Chemical Transformation of Protoberberines. XI. 1) A Novel Synthesis of 2,3,10,11-Tetraoxygenated Protoberberine Alkaloids from Corresponding 2,3,9,10-Tetraoxygenated Protoberberine Alkaloids2)

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2,3,9,10-Tetraoxygenated protoberberin alkaloids, berberine (1a), palmatine (1b), and coptisine (1c), were efficiently converted into the corresponding 12-hydroxy-2,3,10,11-tetraoxygenated protoberberines (6a, 6b, 6c) through an oxidative C8–C8a bond cleavage with m-chloroperbenzoic acid, followed by the enamide photo-cyclization. On successive treatment with diethyl chlorophosphate and sodium in liquid ammonia, the 12-hydroxy derivatives (6a, 6b, 6c) underwent reductive dehydroxylation to produce the corresponding 2,3,10,11-tetraoxygenated protoberberines, tetrahydropseudoberberine (4a), (±)-xylopinine (4b), and tetrahydropseudocoptisine (4c), respectively.

Keywords—2,3,9,10-tetraoxygenated protoberberine; 2,3,10,11-tetraoxygenated protoberberine; berberine; palmatine; coptisine; tetrahydropseudoberberine; xylopinine; tetrahydropseudocoptisine; photo-induced cyclization; oxidative C8–C8a bond fission

Tetraoxygenated protoberberine alkaloids can be classified into two groups, naturally abundant 2,3,9,10-tetraoxygenated protoberberines and 2,3,10,11-tetraoxygenated ones, according to the substitution patterns of oxygen functions in ring A as well as ring D.3) Some of the latter type of alkaloids, pseudoberberine (2a), pseudocoptisine (2c), etc., have recently been isolated.4) 1,2,10,11-Tetraoxygenated protoberberine alkaloids,5) caseadine and caseamine, are also known. These protoberberine alkaloids have been shown to be the biogenetic precursors of related alkaloids such as benzo[c]phenanthridine,6) spirobenzylisoquinoline,7) and phthalideisoquinoline8) alkaloids.

In the course of our continuing studies1,9) on the transformation of protoberberines to benzo[c]phenanthridine alkaloids via a proposed biogenetic route,6) we required the pseudoberberine (2a), a 2,3,10,11-tetraoxygenated protoberberine, for a synthesis of nitidine.10,11)
which has attracted much attention because of its strong antileukemic activity. Although
several methods for the synthesis of protoberberines have so far been developed\(^\text{12)}\) and
pseudoberberine (2a) has been synthesized by conventional means\(^\text{13)}\), a simple conversion of
berberine (1a) into 2a would be of great value as an alternative synthesis of 2a because of the
easy access to the starting material.

The strategy of our transformation is outlined in Chart 2, and is based on the
consideration that pseudoberberine (2a) is the ring D-inverted product\(^\text{14)}\) of berberine (1a).
Therefore, conversion of 1a to 3 via C\(_8\)-C\(_{8a}\) bond cleavage followed by recyclization between
the original C\(_8\) and C\(_{12}\) positions and subsequent removal of the substituent X at C\(_{8a}\) will
afford tetrahydropseudoberberine (4a).

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\text{Chart 2}
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Polyberbine has recently been isolated from Berberis valdiviana PHIL\(^\text{15)}\) and found to be
the oxidative C\(_8\)-C\(_{8a}\) bond cleavage product (3: C\(_8\) = CHO, X = OH) of berberine. Though
polyberbine has been derived from 1a by treatment with m-chloroperbenzoic acid (m-CPBA)
only in low yield (20\%),\(^\text{16,17)}\) this product seems to be a suitable candidate for our strategy.

Treatment of well-dried berberine (1a) with 1.3 eq of m-CPBA in dry tetrahydrofuran (THF) in the presence of 2 eq of sodium hydride in a stream of nitrogen at room temperature
for 1 h afforded polyberbine (5a) in 76\% yield. The yield was considerably improved by
adjusting the reaction conditions. The spectral data of 5a thus obtained are in good agreement
with those described in the literature.\(^\text{16)}\) Irradiation\(^\text{18)}\) of polyberbine (5a) in ethanol with a
400 W high-pressure mercury lamp in a stream of nitrogen for 2 h, followed by reduction of
the resulting quaternary base with sodium borohydride (NaBH\(_4\)), afforded 12-hydroxytetrahydro-
pseudoberberine (6a) in 79\% yield. The salient feature of 6a in the mass spectrum (MS)
is the peaks at m/z 176 and 180 arising from the retro Diels–Alder reaction.\(^\text{12)}\) The proton
nuclear magnetic resonance (\(^1\)H-NMR) spectrum showed only three signals at \(\delta\) 6.81, 6.57,
and 6.20 ppm as singlets in the aromatic region. The hydroxy group at the C\(_{12}\) position in 6a
was, as expected, easily methylated with diazomethane to produce a novel protoberberine, 12-
methoxytetrahydropseudoberberine (7a) in 91\% yield; the structure of this product was
supported by spectral evidence.

Finally reductive removal of the hydroxy group at the C\(_{12}\) position in 6a was realized via the
corresponding phosphate (8a). A solution of 6a in THF was treated with diethyl chlorophosphate to provide the phosphate (8a) which, without purification, was exposed to
sodium in liquid ammonia\(^\text{19)}\) at \(-70\) °C to furnish tetrahydropseudoberberine (4a) in 53\% overall yield from 6a. The synthetic tetrahydropseudoberberine was proved to be identical
with an authentic specimen\(^\text{13)}\) by comparison of their spectra and thin-layer chromatographic
behavior. Thus, we have succeeded in the development of a convenient method for the
synthesis of tetrahydropseudoberberine from easily available berberine.

We next examined the generality of the above transformation method. Similar treatment
of palmatine (1b) and coptisine (1c) with m-CPBA in THF yielded polycarpine (5b)\(^\text{16,20)}\) and
the enamide (5c)\(^\text{21)}\) in 44 and 39\% yields,\(^\text{22)}\) respectively, though these yields are lower than
that in the case of 5a. The structures of 5b and 5c were easily determined on the basis of
spectral evidence. On exposure to sequential irradiation with a high-pressure mercury lamp
and reduction with NaBH₄, polycarpine (5b) and 5c underwent photo-induced cyclization to give 12-hydroxyxylopinine (6b) and 12-hydroxytetrahydropseudocoptisine (6c) in 70 and 65% yields, respectively. Both tetrahydroprotoberberines (6b and 6c) exhibited diagnostic fragmentation peaks at m/z 180 and 192, and at m/z 164 and 176, respectively, in their MS. The hydroxy group at the C₁₂ position in 6b and 6c was reductively removed via 8b and 8c by the same procedure as described for conversion of 6a to 4a, to afford (±)-xylopinine (4b) and tetrahydropseudocoptisine (4c) in 62 and 44% overall yields from 6b and 6c, respectively. The synthetic (±)-xylopinine and tetrahydropseudocoptisine were identical with authentic samples.²³²⁴)

Thus, we have accomplished a novel and convenient synthesis of 2,3,10,11-tetraoxygenated protoberberine alkaloids from the corresponding 2,3,9,10-tetraoxygenated ones. The present method provides an alternative route for the synthesis of 2,3,10,11-tetraoxygenated protoberberines, especially pseudoberberine (2a), because of the easy access to the starting material, berberine (1a).

**Experimental**

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Alumina (Aluminiumoxid 90, Aktivitätsstufe II—III, 70—230 mesh, Merck) and silica gel (Kieselgel 60, 70—230 mesh, Merck) were used for column chromatography. Organic extracts were dried over anhydrous Na₂SO₄. Infrared (IR) spectra were measured with a JASCO A-102 spectrometer. MS with a Hitachi M-80 mass spectrometer, ultraviolet (UV) spectra with a Hitachi 323 spectrometer in MeOH, and ¹H-NMR spectra with a JEOL FX-100 spectrometer in CDCl₃ using tetramethylsilane as an internal standard, unless otherwise stated. Irradiation was carried out with a 100 or 400 W high-pressure mercury lamp equipped with a Pyrex filter (Riko Kagaku Co.).

**Polyberbine (5a)**—Well-dried berberine chloride (1a) (2.1 g, 5.7 mmol) was added portionwise to a stirred suspension of sodium hydride (50% in oil; 550 mg, 11.4 mmol) in dry THF (70 ml) in a stream of nitrogen at room temperature. After 1 h, m-CPBA (1.6 g, 7.4 mmol) in dry THF (30 ml) was added to the reaction mixture at 0 ºC, and the solution was stirred at room temperature for an additional 1 h. Saturated sodium thiosulfate solution (15 ml) and saturated sodium bicarbonate solution (15 ml) were added at once to the reaction mixture and the THF layer was separated. The water layer was extracted with chloroform, and the combined organic layers were washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue on silica gel with ethyl acetate–hexane (1:1) gave polyberbine (5a, 1.59 g, 76%), mp 165—166 ºC (MeOH). IR ν_max(CHCl₃, cm⁻¹): 3500 (OH), 1660 (amide). ¹H-NMR δ: 8.10 (1H, s, CHO), 7.27 (1H, s, olefinic proton), 6.99, 6.46 (2H, AB-q, J=9 Hz, C₆-H and C₅-H), 6.85, 6.58 (each 1H, s, C₄-H and C₅-H), 5.96 (2H, s, OCH₂O), 3.95 (2H, t, J=6 Hz, CH₂CH₂N), 3.89, 3.85 (each 3H, s, OMe ~ 2), 2.85 (2H, t, J=6 Hz, CH₂CH₂N). UV λ_max nm (log ε): 335 (4.30), 221 (4.56). MS m/z: 369 (M+, 100%), 352 (30), 341 (48), 326 (35), 308 (54). Anal. Calcd for C₂₀H₁₉NO₆: C, 65.03; H, 5.19; N, 3.79. Found: C, 65.20; H, 5.36; N, 3.76.

**Polycarpine (5b)**—Palmatine chloride (1b) (379 mg, 1.0 mmol) was oxidized with m-CPBA (280 mg, 1.3 mmol) in THF (total 70 ml) in the presence of sodium hydride (60% in oil; 82 mg, 2.1 mmol). The reaction mixture was treated as described for 5a to give 5b (175 mg, 44%), mp 176—177 ºC (MeOH) (lit.¹⁶ 179—180 ºC). IR ν_max(CHCl₃, cm⁻¹): 3500 (OH), 1660 (amide). ¹H-NMR δ: 8.13 (1H, s, CHO), 7.26 (1H, s, olefinic proton), 6.99, 6.46 (2H, AB-q, J=9 Hz, C₆-H and C₅-H), 6.85, 6.58 (each 1H, s, C₄-H and C₅-H), 5.96 (2H, s, OCH₂O), 3.95 (2H, t, J=6 Hz, CH₂CH₂N), 3.94, 3.90, 3.89, 3.85 (each 3H, s, OMe × 2), 2.88 (2H, t, J=6 Hz, CH₂CH₂N). UV λ_max nm (log ε): 335 (4.30), 221 (4.56). MS m/z: 369 (M⁺, 100%), 352 (30), 341 (41), 326 (35), 324 (36), 308 (54). Anal. Calcd for C₂₁H₂₃NO₆: C, 65.03; H, 5.19; N, 3.79. Found: C, 65.20; H, 5.36; N, 3.76.
(Z)-1,2,3,4-Tetrahydro-1-(2-hydroxy-3,4-methylenedioxyphenylethylidene)-2-formyl-6,7-methylenedioxyisoquinoline (5c) — Coptisine chloride (1c) (195 mg, 0.55 mmol) was oxidized with m-CPBA (593 mg, 2.75 mmol) in THF (total 40 ml) in the presence of sodium hydride (60%; in oil; 113 mg, 2.81 mmol). The reaction mixture was treated as described for 5a to give 5c (75 mg, 39%), mp 177-178 °C (MeOH) (lit.13) 177 °C). The synthetic (Z)-xylopinine was proved to be identical with an authentic sample23) by comparison of their IR and 1H-NMR spectra, and thin-layer chromatographic behavior.

Tetrahydropseudocoptisine (4c) — A solution of 4c (42 mg, 0.12 mmol) in THF was treated with n-BuLi in hexane (0.7 ml, 1.1 mmol) (instead of sodium hydride) and diethyl chlorophosphate (20 mg, 0.12 mmol) and then with hexane (0.7 ml, 1.1 mmol) was added. The reaction mixture was stirred at room temperature for 30 min at the same temperature. A solution of diethyl chlorophosphate (149 mg, 0.63 mmol) and then sodium (58 mg, 2.5 mmol) was added. The reaction mixture was stirred at room temperature for 2 h. After evaporation of the solvent, the residue was neutralized with 10% hydrochloric acid solution and extracted with ethyl acetate. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed on silica gel with ethyl acetate-hexane (1 : 1) to afford 6c (105 mg, 65%), mp 232-233 °C (AcOEt). IR νCHCl3 max cm⁻¹: 3400 (OH). 1H-NMR ν: 6.81, 6.57, 6.20 (each 1H, aromatic protons), 3.83, 3.86 (each 3H, OMe × 2). UV λmax nm (log e): 285 (3.72), 231 (sh, 4.14). MS m/z: 369 (M⁺, 36%), 194 (100). Anal. Calcd for C21H23NO5·1/2MeOH: C, 67.00; H, 6.53; N, 3.63. Found: C, 67.42; H, 6.53; N, 3.56.

Tetrahydropseudoberberine (4a) — A solution of 6a (201 mg, 0.57 mmol) in dry THF (10 ml) was added dropwise to a stirred suspension of sodium hydride (60%; in oil; 38 mg, 0.94 mmol) in dry THF (10 ml) at 0 °C and the resulting THF solution was stirred for 30 min at the same temperature. A solution of diethyl chlorophosphate (149 mg, 0.87 mmol) was added to the THF solution and stirring was continued for 1 h. Saturated ammonium chloride solution was added to the reaction mixture and the THF layer was separated. The water layer was extracted with methylene chloride, and the combined organic layers were washed with water and brine, dried, and concentrated to leave the crude phosphate (8a). A solution of 8a in dry THF (10 ml) was added to liquid ammonia (50 ml) at -70 °C, and then sodium (58 mg, 2.5 mmol) was added. The reaction mixture was stirred for 1 h at the same temperature and solid ammonium chloride (1.5 g) was added to the reaction mixture, which was then warmed to room temperature. Water was added to the THF solution and the THF layer was separated. The water layer was extracted with methylene chloride, and the combined organic layers were washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue on silica gel with methylene chloride–methanol (98 : 2) provided 4a (100 mg, 53%), mp 177—178.5 °C (MeOH) (lit.13) 177 °C). The synthetic (±)-xylopinine was proved to be identical with an authentic sample23) by comparison of their IR and 1H-NMR spectra, and thin-layer chromatographic behavior.

Tetrahydropseudodroserine (4a) — A solution of 6a (201 mg, 0.57 mmol) in dry THF (10 ml) was added dropwise to a stirred suspension of sodium hydride (60%; in oil; 38 mg, 0.94 mmol) in dry THF (10 ml) at 0 °C and the resulting THF solution was stirred for 30 min at the same temperature. A solution of diethyl chlorophosphate (149 mg, 0.87 mmol) was added to the THF solution and stirring was continued for 1 h. Saturated ammonium chloride solution was added to the reaction mixture and the THF layer was separated. The water layer was extracted with methylene chloride, and the combined organic layers were washed with water and brine, dried, and concentrated to leave the crude phosphate (8a). A solution of 8a in dry THF (10 ml) was added to liquid ammonia (50 ml) at -70 °C, and then sodium (58 mg, 2.5 mmol) was added. The reaction mixture was stirred for 1 h at the same temperature and solid ammonium chloride (1.5 g) was added to the reaction mixture, which was then warmed to room temperature. Water was added to the THF solution and the THF layer was separated. The water layer was extracted with methylene chloride, and the combined organic layers were washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue on silica gel with methylene chloride–methanol (98 : 2) provided 4a (100 mg, 53%), mp 177—178.5 °C (MeOH) (lit.13) 177 °C). The synthetic (±)-xylopinine was proved to be identical with an authentic sample23) by comparison of their IR and 1H-NMR spectra, and thin-layer chromatographic behavior.

Tetrahydropseudocoptisine (4c) — A solution of 4c (42 mg, 0.12 mmol) in THF was treated with n-BuLi in hexane (0.7 ml, 1.1 mmol) (instead of sodium hydride) and diethyl chlorophosphate (20 mg, 0.12 mmol) and then with...
sodium (10 mg × 2, total 0.9 mmol) in liquid ammonia as described for 4a to give 4c (22 mg, 44%), mp 213—214 °C (EtOH) (lit.24) 214—215 °C). The synthetic tetrahydropseudocoptisine was proved to be identical with an authentic sample24) by comparison of their IR and ¹H-NMR spectra, and thin-layer chromatographic behavior.

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References and Notes

2) A part of this work was published in a preliminary communication: M. Hanaoka, M. Marutani, K. Saitoh, and C. Mukai, Heterocycles, 23, 2927 (1985).
17) The reaction was carried out in methylene chloride at —78 °C in the presence of sodium bicarbonate.¹⁸a
22) M. Shamma obtained 5b¹⁶a) and 5c¹²¹ in 40 and 40—50% yields, respectively.