinolone alkaloid.

A solution of tetrahydroberberine (**1**) in methanol containing a catalytic amount of rose bengal was irradiated with a high-pressure mercury lamp (100W, with a Pyrex filter) in a stream of oxygen for 3.5 h at room temperature to give berberal [**2**, mp 150—151°C (lit.[12] mp 148—150°C)], noroxyhydrastinine [**3**, mp 187—187.5°C (lit.[11] mp 182—183°C)], and *O*-methylpseudopianic acid (**4**, mp 91.5—92°C) in 32, 20, and 14% yields, respectively. The structures of the products were elucidated by analysis of their spectral data (see "Experimental."). Further confirmation of their structures was obtained by methanolysis of **2**. Heating of **2** in methanol saturated with hydrogen chloride under reflux for 3.5 h yielded **3** (74%), **4** (5%), and pseudopianic acid [**5**, 42%, mp 122.5—123.5°C (lit.[12] mp 121—122 °C)].

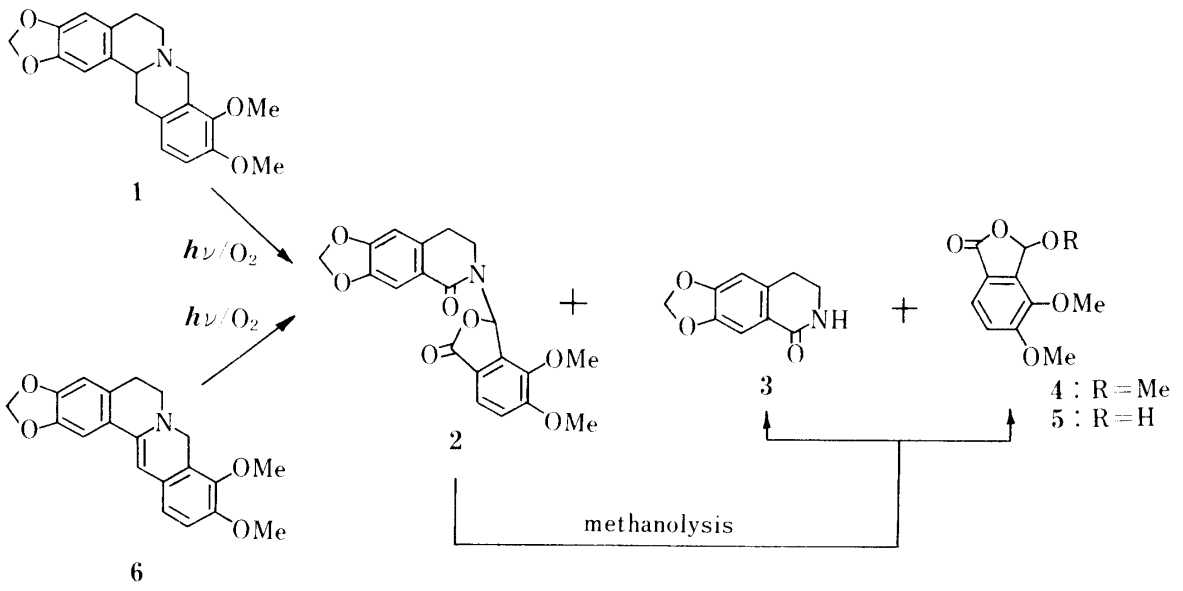

Chart 2

Upon irradiation in a stream of nitrogen instead of oxygen, **1** was recovered unchanged. Photooxygenation of **1** without rose bengal gave **2** (18%) along with the starting material (50%). The present photooxygenation, therefore, should involve singlet oxygen. The possibility that **3** and **4** are secondary products derived from **2** was ruled out by the fact that **2** was recovered unchanged after irradiation under the same photooxygenation conditions or after being refluxed in methanol.

A possible mechanism for the above reaction is shown in Chart 3, namely **1** would be oxidized to dihydroberberine (**6**) *via* the zwitterionic intermediate[13] (**7**) and **6** would be further oxidized *via* the dioxetane[10] (**8**) and **9** to the acid (**10**), which might cyclize to give **2** or **3** and **4** by fission of the C–O bond (path a) or C–N bond (path b), respectively.

As dihydroberberine (**6**) would be an important intermediate in this reaction according to the above mechanism, photooxygenation of **6** was investigated.[14] Upon irradiation under conditions similar to those used for **1**, **6** disappeared within 5 min to give **2**, **3**, and **4** in 53, 18, and 8% yields, respectively. The involvement of the intermediate **6** in the photooxygenation of **1** was supported by the observation that the oxygenation of **6** proceeded much faster than that of **1** to afford the same products as those from **1**. Thus, it was found that preferential oxygenation at C_{13} and C_{14} as well as C_8 and easy cleavage of the C_{13}–C_{14} bond occurred to give the isoquinolone alkaloid noroxyhydrastinine (**3**) in the photooxygenation of tetrahydroberberine (**1**) *via* dihydroberberine (**6**).

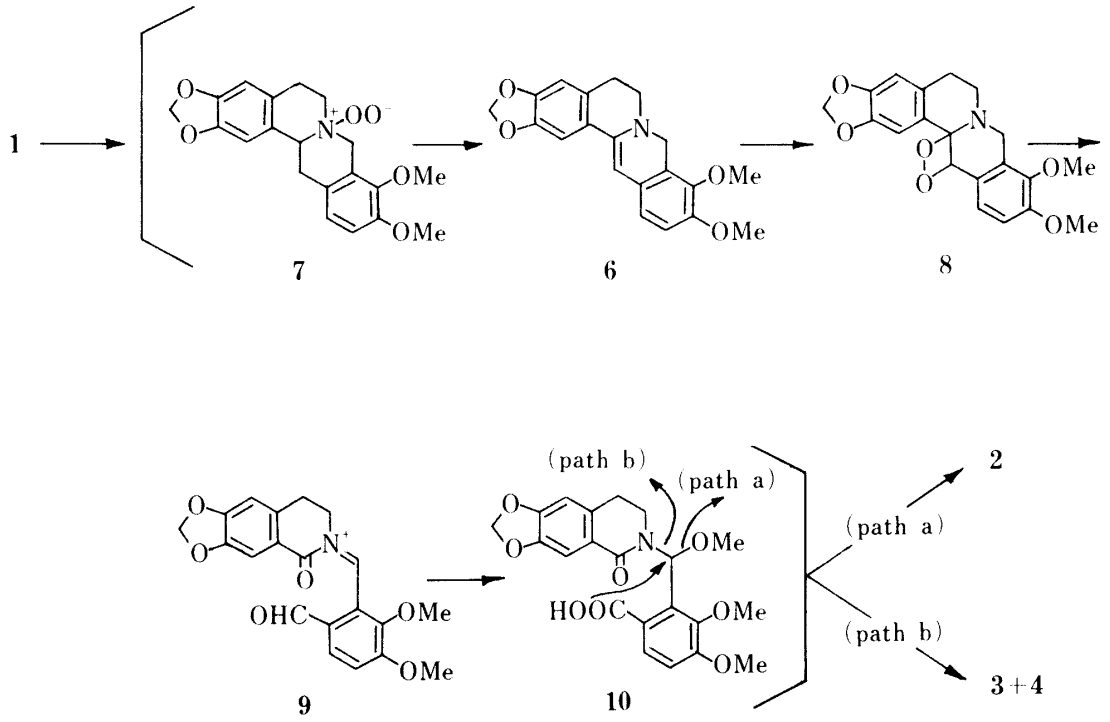

Chart 3

The isoquinolone alkaloids are considered to be biogenetically derived by oxidation of the benzylisoquinoline alkaloids,[11,15] and photooxygenation of laudanosine has been found to provide *N*-methylcorydaldine, an isoquinolone alkaloid.[16] The present ready transformation of berberines into noroxyhydrastinine by photooxygenation suggests that the protoberberine alkaloids might be also precursors of the isoquinolone alkaloids.

Experimental

All melting points are uncorrected. Alumina (Brokmann grade II—III, Merck) and silica gel (Kieselgel GF_{254} Typ 60, Merck) were used for column and thin-layer chromatography (TLC), respectively. ^{1}H-Nuclear magnetic resonance (^{1}H-NMR) spectra in $CDCl_3$ were measured with a JEOL PS-100 machine (tetramethylsilane as an internal standard), infrared (IR) spectra with a JASCO IR-G spectrophotometer, mass spectra with a JEOL JMS-01SG mass spectrometer, and ultraviolet (UV) spectra in MeOH with a Hitachi Model 323 machine. Irradiation was carried out with 100W high-pressure mercury lamp (Riko Kagaku Co.) with a Pyrex filter.

Photooxygenation of Tetrahydroberberine (1)——a) In the Presence of Rose Bengal: A solution of tetrahydroberberine (**1**, 100 mg, 0.30 mmol) in methanol (100 ml) was irradiated in a stream of oxygen for 3.5 h at room temperature in the presence of rose bengal (5 mg). The reaction mixture was evaporated to dryness and the residue was chromatographed on alumina with *n*-hexane–$CHCl_3$ (1: 3) to give berberal (**2**, 36 mg, 32%) as colorless scales, mp 150—151°C (from AcOEt). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1767 (lactone), 1665 (amide). ^{1}H-NMR δ: 3.36—3.72 (4H, m, $-CH_2CH_2-$), 3.89, 4.00 (each 3H, each s, OMe×2), 6.04 (2H, s, O–CH_2–O), 6.62 (1H, s, C_4–H), 7.20 (1H, d, J=8.5 Hz, C_{11}–H), 7.64 (1H, s, C_1–H), 7.71 (1H, d, J=8.5 Hz, C_{12}–H), 8.02 (1H, s, O–CH–N). MS *m/e*: 383 (M^+). UV λ_{max} nm (log ε): 223.5 (4.72), 264.5 (4.27), 307 (3.96). *Anal.* Calcd for $C_{20}H_{17}NO_7$: C, 62.66; H, 4.47; N, 3.65. Found: C, 62.56; H, 4.31; N, 3.81. Further elution with the same solvent afforded noroxyhydrastinine (**3**, 11 mg, 20%) as colorless needles, mp 187—187.5°C (from benzene). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3425 (NH), 1660 (CO). ^{1}H-NMR δ: 2.85 (2H, t, J=6.5 Hz, $-C\underline{H}_2CH_2-$N), 3.49 (2H, t, J=6.5 Hz, $-CH_2C\underline{H}_2-$N), 5.90 (2H, s, O–CH_2–O), 6.48 (1H, br s, NH), 6.55 (1H, s, C_5–H), 7.39 (1H, s, C_8–H). MS *m/e*: 191 (M^+). *Anal.* Calcd for $C_{10}H_{11}NO_3$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.60; H, 4.65; N, 7.21. From the next eluate, *O*-methylpseudopianic acid (**4**, 9 mg, 14%) was obtained as colorless needles, mp 91.5—92°C (from *n*-hexane). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1768 (CO). ^{1}H-NMR δ: 3.64, 3.99, 4.01 (each 3H, each s, OMe×3), 6.38 (1H, s, –CH–O), 7.11 (1H, d, J=8.0 Hz, Ar–H), 7.59 (1H, d J=8.0 Hz, Ar–H). MS *m/e*: 224 (M^+). *Anal.* Calcd for $C_{11}H_{12}O_5$: C, 58.92; H, 5.40. Found: C, 58.68; H, 5.56. Finally a mixture

of unknown compounds (19 mg) was eluted.

b) In the Absence of Rose Bengal: A solution of **1** (400 mg, 1.2 mmol) in methanol (250 ml) was irradiated in a stream of oxygen at room temperature for 6 h. Work-up as described above gave **2** (80 mg, 18%) and **1** (201 mg, 50%).

Photooxygenation of Dihydroberberine (6)——A solution of dihydroberberine (**6**, 200 mg, 0.59 mmol) in methanol (250 ml) containing rose bengal (5 mg) was irradiated in a stream of oxygen for 5 min at room temperature. The solvent was evaporated off, and the residue was chromatographed on alumina with *n*-hexane–$CHCl_3$ (1: 3) to give **2** (120 mg, 53%), **3** (20 mg, 18%), **4** (11 mg, 8%), and an unknown mixture (20 mg). They were identical with the corresponding specimens obtained above.

Methanolysis of Berberal (2)——A solution of **2** (100 mg, 0.26 mmol) in methanol (100 ml) saturated with dry HCl gas was refluxed for 3.5 h, then cooled. The solvent was evaporated off under reduced pressure and the residue was made alkaline with saturated $NaHCO_3$ aq. solution, then extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated. The yellowish residue was separated by preparative thin-layer chromatography on silica gel with $CHCl_3$–AcOEt (4: 1) to afford **3** (37 mg, 74%) and **4** (3 mg, 5%). The above aqueous alkaline solution was acidified with 10% HCl and extracted with $CHCl_3$. The organic layer was washed with water, dried over Na_2SO_4, and concentrated to give pseudopianic acid (**5**, 23 mg, 42%) as colorless needles, mp 122.5—123.5°C (*n*-hexane). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3300 (OH), 1767 (CO). ^{1}H-NMR δ: 3.94, 4.02 (each 3H, each s, OMe×3), 4.66 (1H, s, OH), 6.68 (1H, s, –CH–O), 7.04 (1H, d, J=8.2 Hz, Ar–H), 7.52 (1H, d, J=8.2 Hz, Ar–H). MS *m/e*: 210 (M^+). *Anal.* Calcd for $C_{10}H_{10}O_5$: C, 57.14; H, 4.84. Found: C, 57.06; H, 4.85.

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