Chemical Transformation of Protoberberines. XII.1) A Novel Synthesis of Rheoaine Alkaloids. An Alternative Synthesis of a Key Intermediate, Benzindenoazepine, for a Synthesis of (±)-cis-Alpinigenine and (±)-cis-Alpinine from Palmatine2)

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A formal synthesis of (±)-cis-alpinigenine (3) and (±)-cis-alpinine (4) was achieved by conversion of palmatine (7) into the key intermediate, benzindenoazepine (16), via the ring D-inverted 2,3,11,12-tetraoxygenated phenolbetaine (14) and the 8,14-cycloberbine (15) through photooxygenation, photochemical valence isomerization, and regioselective C–N bond cleavage of 15 as crucial reactions.

Keywords — rhoeadine alkaloid; protoberberine alkaloid; cis-alpinigenine; cis-alpinine; palmatine; benzindenoazepine framework; 8,14-cycloberbine; photooxygenation; photochemical isomerization; regioselective C–N bond cleavage

Rhoeadine alkaloids (1)3) possess a unique framework having a benzazepine system fused with a six-membered hemiacetal or acetal. These alkaloids have been shown to be biosynthesized from the corresponding protoberberines (2).4–6) Among several successful syntheses,7–12) those through benzindenoazepines9,10,12) such as 6 (R = Me)10) are of great interest from the viewpoints of both biosynthesis and chemical transformation.

On the basis of biogenetic considerations, we planned a novel synthetic route to rhoeadine alkaloids (Chart 1). The protoberberine (2) is transformed to the ring D-inverted protoberberine (5) and then to the benzindenoazepine (6), which has already been converted to rhoeadine alkaloids (1).
In the previous papers, we have demonstrated a convenient transformation of a natural 2,3,9,10-tetraoxygenated protoberberine (2) into a ring D-inverted unnatural 2,3,11,12-tetraoxygenated protoberberine (5) via a spirobenzylisoquinoline,13) as well as an efficient synthesis of a benzindenoazepine system from a protoberberinephenolbetaine via an 8,14-cycloberbine.2,14) Now we describe a novel and convenient synthesis of the key intermediate, benzindenoazepine (6), for total synthesis of (+)-cis-alpinigenine (3)15) and (+)-cis-alpinine (4)15) from a protoberberine alkaloid, palmatine (7) according to our novel pathway mentioned above.

Irradiation of palmatine (7) in methanol in the presence of sodium methoxide and rose bengal with a halogen lamp in a stream of oxygen at 0 °C followed by alumina column chromatography afforded 8-methoxypalmatinephenolbetaine (8)16) in 60% yield. The structure of 8 was well established by the appearance of a low-field signal due to H-1 at δ 9.26 ppm as well as five methoxy signals in the proton nuclear magnetic resonance (1H-NMR) spectrum. Further irradiation17) of 8 in methanol with a mercury lamp in a stream of nitrogen effected valence isomerization to give the presumed intermediate (9), which immediately decomposed to afford the spirobenzylisoquinoline (10) in 81% yield through solvolysis in methanol. The product showed a carbonyl band at 1710 cm⁻¹ in the infrared (IR) spectrum and a high-field signal due to H-1 at δ 6.28 ppm (diagnostic of a spirobenzylisoquinoline skeleton)18) and six methoxy signals in the 1H-NMR spectrum. Sodium borohydride reduction of 10 afforded stereoselectively17) the hydroxy-acetal (11) in a quantitative yield. The trans relationship between the nitrogen and the hydroxy group in 11 was supported by the H-13 signal at δ 4.92 ppm in the 1H-NMR spectrum.17) Deacetalization of 11 with 10% hydrochloric acid afforded quantitatively the hydroxy-ketone (12).

On exposure to 10% sodium hydroxide in ethanol,13) 12 underwent retro-aldol reaction, recyclization, and dehydration successively to afford the expected ring D-inverted protoberberine (14) via the keto-aldehyde (13) in a quantitative yield. The structure of 14 was
supported by the chemical shift of an AB-quartet (7.38 and 7.25 ppm) due to the protons on ring D in comparison with that (8.52 and 7.43 ppm) of 8.

The structure of 14 was fully confirmed by an alternative and conventional synthesis. The protoberberine (18)\(^{19}\) was synthesized starting from 3,4-dimethoxyphenethylamine and 2,3-dimethoxyphenylacetic acid by a modification of the reported method.\(^{20}\) Reduction of 18 with lithium aluminum hydride (LAH) in tetrahydrofuran (THF) followed by oxidation with \(m\)-chloroperbenzoic acid (\(m\)-CPBA) in dichloromethane afforded the betaine (14) in 63\% yield. The product was identical with that obtained above.

Thus, we succeeded in the ring D inversion of palmatine (7) to the protoberberine (14), and therefore the next step is the transformation of 14 to the benzindenoazepine framework.

Irradiation\(^{17}\) of 14 in methanol with a mercury lamp in a stream of nitrogen afforded the 8,14-cycloberbine (15) in 78\% yield; this product showed a singlet due to the proton on the aziridine ring at \(\delta\) 3.79 ppm in the \(^1H\)-NMR spectrum. Treatment of 15 with \(p\)-toluenesulfonic acid (\(p\)-TsOH)\(^{14}\) effected regioselective C\(_{14}\)-N bond cleavage to afford the benzinde-noazepine (16) in 58\% yield. The product was identical with an authentic sample\(^1\) in IR and \(^1H\)-NMR spectra and thin layer chromatographic behavior. Since 17 has already been converted to (\(\pm\))-cis-alpinigenine (3) and (\(\pm\))-cis-alpine (4),\(^{10}\) the present synthesis of 17 amounts to a formal synthesis of these alkaloids.

Thus, we have developed a novel synthesis of (\(\pm\))-cis-alpinigenine and (\(\pm\))-cis-alpine and have provided a new general method for synthesis of rhoeadine alkaloids.

**Experimental**

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Organic extracts were dried over anhydrous Na\(_2\)SO\(_4\) and concentrated \textit{in vacuo}. Column chromatography was carried out with alumina (Aluminiumoxid 90, Aktivitätstufe II—III, 70—230 mesh, Merck) and silica gel (Kieselgel 60, 70—230 mesh, Merck). Preparative thin-layer chromatography (pTLC) was performed on alumina (Aluminiumoxid GF\(_{254}\), Typ 60/E, Merck). IR spectra were measured with a JASCO A-102 spectrometer, mass spectra (MS) with a Hitachi M-80 spectrometer, and \(^1H\)-NMR spectra with a JEOL FX-100 spectrometer in CDC\(_3\) using tetramethylsilane as an internal standard, unless otherwise stated. Irradiation was carried out with a 100W high-pressure mercury or halogen lamp with a Pyrex filter (Riko Kagaku Co.).

**5,6-Dihydro-2,3,8,9,10-pentamethoxydibenzo[a,g]quinolinizinium-13-olate (8-Methoxypalmatinephenolbetaine) (8)** — Palmatinium chloride (7) (505 mg) and rose bengal (1% methanol solution, 0.1 ml) were dissolved in a solution of methanol (50 ml) containing sodium methoxide (prepared from Na, 100 mg), and the resulting solution was irradiated with a halogen lamp at 0 °C for 20 min in a stream of oxygen. The reaction solution was adjusted to pH 7—8 with conc. HCl and concentrated at 30—35 °C. Aqueous K\(_2\)CO\(_3\) was added to the residue and the mixture was extracted with CH\(_2\)Cl\(_2\). The CH\(_2\)Cl\(_2\) layer was washed with sat. NaCl, dried, and concentrated. The residue was chromatographed on Al\(_2\)O\(_3\) with CH\(_2\)Cl\(_2\) and CH\(_2\)Cl\(_2\)-MeOH (99 : 1). The fraction eluted with CH\(_2\)Cl\(_2\)-MeOH was concentrated and the residue was washed with AcOEt to give the betaine (8) (310 mg, 60\%) as an orange powder. MS \(m/z\) (%): 397 (M\(^+\), 53), 382 (100). High-resolution MS \(m/z\): Calcld for C\(_{22}\)H\(_{23}\)NO\(_6\): 397.1523. Found: 397.1518. \(^1H\)-NMR \(\delta\): 9.26 (1H, s, C\(_6\)-H), 8.52, 7.43 (2H, AB-q, \(J=9.5\) Hz, C\(_{2}\)- and C\(_{11}\)-H), 6.70 (1H, s, C\(_4\)-H), 4.66 (2H, t, \(J=5.5\) Hz, C\(_6\)-H), 4.03 (6H, s, OCH\(_3\) \(\times 2\)), 4.00 (3H, s, OCH\(_3\)), 3.91 (6H, s, OCH\(_3\) \(\times 2\)), 3.01 (2H, t, \(J=5.5\) Hz, C\(_5\)-H).

**2,3,8,8,9,10-Hexamethoxynorochotensan-13-one (10)** — A solution of the betaine (8) (309 mg) in MeOH (200 ml) was irradiated with an Hg lamp at 0 °C for 1 h in a stream of nitrogen. The solution was evaporated off and the residue was chromatographed on Al\(_2\)O\(_3\) with CH\(_2\)Cl\(_2\) to give the spiropyrrolizinium (10) (134 mg, 66\%) as colorless needles, mp 168—169 °C (MeOH). IR \(\nu_{\text{CHCl}}\) cm\(^{-1}\): 1710 (CO). MS \(m/z\) (%): 429 (M\(^+\), 91), 414 (77), 398 (62), 382 (100). \(^1H\)-NMR \(\delta\): 7.63, 7.22 (2H, AB-q, \(J=8.5\) Hz, C\(_{12}\)- and C\(_{13}\)-H), 6.60 (1H, s, C\(_4\)-H), 6.28 (1H, s, C\(_2\)-H), 3.99, 3.90, 3.84, 3.46, 3.33, 3.21 (each 3H, s, OCH\(_3\) \(\times 6\)). Anal. Calcld for C\(_{23}\)H\(_{27}\)NO\(_7\): C, 64.32; H, 6.34, N, 3.26. Found: C, 64.12; H, 6.31; N, 3.34.

**rel-(13R,14S)-2,3,8,8,9,10-Hexamethoxynorochotensan-13-ol (11)** — Sodium borohydride (100 mg) was added portionwise to a stirred solution of the ketone (10) (134 mg) in MeOH (10 ml)—CHCl\(_3\) (3 ml) under ice cooling, and the mixture was stirred at the same temperature for 2 h. The solvents were evaporated off and the residue was taken
up in CHCl₃. The CHCl₃ layer was washed with sat. NaCl, dried, and concentrated. The residue was chromatographed on Al₂O₃ with CH₂Cl₂ to afford the alcohol (11) (110 mg, 98%) as colorless plates, mp 147—148 °C (iso-
Pr₂O). IR νCHCl₃ cm⁻¹: 3550 (OH). MS m/z (%): 416 (M⁺ - 15, 46), 399 (32), 368 (100). ¹H-NMR δ: 7.11 (1H, dd, J = 8.5, 1 Hz, C₁-H), 7.00 (1H, d, J = 8.5 Hz, C₁₁-H), 6.62 (1H, s, C₅-H), 6.13 (1H, s, C₁-H), 4.92 (1H, dd, J = 10, 1 Hz, C₁₂-H). 1H-ν (d, J = 1 Hz, by addition of D₂O), 3.89, 3.86, 3.84, 3.36, 3.35, 3.20 (each 3H, s, OCH₃ x 6). Anal. Calcd for C₁₅H₁₄NO₅: C, 64.02; H, 6.77; N, 3.81. Found: C, 64.12; H, 6.82; N, 3.81.

**rel-(15R,14S)-15-Hydroxy-2,3,9,10-tetramethoxychroman-8-one (12)** — Hydrochloric acid (10%, 6 ml) was added to a solution of the acetal (11) (110 mg) in MeOH (6 ml) and the reaction mixture was heated under reflux for 1 h. After evaporation of the MeOH, the residue was made alkaline with aqueous K₂CO₃, and extracted with CH₂Cl₂. The CH₂Cl₂ layer was washed with sat. NaCl, dried, and concentrated. The crude hydroxy-ketone (12) (98 mg, 100%) was recrystallized from iso-Pr₂O to give colorless plates, mp 125.7—129.5 °C. IR ν(CHCl₃ cm⁻¹: 3550 (OH), 1710 (CO). MS m/z (%): 385 (M⁺, 100), 326 (45), 192 (47). ¹H-NMR δ: 7.38 (1H, dd, J = 8 Hz, C₁-H), 7.30 (1H, d, J = 8 Hz, C₁₁-H), 6.66 (1H, s, C₅-H), 5.96 (1H, s, C₁-H), 5.16 (1H, d, J = 0.7 Hz, C₁-H), 4.03, 3.94, 3.84, 3.47 (each 3H, s, OCH₃ x 4). Anal. Calcd for C₁₅H₁₄NO₃: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.41; H, 5.98; N, 3.52.

**5,6-Dihydro-2,3,11,12-tetramethoxybenzo[a,g]quinolizinium-13-olate (13) (14)** — A solution of the hydroxy-ketone (12) (116 mg) and 10% aqueous NaOH (2 ml) in EtOH (6 ml) was heated under reflux with stirring for 40 min. The EtOH was evaporated off and the residue was extracted with CH₂Cl₂. The CH₂Cl₂ layer was washed with sat. NaCl, dried, and concentrated. The residue was chromatographed on Al₂O₃ with CH₂Cl₂—MeOH (49:1) to afford the betaine (14) (110 mg, 100%) as yellow needles, mp 162-164 °C (MeOH). MS m/z (%): 367 (M⁺, 85), 352 (100), 334 (33). High-resolution MS m/z: Caled for C₁₅H₁₄NO₃: 367.1413. ¹H-NMR δ: 7.81 (1H, s, C₁-H), 7.01, 6.66 (2H, AB-q, J = 8 Hz, C₉- and C₁₀-H), 6.54 (1H, s, C₄-H), 4.03, 3.94, 3.84, 3.47 (each 3H, s, OCH₃ x 4). Anal. Calcd for C₁₅H₁₄NO₃: C, 68.65; H, 5.76; N, 3.81.

**2,3,11,12-Tetramethoxy-8,14-cycloberbin-13-one (15)** — A solution of the betaine (14) (110 mg) in MeOH (150 ml) was irradiated with an Hg lamp at room temperature for 1 h in a stream of nitrogen. The solvent was evaporated off and the residue was chromatographed on SiO₂ with CH₂Cl₂—MeOH (4:1) to afford the dihydrobase (15) (105.7 mg) and p-TsOH (71 mg) in anhyd. C₆H₆ (10 ml) was heated under reflux for 1.5 h with stirring. The C₆H₆ was evaporated off and the residue was chromatographed on Al₂O₃ with CH₂Cl₂ to afford the dihydro base (1.529 g). A solution of m-CPBA (1.32 g) in CH₂Cl₂ (20 ml) was added dropwise to a stirred solution of the dihydro base (1.529 g) in CH₂Cl₂ (50 ml) at -20 °C for 15 min in a stream of nitrogen, and the mixture was stirred at room temperature for a further 1 h at the same temperature. The reaction temperature was allowed to rise to 0 °C, finely powdered Na₂SO₃ (2 g) was added to the reaction solution and the mixture was stirred vigorously at room temperature for 1 h. The inorganic precipitates were filtered off and the filtrate was concentrated to dryness. The residue was treated as described in 1) to afford the betaine (14) (1.064 g, 63%) which was identical with that obtained in 1).

**2,3,11,12-Tetramethoxy-7-methylbenzo[d]indeno[1,2-b]azepin-13-one (17)** — Sodium hydride (40 mg, 50%, mineral oil dispersion) was added to a solution of the azepine (16) (59 mg) in HMPA (0.5 ml) and anhyd. C₆H₆ (2 ml). The resulting solution was stirred at room temperature for 15 min. Dimethyl sulfate (3 drops) was added to the stirred solution and stirring was continued at room temperature for 1 h. Aqueous NH₄ (28%, 1 ml) was added to the reaction mixture and stirring was continued at room temperature for 30 min. The reaction mixture was extracted with CHCl₃. The CHCl₃ layer was washed with water, dried, and evaporated to dryness. The residue was subjected to pTLC [Al₂O₃, C₆H₆—AcOEt (4:1)] to afford the N-methyl derivative (17) (48 mg, 78%) as reddish purple prisms, mp 164—166 °C (MeOH) (lit. 190—191 °C). IR ν(CHCl₃ cm⁻¹: 1650 (CO). MS m/z (%): 381 (M⁺, 100), 366 (53). ¹H-NMR δ: 7.81 (1H, s, C₁-H), 7.01, 6.66 (2H, AB-q, J = 8 Hz, C₉- and C₁₀-H), 6.54 (1H, s, C₄-H), 4.01, 3.94, 3.87, 3.85 (each 3H, s, OCH₃ x 4), 3.95—3.60 (2H, m, C₅-H), 3.40—2.80 (2H, m, C₅-H). Anal. Calcd for C₂₁H₂₁NO₅: C, 69.28; H, 6.08; N, 3.67. Found: C, 69.18; H, 6.13; N, 3.39. The product was identical with an authentic specimen (IR and ¹H-NMR spectra, and mixed melting point).
The yellow precipitates were collected by filtration to give the quaternary base (18) (3.9 g, quant.) as yellow needles, mp 138-138.5 °C (lit. mp 130-130.5 °C). IR νCHCl3 max cm⁻¹: 1650 (CO). MS m/z: 359 (M⁺). ¹H-NMR δ: 7.11-6.53 (6H, m, Ar-H), 5.88 (1H, brs, NH), 3.87, 3.85, 3.83, 3.78 (each 3H, s, OCH3 ≈ 4), 3.53 (2H, s, COCH2), 3.39 (2H, t, J = 6.5 Hz, NHCH2), 2.67 (2H, t, J = 6.5 Hz, ArCH2CH2). Anal. Calcd for C20H25NO5: C, 66.83; H, 7.01; N, 3.90. Found: C, 66.83; H, 7.08; N, 3.92.

Sulfur dioxide gas was passed through a suspension of the precipitates in water (20 ml) for 2 h with stirring. After the reaction mixture had cooled to room temperature, the precipitates were collected by filtration. A solution of the crude amine (8.5 g) and 37% HCHO (105 ml) in MeOH (105 ml) was added dropwise to a refluxing solution of the tetrahydroprotoberberine (8.2 g, 97%) which was recrystallized from MeOH to afford pale yellow needles, mp 167-167.5 °C (lit. mp 162-163 °C). IR νCH₃ max cm⁻¹: 3200 (CH₃), 3050 (CH). ¹H-NMR δ: 6.81 (1H, s, C₄-H), 6.79 (2H, s, C₉- and C₁₀-H), 6.62 (1H, s, C₆-H), 3.92, 3.87, 3.85, 3.81 (each 3H, s, OCH₃ × 4). Anal. Calcd for C₂₅H₂₃NO₄: C, 70.96, H, 7.09; N, 3.94. Found: C, 70.95; H, 7.10; N, 4.03.

A solution of I₂ (7.3 g) in EtOH (40 ml) was added dropwise to a refluxing solution of the tetrahydroprotoberberine (3.0 g) and AcOK (4.7 g) in EtOH (200 ml) with stirring for 1 h, and stirring was continued at the same temperature for 1.5 h. After the reaction mixture had cooled to room temperature, the precipitates were collected by filtration. The yellow precipitates were washed with water, dried, and concentrated to leave the oily imine (8.5 g). Sodium borohydride (1.2 g) was added portionwise to a solution of the imine (8.5 g) in MeOH (130 ml) and stirring was continued at room temperature for 6 h. The MeOH was evaporated off and the residue was taken up in CHCl₃ and washed with water, dried, and concentrated to leave the oily imine (8.5 g, quant.). A solution of the crude amine (8.5 g) and 37% HCHO (105 ml) in MeOH (105 ml) was added dropwise to a refluxing solution of the tetrahydroprotoberberine (8.2 g, 97%) which was recrystallized from MeOH to afford pale yellow needles, mp 167-167.5 °C (lit. mp 162-163 °C). IR νCH₃ max cm⁻¹: 3200 (CH₃), 3050 (CH). ¹H-NMR δ: 6.81 (1H, s, C₄-H), 6.79 (2H, s, C₉- and C₁₀-H), 6.62 (1H, s, C₆-H), 3.92, 3.87, 3.85, 3.81 (each 3H, s, OCH₃ × 4). Anal. Calcd for C₂₅H₂₃NO₄: C, 70.96, H, 7.09; N, 3.94. Found: C, 70.95; H, 7.10; N, 4.03.

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References and Notes

21) All spirobenzylisoquinolines in this paper were named and numbered according to the spirobenzylisoquinoline alkaloid skeleton, ochotensan.23)
22) The numbering of the benzindenoazepines described in this paper is in accord with that for protoberberines.